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INFLUÊNCIA DO TIPO DE PARTO NA COMPOSIÇÃO DA MICROBIOTA INTESTINAL INFANTIL: UMA REVISÃO SISTEMÁTICA DE LITERATURA, CONSIDERANDO O PAPEL DO ALEITAMENTO MATERNO

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Luciana Princisval da Silva

Dissertação apresentada ao Programa de Pós-Graduação em Nutrição (PPGN), do Instituto de Nutrição Josué de Castro da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários à obtenção do título de **mestre em Nutrição Humana.**

Orientador: Gilberto Kac
Co-orientadora: Fernanda Rebelo Santos

Rio de Janeiro
Fevereiro 2020

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Examinada por:

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Prof. Dr. Gilberto Kac (orientador) - Universidade Federal do Rio de Janeiro (UFRJ)

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Dedico essa dissertação a meus pais, minha irmã e minha avó. O zelo e dedicação de vocês foram essenciais.

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Epígrafe

“A fé na vitória tem que ser inabalável.”
(Marcelo Falcão/Tom Saboia)

Sumário

Lista de Quadros

Board List

Lista de Tabelas

Table List

Lista de Figuras

List of Figures

Lista de Anexos

Lista de abreviatura e siglas (bilíngue)

Abreviatura/Sigla	Significado
BF	*Breastfeeding*
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CBF	*Complementary breastfeeding*
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
CS	*Cesarean section*
DGGE	*Denaturing gradient gel electrophoresis and degenerating gradient gel electrophoresis*
EBF	*Exclusive breastfeeding*
EMBASE	*Electronic database of publisher Elsevier*
FISH	*Fluorescence in situ hybridization*
GRADE	*Grading of Recommendations, Assessment, Development and Evaluation*
HMOs	Oligossacarídeos do leite humano (*Human milk oligosaccharide*)
MA	Meta-análise
MBF	*Mixed breastfeeding*
MEDLINE	*Medical Literature Analysis and Retrieval System Online*
MESH	*Medical Subject Headings*
MOOSE	*Meta-analysis of Observational Studies in Epidemiology*
OMS	Organização Mundial da Saúde
PCR	*Polymerase chain reaction*
PPGN	Programa de Pós-Graduação em Nutrição
PRISMA	*Preferred Reporting Items for Systematic reviews and Meta-Analyses*
PROSPERO	*International Prospective Register of Systematic Reviews*
PUBMED	*US Natural library of medicine*
RN	Recém-nascido
RSL	Revisão sistemática de literatura
SCOPUS	*Elsevier's scientific abstracts and citations database*
VD	*Vaginal delivery*

Apresentação

O presente documento foi elaborado a partir do projeto de pesquisa desenvolvido para a dissertação de mestrado acadêmico no Programa de Pós-Graduação em Nutrição (PPGN). O projeto intitula-se 'Influência do tipo de parto com a composição da microbiota intestinal infantil até os seis meses de idade: uma revisão sistemática de literatura, considerando o papel do aleitamento materno'. O presente trabalho está estruturado com as seguintes seções: Resumo/*abstract*, introdução, referencial teórico, objetivos, justificativa, hipótese, métodos, resultados, conclusão, referências e anexos.

A coleta de dados contemplou as etapas de busca bibliográfica, leitura dos estudos, extração dos dados e avaliação da qualidade. As etapas de extração dos dados e avaliação da qualidade foram realizadas com o auxílio de formulários desenvolvidos exclusivamente para o estudo. Os resultados da dissertação foram apresentados em formato de artigo, contidos no manuscrito que será submetido para publicação. Apesar de o manuscrito já estar finalizado, o mesmo será atualizado para permitir a inclusão de artigos publicados no ano de 2019.

O manuscrito deverá ser publicado em alguma revista com conceito Qualis A1 segundo área de Nutrição da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), como a *Gut Pathogens* ou *Clinical Journal of microbiology and infection*.

A aluna foi apoiada pelas instituições de fomento CAPES e do Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), por meio de bolsa de mestrado.

Resumo da dissertação apresentada ao PPGN/UFRJ como parte dos requisitos necessários para a obtenção do grau de **mestre em Nutrição Humana**.

INFLUÊNCIA DO TIPO DE PARTO NA COMPOSIÇÃO DA MICROBIOTA INTESTINAL INFANTIL: UMA REVISÃO SISTEMÁTICA DE LITERATURA, CONSIDERANDO O PAPEL DO ALEITAMENTO MATERNO

Luciana Princisval da Silva

Fevereiro /2020

Orientador: Gilberto Kac

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RESUMO

A microbiota desempenha funções importantes à saúde do hospedeiro e alterações na sua composição podem estar associadas a desfechos negativos. O parto cesáreo pode estar associado negativamente à microbiota intestinal infantil e a amamentação pode modificar essa associação. O objetivo deste estudo foi sistematizar as evidências de associação entre o tipo de parto e a microbiota intestinal de crianças até os seis meses de idade e avaliar o potencial papel da amamentação nessa associação. Trata-se de uma revisão sistemática de literatura, que foi registrada no *International Prospective Register of Systematic Reviews (*PROSPERO). As bases de dados foram: Medline/Pubmed, *Web of Science*, Scopus, Embase, *Trip Medical Database* e *Open Grey*. O risco de viés foi avaliado com o auxílio do *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE). Foram incluídos estudos de coorte prospectiva, que realizaram ≥2 coletas fecais da criança ao longo dos seis meses de vida, que apresentassem informações sobre o tipo de parto (vaginal e cesárea) e a comparação da microbiota intestinal entre os tipos de parto. O uso de probiótico materno-infantil, e condições que possam alterar a microbiota foram considerados como critérios de exclusão. Foram selecionados 2.096 resumos para leitura e 217 artigos foram lidos na íntegra. Após essas etapas, 31 estudos foram selecionados para a extração de dados por meio do formulário desenvolvido para este estudo. Crianças nascidas por parto cesáreo apresentaram menor colonização do gênero *Bifidobacterium* e *Bacteroides* (e *Bacteroides fragilis*), ao longo dos seis meses de vida. O grupo nascido de parto cesáreo apresentou menor colonização do gênero *Lactobacillus* no terceiro mês e das espécies *Bifidobacterium longum, Bacteroides*

vulgatus e *Bacteroides uniformis* no primeiro mês de vida e *Escherichia coli* na primeira semana de vida, enquanto *Clostridium perfringens* esteve aumentado no terceiro mês. Crianças nascidas por parto cesáreo e em amamentação exclusiva apresentaram a microbiota mais semelhante à de nascidos por parto vaginal. Resultados para *Bifidobacterium* foram mais prevalentes na Ásia, e *Bacteroides* e *E.coli* no Centro e Sul Europeu, respectivamente. Dezesseis por cento dos estudos apresentaram baixo risco de viés. Os gêneros *Bifidobacterium* e *Bacteroides* (e *B. fragilis*) foram potencialmente inferiores em crianças nascidas por parto cesáreo. Ainda nesse grupo, há tendências de que a colonização do gênero *Lactobacillus* e das espécies *B. longum, B. catenulatum, B. vulgatus, B. uniformis* e *E. coli* sejam menores e *C. perfringens* ser aumentada. Os resultados dessas associações podem ser modificados pela amamentação, no entanto, ainda são necessários mais estudos que confirmem esses resultados. Supostamente, a colonização dos gêneros *Bifidobacterium* é maior em crianças da Ásia, enquanto *Bacteroides* na Europa Central e *E. coli* na Europa Nórdica. Supõe-se que os trinta e um estudos gerem baixa evidência sobre o tema.

Palavras-chave: microbiota, tipo de parto, revisão sistemática de literatura, intestino, lactente, aleitamento materno, bifidobacterium, bacteroides.

IMPACT OF MODE OF DELIVERY ON INFANT GUT MICROBIOTA COMPOSITION UP TO 6 MONTHS OF AGE: SYSTEMATIC LITERATURE REVIEW, CONSIDERING THE ROLE OF BREASTFEEDING

Luciana Princisval da Silva

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Advisors: Gilberto Kac

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ABSTRACT

The microbiota performs important role in the health of the host and changes in this composition may be associated with negative outcomes. Cesarean section may be negatively associated with infant gut microbiota and breastfeeding may modify this association. This dissertation aims to systematize the evidence of an association between the mode of delivery and the gut microbiota of infants up to six months of age and to evaluate the potential role of breastfeeding in this association. This is a systematic review of the literature, which was registered in the International Prospective Register of Systematic Reviews (PROSPERO). The databases were: Medline/Pubmed, Web of Science, Scopus, Embase, Trip Medical Database and Open Grey. The risk of bias was assessed with the aid of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). Prospective cohort studies, which performed ≥2 fecal collections from the infant over the six months of life, that included information on the mode of delivery (vaginal and cesarean) and the comparison of the gut microbiota between mode of delivery, were included. The use of maternal and infant probiotics, and conditions that may alter the microbiota were considered as exclusion criteria. 2,096 abstracts were selected for reading and 217 articles were read in full. After these steps, 31 studies were selected for data extraction using the form developed for this study. Infants born by cesarean section had lower colonization of the genus *Bifidobacterium* and *Bacteroides* (and *Bacteroides fragilis*), over the six months of life. The group born by cesarean section showed less colonization of the genus *Lactobacillus* in the third month and of the species *Bifidobacterium longum*, *Bacteroides vulgatus* and *Bacteroides uniformis* in the first month of life and *Escherichia coli* in the first week of life, while *Clostridium perfringens* was increased in the third month. Infants born by cesarean section and exclusively

breastfeeding had the most similar microbiota to those born by vaginal delivery. Results for *Bifidobacterium* were more prevalent in Asia, and *Bacteroides* and *E.coli* in Central and Southern Europe, respectively. Sixteen percent of the studies had a low risk of bias. The genus *Bifidobacterium* and *Bacteroides* (and *B. fragilis*) were potentially inferior in infants born by cesarean section. Also in this group, there are trends that the colonization of the genus *Lactobacillus* and the species *B. longum*, *B. catenulatum*, *B. vulgatus*, *B. uniformis* and *E. coli* are smaller and *C. perfringens* be increased. The results of these associations can be modified by breastfeeding, however, further studies are needed to confirm these results. The colonization of the genera *Bifidobacterium* is supposed to be greater in children in Asia, while *Bacteroides* in Central Europe and *E. coli* in Nordic Europe. It is supposed that the thirty-one studies generate low evidence on the subject.
Key-word: microbiota, mode of delivery, systematic review of literature, gut, infant, breastfeeding, bifidobacterium, bacteroides.

1. Introdução

O trato gastrointestinal é composto por vírus, fungos, *archae* e em especial bactérias, que compõe 90% da população do organismo. Esse conjunto de microrganismos é denominado microbiota intestinal (LEDERBERG; MCCRAY, 2001; TURNBAUGH et al., 2007). Resumidamente, a microbiota é composta por bactérias potencialmente benéficas à saúde (mutualistas e comensais) e por bactérias patogênicas (oportunistas). O intestino é um importante reservatório desses microrganismos, e dessa forma, a maior parte dessas bactérias reside nesse órgão (PALMER et al., 2007). Essas bactérias interagem com o organismo humano em relação de simbiose (mutualismo), o que resulta em manutenção da saúde do hospedeiro (PETERSON et al., 2009; CLEMENTE et al., 2012; COSTELLO et al., 2012). A disbiose é uma condição na qual há desequilíbrio dessas bactérias que interagem beneficamente com o hospedeiro (LEY, 2010; JARCHUM; PAMER, 2011; HUMAN MICROBIOME PROJECT, 2012). Em condições normais, a concentração desses microrganismos está em equilíbrio, porém quando há desproporcionalidade entre ambos pode gerar impacto à saúde (BÄCKHED et al., 2012; BELIZÁRIO; FAINTUCH et al., 2018). Essas bactérias e seus metabólitos agem na fisiologia humana, desempenhando papel importante na manutenção da saúde, e dessa forma, relações de desequilíbrio podem favorecer o desenvolvimento de doenças (ABRAHAMSSON et al., 2012; COSTELLO et al., 2012; ABRAHAMSSON et al., 2014; DELZENNE et al., 2015; GREENHALGH et al., 2016).

Há evidências de que o intestino infantil seja colonizado no período perinatal (AAGARD et al., 2014; COLLADO et al., 2016) e diante disso, a microbiota apresenta papel importante, pois atua em mecanismos de proteção à saúde (defesa contra microrganismos patogênicos) e na digestão e metabolização de compostos do leite materno e fórmula infantil (GUARNER; MALAGELADA, 2003; PENDERS et al., 2013; SHREINER ; KAO; YOUNG, 2015). A quantidade exata de microrganismos que compõe a microbiota ainda é desconhecida, no entanto sabe-se que nos primeiros meses de vida, os filos mais encontrados são *Proteobacteria*, *Actinobacteria*, *Firmicutes* e *Bacteroidetes* (KOENIG et al., 2011; SPOR et al., 2011; OTTMAN et al., 2012; LANDMAN et al., 2016).

O tipo de parto é um fator reconhecidamente importante e que influencia a colonização bacteriana do recém-nascido (RN). Diversos estudos relatam que a

composição da microbiota de crianças nascidas por parto cesáreo é diferente das nascidas por parto vaginal (NURIEL-OHAYON et al., 2016; RUTAYISIRE et al., 2016; DOBBLER et al., 2019). A microbiota intestinal infantil em crianças em aleitamento materno possui uma menor diversidade de bactérias (HARMSEN et al., 2000; BÄCKHED et al., 2015; RAUTAVA, 2016), porém estudos demonstram haver maior diversidade de bactérias em crianças nascidas por parto cesáreo (AZAD et al., 2013; HO et al., 2018). O leite materno é o único alimento preconizado durante os seis primeiros meses de vida (OMS, 2007). Assim, espera-se que a microbiota intestinal seja menos diversa nesse período. Ao comparar a microbiota intestinal de crianças nascidas de parto normal e cesáreo, respectivamente, há quase unanimidade sobre a diferença entre a composição da microbiota de ambos, porém muitos estudos só consideram o efeito do tipo de parto nessa associação, e não combinam esse efeito ao tipo de aleitamento (PHAM et al., 2016; RUTAYISIRE et al., 2016).

Independentemente de o tipo de parto estar associado a microbiota infantil, é necessário que o papel modificador de efeito do aleitamento materno seja considerado no estudo dessas associações (MILANI et al., 2017; HO et al., 2018). Dessa forma, é possível observar se ainda há vieses sobre a referida associação. Diversos estudos já foram conduzidos sobre o assunto, mas a descrição comparativa de determinados grupos de bactérias por tipo de parto não reflete o efeito na saúde infantil, e a partir disso ainda é necessário que estudos futuros associem determinados grupos de bactérias em doenças (RUTAYISIRE et al., 2016).

2. Referencial teórico

2.1 Tipo de parto

O ato de nascer ocorre com ausência de complicações na maior parte dos casos (OMS, 2018). No entanto, estudos demonstram que mulheres sem risco podem ser submetidas à intervenções durante o parto, como indução medicamentosa, uso de ocitocina e antibióticos, realização de episiotomia e aminiostomia, parto instrumental (fórceps) e cesáreo (COULM et al., 2012; EUROPEAN PERINATAL HEALTH REPORT, 2013; RENFREW et al., 2014; BRASIL, 2017; OMS, 2018).

A grande parte dos 140 milhões de partos por ano ocorram sem complicações para a mãe e para o RN (UNICEF, 2016b), no entanto a escolha do tipo de parto ainda é tema controverso em vários países (OMS, 1985; SOUZA et al., 2014). Ainda assim, dados de 121 países demonstraram que as prevalências de parto do tipo cesáreas aumentaram de 6,7% em 1990 para 19,1% em 2014 (OMS, 2018). Esse aumento ocorreu sem nenhuma razão justificável segundo diversos autores (MAZZONI et al., 2011; LIU et al., 2013; MAZZONI et al., 2016). Estudos mostram que o parto cesáreo não é a preferência entre gestantes saudáveis e, ainda que condutas sem o consentimento da mulher não sejam éticas, intervenções médicas desnecessárias que interferem no processo natural do parto ainda são prevalentes (MAZZONI et al., 2011; MAZZONI et al., 2016; OMS, 2018).

A escolha do tipo de parto deve ser de acordo com os benefícios e riscos envolvidos (UNICEF, 2017). O parto vaginal, definido como parto normal, inicia-se de forma espontânea, gerando baixo risco durante o trabalho de parto até o nascimento. O RN nasce espontaneamente, em posição cefálica de vértice, entre 37 e 42 semanas completas de gestação, conferindo baixo risco ao binômio mãe-filho no período pós-parto (OMS, 1996). O parto cesáreo é um procedimento cirúrgico que inclui incisão abdominal para extração do concepto do útero materno durante o trabalho de parto, o que pode reduzir a mortalidade materna e fetal em casos de gestações complicadas (OMS, 1985). O parto instrumental, mais conhecido como fórceps ou ventosa, não é mais utilizado, e é caracterizado pela aplicação de um instrumento (ventosa, fórceps ou espátula) para auxílio da extração do feto (HOOK; DAMOS, 2008). Não há evidência que os partos cirúrgicos eletivos e o instrumental tragam benefícios, muito pelo contrário, podem gerar riscos à saúde materno-fetal a curto ou longo prazo, como sequelas ou morte, além de aumentar gastos desnecessários (OMS, 1985; BELIZAN et al., 2007; LOURENÇO et al., 2012; NASCER NO BRASIL, 2012; OMS, 2015; MASCARELLO et al., 2018). O uso

de medicamentos, maior tempo de internação, a maior demanda por profissionais e o consumo de energia em sala de cirurgia são alguns dos fatores que contribuem para o maior custo nesse tipo de parto quando comparado ao parto vaginal (ENTRINGER; PINTO; GOMES, 2018).

A Organização Mundial da Saúde (OMS) alerta que não há justificativa para que ocorram prevalências de parto cesáreo superiores a 15%, dado que trata-se de um procedimento cirúrgico (OMS, 1985; NASCER NO BRASIL, 2012; OMS, 2015). Entretanto, atualmente destacam-se prevalências de nascimentos do tipo cesariana em 56% dos partos ocorridos no Brasil e 16% no mundo (OMS, 2013; OMS, 2015; DATASUS, 2017). Um estudo com dados provenientes da Pesquisa Nacional e Demografia e Saúde da Criança e da Mulher (PNDS) de 2006, demonstrou prevalência de 33,2% e 77,2% de cesarianas realizadas em hospitais do setor público e privado, respectivamente (REBELO et al., 2010). Posteriormente, os resultados do estudo 'Nascer no Brasil', um inquérito nacional sobre a situação atual da atenção ao parto e nascimento, revelou prevalências de 52% e 88% de partos cesáreos realizados nos setores públicos e privados, respectivamente (NASCER NO BRASIL, 2012).

Estudos revelaram que a realização de um parto cesáreo em gestações complicadas pode reduzir o risco de mortalidade materno-infantil (BELIZAN et al., 2007; OMS, 2009; OMS, 2015; MASCARELLO et al., 2017). Esse tipo de parto, apesar de ser uma via supostamente segura para o RN, pode gerar desfechos maternos desfavoráveis, como ruptura uterina, infertilidade e complicações em gestações futuras (SU, 2007; SOUZA et al., 2014; KEAG et al., 2018; SANDALL et al., 2018). A realização de cesarianas deve ser sempre justificada segundo critérios clínicos, como o diagnóstico de placenta prévia ou de posicionamento fetal inadequado, hipertensão arterial materna não controlada, e hiperglicemia materna não controlada (BRASIL, 2010). Assim como qualquer cirurgia, a realização de cesariana confere riscos, e as complicações podem ser agravadas em locais sem infraestrutura ou condições adequadas para realização de tal procedimento ou nos quais haja incapacidade de tratar possíveis complicações pós-operatórias (OMS, 1985).

Apesar de evidências mostrarem indícios de efeitos à saúde, mais estudos neste âmbito devem ser conduzidos para elucidar os efeitos imediatos e em longo prazo da realização do parto cesáreo sobre a saúde materno-infantil (OMS, 2015). Diversos autores vêm demonstrando possíveis associações do parto cesáreo com desfechos infantis desfavoráveis, entre eles, o risco aumentado para obesidade infantil (HUH et al., 2012; KEAG et al., 2018), diabetes mellitus (VEHIK; DABELEA, 2012), doença celíaca

(MÅRILD et al., 2012), asma (SEVELSTED et al., 2016; KEAG et al., 2018) e alterações cognitivas (POLIDANO et al., 2017). Além dessas alterações, destaca-se a presença de modificações na diversidade bacteriana intestinal (RUTAYISIRE et al., 2016). O tipo de parto vem sendo amplamente associado à composição bacteriana intestinal do RN, porém essa relação complexa ainda precisa ser melhor elucidada (NURIEL-OHAYON et al., 2016; RUTAYISIRE et al., 2016; SANDALL et al., 2018).

2.2 Composição da microbiota intestinal infantil

Um conjunto de microrganismos presentes em um meio específico é definido como microbiota, que é constituído por trilhões de células microbianas (LEDERBERG; MCCRAY, 2001; TURNBAUGH et al., 2007). A combinação dessas células e o conjunto de genes é denominado microbioma (TURNBAUGH et al., 2007). Esse conjunto de bactérias interage dinamicamente com seu hospedeiro e o ambiente (PETERSON et al., 2009; COSTELLO et al., 2012; CLEMENTE et al., 2012). A maior parte dessas bactérias são encontradas no intestino, que é um importante reservatório e o que apresenta a maior diversidade quando comparada a outras partes do corpo. Essas bactérias parecem apresentar um papel importante na saúde humana, como a preparação do sistema imune do hospedeiro. Essas bactérias também podem causar doenças na presença de disbiose (PALMER et al., 2007; LEY, 2010; JARCHUM; PAMER, 2011; HUMAN MICROBIOME PROJECT, 2012).

A microbiota, em razão de apresentar alto potencial de interferência na fisiologia humana, quando em condições de desequilíbrio pode estar associada à obesidade, desnutrição, alergias, diabetes tipo 2, doenças inflamatórias da pele e do trato gastrointestinal (ABRAHAMSSON et al., 2012; COSTELLO et al., 2012; ABRAHAMSSON et al., 2014; DELZENNE et al., 2015;GREENHALGH et al., 2016). Esses microrganismos podem interferir em funções metabólicas, como proteção contra patógenos ou em relação de comensalismo, na qual o sistema imune tolera a presença de bactérias no organismo (SHREINER; KAO; YOUNG, 2015). Diante disso, a microbiota intestinal apresenta grande importância logo após o nascimento e no período da infância, pois além de atuar na proteção contra microrganismos patogênicos, também age na digestão e na metabolização de compostos do leite materno e de fórmula infantil, no sistema imune, na homeostase, no crescimento e proliferação celular e no

desenvolvimento cerebral (GUARNER; MALAGELADA, 2003; PENDERS et al., 2013; SHREINER; KAO; YOUNG, 2015; MARTIN et al., 2016).

Durante mais de um século acreditava-se na hipótese do ‘útero estéril’, na qual o RN nascia estéril (TISSIER, 1900). Porém ao longo dos anos, diversos estudos passaram a contestar o dogma e demonstraram haver presença de bactérias nesse órgão, e que essas possivelmente poderiam ser transferidas verticalmente pela placenta ao feto. Dessa forma, o feto já estaria em contato com bactérias maternas desde antes do nascimento (AAGARD et al., 2014; COLLADO et al., 2016; ZHU et al., 2018; STINSON et al., 2019). Intrigantemente, alguns estudos mais recentes demonstraram não haver colonização na placenta, revelando que esse órgão não apresenta bactérias com capacidade de colonização (LEIBY et al., 2018; GOFFAU et al., 2019; SEGATA, 2019).

O desenvolvimento da microbiota é um processo dinâmico e progressivo, além de apresentar diferenças significativas na composição e diversidade ao longo da vida (DOMINGUEZ-BELLO et al., 2011). A microbiota intestinal é estabilizada ao longo do tempo, e dessa forma, o RN apresenta menor diversidade de bactérias do que a de um adulto (DOMINGUEZ-BELLO et al., 2011; YANG et al., 2016). A microbiota infantil alcança a maturidade e diversidade semelhante a de um adulto saudável somente a partir dos 2-3 anos de idade (KOENIG et al., 2011; YATSUNENKO et al., 2012). A composição da microbiota intestinal apresenta grande variedade intra-individual, porém após o nascimento, a mesma é geralmente composta por microrganismos anaeróbios e facultativos, o que reduz as concentrações de oxigênio no intestino e consequentemente favorece uma maior proliferação de bactérias anaeróbicas nesse órgão (KOENIG et al., 2011; DEL CHIERICO et al., 2015). A microbiota pode ser classificada taxonomicamente em filo, classe, ordem, família, gênero e espécie (RINNINELLA et al., 2019). Durante o período neonatal, a microbiota intestinal é composta inicialmente pelos filos *Proteobacteria*, *Actinobacteria*, e posteriormente também por *Firmicutes* e *Bacteroidetes* (SPOR et al., 2011; OTTMAN et al., 2012; LANDMAN et al., 2016).

Destacam-se os gêneros *Escherichia* (espécie *Escherichia coli*) no filo *Proteobacteria*, *Bifidobacterium* (espécie *Bifidobacterium longum*) no filo *Actinobacteria*, *Clostridium* (espécie *Clostridium perfringens*) e *Lactobacillus* no filo *Firmicutes*, *Bacteroides* (espécie *Bacteroides fragilis)* e *Prevotella* no filo *Bacteroidetes* (RINNINELLA et al., 2019). Essas bactérias têm ações específicas no organismo, e diante disso, os gêneros *Bifidobacterium* e *Lactobacillus* são reconhecidos por apresentarem papel probiótico e dessa forma, reduzirem o crescimento de patógenos intestinais

(PANNARAJ et al., 2017). A espécie *B. longum* possui ação importante na digestão de compostos bioativos (UNDERWOOD et al., 2015). O gênero *Bacteroides* (espécie *B. fragilis)* apresentam papel importante na maturação celular e resistência à patógenos (WEXLER et al., 2017). A espécie *C. perfringens* pode levar a produção de toxinas e consequentemente aumentar o risco de desenvolvimento de doenças (KIU et al., 2018). O gênero *Prevotella* na maior parte dos casos atua como uma bactéria comensal, ou seja, não há aumento do risco de doenças para o indivíduo (PRECUP; VODNAR, 2019). Por outro lado a espécie *E. coli*, que também possui ação comensal, além de atuar no metabolismo e no processo celular, também produz fatores de virulência, que podem aumentar o risco de doenças (RILEY, 1993; MULLIGAN; FRIEDMAN, 2017).

Ainda no período neonatal, há muitos fatores que podem influenciar na formação da microbiota intestinal, entre eles o uso de antibiótico, uso de fórmulas infantis, a amamentação e em especial, o tipo de parto (LOZUPONE et al., 2012; MUELLER et al., 2015; MARTIN et al., 2016). Sendo assim, diversos estudos sugerem que o tipo de parto (cesárea ou vaginal) pode ter efeito negativo na transferência microbiana inicial da mãe para o RN (NURIEL-OHAYON et al., 2016; RUTAYISIRE et al., 2016; DOBBLER et al., 2019). Em condições normais, a microbiota da vagina é composta quase integralmente pelo gênero *Lactobacillus*, que são responsáveis pela produção de ácido lático por meio da fermentação. Dessa forma, esse gênero contribui para a manutenção de um ambiente ácido, e consequentemente reduz a proliferação de microrganismos patogênicos (BOSKEY et al., 1999; TACHEDJIAN et al., 2017). Os RN por parto vaginal são rapidamente colonizados pelas bactérias presentes na vagina materna, enquanto os nascidos por parto cesáreo apresentam colonização pelas bactérias presentes na pele materna (DOMINGUEZ-BELLO et al., 2010; BÄCKHED et al., 2015; NAYFACH et al., 2016). A ausência desse contato com a microbiota materna vaginal faz com que esses RN sejam expostos a um ambiente mais estéril após o nascimento, o que consequentemente pode gerar maior risco de desordens imunológicas e metabólicas (MARTIN et al., 2016; SEVELSTED et al., 2015).

Nesse contexto, um estudo piloto realizado por Dominguez-Bello et al. (2016) selecionou 59 RN de parto cesáreo expondo-os à uma gaze com fluídos da microbiota vaginal materna imediatamente após o parto. A exposição ocorreu nos lábios, face, tórax, braços, pernas, órgãos genitais e ânus dos RN. Em relação à microbiota de todo o corpo, os autores demonstraram que essa intervenção gerou resultados nos quais foram observados maior semelhança de bactérias presentes na microbiota vaginal até o primeiro

mês de vida, quando comparado aos nascidos de parto cesáreo não expostos à microbiota vaginal. Foram observadas concentrações significativas de *Lactobacillus* na microbiota intestinal imediatamente após o nascimento tanto nos RN expostos como nos que nasceram de parto vaginal. Porém, ao realizar a comparação da composição bacteriana dos RN de acordo com o tipo de parto, encontrou-se diferença somente nas microbiotas oral e cutânea dos RN de parto cesáreo (DOMINGUEZ-BELLO et al., 2016). Esses resultados sugerem que os microrganismos podem ser parcialmente restaurados em nascidos de parto cesáreo, demonstrando o benefício do parto vaginal, e tem como direções futuras, a realização de estudos em amostras maiores, além de avaliar essa prática nos efeitos à saúde infantil em longo prazo.

O tipo de parto tem sido observado como o fator que mais modifica a colonização intestinal no início da vida (BIASUCCI et al., 2008; DOMINGUEZ-BELLO et al., 2010; JAKOBSSON et al., 2014; RUTAYISIRE et al., 2016). Alguns estudos observaram que o tipo de parto pode alterar a composição da microbiota intestinal durante os seis primeiros meses de idade (GRÖNLUND et al., 1999; PENDERS et al., 2006; DOMINGUEZ-BELLO et al., 2010; HESLA et al., 2014). Um estudo de revisão narrativa realizado em 2016 destacou que há mudanças intensas na composição, diversidade e riqueza da microbiota intestinal em RN de diferentes tipos de parto (NURIEL-OHAYON, 2016). Ainda que estudos atuais retornem ao princípio do ‘útero estéril’ e consequentemente a ausência do contato bacteriano vertical (LEIBY et al., 2018; GOFFAU et al., 2019; SEGATA, 2019), diversos estudos contribuem para a possível colonização precoce no momento do parto (JIMÉNEZ et al., 2008; COLLADO et al., 2016; RUTAYISIRE et al., 2016). Esses resultados são relevantes para melhorar o entendimento sobre a importância da microbiota intestinal no início da vida (NURIEL-OHAYON, 2016; RUTAYSIRE et al., 2016).

2.3 Tipo de parto como preditor da composição da microbiota intestinal infantil

A associação entre o tipo de parto e microbiota já foi investigada por diversos estudos ao longo dos anos (MUNYAKA et al., 2014; MILANI et al., 2017). Esse conjunto inicial de estudos possibilitou que em 2016 fosse publicada uma revisão sistemática de literatura (RSL) com o objetivo de avaliar a diversidade e padrão de colonização da microbiota intestinal durante o primeiro ano de vida (RUTAYSIRE et al., 2016). Os autores observaram uma menor concentração dos gêneros de bactérias como *Bifidobacterium*,

Bacteroides e *Lactobacillus*, enquanto os gêneros *Enterobacter*, *Klebsiella*, *Clostridium*, *Veillonella*, *Haemophilus* e *Enterococcus* foram encontrados em maiores concentrações em RN por cesariana (**Quadro 1**).

Rutayisire et al. (2016) observaram que a primeira semana de vida foi caracterizada por uma concentração reduzida de *Bifidobacterium*, *Bacteroides* e *Lactobacillus* em RN por parto cesáreo (GRÖNLUND et al., 1999; MITSOU et al., 2008; KABEERDOSS et al., 2013; HESLA et al., 2014; JAKOBSSON et al., 2014; DOGRA et al., 2015). Por outro lado, dois estudos citados na revisão divergiram em relação aos resultados do filo *Proteobacteria*. Um observou concentração aumentada e outro reduzida em RN por parto cesáreo (KABEERDOSS et al., 2013; HESLA et al., 2014). Até o primeiro mês de vida, o gênero *Bifidobacterium* e os filos *Bacteroidetes* e *Firmicutes* foram menores no grupo de crianças nascidas por cesariana (GRÖNLUND et al., 1999; HUURRE et al., 2008; MITSOU et al., 2008; KABEERDOSS et al., 2013; HESLA et al., 2014; JAKOBSSON et al., 2014). Até o terceiro mês, o gênero *Bifidobacterium* e o filo *Bacteroidetes* também apresentaram uma menor colonização nesse grupo (GRÖNLUND et al., 1999; KABEERDOSS et al., 2013; HESLA et al., 2014; JAKOBSSON et al., 2014; DOGRA et al., 2015).

Essa revisão demonstrou que o padrão de colonização da microbiota intestinal foi significativamente associado ao tipo de parto nos três primeiros meses de vida. No entanto, esse padrão se alterou após os seis meses de idade (RUTAYISIRE et al., 2016). Ainda há necessidade que novos estudos investiguem a diversidade e os níveis de colonização da microbiota intestinal infantil em relação ao tipo de parto e como essa microbiota pode impactar na saúde ao longo da vida. Apesar de o tipo de parto ser um importante determinante da composição bacteriana nos primeiros meses de vida, também é necessário que outros fatores determinantes sejam considerados. Entre eles destaca-se o método de análise, o tipo ou duração do aleitamento materno, a localização geográfica e o uso de antibióticos pelo grupo materno-infantil (YATSUNENKO et al., 2012; MILANI et al., 2017). Esses fatores são potenciais modificadores da associação entre o tipo de parto e a microbiota intestinal (MILANI et al., 2017). O aleitamento materno destaca-se como um dos fatores que mais podem interferir nessa associação (HARMSEN et al., 2000; LOZUPONE et al., 2012; PRIOR et al., 2012; MUELLER et al., 2015).

Quadro 1. Estudos que avaliaram a composição da microbiota intestinal associado ao tipo de parto.

Autor, ano	País	Tamanho amostral (PV/PC)	Tempo de coleta fecal	Efeito do PC na microbiota
Grönlund et al., 1999	Finlândia	64 (34/30)	3 - 5, 10 dias; 1, 2 e 6 meses	Até 7 dias Actinobacteria: *Bifidobacterium* – ↓ Bacteroidetes: *Bacteroides* - ↓ 8 a 30 dias Actinobacteria: *Bifidobacterium* – ↓ Bacteroidetes: *Bacteroides* – não detectado em nascidos por PC Firmicutes: *Clostridium* – ↑ 31 a 90 dias Bacteroidetes: *Bacteroides* – ↓ 91 a 180 dias Bacteroidetes: *Bacteroides* – ↓ ➔ Avaliou o efeito do tipo de parto na colonização bacteriana.
Huurre et al., 2008	Finlândia	165 (141/24)	1, 3 e 6 meses	8 a 30 dias Actinobacteria: *Bifidobacterium* – ↓ ➔ Avaliou o impacto do tipo de parto na microbiota, e sua relação com a imunidade.
Mitsou et al., 2008	Grécia	82 (34/48)	4 dias; 1 e 3 meses	Até 7 dias Actinobacteria: *Bifidobacterium* – ↓ Firmicutes: *Lactobacillus* – ↓ 8 a 30 dias Actinobacteria: *Bifidobacterium* – não detectado em nascidos por PC. ➔ Avaliou o efeito do tipo de parto no desenvolvimento da microbiota intestinal e padrão de colonização de ácido lático e *Bifidobacterium.*
Kabeerdoss et al., 2013	Índia	83 (73/10)	1, 2, 4, 7, 14 dias; 1, 3 e 6 meses	Até 7 dias Proteobacteria: *Enterobacteriaceae* – ↓ Bacteroidetes: *Bacteroides* e *Prevovella* – ↓ Firmicutes: *Lactobacillus* – ↓ 8 a 30 dias Bacteroidetes: *Bacteroides* e *Prevotella* – ↓ 31 a 90 dias Actinobacteria: *Bifidobacterium* – ↓ Bacteroidetes: *Bacteroides* e *Prevotella* – ↓ ➔ Avaliou o desenvolvimento da microbiota de acordo com tipo de parto, condição socioeconômica, peso ao nascer e tipo de alimentação.
Jakobsson et al., 2014	Suécia	24 (15/9)	7 dias; 1, 3 e 6 meses	Até 7 dias

				Bacteroidetes: *Bacteroides* – ↓ 8 a 30 dias Bacteroidetes: *Bacteroides* – ↓ Firmicutes: *Enterococcus* – ↑ 31 a 90 dias Bacteroidetes: *Bacteroides* – ↓ ➔ Avaliou a microbiota e padrão de colonização de acordo com o tipo de parto, e associação com resposta imune.
Hesla et al., 2014	Suécia	128 (109/19)	6, 21 dias; 2 e 6 meses	Até 7 dias Actinobacteria: *Bifidobacterium* – ↓ Proteobacteria: *Enterobacteriaceae* e *Haemophilus* – ↑ Bacteroidetes: *Bacteroides* – ↓ Firmicutes: *Clostridiaceae* e *Veillonella*: ↑ 8 a 30 dias Actinobactéria: *Bifidobacterium* – ↓ Proteobacteria: *Enterobacteriaceae* e *Haemophilus* – ↑ Bacteroidetes: *Bacteroides* - ↓ Firmicutes: *Clostridium* e *Veillonella*: ↑ 31 a 90 dias Proteobacteria: *Enterobacteriaceae* – ↑ Bacteoidetes: *Bacteroides* - ↓ Firmicutes: *Clostridium*- ↑ 91 a 180 dias Proteobacteria: *Enterobacteriaceae* – ↑ Firmicutes: *Clostridiales* – ↑ ➔ Avaliou o impacto a exposição precoce ao estilo de vida antroposófico na microbiota intestinal.
Dogra et al., 2015	Singapura	75 (57/18)	3, 21 dias; 3 e 6 meses	Até 7 dias Actinobacteria: *Bifidobacterium* – ↓ Firmicutes: *Klebsiella* – ↑ 31 a 90 dias Actinobacteria: *Bifidobacterium* – ↓ 91 a 180 dias Actinobacteria: *Bifidobacterium* – ↓ ➔ Avaliou o efeito de fatores ambientais, incluindo o tipo de parto no desenvolvimento da microbiota, associado ao aumento de adiposidade.

Nota: PV – parto vaginal; **PC** – parto cesáreo; ↓- menor; ↑ - maior.

2.4 Aleitamento materno como potencial modificador da composição da microbiota intestinal infantil

O leite humano é composto por vitaminas, minerais, proteínas, lipídios e carboidratos (NOMMSEN et al., 1991; BALLARD et al., 2013). A lactose e os oligossacarídeos são os carboidratos que estão em maiores concentrações entre os diversos compostos (BALLARD et al., 2013). Os oligossacarídeos do leite humano (HMO - *human milk oligosaccharides*, da sigla em inglês), são compostos bioativos e carboidratos não digeríveis no intestino delgado, mas no cólon são fermentados por algumas bactérias e transformados em ácido graxo de cadeia curta (YU et al., 2013; BODE, 2012). Essa transformação gera um meio mais ácido, que favorece o crescimento do gênero *Bifidobacterium* no intestino (YU et al., 2013). Sendo assim, os HMO reduzem a capacidade de crescimento de microrganismos patogênicos (BODE, 2012; RAY et al., 2019). Os HMO atuam como prebióticos, pois à medida que servem de substrato para o crescimento de bactérias não patogênicas, reduzem a colonização de bactérias patogênicas no intestino (YU et al., 2013).

Além de oligossacarídeos, o leite materno também é composto por diversas bactérias (microbiota do leite), em especial *Bifidobacterium* e *Lactobacillus*, que atuam como probióticos e podem modular a microbiota intestinal infantil (MARTIN et al., 2007; HUNT et al., 2011; PANNARAJ et al., 2017). Assim, a modulação intestinal é potencializada pela ação prebiótica e probiótica do leite humano (BODE, 2009; COLLADO et al., 2014; PANNARAJ et al., 2017). O leite materno é o alimento padrão-ouro para a saúde infantil, e diante disso a OMS recomenda que o mesmo seja oferecido por dois anos ou mais, e que crianças sejam amamentadas exclusivamente até o sexto mês de vida (OMS, 2007). O aleitamento materno exclusivo é definido como aquele em que é consumido somente o leite materno, com ausência de outros líquidos e sólidos. Mesmo sendo considerado o alimento ideal, a prevalência de amamentação exclusiva até os seis meses no Brasil é de apenas 39,8% (PNDS, 2006; UNICEF, 2016a) e 38% no mundo (OMS, 2013).

Além de todos os benefícios já conhecidos, o aleitamento materno é um dos fatores que podem modular o intestino nos primeiros meses de vida (GUARALDI; SALVATORI, 2012; CARVALHO-RAMOS, et al., 2018). Estudos têm demonstrado que crianças em aleitamento materno apresentam maiores concentrações de *Bifidobacterium*, quando comparadas às usuárias de fórmulas infantis, e essa diferença pode ser vista rapidamente após a transição do

leite materno para a fórmula infantil (HARMSEN et al., 2000; O'SULLIVAN et al., 2015; THOMPSON et al., 2015; DAVIS et al., 2016; GREGORY et al., 2016; SORDILLO et al., 2017). A concentração dos filos *Bacteroidetes* (especialmente *Bacteroides)*, *Firmicutes* (especialmente *Clostriales)*, dos gêneros *Eubacterium* e *Veillonella* foram aumentadas em crianças não amamentadas exclusivamente (HO et al., 2018). A microbiota intestinal, em condições de amamentação, é composta majoritariamente por *Bifidobacterium* e *Lactobacillus*, ou seja, menos diversa. Por outro lado, em adição à essas, quando em uso de fórmula infantil, apresentam uma maior diversidade de bactérias no intestino, como *Clostridium*, *Enterobacter* e *Citrobacter* (HARMSEN et al., 2000; BÄCKHED et al., 2015; RAUTAVA, 2016).

O leite materno é responsável por uma microbiota menos diversa, e dessa forma destaca-se como um dos fatores de confusão que podem modificar o efeito da associação entre o tipo de parto e a colonização intestinal infantil, pois além de estar associado a modificações na microbiota infantil, também pode estar associado a maior dificuldade na amamentação durante a primeira hora de vida em RN de parto cesáreo (HARMSEN et al., 2000; PRIOR et al., 2012). Alguns estudos demonstram que essa variável pode afetar positivamente a microbiota intestinal de crianças nascidas por parto cesáreo. Diante disso, crianças nascidas por parto cesáreo e não amamentadas exclusivamente apresentam microbiota intestinal mais diversa, quando comparadas às amamentadas exclusivamente (HO et al., 2018).

Uma meta-análise com sete estudos de cinco países avaliou o efeito do aleitamento exclusivo na microbiota intestinal até os dois anos de idade (HO et al., 2018). Nesse estudo, um total de 1.825 amostras de fezes de crianças até os seis meses de idade foram analisadas e apresentaram uma diferença notável entre crianças amamentadas e não amamentadas ao longo desse período, como menores concentrações de *Bifidobacterium* e *Enterococcus* e maiores concentrações de *Lactobacillus*, *Coriobacterium*, *Prevotella* e *Clostridium* em crianças não amamentadas (HO et al., 2018). Além disso, quando as análises para a presença ou ausência da amamentação foram estratificadas pelo tipo de parto, observou-se que a microbiota intestinal de crianças nascidas por parto cesáreo apresenta maior suscetibilidade aos efeitos da ausência da amamentação exclusiva (HO et al., 2018).

Dessa forma, ao considerar que o tipo de parto seja o maior contribuinte para mudanças na colonização intestinal, o aleitamento materno destaca-se como um potencial modificador da colonização intestinal para um perfil mais semelhante ao de crianças nascidas por parto vaginal (AZAD et al., 2013; HO et al., 2018). Sendo assim, torna-se necessário investigar a modificação

de efeito na referida associação, de forma que crianças nascidas por parto cesáreo, tenham a capacidade de desenvolver uma microbiota mais semelhante aos nascidos por parto vaginal.

2.5 Localização geográfica

A composição da microbiota é uma variável que pode ser influenciada por fatores fisiológicos do indivíduo e ambientais (YATSUNENKO et al., 2012; SHREINER et al., 2015). Os fatores ambientais incluem o estilo de vida, as condições higiênico-sanitárias, condição climática, o padrão de alimentação, bem como o tipo e duração do aleitamento materno (GRZEŚKOWIAK et al., 2012; YATSUNENKO et al., 2012; HO et al., 2018). Devido ao padrão sociocultural e sanitário específico de cada região, essas variáveis diferem bastante em relação aos países ao redor do mundo. O aleitamento materno é um importante fator para a colonização bacteriana infantil, e diante disso, a localização geográfica também é uma variável que possivelmente pode influenciar na composição da microbiota intestinal (YATSUNENKO et al., 2012; HO et al., 2018). Ainda que a OMS recomende a oferta do leite materno por dois anos ou mais, o padrão de aleitamento é variável ao redor do mundo (OMS, 2007; OMS, 2013).

Um estudo realizado em cinco países europeus demonstrou haver maior proporção de *Bifidobacterium* em lactentes nascidos na Europa Central (Alemanha e Escócia), e de *Bacteroides*, *Lactobacillus* e *E. coli* em crianças nascidas na região Sul da Europa (Itália e Espanha), enquanto resultados para a espécie *C. perfringens* foi semelhante entre os lactentes, independente da região de nascimento, ainda que ajustado para o tipo de aleitamento (FALLANI et al., 2011). Uma coorte realizada em dois continentes diferentes (África - Malawi e América – Venezuela e Estados Unidos da América) avaliou a microbiota intestinal infantil até os três anos de idade. Inicialmente, ao comparar a semelhança entre comunidade bacteriana, o estudo demonstrou maior diferença significativa entre a microbiota intestinal de crianças americanas em relação à de outras regiões. Além disso, essas crianças também apresentaram maior abundância de *Prevotella* ao longo dos três anos de idade, quando comparados às crianças da Venezuela e África (YATSUNENKO et al., 2012).

Grześkowiak et al. (2012), quando comparou a microbiota intestinal de lactentes de seis meses de idade em dois países de continentes diferentes (Malawi e Finlândia), demonstrou maior proporção de *Bifidobacterium*, *Bacteroides* e *Prevotella* em crianças do Malawi, quando comparadas às crianças Finlandesas. Enquanto as contagens celulares das espécies *Bifidobacterium catenulatum* e *Clostridium difficile* foram extremamente superiores no grupo

de crianças finlandesas. Por outro lado, em oposição às crianças finlandesas, as espécies *Bifidobacterium adolescentis*, *C. perfringens* e *Staphylococcus aureus* não foram detectadas em crianças nascidas no Malawi. No entanto, o padrão de tipo de nascimento e amamentação é diferente entre ambos os grupos, no qual todas as crianças nascidas no Malawi, além de terem nascido por parto vaginal, estavam sendo amamentadas no período de seis meses de idade.

Diante disso, ao considerar que o padrão de alimentação infantil, bem como a amamentação (tipo e duração), pode estar diretamente relacionado ao país de condução do estudo (YATSUNENKO et al., 2012; HO et al., 2018), é necessário que os resultados demonstrados nos estudos sobre a composição da microbiota intestinal para os diferentes tipos de parto sejam descritos de acordo com a localização geográfica.

2.6 Justificativa

A prevalência de parto cesáreo foi de 56% no Brasil em 2016 (DATASUS, 2017) e 16% no mundo (OMS, 2013). Esse tipo de parto pode estar associado de forma negativa à composição da microbiota infantil, e consequentemente ao aumento de complicações na saúde infantil em longo prazo, como distúrbios imunológicos (alergias) e metabólicos (obesidade, diabetes mellitus e doenças do trato gastrointestinal).

Diversos estudos já foram realizados e mostraram que a composição da microbiota pode ser influenciada pelo tipo de parto. Diante disso, uma revisão sistemática foi publicada com a mesma temática. No entanto, o referido estudo, além de avaliar a microbiota até o primeiro ano de vida, apresenta algumas diferenças, como, não considerar o efeito isolado da amamentação e não avaliar a qualidade metodológica dos estudos selecionados.

O aleitamento materno, em conjunto com o tipo de parto, é um dos fatores que mais podem modificar a colonização intestinal até os seis meses de idade (HARMSEN et al., 2000; HO et al. 2018). Além disso, também é possível que o aleitamento materno modifique positivamente a microbiota intestinal de crianças nascidas por parto cesáreo, deixando-a mais semelhante aos nascidos por parto vaginal. No entanto, poucos estudos consideram o efeito da amamentação na associação entre o tipo de parto e a microbiota infantil. Além da amamentação, outros vieses podem afetar a qualidade dos resultados, sendo assim, ressaltamos a importância da avaliação da qualidade dos estudos. Dessa forma, o presente estudo é muito necessário, pois além de adicionar estudos à revisão anterior irá considerar o papel da amamentação na associação entre tipo de parto e a microbiota intestinal, mas também vai discutir a qualidade metodológica desses estudos e consequentemente a qualidade das evidências.

Visando adicionar novas evidências a RSL já publicada, torna-se necessário resumir os resultados e estimar a magnitude do efeito do tipo de parto na composição bacteriana intestinal durante os seis meses, avaliar o potencial papel modificador de efeito da amamentação nessa associação e a qualidade das evidências obtidas. Dessa forma, os resultados desse estudo podem sintetizar as evidências sobre a referida associação e seu papel modificador e contribuir para a promoção da qualidade de vida neonatal e infantil por meio do melhor esclarecimento sobre benefícios do tipo de parto e do aleitamento materno à saúde infantil.

3. Objetivos

3.1 Objetivo geral

Sintetizar e sistematizar os resultados de estudos que avaliaram a associação do tipo de parto com a composição da microbiota intestinal infantil até os seis meses pós-parto, considerando o papel da amamentação.

3.2 Objetivos específicos

- Revisar a literatura e resumir as evidências sobre a associação do tipo de parto com a microbiota intestinal infantil até os seis meses pós-parto;
- Avaliar o papel da amamentação nos estudos selecionados e seu potencial modificador de efeito na relação entre o tipo de parto e a composição da microbiota intestinal infantil;
- Descrever os resultados da microbiota intestinal e tipo de parto de acordo com a localização geográfica.

4. Hipótese

O presente estudo testará duas hipóteses:

i. Crianças nascidas por parto cesáreo apresentam microbiota intestinal distinta em termos de composição de bactérias, ao longo dos seis meses de idade, quando comparadas às nascidas por parto vaginal.

ii. A amamentação pode atuar como um modificador de efeito na microbiota intestinal em crianças nascidas por parto cesáreo quando amamentadas, que tendem a ter a composição da microbiota intestinal mais semelhante à de crianças nascidas por parto vaginal.

5. Método

5.1 Desenho de estudo

O desenho de estudo é uma RSL de publicações que avaliaram a associação do tipo de parto com a microbiota intestinal infantil até os seis meses de idade. Após a seleção dos estudos, considerou-se o papel da amamentação como modificador do efeito entre o tipo de parto e a microbiota intestinal infantil. O estudo foi conduzido de acordo com os *guidelines* do *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) (MOHER et al., 2009) e MOOSE (2000).

5.2 Registro do protocolo

O PROSPERO é uma base de dados internacional para registro de revisões sistemáticas na área de saúde. Seu objetivo principal é fornecer informações relevantes sobre as revisões registradas, a fim de evitar duplicações, além de permitir a comparação da revisão concluída com o que havia sido planejado no protocolo (*CENTRE FOR REVIEWS AND DISSEMINATION, 2009).* A presente revisão foi registrada com o seguinte título no PROSPERO (nº 42017071285)**:** '*Association of mode of delivery and changes in the composition of infant gut microbiota up to 6 months: a systematic review of literature, considering the role of breastfeeding*'.

5.3 Critérios de elegibilidade

Para a definição dos critérios de elegibilidade foi utilizada a estratégia PECOS (LIBERATI et al., 2009), na qual cada letra se refere à definição de um item: (P - população) pares de mães/filho; (E – exposição) ter informação sobre o tipo de parto (parto cesáreo x parto vaginal) como exposição; (C - grupo de comparação) ter realizado a comparação da composição da microbiota intestinal entre os nascidos de parto cesáreo *versus* parto normal até os 6 meses, pelo menos em algum momento; (O – resultado/desfecho) ter realizado a avaliação da microbiota intestinal infantil até os seis meses de idade de forma longitudinal, i.e. mais de uma amostra de fezes analisada em tempos distintos nos seis primeiros meses de vida da criança; (S – desenho do estudo) ter desenho de estudo do tipo coorte.

Os seguintes critérios de exclusão foram adotados: estudos que avaliaram RN pré-termos (<37 semanas gestacionais), RN com baixo peso ao nascer (<2500g), RN com diagnóstico de doenças (fibrose cística infantil, síndrome da imunodeficiência adquirida materna SIDA/HIV)),

uso materno-infantil de probióticos, avaliação de somente um gênero/espécie de bactéria, publicações na forma de resumo e estudos que não foram publicados na língua inglesa. Para serem incluídos na RSL, os estudos deveriam atender os critérios de inclusão e exclusão.

5.4 Estratégia de busca

A busca foi realizada por três investigadores no período de Abril de 2018 até Fevereiro de 2020, nas seguintes bases de dados eletrônicas: Pubmed, *Web of Science* (ISI), Scopus, Embase, *Trip Medical Database* e *Open Grey*. As palavras-chave e suas combinações estão detalhadas no **Quadro 2**.

Quadro 2. Bases de dados utilizadas e estratégias de busca.

Base de dados	Período de tempo	Palavras-chave e suas combinações	Observações
Cochrane *Library* e PROSPERO	5 de Abril de 2018	Busca por estudos de revisão sistemática com a mesma temática.	Não foram obtidos resultados.
Pubmed	19 de Fevereiro de 2020	*(("microbiota"[All Fields] OR "microbiome"[All Fields] OR "gut microbiota"[All Fields] OR "intestinal microbiota"[All Fields] OR "intestinal microbiome"[All Fields] OR "gut microbiome"[All Fields] OR "microorganisms"[All Fields] OR "lactobacillus"[All Fields] OR "bifidobacterium"[All Fields] OR "bacteroides"[All Fields] OR "clostridium"[All Fields] OR "staphylococcus"[All Fields] OR "pathogenic bacteria "[All Fields] OR "beneficial bacteria"[All Fields]) AND ("Mode of delivery"[All Fields] OR "Delivery mode"[All Fields] OR "C-section"[All Fields] OR "cesarean section"[All Fields] OR "caesarean section"[All Fields] OR "vaginal delivery"[All Fields] OR "normal delivery"[All Fields]) AND ("newborn"[All Fields] OR "neonate"[All Fields] OR "infant"[All Fields])) OR ("Microbiota"[Mesh] AND "Cesarean Section"[Mesh]) AND "Infant"[Mesh]*	Uso do 'medical subject headings' (MESH).
Web of science	18 de Fevereiro de 2020	*((microbiota OR microbiome) AND (mode of delivery OR cesarean section OR caesarean section OR c-section OR vaginal delivery) AND (infant OR newborn OR neonate))*	-
Scopus	18 de Fevereiro de 2020	((("infant" OR "newborn" OR "neonate") AND ("microbiota" OR "microbiome" OR "gut microbiota") AND ("mode of delivery" OR "delivery mode" OR "c-section" OR "caesarean section" OR "cesarean-section" OR "vaginal delivery" OR "normal delivery")))	-
Embase	18 de Julho de 2018	*('microbiota' OR 'microbiome' OR 'gut microbiota') AND ('delivery mode' OR 'mode of delivery' OR 'cesarean section' OR 'caesarean section' OR 'vaginal delivery' OR 'normal delivery') AND ('newborn' OR 'infant')*	Maior parte resumos de congressos e conferências.
Trip Medical Database	21 de Novembro de 2018	*mode of delivery and microbiota* e *delivery mode and microbiota*	Literatura cinzenta (*Grey literature*).
Open Grey	18 de Fevereiro de 2020	*mode of delivery and microbiota* e *delivery mode and microbiota*	Literatura cinzenta (*Grey literature*).

5.5 Gerenciamento em *softwares* de referências

Todas as referências foram exportadas para o gerenciador de referências Endnote versão X8®. Os estudos duplicados foram encontrados e excluídos. Então, resumos e textos completos foram adicionados ao gerenciador de revisões sistemáticas Covidence®, para seleção dos estudos de acordo com os critérios de inclusão pré-selecionados e para a extração de dados.

5.6 Seleção dos estudos

A seleção dos estudos foi realizada por três investigadores (LP, ACC e FR). Esses foram selecionados para a leitura dos artigos completos (Pubmed, *Web of Science* e *Scopus*). Após essa leitura, os artigos foram selecionados para inclusão na RSL. Essa etapa foi realizada por dois avaliadores independentes (LP e ACC) e as discordâncias dirimidas por um terceiro revisor (FR). Os resumos disponíveis no *Embase* eram em sua maioria publicados em congressos e conferências. Após a seleção dos resumos de acordo com os critérios de inclusão, somente dois estudos estavam disponíveis na forma de artigo. Sendo assim, os primeiros autores ou orientadores foram contatados por *e-mail*, solicitando confirmação dos critérios de elegibilidade (**Anexo 1 e 2**). Os estudos que foram classificados como elegíveis foram incluídos na extração de dados.

5.7 Extração de dados

Foi elaborado um formulário próprio para a extração de dados que foi baseado em um modelo proposto pela *Cochrane Handbook* (2011). Esse formulário considerou os principais fatores de confusão descritos na literatura. Essa fase dos trabalhos foi realizada majoritariamente (85%) pelo primeiro avaliador (LP) e 15% pelo segundo avaliador (ACC). O formulário foi inserido no Covidence® para que a extração de dados fosse realizada por ambos avaliadores, e em caso de discordância, o terceiro revisor foi considerado na resolução das mesmas.

Para a RSL, os dados foram sistematizados de acordo com os seguintes critérios: autor, ano de publicação; desenho do estudo, duração do estudo, país no qual o estudo foi conduzido; tamanho amostral; número de vezes e tempo de coleta de fezes, etnia, características sócio demográficas (renda e escolaridade), contato com irmãos/crianças, índice de massa corporal materno, uso de antibióticos materno/infantil, idade gestacional ao nascer, amamentação (exclusiva, predominante ou mista e tempo de duração), uso de fórmula infantil ou outros alimentos, tipo de parto, método de análise da microbiota, abundância relativa, frequência de colonização e análise estatística (**Anexo 3**).

Quando os dados não estavam disponíveis no estudo, o primeiro autor foi contatado por e-mail, solicitando-se o envio de dados adicionais. Em caso de não obtenção de resposta, a solicitação foi

feita ao segundo autor. Os estudos para os quais não obtivemos resposta, ou que os artigos ainda não tivessem sido publicados, foram excluídos da extração de dados.

5.8 Avaliação da qualidade dos estudos (risco de viés)

A avaliação da qualidade metodológica dos estudos foi realizada por meio de um instrumento criado exclusivamente para o estudo (**Supplementary Board 2**). O instrumento foi criado tendo como base o modelo desenvolvido pelo *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE) (GRADE *WORKING GROUP*). O instrumento é composto por seis domínios que abrangem os seguintes itens: (1) amostra de participantes; (2) confidencialidade sobre a exposição (tipo de parto); (3) diferença na avaliação/coleta da microbiota intestinal; (4) controle pelos fatores de confusão (aleitamento materno e uso de antibiótico); (5) método de análise da microbiota intestinal e (6) seguimento do estudo (dados faltantes). Para cada item foram atribuídas três opções de resposta (*Definitely yes* – low risk of bias, *Unclear, Definitely no - high risk of bias*). A classificação foi realizada em cada estudo (intra–estudo), definida como: baixo risco de viés (todos os domínios "*low*"), risco intermediário de viés (um domínio "*high*" ou "*unclear*") ou alto risco de viés (≥ dois domínios "*high*" ou "*unclear*"). Após essa etapa, o risco de viés entre os estudos (evidência acumulada), definido pela classificação do mais frequente, foi classificado em alto ou baixo risco de viés.

6. Resultados

Modelo de manuscrito a ser submetido nas revistas *Gut Pathogens* ou *Clinical Journal of microbiology and infection.*

6.1 Manuscrito

Impact of delivery mode on infant gut microbiota composition up to 6 months of age: systematic literature review, considering the role of breastfeeding

Abstract

Background: Evidence has shown that cesarean section (CS) and breastfeeding can influence the infant gut microbiota. This systematic literature review (SLR) aims to evaluate evidence of association between the mode of delivery and infant gut microbiota up to six months of age and the role of breastfeeding in this association. **Methods:** A SLR was performed on six databases (Pubmed, Web of Science, Scopus, Embase, Medical Database and Open Grey) from inception to 2020. Observational studies with ≥2 infant stool collections in the first six months of life and with comparison of gut microbiota between modes of delivery (CS vs. vaginal delivery) were included. Studies that focused on maternal or infant conditions or diseases that may impact the microbiota were excluded. **Results:** Data from 31 studies meeting inclusion criteria were extracted and evaluated. Infants born by CS had lower abundance of the genus *Bifidobacterium* and *Bacteroides* (and *B. fragilis*) at almost all points. Colonization of the genus *Lactobacillus* (third month) and the species *Bifidobacterium longum* (first month), *Bifidobacterium catenulatum* (one week), the species *B. vulgatus* and *B. uniformis* (one month) and *Escherichia coli* (one week) was reduced in infants delivered by CS, while *Clostridium perfringens* (third month) was increased in those infants. Geographic location can presume the bacterial colonization. Infants born by CS and exclusively breastfed showed greater similarity with the microbiota of infants born by vaginal delivery. Sixteen percent of the studies had a low risk of bias at the intra-study level. **Conclusion**: The genus *Bifidobacterium* and *Bacteroides* (and *B. fragilis*) are potentially reduced in infants born by CS. There are trends that the genus *Lactobacillus* and the species *B. longum, B. catenulatum, B. bifidum, B. vulgatus, B. uniformis, E. coli* and *C. perfringens* differ between delivery modes. Geographic location of the study development could influence the bacterial colonization. The effect modification of breastfeeding on microbiota associations with delivery mode should be highlighted.

Keywords: microbiota, mode of delivery, breastfeeding, systematic review of literature

Protocol registration number: PROSPERO nº 42017071285.

Background

The gut microbiota is very important from birth up to early childhood (1,2). Gut microbial communities can impact infant health by providing protection against pathogenic microorganisms, aiding in digestion and metabolization of breast milk and infant formula compounds, promoting immune system development, maintaining intestinal homeostasis, impacting cell growth and proliferation and brain development (3,4,5). The microbiota succession in early life is a dynamic and progressive process (6). The gut microbiota stabilizing over time in bacterial composition and diversity, and thus, newborn has less bacterial diversity than an adult (1,7,8). The infant microbiota reaches maturity and diversity similar to that of a healthy adult at around 2-3 years of age (1,9). During the neonatal period, the gut microbiota is composed mainly of the phylum *Proteobacteria*, *Actinobacteria*, *Firmicutes* and *Bacteroidetes* (10,11,12). These include the genus *Escherichia*, *Bifidobacterium*, *Clostridium*, *Lactobacillus, Bacteroides* and *Prevotella* (13).

The composition of infant microbiota may be influenced by several factors, including mode of delivery, breastfeeding, infant diet, antibiotic use and geographic location (9,14,15). Unlike vaginal delivery (VD), cesarean section (CS) circumvents infants' exposure to the maternal vaginal microbiota (16,17,18). Several studies suggest that CS may have a negative effect on the mother's initial microbial transfer to the newborn (19,**20**). Vaginally born neonates are initially colonized by bacteria present in the maternal vagina and gut, while those born by CS are colonized by bacteria present on the maternal skin (7,21,22). Abnormal progression of infant gut microbiota composition and diversity in early life, as occurs with CS, may impact the development of immune and metabolic disorders such as allergy, obesity, and type 2 diabetes mellitus in later life (16, 23, 24, 25,26).

The occurrence of CS has been steadily increasing over the years, and data show a worldwide prevalence of 16% (27). Current evidence suggests that the mode of delivery is the factor that most modifies early gut colonization (7,20,28,29). Some cross-sectional studies have observed that the mode of delivery alters the composition of the microbiota during the first six months of life (7,30,31). One study highlighted changes in gut colonization between delivery mode, such as increased *Prevotella* and *Lactobacillus* and reduced *Streptococcus* and *Enterobacteriaceae* in vaginal deliveries. In addition, infants born vaginally also showed similarity to the maternal gut microbiota, and infants born by CS had a higher proportion of antibiotic resistance genes in their microbiome **(19).** These differences in the microbiota associated with delivery mode do not seem to persist after sixth months of life (20).

Breastfeeding is also an important factor that can have a substantial influence on infant gut bacterial composition (32,33,34,35). Besides the presence of various bacteria, human milk is composed mainly of carbohydrates, including human milk oligosaccharides (HMOs) (36,37,38,39). HMOs promote the growth of the genus *Bifidobacterium* in the infant gut (38,40). During

breastfeeding, several studies demonstrate that the infant gut microbiota has higher levels of *Bifidobacterium* and *Lactobacillus* (2, 41,42 43). Phylum *Bacteroidetes* (especially *Bacteroides*), *Firmicutes* (especially *Clostriales*), genus *Eubacterium* and *Veillonella* were increased in infants who were not exclusively breastfed (44).

Studies have shown an association between breastfeeding and infant gut microbiota (45,46,47). In 2018, a meta-analysis showed that infants who were exclusively breastfed for two months showed a more stable colonization pattern when compared with non-breastfed infants (44). Given that both delivery mode and breastfeeding can influence the succession of the infant gut microbiota, it is important to understand their combined effects on the microbiota in early life. Thus, the aim of this manuscript is to systematically review studies that have evaluated the association between mode of delivery and infant gut microbiota longitudinally in the first six months of life, to evaluate the role of breastfeeding as an effect modifier of this relationship, and describe the results according to geographic location.

Methods

This is a systematic literature review (SLR) registered at the International Prospective Register of Systematic Reviews - PROSPERO (nº CRD42017071285). PECOS strategy was used to define the inclusion and exclusion criteria according to O'Connor et al. (2008), in wich P (population) pairs of mothers and infants; E (exposure) mode of delivery; C (comparison group) mode of delivery – VD and CS ; O (outcome) composition of gut microbiota; and S (study design) cohort studies. The inclusion criteria have been defined as: data allowing comparision of gut microbiota between VD and CS; microbiota data measured at least twice in the first six months of life; studies with cohort design; and publication in English. The following exclusion criteria were considered: preterm infants (< 37 gestational week at birth); low birth weight infants (< 2500g); maternal-infant diseases (e.g. cystic fibrosis and human immunodeficiency virus); use of maternal-infant probiotic; evaluation of only one bacterial taxa; publication of abstracts only.

The study was conducted according the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) (48), and in four stages: bibliographic search, selection of studies, data extraction and quality evaluation of the included studies. All steps were performed by two independent reviewers (LP and ACC) and disagreements were resolved by a third reviewer (FR). The searches were performed from April 2018 to February 2020 in the following bibliographic databases: Pubmed, Web of Science, Scopus, Embase, Medical Database and Open Grey. Search strategy with detailed keywords are available in the **Supplementary Board 1**.

The titles and abstracts were first examined to remove irrelevant results. Secondly, full text of potentially relevant abstracts were read and checked for elegibility criteria. Studies that met all

elegibility criteria had the data extracted through a specific data extraction form based on Cochrane reccomendations (49). The following variables were extracted from each study: author, year, country, sample size, infant age at stool collection, maternal and infant antibiotic use, gestational age at birth, breastfeeding, method of microbiota analysis and frequency of colonization/relative abundance/diversity and richness of bacteria used for data analysis. Data on duration and feeding mode and was collected, and was categorized into exclusive breastfeeding (EBF - breast milk only); mixed breastfeeding (MBF - breast milk + formula feeding); Complementary breastfeeding (CBF - breast milk + food).

For data analysis the results were grouped according to time stool was collected (up to sixth months) and the colonization/relative abundance/diversity/richness of bacteria identified. After the synthesis of all data, to summarize this multitude of results, only the groups of bacteria evaluated in the same period by more than one author were included.

A tool based on Grading Recommendations, Assessment, Development and Evaluation Recommendations (GRADE) (50) was designed exclusively for this study with the purpose of evaluating the risk of bias/quality assessment (**Supplementary Board 2**). The assessment of risk of bias according to domains classification considers information that interferes on the study outcome definition. For this evaluation, we used six domains with the following items: (1) selection bias; (2) validity of information about exposures; (3) information bias on stool collection protocol; (4) control for confounders (antibiotic use and breastfeeding); (5) validity of microbiota results (genetic sequencing and molecular techniques); (6) adequate follow-up of the study, including available outcome data. The quality assessment was performed based on the risk of bias classification (low, high or unclear) in each domain, and the results are presented for each study (intra - study) and for the accumulated evidence (between study). The accumulated evidence was defined as the most frequent classification among studies, and was classified as ‘low’ or ‘high’. Intra-study results were defined as: (1) Low risk of bias if all domains are ‘low’; (2) Intermediate risk of bias if the study presented a domain classified as ‘high’ or ‘unclear’; (3) High risk of bias if the study presented two or more domains as ‘high’ or ‘unclear’.

Results

Study selection

The study selection process involved the search for manuscripts and conference proceedings abstracts, which generated 2,096 publications. Among these, 824 duplicates were excluded. Thus 1,272 documents were selected for title and abstract screening. As a result, 217 were selected for full

manuscript reading. Finally, a total of 31 manuscripts were elegible for the SLR and had their data extracted, comprising a total of 3,313 infants studied. (**Figure 1**).

Study characteristics

Among the eligible manuscripts, the average gestational age at birth ranged between 37 and 40 gestational weeks. Thirteen studies were conducted in Europe, three in North America, and two were multicenter (Europe and North America). Eleven studies were conducted in Asia, and only one in Africa. The majority of studies (n = 23) reported antibiotic use. Among them, ten reported that mothers used antibiotic before or during the study follow-up, eight reported use by the mother-child dyad, while five of them showed use only in infants. In average, 46% of women (n=14) and 21% of children (n=8) made use of antibiotic among these studies (**Supplementary Table 1**).

Twelve studies used the molecular polymerase chain reaction (PCR) technique, in association with genetic techniques (DNA extraction + rRNA sequencing), one of them associated cytogenetic fluorescence in situ hybridization (FISH) technique; thirteen studies performed only genetic techniques; five studies used bacterial culture techniques, two of them, associated genetic and molecular techniques; one study used only FISH technique; one study used only PCR technique (**Table 1**). All these studies presented data on feeding mode, and all infants were breastfed at least during the study follow-up **(Supplementary Table 2)**.

Most studies (n=18) performed three or four stool collections during follow-up. Eight studies collected more than four samples. Of the thirty-one studies, only ten presented results adjusting for the 'mode of feeding' variable (29,51,52,53,54,55,56,57,58,59). Five studies stratify for this variable within each delivery mode (35,60, 61,62, 63). Six of these studies presented results for the mode of feeding independent of the mode of delivery (second exposure) (64,65,66, 67, 68,69). Ten studies did not present results adjusting or categorizing by the mode of feeding variable (70,71,72,73,74,75,76,77,78,79) (**Table 2**).

Data analysis

Bacterial colonization according to mode of delivery

Despite the difference in the stool collection period, days 2, 3, 4, 6, 7 and 30 were characterized by reduced colonization and relative abundance of *Bifidobacterium* in infants born by CS (51,52,55,58,61,62,63,64,66,70,72,76).The third month was evaluated in five studies, two of them found lower colonization of *Bifidobacterium* in infants born by CS (61,78) and two did not perform a statistical test (52,65). Only one study found a higher colonization in this period (61).

Three studies found reduced colonization of the species *Bifidobacterium longum* in the first month in infants born by CS (55,58,61). Two studies found reduced colonization of species *Bifidobacterium catenulatum* at first week of life in infants born by CS (58,61). On the other hand, in the first month of life, the results for the species *Bifidobacterium bifidum* were contradictory (58,61).

Two authors found reduced colonization of the genus *Bacteroides* in infants born by CS at the third (74,78) and sixth months (70,78). The species *Bacteroides fragilis* was more likely to occur in infant stools collected at the first (58,61), third (61,62) and sixth months (61,62,64). All studies with stool data for one, three and six months found reduced colonization of *B. fragilis* in infants born by CS. The first month of life stood out by the lower colonization of the species *Bacteroides vulgatus* and *Bacteroides uniformis* in infants born by CS (58,61).

In the third month, two studies revealed reduced *Lactobacillus* colonization in infants born by CS, but one of them did not present the significance of this association, i.e. p-value was not shown (52, 62). In the first week of life, two studies found different results for the species *Clostridium perfringens*: higher colonization in infants born by CS (61), while the other found no difference between mode of delivery (58). In the first month, three studies found increased colonization of *Clostridium perfringens* in infants born by CS (61, 62,70), but results were contradictory for this species at six months (61,62).

The results for the *Enterobacteriaceae* family was presented by two authors during the first month, but only one found reduced colonization in infants born by CS (60,73). Four studies also found reduced colonization of *Escherichia coli* in the seven days of life among the CS group (29,56,58,71) (**Table 3**).

Association of mode of delivery on gut microbiota according to geographic location

The majority of included studies were from Asia (n=8) and Europe (Central, Nordic and Balkan Peninsula) (n=8). Only one study was from North American and Eastern Europe region. It was observed that the genus *Bifidobacterium* was found fourteen times among eight Asian studies (51,55,62,63,64,65,73,76), seven times in two Central European studies (61,78), five times in four Nordic European studies (66,70,71,72), three times in the study of the Balkan Peninsula (52), and twice in study of Eastern Europe. The species *B. longum* was found in one study from Asia and others in Central and Eastern Europe (55,58,61), while results for the species *B. catenulatum* and *B. bifidum* were found in a study of Central Europe e other in Eastner Europe (58,61).

Results for the genus *Lactobacillus* was found by an Asian study and another from the Balkan Peninsula (52, 62). The species *C. perfringens* was found by a study of Nordic Europe, one from Central Europe, one from Asia, and one from Eastern Europe (58,61, 62,70). Most studies that found a difference in the *Bacteroides* genus according to mode of delivery, were conducted in Central Europe, and only one in Nordic Europe (61,70,74,78). The difference in *B. fragilis* between mode of delivery was concentrated in studies conducted in Asia and Central Europe, and one conducted in Eastern Europe (58,61,62,64). Meanwhile, results from species *B. vulgatus* and *B. uniformis* was concentrated in studies from Central and Eastern Europe (58,61). The species *E. coli* was found in

two studies conducted in Nordic Europe (56,71), one in Central Europe (29), and one in Eastern Europe (58) (**Table 4**).

Considering the role of breastfeeding

Of the results that were controlled by the variable breastfeeding (n=10) (29,51,52, 53,54,55,56,57,58,59), six studies used as eligibility criteria: EBF (n=2) (51, 52) and MBF (n=4) (54,55,57 58). Four studies showed results adjusted for this variable (53; 56, 29; 58). Yap et al. (2011) (53) showed no difference between richness in the third month of life, even after adjusting for EBF (53). Moreover, after adjusting for breastfeeding, Reyman et al. (2019) (29) did not find difference between the abundance of *Bifidobacterium*.

Among the results that were presented regardless of the mode of delivery (n=6) (64,65,66,67,68,69). Tsuji et al. (2012) (64) demonstrated a higher total bacterial counts and prevalence of *C. coccoides* and *Atopobium* cluster in infants who were using infant formula, when compared infants in EBF. The genus *Bifidobacterium* was similar between both groups (64). This comparison was difficult in the study of Kabeerdoss et al. (2013) (65), since most infants were on EBF or MBF from birth. Despite demonstrating that cessation of breastfeeding at 90 days did not generate significance in the bacterial abundance, infants who received MBF in this period had a lower abundance of *Enterobacteriaceae*, compared to infants in EBF (65).

Hesla et al. (2014) (66) demonstrated that breastfeeding significantly influenced the gut microbiota at six months of age, and showed a greater relative abundance of *Bifidobacterium* in infants who were in EBF. When analyzed in isolation, the mode of delivery and breastfeeding had the greatest impact on the gut microbiota and strong association with the genus *Bifidobacterium* (66). Another study that also analyzed breastfeeding independently, showed greater relative abundance of *Bifidobacterium* sp. during the breastfeeding period, while that of *Bacteroides* sp. was significantly higher after the introduction of solid foods (67). On the other hand, Brazier et al. (2017) (68) and Yang et al. (2019) (69) found no difference for diversity and richness between feeding mode categories (68,69). However, Yang et al. (2019) (69) observed a greater abundance of *Bacteroidetes* than *Firmicutes* in the group that were in MBF.

Among the fifteen studies that considered the role of breastfeeding, only five showed results stratified for this variable (35,61,62,63). Martin et al. (2016) (61) revealed that infants born by VD that were EBF had more colonization by *B. bifidum* and *Lactobacillus gasseri* compared with infant who were in the MBF group or born by CS. The group of infants born by CS and who were in EBF showed greater similarity to the microbiota of the VD group. The *L. gasseri* species was more prevalent in EBF infants, and thus the VD group in EBF favored the colonization of *B. bifidium* and *L. gasseri* subgroup. Infants born by CS who were in MBF showed higher colonization of *Lactobacillus reuteri* compared to EBF infants (61).

Sakwinska et al. (2017) (63) compared the microbiota of VD and type of breastfeeding and observed that infants who were in MBF had lower colonization of *Bifidobacterium* and larger colonization of *Enterobacteriaceae*, *Klebsiella*, *Escherichia* and *Streptococcus* compared to EBF. After comparing this group (VD + MFD) with those born by CS and who were in the MBF group, they had reduced colonization of *Bifidobacterium*, increased *Klebsiella* and absence of the genus *Bacteroides* (63). Nagpal et al. (2017) (62) observed that difference in *C. perfringens* carriage was greater between the CS group (breastfed versus non-breastfed) when compared to the two VD groups. The CS in breastfeeding presented higher carriage of *B. fragilis*, *B. longum*, *B. breve* and *Lactobacillus* (62). On the other hand, in an American study, although the abundance of bacteria was greater in infants born by CS in MBF over the six months of life, there was no difference between microbial richness and diversity by categorizing the mode of delivery and MBF or exclusive formula use (60). When categorizing the results in different types of breastfeeding (BF and FF), the results by Akagawa et al. (2019) (35) observed no different for the diversity between groups, although the abundance of *Bacteroidales* was higher in the VD, regardless of feeding mode **(Table 2**).

Quality assessment (risk of bias)

Fifty-three percent of the studies (n = 17) had a high risk of bias, 31% (n = 10) an intermediate risk and 16% (n = 5) a low risk. The risk of bias between studies (accumulated evidence) is high as only five studies had a maximum score in this classification. The domains 'Selection', 'Confounders' (breastfeeding and antibiotic use), 'Analysis method' and 'Follow up' were the main factors responsible for the majority of bias. **(Table 5** and **Figure 2**).

Discussion

This SLR has several interesting findings. Only eleven bacterial taxa could be grouped synthesized based on the 31 studies that met inclusion criteria. The studies included in this SLR have shown that CS delivery leads to differential infant microbiota colonization patterns compared to infants born by VD. Synthesis of these studies further suggests that there may be differences in bacterial taxa associated with CS deliveries that are dependent on geographic location. Further, focused assessment of studies that considered both mode of delivery and breastfeeding revealed that while a few studies have reported that breastfeeding may modify the effect of delivery on the infant gut microbiota, few studies have adequately addressed this relationship to draw conclusions too.

The absence of initial maternal vaginal contact could explain differences in the infant gut microbiota (18). However, other clinical practices associated with CS, such as intrapartum maternal antibiotic which is indicated for CS, could mediate differences in the infant microbiota (80). The abundance of the genus *Bifidobacterium* on days two, three, four, six, seven and 30 was lower in infants born by CS. In the third month two studies showed lower abundance of *Bifidobacterium* in

infants born by CS (52,78), while one showed higher abundance in this group (61). The sixth month also presented conflicting results (61,78): as in the third month, intriguingly, Martin et al. (2016) (61) showed higher abundance of *Bifidobacterium* in infants born by CS, contrary to findings in other studies (**19,**20**)**. Differences in exposure to antibiotics by the mother-child dyad and feeding mode may explain these conflicts. Martin et al. (2016) (61) has no exposure to antibiotics and within six months most infants were in CBF, while Pham et al. (2016) (78) showed higher prevalence of MBF in this period. Apparently, the use of antibiotics associated with partial exposure to breast milk influenced the colonization of the *Bifidobacterium* (61), agreeing with Rutayisire et al. (2016) (20).

The species *B. longum (*especially subsp. *infantis)* is the only one with the high capacity to digest the HMO and generate a positive impact on the gut barrier (81,82). In experimental models, *B. catenulatum* species has been reported as probiotic bacteria, acting on liver health and activating enzyme (83,84). Colonization of the species *B. longum* and *B. catenulatum* were also reduced in infants born by CS in the first month and week of life, respectively (55,58,61,69). The species *B. bifidum* also ferment the HMO, besides to activate the innate immunity, adhere to the mucosa and contribute to the aggregation of other bacteria, preventing the dysfunction and the development of diseases (85). Unlike those species, results for *B. bifidum* were different between two studies: lower (61) and higher (58) in the first month of life in infants born by CS. Both differ by exposure to antibiotics, feeding and analysis method, where Martin et al. (2016) (61) has no exposure to antibiotics and within first month, most infants were in EBF, and in addition used the gene sequencing, while Priputnevich et al. (2019) (58) despite having been exposed to antibiotics, used a molecular analysis method (MALDI – TOF).

It is noteworthy that differences in the genus *Bifidobacterium* predominated among the synthesized studies, consistent with other literature (21,41,43,86). Most studies were conducted focusing on periods varying from three to seven days and one and three months of life, with similar results, with the exception of the third month for *Bifidobacterium*. This genus can be modulated by mode of delivery, as the vaginal microbiota has strains of this bacteria that can be transmitted to the infant (87,88). However further studies relating *B. longum, B. catenulatum* and *B. bifidum* to the mode of delivery are needed.

The genus *Bacteroides* and the species *B. fragilis* also play an important role in human health, contributing to the cellular maturation of the host immune system and the pathogen resistance (89,90). Infants born by CS between the first, third and sixth month of life were characterized by a lower abundance of the genus *Bacteroides* (and species *B. fragilis*). The species *B. vulgatus* had immunomodulatory role influencing secretion of cytokines (91). *B. uniformis* species is a mucin degraded that metabolize glycan, canning increase by breastfeeding and fiber intake (92). This bacteria improve inflammation, immune system and metabolic disfunction associated to obesity (93).

In first month of life, the colonization of *B. vulgatus* and *B. uniformis* were lower in gut of infants born by CS (58,61). These infants were more likely to be colonized by opportunistic and pathogenic bacteria (89).

Studies observed the beneficial health effects of *Lactobacillus* (41,94). This genus produces lactic acid, which has antiviral and antibacterial function, favoring the maintenance of eubiosis (95). The abundance of the genus *Lactobacillus* was reduced in the microbiota of infants born by CS. *Lactobacillus* is frequently the dominant genus found in the maternal vagina (7,95,96), what have led some to suggest that probiotic *Lactobacillus* could be deliveried as a supplement to cesarean-delivered infants, to reduce allergic diseases that develop later in life (7,97). This genus is also present in breast milk, so breastfeeding could be a natural way to provide *Lactobacillus* to the infant (7,98).

The species *C. perfringens* has negative effect on health. It produces toxins that can induces gut infections or tissue necrosis like preterm necrotizing enterocolitis (99,100). At the first month, the colonization of the species *C. perfringens* was higher in infants born by CS, while the sixth months the results were contradictory (61,62). Such results are intriguing, as this species is potentially pathogenic and found only in dysbiosis conditions (62). Infants born by CS are more colonized by anaerobic bacteria, which may favor the growth of opportunistic bacteria such as *C. perfringens* (101). Nevertheless, Martin et al. (2016) (61) found lower colonization in infants born by CS, and this result can be explained by the absence of antibiotic exposure, unlike Nagpal et al. (2017) (62), who reported the presence of this exposure.

The species *E. coli* has some pathogenic categories and may be associated with intestinal and urogenital tract infection (102,103). Due to its high capacity for proliferation in the gut, it is possibly transmitted by maternal stool. Fecal transmission of this bacterium can be increased in unhealthy conditions in the hospital environment (104,105). Under normal conditions, during vaginal birth, these bacteria is responsible for the intestinal colonization of the newborn in the first days of life (56,104). In this SLR, the species *E. coli* presented reduced colonization in the CS group at the first week of life (56,71). Although studies on the association of this bacteria with the mode of delivery are still scarce, these findings corroborate what was found in Nowrouzian et al. (2003) (105).

The microbiota composition can be influenced by the exposure to antibiotics (14,15). Exposure to antibiotics (directly or indirectly) may alter the composition of the gut microbiota (dysbiosis), and impair the bacterial-host homeostasis relationship, increasing the risk of diseases such as allergies and diabetes (106). Two studies at six months found contradictory results for the genus *Bifidobacterium*. Infants born by CS who were not exposed to antibiotics showed greater colonization of this genus (78), while in the study in which these infants were exposed to antibiotics, colonization of *Bifidobacterium* was lower (61). This exposure also influenced colonization of *C.*

perfringens at six months (61,62). The effect of antibiotic use on microbiota may be of long term, however there is no definite time for the effect (30,34,107,108).

Breastfeeding is a potential determinant of infant gut microbiota that could mediate, at least to some degree, changes in the gut microbiota associated with mode of delivery (2,61). The compounds of human milk, especially HMOs, stimulate the growth of potentially health promoting bacteria and inhibits the growth of pathogens (109). To considere breastfeeding in analysis of association between mode of delivery and microbiota is important.

Despite this, in this SRL only eleven studies controlled the results for breastfeeding. Within these studies, Nagpal et al. (2017) (62) demonstrated greater *C. perfringens* among infants born by CS than who born to VD, regardless of feeding. However, when the infants born by CS were breastfed, presented higher *B. fragilis*, *B. longum*, *Bifidobacterium breve* and *Lactobacillus* compared who no BF. In the same manner, Martin et al. (2016) (61) found those born by CS and who were breastfed presented a more similar gut microbiota to infants born by VD. These finds probably sugest an effect of BF in gut microbiota of infants born to CS, similar to Hill et al., (2017) (110) results, that shows that BF for more than four months impacted in gut microbiota of full-term born by CS, in 24 months postpartum.

Despite that, is important consider the formula intake. Sakwinska et al. (2017) (63) observed lower colonization of *Bifidobacterium* and higher colonization of *Enterobacteriaceae, Klebsiella, Escherichia* and *Streptococcus* in infants born by VD in MBF (vs EBF). Compared with previous group, infants born by CS who were in MBF had lower colonization of *Bifidobacterium,* higher colonization of *Klebsiella* and absence of the genus *Bacteroides*. Additionally, Martin et al., (2016) (61) demonstrated that Infant born by VD with EBF had higher abundance of the species *B. bifidum* and *L. gasseri* subsp. when compared to those who were born by CS or were the MBF group. These findings are in acordance with Liu et al., (2019) (111) results, who described that EBF could counteract partialy of the deleterious effects of CS in infant gut microbiota. In contrast, in this RSL two studies showed no difference in bacterial diversity and richness according to feeding mode (35,60). These studies results may have been influenced by the comparison groups used, MBF and FF, both with formula intake, despite in different amounts. More infant microbiota studies comparing CS to VD that consider breastfeeding with formula use are needed.

Geographic location can be a factor that influences gut microbiota, as it can vary widely among human populations around the world (9,112,113). According to results described for this variable, it has been suggested that gut colonization of the genus *Bifidobacterium* is favored in Asia, while *Bacteroides* are favored in Central Europe, and *E. coli* in Nordic Europe, due to lifestyle and feeding mode (114,115). Subramanian et al. (2014) (115) also found higher levels of *Bifidobacterium* in Asian children. Fallani et al. (2011) (114) also found a higher proportion of *Bacteroides* in Central

European infants when compared to those born in other regions of Europe (Fallani et al., 2011) (114). Contrary to our findings, the proportion of *E. coli* was higher in Southern Europe when compared to Nordic and Central Europe, even after adjusting for feeding (Fallani et al., 2011) (114). However, the studies included in this SLR have not been performed in Southern Europe, making it impossible to compare. In addition, all studies included in this SLR were not focused on analyzing the microbiota according to the geographic location, making it difficult to compare these results with the literature.

Bacterial culture provides less information about the microbiota, as many taxa cannot be easily cultured and abundance information is not obtained compared to broad range sequencing methods, thus it is an important factor to be considered in the interpretation of results from different studies (116,117). Even so, only three of the 31 studies in this SLR employed just culture methods. Overall, these studies would have little impact on the interpretation of results from the SLR.

The current SLR found that only five studies presented low risk of bias when the quality of intra-individual studies was assessed. This may compromise the quality of the accumulated evidence. Our findings suggest that the combination of these results shows that the thirty-one manuscripts yield little evidence on this topic, but recommendation studies and guidelines need to confirm this by assessing overall quality of evidence. These results indicate that more studies with good methodological quality and with great effort to avoid bias need to be carried out. The presence of bias is unavoidable in certain situations, but control by breastfeeding mode and antibiotic exposures are crucial to study infant microbiota.

The present study had the limitations of not being able to synthesize the results according to breastfeeding status, as some studies did not show results categorized according to this variable. Therefore, further studies are needed to associate the mode of delivery and breastfeeding/antibiotics with the infant gut microbiota. The difference in presentation measures and the lack of data (in values) on microbiota results in several studies makes it difficult to statistically combine the results and conduct a formal meta-analysis. Given this, a software developed by Gonzales et al. (2018) (118) allows microbiota data be added by the author of the manuscript. Therefore, we suggest that all data be provided in supplementary material or software to facilitate the conduct of this type of study. Yet, this SLR has strengths that should be highlighted, such as the various databases searched and additional sources that allowed a wide access, such as gray literature and the consideration of feeding and geographic location in the results. Therefore, it adds evidence to the existing ones and shows that future studies with similar methodological processes and data are necessary for possible comparisons, in addition to adequate control of feeding mode and antibiotic use. In addition, future studies in territories where few publications were found or no study was included in the SLR, such as the South American one, are essential for a better understanding of the association explored by this manuscript and the influence of geographic location.

Conclusion

Infants born by CS are less colonized by *Bifidobacterium* and *Bacteroides* (and the species *B. fragilis, B. vulgatus* and *B. uniformis)*. Breastfeeding is a potent confounder of this association, however, further studies considering the role of this variable are still needed. The species *B. longum* and *B. catenulatum* have shown similar results as the genus *Bifidobacterium*. However, studies considering the association between this species are still scarce. The genus *Lactobacillus* and the species *E. coli*, although apparently reduced in infants born by CS, as shown in the literature, still need to be further explored by other studies. The colonization of the species *C. perfringens* tends to be higher in CS during the first month of life, but further studies are also needed. Thus, infants born by CS are less colonized by bacteria that can increase development of diseases. Conditions such lifestyle and maternal-infant feeding pattern specific to each geographic location can influence the initial colonization of gut microbiota. Overall, the intra-study quality is low (high risk of bias), and our findings suggest that biases may influence the quality of general evidence, and thus further studies with minimal biases need to be performed.

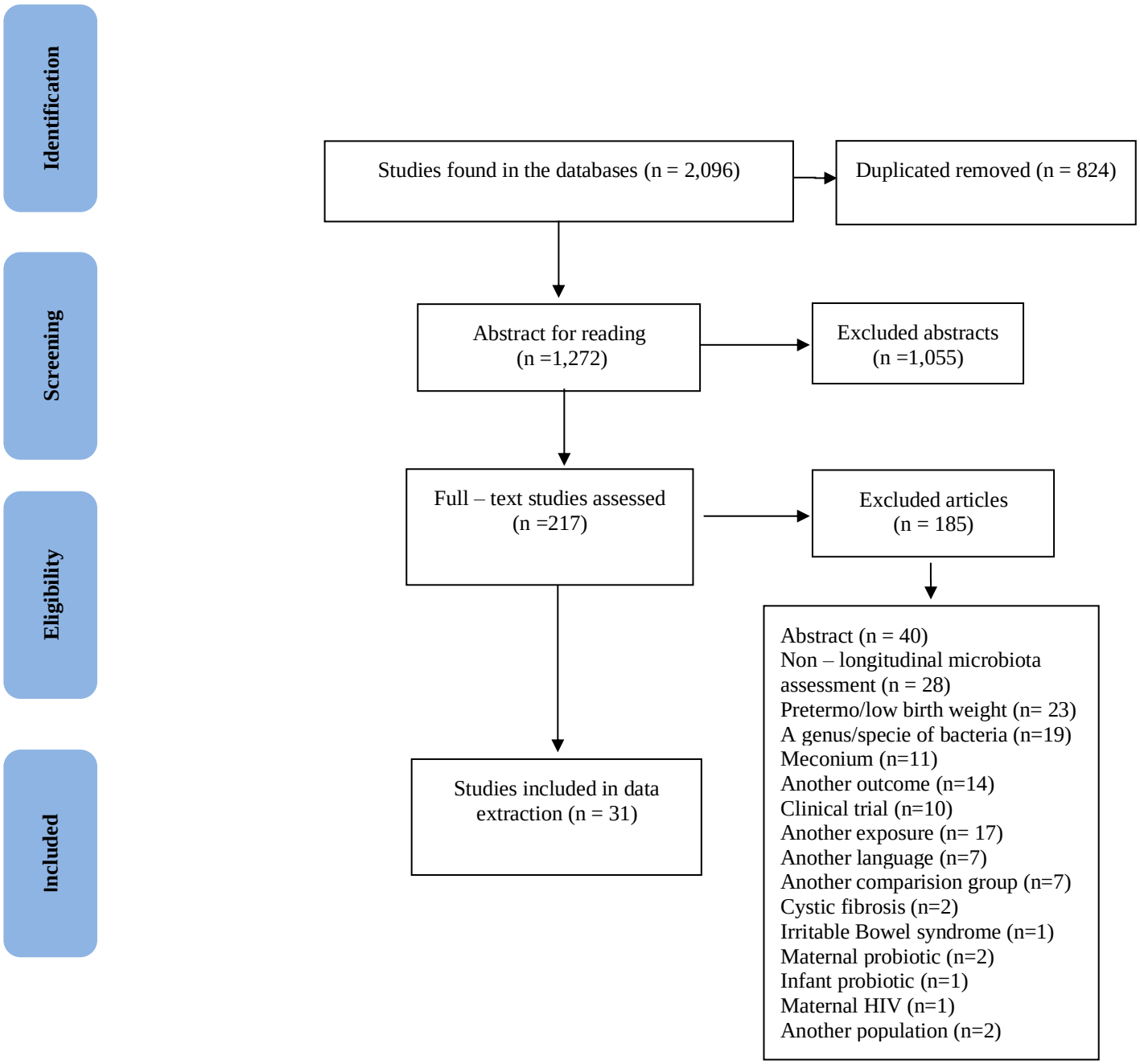

Figure 1. Study selection flowchart (PRISMA, 2009).

Table 1. Characteristics of the studies.

Author, year	Country	Sample size (n)		Gestational age at birth (mean/w)			Period for stool collection	Antibiotic use	Analysis method
		VD	CS	Total	VD	CS			
Gronlund et al., 1999	Finland	34	30	-	40.0	39.0	3, 5, 10, 30 and 180 d	M	Bacterial culture
Adlerberth et al., 2006	Sweden	99	17	-	-	-	1, 2, 4 and 8 w; 6 mo	M/C	Bacterial culture
Chen et al., 2007	China	20	20	-	39.1	39.4	1 - 7 d	M	DNA extraction and 16s RNA
Huurre et al., 2008	Finland	141	24	-	39.5	39.2	1, 3, 6 mo	NC	FISH
Mitsou et al., 2008	Greece	37	30	-	39.4	38.7	4, 30 and 90 d	-	DNA extraction, sequencing and PCR amplification
Tanaka et al., 2009	Japan	23	3	39.0	-	-	1 - 5 d; 1 and 2 mo	M/C	DNA extraction and 16S rRNA amplification
Yap et al., 2011	Singapore/ Indonesia	32	42	-	-	-	3 d; 1, 3 mo	M	DNA extraction, 16S rRNA amplification + PCR + FISH + flow cytometry
Tsuji et al., 2012	Japan	134	17	-	-	-	1 and 3 d; 1 w; 3 and 6 mo	C	DAPI staining, RNA extraction RT-PCR and DNA extraction and qPCR amplification
Kabeerdoss et al., 2013	India	73	10	~ 37.9	-	-	1, 2, 4, 7, 14, 28, 90 ,180 d	-	DNA extraction and 16S rRNA gene sequencing
Hesla et al., 2014	Sweden	94	16	-	-	-	6 d; 3 w; 2 and 6 mo	M	DNA extraction and 16S rRNA gene sequencing
Jakobsson et al., 2014	Sweden	15	9	-	-	-	1 w; 1, 3 and 6 mo	C	DNA extraction and 16S rRNA gene amplification
Del Chierico et al., 2015	Italy	6	25	39.0	-	-	1,2,3,7, 15 and 30 d	-	DNA extraction and HITChip microarray
Dogra et al., 2015	Singapore	57	18	38.8	-	-	3 d; 3 w, 3 and 6 mo	M	DNA extraction and 16S rRNA sequencing
Liu et al., 2015	China	25	16	-	39.4	39.1	2 and 4 d	-	DNA extraction, 16s RNA sequencing + PCR + DGGE
Bokulich et al., 2016	USA	24	19	39.2	-	-	12 – 24h PP; 1,2,3,4,5 and 6 mo	M/C	16s rRNA sequencing + qPCR

Brumbaugh et al., 2016	USA	11	12	-	39.6	39.2	2 and 6 w	M	DNA extraction, 16S rRNA sequencing + PCR
Lee et al., 2016	South Korea	3	3	39.1	38.6	39.6	1 – 3 d; 1 and 6 mo	-	DNA extraction and 16s RNA sequencing
Martin et al., 2016	Belgium	80	28	-	-	-	MC; 2 d; 1 w; 1, 3 and 6 mo	-	DNA extraction + qPCR, RNA extraction + RT-qPCR and 16S/23S RNA sequencing and amplification
Pham et al., 2016	SWI	29	11	-	-	-	2 w; 1, 3 and 6 mo	M/C	Culture-based methods + DNA extraction, 16s rRNA (V1-3) sequencing + qPCR and high throughput sequencing methods.
Stokholm et al., 2016	Denmark	549	151	39.9	40.0	39.2	7 d and 1 mo	M/C	Bacterial culture
Yassour et al., 2016	Finland/ USA	35	4	38.5	39.6	38.4	2, 3, 4, 5 and 6 mo	C	DNA extraction, 16S rRNA sequencing
Brazier et., 2017	Gabon/ Republic of the Congo	7	8	~ 40.2	~ 40.2	~ 40.2	MC; 2, 7 and 28 d	NC	DNA extraction, PCR amplification 16s rRNA (V3)
Nagpal et al., 2017	Japan	76	13	-	-	-	7 d; 1, 3 and 6 mo	C	DNA extraction, RT-qPCR and 16S/23S RNA sequencing
Sakwinska et al., 2017	Singapore	34	8	38.9	-	-	3 d; 3 w	M	PCR
Stearns et al., 2017	Canada	67	7	-	40.0	39.6	3, 10 d; 6 and 12 w	M/C	DNA extraction and 16s rRNA sequencing
Korpela et al., 2018	USA/ Italy/ Sweden	122	25	-	-	-	MC (USA, Italy), 1 w (Sweden), 6 w (USA), 4 mo (Sweden)	M/C	DNA extraction and sequencing
Akagawa et al., 2019	Japan	20	16	39.1	39.5	38.8	4 d and 1 mo	M	DNA extraction and 16S rRNA gene sequencing
Priputnevich et al., 2019	Russia	33	33	~ 39.0	-	-	1, 7, 30 d	M	Bacterial culture + MALDI-TOF MS + DNA extraction and 16S rRNA sequencing
Reyman et al., 2019	Netherland	74	46	~ 39.4	39.75	39.12	2h; 24 – 36h; 7, 14 d; 1, 2, 4 and 6 mo	M/C	DNA extraction, 16S rRNA sequencing + PCR
Shao et al., 2019	United Kingdom	314	282	39.5	39.5	39.5	4, 7 and 21 d	M	DNA extraction and 16S rRNA sequencing
Yang et al., 2019	China	46	56	39.0	-	-	1, 42 d; 3 and 6 mo	C	DNA extraction, 16S rRNA sequencing + PCR

Note: VD – vaginal delivery, **CS** – cesarean- section; **d** – day (s); **MC** - meconium; **w**- week (s); **mo** - month(s); **FISH** - fluorescence in situ hybridization; **PCR** – polymerase chain reaction; **DGGE** - denaturing gradient gel electrophoresis and degenerating gradient gel electrophoresis; **USA** – United States of America; **SWI** – Switzerland; **MALDI-TOF MS** – matrix-assisted laser desorption/ionization – time of flight spectofotometry mass ;**M** – Mother; **C** – Child; **NC** – not clear.

Table 2. Study objectives and ways breastfeeding covariable was analyzed

Author, year	Objectives	Control for breastfeeding
Gronlund et al., 1999	To study the duration of the effect of external factors on gut colonization between delivery mode	No adjustment/ stratification for BF
Adlerberth et al., 2006	To characterize gut colonization in infants with high risk of developing allergy	No adjustment/ stratification for BF
Chen et al., 2007	To investigate the effects of different delivery on *Bifidobacterium* and *Lactobacillus* in breaste-fed neonates	Controlled: all were exclusively breastfed
Huurre et al., 2008	To evaluate difference on gut microbiota between mode of delivery, and the possible effect on mucosal immunity	No adjustment/ stratification for BF
Mitsou et al., 2008	To explore the development of intestinal microflora and the colonization pattern of lactic acid bacteria and *Bifidobacterium* in healthy infants and to investigate the potential role of mode of delivery on gut microbiota development	The effect on the delivery mode was performed with all those were breastfed
Tanaka et al., 2009	To investigate the influence of antibiotic treatment in newborn infants on the development of gut microbiota	No adjustment/ stratification for BF
Yap et al., 2011	To investigate the influence of demographic factors on determining the microbial colonization of the infant colon in Singapore and Indonesia	The relative abundance of *Lactobacillus – Enterococci* was higher in EBF (6 months) in all points ($p<0.05$); There's no difference between the Richness (3 months) after the adjustment for EBF
Tsuji et al., 2012	To describe the range of profiles that constitute gut microbiota in infant after birth until 3 years as well as the influence of various factors	Total bacterial counts and the prevalence of *C. Coccoides* and the *Atopobium* cluster in infants fed formula milk (started on 7 days) were higher than in EBF (3 months); *Bifidobacterium* was similar between the groups. *It was not adjusted, but BF entered as one of the exposures
Kabeerdoss et al., 2013	To examine and elucidate the development of the gut microbiota in neonatal life until 6 months in development country and to ascertain differences in gut composition according mode of delivery, socioeconomic status, feeding practices and birth weigh	The majority of infants were BF from birth, making it difficult to compare the effect of BF and bottlefeeding on the microbiota. Cessation of BF by day 90 was not associated with significant alteration in abundance of these microbial communities (data not shown). Infants who received supplemental cows' milk (in addition to BF) by day 90 had lower numbers of *Enterobacteriaceae* than infants in EBF. *It was not adjusted, but BF entered as one of the exposure

Hesla et al., 2014	To investigate how anthroposofic lifestyle affects the gut microbiota of healthy lifestyle	BF significantly influenced the gut microbiota at 6 months, but not at 2 months (inverse relationship); The relative abundance of *Bifidobacterium* was higher in infants EBF (6 months); intermediate in MFD; lower in NBF. Even though BF might be delayed among in CS, the proportion of infants who had been fed with FF during the 1st week was low and similar between the mode of delivery, so the difference in abundance relative between the groups can not be explained by type of BF; Mode of delivery and BF had a major impact on gut microbiota and strongly affected the *Bifidobacterium.* *It was not adjusted, but BF entered as one of the exposures
Jakobsson et al., 2014	To address how microbiota development in infants is affected by mode of delivery, and relate difference in colonization patterns to the maturation of a balanced Th1/Th2 immune response	No adjustment/ stratification for BF; Did not evaluate the effect of BF on the variables used (relative abundance; diversity; richness, colonization)
Del Chierico et al., 2015	To investigate the chronological succession and network of interactions of gut microbiota operational taxonomic units (OTUs)	No adjustment/ stratification for BF; Did not evaluate the effect of BF on the variables used (relative abundance; diversity; richness, colonization)
Dogra et al., 2015	To investigate the effect of environmental factors (mode of delivery, duration of gestation) on the trajectories of microbial development, along with the associative relationships with later adiposity	No adjustment/ stratification for BF; The major was in EFF until 6 months; The majority of infants was in MFD at 3 days of life. Limitation on the discriminatory power to detect the effects of infant feeding
Liu et al., 2015	To describe the influence of the mode of delivery on the diversity of the gut microbiota during early colonization in Chinese infants	Controlled: all were in MFD
Bokulich et al., 2016	To profile microbial development during the first two years of life, and identify multiple disturbances associated with antibiotic exposure, CS and diet	Categorized for mode of feeding; No difference on microbiota composition (richness; diversity) between the 2 groups until 6 months (MFD and EFF)
Brumbaugh et al., 2016	To investigate the relationship between delivery mode, initial bacterial inoculation of infant oropharynx and intestinal colonization	No adjustment/ stratification for BF; equal BF intensity between delivery groups
Lee et al., 2016	To identify the effects of delivery mode on the composition of gut microbiota in infants after controlling for confounding factors (perinatal antibiotics and probiotics and feeding type)	Controlled for mode of feeding: chose participants who were on MFD

Martin et al., 2016	To describe the dynamics of the early colonization during the first six months of life and identify factors that can drive changes in the can drive changes in the composition of the gut microbiota in early life	The colonization of *L. reuteri*, *L. reuteri* subgroup and *B. bifidum* was dependent on interaction between mode of delivery and feeding mode; VD EBF was more colonizated by *B. bifidum*, *L. gasseri* subgroup, compared to VD MFD or CS; CS EBF showed a level more similar to VD; L. gasseri subgroup were more frequently detected in EBF; VD + EBF favor the colonization by *B. bifidum* and *L. gasseri* subgroup, and the BF can compensate, favoring the colonizaion os these species; CS + MFD was more colonizated by *L. reuteri* subgroup, while CS + EBF was less colonizated by this specie; *Feeding mode as second exposure (EBF x MFD): - Lower in total bacterial counts in EBF (3 months); - Higher counts of *Staphylococcus* (3 months); Infants exposed to FF was more colonized by *Enterococcus*, *C. coccoide*, *Atopobium*, *B. vulgatus* and *B. longum* subsp. *Longum;* The counts of *Bifidobacterium* was lower in EBF (especially at earlier time point); The colonization of C. perfringens and L. casei subgroup were lower in EBF (3 months); The colonization of *C. leptum* was higher in infants exposed to FF (3 months); Effect on diet of first 3 months on stool collection at 6 months EBF was higher counts of *Bifidobacterium*, *L. casei* subgroup L. gasseri and *B. adolescentis* at 6 months; The prevalence of *Atopobium* AND C. coccoide was higher in infants were exposed to solid food ; The colonization of *Enterobacteriaceae* and *Staphylococcus* was lower in infants were exposed to solid food; The prevalence of *B. longum* subsp. l*ongum* was higher after introduction of solid food
Pham et al., 2016	To investigate the colonization pattern of gut microbiota using a combination of culture – based methods, molecular and high – throughput sequencing methods, focusing on the functional groups of microbes contributing to a healthy throphic chain, and the fate of lactate as an important intermediate metabolic	No adjustment/ stratification for BF
Stokholm et al., 2016	To analyze the effects of delivery mode on the colonization patterrn of both the intestinal tract and airway during the first year of life	Adjusted for duration of EBF

Yassour et al., 2016	To report a longitudinal study of the gut microbiome based on DNA sequence analysis of monthly stool samples	BF period was correlated with higher relative abundance of *Bifidobacterium* sp. The presence *Bacteroides* sp. was significant at the earliest time points, after introduction of solid food
Brazier et., 2017	To analyze the different steps involved in the infant gut bacterial/virus seeding an to monitor the changes of the gut microbiota community in the early days of life	*Feeding as a second exposure: There is no difference in diversity (Shannon index) and richness between the feeding mode
Nagpal et al., 2017	To investigate the intestinal carriage of a-toxigenic and enterotoxigenic *Clostridium perfrigens* during infancy, focusing on its association with other gut microbes and mode of delivery and feeding	Infants started FF (day 7) and (after 3 months): There is no difference in *C. perfringens*, but the infants in FF was more colonizated by a-toxigenic C. perfringens (1 and 3 months); Higher carriage of *Bifidobacterium*, *Lactobacillus*, *C. coccoide*, *Atopobium* and *C. perfringens* in MFD; Categorized (VD BF, VD FF, CS BF, CS FF): The difference in *C. perfringens* carriage was higher in CS BF x CS FF than VD BF x VD FF; Higher carriage of *B. fragilis, B. longum, B. breve and Lacyobacillus* in CS BF
Sakwinska et al., 2017	To characterize the microbiota of mother – infant pairs, and to describe the impact of delivery and feeding mode on the first stages of colonization and establishment of gut and nasal microbiota	Feeding mode was associated with difference in the overall composition of gut microbiota at day 3; Categorized: VD MFD (compared to VD EBF) shows colonization of *Bifidobacterium* lower, and higher of *Enterobacteriaceae*, *Klebsiella*, *Escherichia* and *Streptococcus.* CS MFD (compared to VD MFD) shows lower colonization of *Bifidobacterium*, higher of *Klebsiella* and absence of *Bacteroides.*
Stearns et al., 2017	To compare bacterial community sucession in infants born vaginally (with and without antibiotic) and CS	Controled: all were MFD
Korpela et al., 2018	To compiled a cohort of family members that allow us to assess strain persistance and intra-family strain transmission at birth and later in life, identifying strain transmission at different ages up to adulthood	No adjustment/stratification for BF

Akagawa et al., 2019	To characterize the gut microbiota of Japanese neonates and to clarify whether BF can correct dysbiosis in CS neonates.	Categorized (VD BF, VD FF, CS BF, CS FF) at 4 months: - *Bacteroidales*: higher in VD BF/FF (compared to CS BF/FF); - Diversity (Shannon): no difference between feeding mode groups.
Priputnevich et al., 2019	To apply the methods of culturomics, proteomics and molecular genetic technologies to investigate the development of gut microbiota in health newborn according delivery mode	Controlled: all were (at least) MBF
Reyman et al., 2019	To report on differences in the fecal microbiota between CS and VD infants over the first year of life, independent of maternal antibiotics	BF (covariable): - *Bifidobacterium*: higher in VD (compared to CS), even controlled for this variable
Shao et al., 2019	To characterize the trajectory of the acquisition and development of the gut microbiota during the neonatal period	Adjusted for EBF and MBF
Yang et al., 2019	To provide additional evidence for the signatures of gut microbiota after birth and investigate potential impacts of various factors on the gut microbiota	*Feeding as a second exposure (MBF and FF dominant): - No difference between richness and diversity; - *Bacteroidetes* was higher than *Firmicutes* in MBF (compared to FF dominant); - *Haemophilus*: higher in MBF; - *Peptoclostridium* and *Erysipelaclostridium*: higher in FF dominant at 42 days; - *Enterococcus* and *Lactococcus*: higher in FF dominant at 3 months; - - *Mogibacterium, Lactococcus, Eggerthella, Lachnoclostridium, Lachnospiraceae, Peptoclostridium, Lachnospiraceae* and *Intestinibacter:* Higher in MBF at 6 months.

Note: EBF – Exclusive breastfeeding; **MFD** – Mixed breastfeeding; **NBF** – No breastfeeding; **BF** – Breastfeeding; **FF-** Formula feeding; **EFF** – Exclusive formula feeding; **VD** – Vaginal delivery; **CS** – Cesarean delivery.

Table 3. Summary of findings for the mode of delivery on gut microbiota over six months.

Bacteria group	Period of collection	Total of studies	Effect on CS gut microbiota
Bifidobacterium	2 d	2	2↓
	3 d	4	4 ↓
	4 d	2	2 ↓
	6 d	2	2↓
	1 wk	7	5 ↓; 1↓ (MD); 1↓*
	1 mo	7	6↓; 1↓ (MD)
	3 mo	5	1↓; 2↓ (MD); 1↓*; 1↑
	6 mo	2	1↓; 1↑
Bifidobacterium longum	1 mo	3	2↓; 1↓ (MD)
Bifidobacterium bifidum	1 mo	2	1↓; 1↑ (MD)
Bifidobacterium catenulatum	1 wk	2	2↓
Lactobacillus	3 mo	2	1↓; 1↓ (MD)
Clostridium perfringens	1 wk	2	1↑; 1 (ND)
	1 mo	3	3↑
	6 mo	2	1↓; 1↑
Bacteroides	1 mo	2	1↓; 1↓ (MD)
	3 mo	2	2↓
	6 mo	2	2↓
Bacteroides fragilis	1 mo	2	1↓; 1↓ (MD)
	3 mo	2	2↓
	6 mo	3	3↓
Bacteroides vulgatus	1 mo	2	1↓; 1↓ (MD)
Bacteroides uniformis	1 mo	2	1↓; 1↓ (MD)
Enterobacteriaceae	1 mo	2	1↓ (MD); 1 (ND)*
Escherichia coli	1 wk	4	3↓; 1↓*

Note 1: Only groups of bacteria that were found in the same period by more than one study are shown in this table (see more in supplementary table 3); **d –** days; **wk** – week (s); **mo** – month (s); **CS –** Cesarean section; ↓ - Lower compared to VD; ↑- Higher compared to VD; **MD –** Missing data; **ND –** No difference; ***** - Not significant results (p- value ≥ 0.05).
Note 2: *Enterobacteriaceae* family could not be synthesized, as only one presented a different result between the groups.

Table 4. Summary of findings for the mode of delivery on gut microbiota over six months according geographic location.

Bacteria group	Region	Period of collection	Effect on CS gut microbiota	Author, year
Bifidobacterium	Asia	2 d	↓	Chen et al., 2007
	Central Europe		↓	Martin et al., 2016
	Nordic Europe	3 d	↓	Gronlund et al., 1999
	Asia		↓	Chen et al., 2007
	Asia		↓	Dogra et al., 2015
	Asia		↓	Sakwinska et al., 2017
	Asia	4 d	↓	Chen et al., 2007
	Balkan Peninsula		↓	Mitsou et al., 2008
	Asia	6 d	↓	Chen et al., 2007
	Nordic Europe		↓	Hesla et al., 2014
	Nordic Europe	1 wk	↓*	Adlerberth et al., 2006
	Asia		↓	Chen et al., 2007
	Asia		↓ (MD)	Tanaka et al., 2009
	Asia		↓	Tsuji et al., 2012
	Central Europe		↓	Martin et al., 2016
	Asia		↓	Nagpal et al., 2017
	Eastern Europe		↓	Priputnevich et al., 2019
	Nordic Europe	1 mo	↓	Gronlund et al., 1999
	Nordic Europe		↓	Huurre et al., 2008
	Balkan Peninsula		↓	Mitsou et al., 2008
	Asia		↓	Tsuji et al., 2012
	Asia		↓	Lee et al., 2016
	Central Europe		↓	Martin et al., 2016
	Eastern Europe		↓ (MD)	Priputnevich et al., 2019
	Balkan Peninsula	3 mo	↓ (MD)	Mitsou et al., 2008
	Asia		↓ (MD)	Kabeerdoss et al., 2013
	Central Europe		↑	Martin et al., 2016
	Central Europe		↓	Pham et al., 2016
	Asia		↓*	Nagpal et al., 2017
	Central Europe	6mo	↑	Martin et al., 2016
	Central Europe		↓	Pham et al., 2016
Bifidobacterium catenulatum	Central Europe	1 wk	↓	Martin et al., 2016
	Eastern Europe		↓	Priputnevich et al., 2019
Bifidobacterium longum	Asia	1 mo	↓	Lee et al., 2016
	Central Europe		↓	Martin et al., 2016
	Eastern Europe		↓ (MD)	Priputnevich et al., 2019
Bifidobacterium bifidum	Central Europe	1 mo	↓	Martin et al., 2016
	Eastern Europe		↑ (MD)	Priputnevich et al., 2019

Lactobacillus	Balkan Peninsula	3 mo	↓ (MD)	Mitsou et al., 2008
	Asia		↓	Nagpal et al., 2017
Clostridium perfringens	Central Europe	1 wk	↑	Martin et al., 2016
	Eastern Europe		ND	Priputnevich et al., 2019
	Nordic Europe	1 mo	↑	Gronlund et al., 1999
	Central Europe		↑	Martin et al., 2016
	Asia		↑	Nagpal et al., 2017
	Central Europe	6 mo	↓	Martin et al., 2016
	Asia		↑	Nagpal et al., 2017
Bacteroides	Central Europe	3 mo	↓	Jakobsson et al., 2014
	Central Europe		↓	Pham et al., 2016
	Nordic Europe	6 mo	↓	Gronlund et al., 1999
	Central Europe		↓	Pham et al., 2016
Bacteroides fragilis	Central Europe	1 mo	↓	Martin et al., 2016
	Eastern Europe		↓ (MD)	Priputnevich et al., 2019
	Central Europe	3 mo	↓	Martin et al., 2016
	Asia		↓	Nagpal et al., 2017
	Asia	6 mo	↓	Tsuji et al., 2012
	Central Europe		↓	Martin et al., 2016
	Asia		↓	Nagpal et al., 2017
Bacteroides vulgatus	Central Europe	1 mo	↓	Martin et al., 2016
	Eastern Europe		↓ (MD)	Priputnevich et al., 2019
Bacteroides uniformis	Central Europe	1 mo	↓	Martin et al., 2016
	Eastern Europe		↓ (MD)	Priputnevich et al., 2019
Enterobacteriaceae	Asia	1 mo	ND*	Tanaka et al., 2009
	North America		↓ (MD)	Bokulich et al., 2016
Escherichia coli	Nordic Europe	1 wk	↓	Adlerberth et al., 2006
	Nordic Europe		↓	Stokholm et al., 2016
	Eastern Europe		↓*	Priputnevich et al., 2019
	Central Europe		↓ (C%); ND (RA %)	Reyman et al., 2019

Note 1: Only groups of bacteria that were found in the same period by more than one study are shown in this table (see more in supplementary table 4); **d –** days; **wk** – week (s); **mo** – month (s); **CS –** Cesarean section; ↓ - Lower compared to VD; ↑- Higher compared to VD; ***** - Not significant results (p- value ≥ 0.05); **MD** – missing data; **ND** – no difference. **Note 2**: European continent was grouped in **Central Europe** (Switzerland; Belgium); **Nordic Europe** (Finland, Sweden, Denmark); **Balkan Peninsula** (Greece); **North America continent** (United States of America); **Asian continent** (China, Singapore, Japan, South Korea, India); **Eastern Europe** (Russia).

Table 5. Risk of bias assessment (accumulated evidence).

Author, year	Selection	Exposure	Outcome assessment	Confounders		Analysis method	Follow up	Risk of bias intra – study	Risk of bias between study
				BF	AB				
Gronlund et al., 1999	Low	Low	Low	High	Low	High	High	High	
Adlerberth et al., 2006	Low	Low	Low	High	High	High	High	High	
Chen et al., 2007	Low	Low	Low	Low	Low	Low	Low	Low	
Huurre et al., 2008	Low	Low	Low	High	NC	High	Low	High	
Mitsou et al., 2008	Low	Low	Low	Low	Low	Low	High	Intermediate	
Tanaka et al., 2009	Low	Low	Low	High	Low	Low	High	High	
Yap et al., 2011	High	Low	Low	Low	Low	Low	High	High	
Tsuji et al., 2012	Low	Low	Low	High	Low	Low	High	High	
Kabeerdoss et al., 2013	Low	Low	Low	High	Low	Low	High	High	
Hesla et al., 2014	High	Low	Low	High	Low	Low	Low	High	
Jakobsson et al., 2014	Low	Low	Low	High	Low	Low	Low	Intermediate	
Del Chierico et al., 2015	Low	Low	Low	High	Low	Low	High	High	
Dogra et al., 2015	High	Low	Low	High	NC	Low	High	High	High
Liu et al., 2015	Low	Low	Low	Low	Low	Low	Low	Low	
Bokulich et al., 2016	Low	Low	Low	Low	Low	Low	Low	Low	
Brumbaugh et al., 2016	Low	Low	Low	High	Low	Low	Low	Intermediate	
Lee et al., 2016	Low	Low	Low	Low	Low	Low	Low	Low	
Martin et al., 2016	Low	Low	Low	Low	Low	Low	High	Intermediate	
Pham et al., 2016	Low	Low	Low	High	High	Low	High	High	
Stokholm et al., 2016	Low	Low	Low	Low	Low	High	High	High	
Yassour et al., 2016	Low	Low	Low	High	High	Low	High	High	
Brazier et., 2017	High	Low	Low	High	NC	Low	Low	High	
Nagpal et al., 2017	Low	Low	Low	Low	NC	Low	High	High	
Sakwinska et al., 2017	Low	Low	Low	Low	Low	Low	High	Intermediate	
Stearns et al., 2017	Low	Low	Low	Low	Low	Low	High	Intermediate	
Korpela et al., 2018	High	Low	Low	High	High	Low	High	High	
Akagawa et al., 2019	Low	Low	Low	Low	Low	Low	Low	Low	
Priputnevich et al., 2019	Low	Low	Low	Low	Low	Low	High	Intermediate	
Reyman et al., 2019	Low	Low	Low	Low	Low	Low	High	Intermediate	
Shao et al., 2019	High	Low	Low	Low	Low	Low	High	Intermediate	
Yang et al., 2019	Low	Low	Low	High	Low	Low	High	Intermediate	

Note: BF – breastfeeding; **AB** – antibiotic**; NC –** not clear**;** all domains "Low" – **Low risk of bias**; one domain "High" – **Intermediate risk of bias**; ≥ 2 domains "High" or "NC"- **High risk of bias**; **Note 2: Risk of bias intra – study -** risk of bias withing each specific study; **Risk of bias between study -** risk of bias between studies (accumulated evidence).

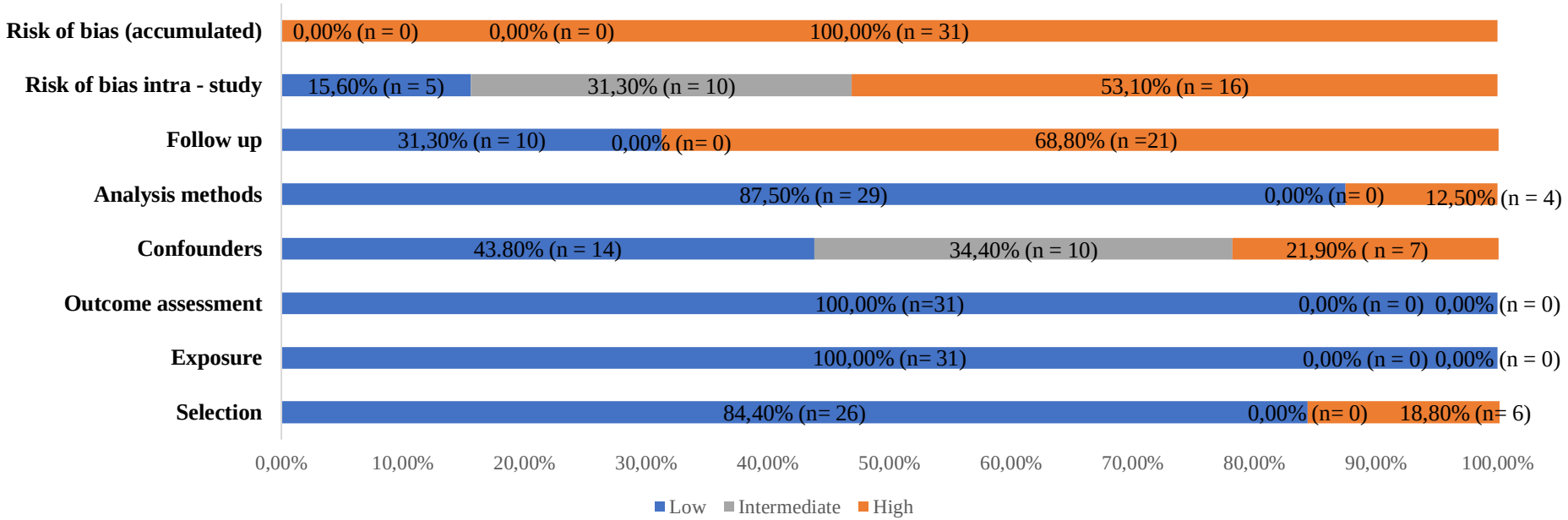

Figure 2. Risk of bias graph according each domain (n=31).

Note: All domains "Low" – **Low risk of bias**; one domain "High" – **Intermediate risk of bias**; ≥ 2 domains "High" or "NC"- **High risk of bias**.

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Supplementary Board 1. Databases used and search strategies.

Database	Period of time	Keywords and their combinations	Observations
Cochrane Library and PROSPERO	April 5, 2018	Search for systematic review studies with the same theme.	No results were obtained.
Pubmed	February 19, 2020	(("microbiota"[All Fields] OR "microbiome"[All Fields] OR "gut microbiota"[All Fields] OR "intestinal microbiota"[All Fields] OR "intestinal microbiome"[All Fields] OR "gut microbiome"[All Fields] OR "microorganisms"[All Fields] OR "lactobacillus"[All Fields] OR "bifidobacterium"[All Fields] OR "bacteroides"[All Fields] OR "clostridium"[All Fields] OR "staphylococcus"[All Fields] OR "pathogenic bacteria "[All Fields] OR "beneficial bacteria"[All Fields]) AND ("Mode of delivery"[All Fields] OR "Delivery mode"[All Fields] OR "C-section"[All Fields] OR "cesarean section"[All Fields] OR "caesarean section"[All Fields] OR "vaginal delivery"[All Fields] OR "normal delivery"[All Fields]) AND ("newborn"[All Fields] OR "neonate"[All Fields] OR "infant"[All Fields])) OR ("Microbiota"[Mesh] AND "Cesarean Section"[Mesh]) AND "Infant"[Mesh]	Medical subject headings (MESH).
Web of Science	February 18, 2020	((microbiota OR microbiome) AND (mode of delivery OR cesarean section OR caesarean section OR c-section OR vaginal delivery) AND (infant OR newborn OR neonate))	-
Scopus	February 18, 2020	((("infant" OR "newborn" OR "neonate") AND ("microbiota" OR "microbiome" OR "gut microbiota") AND ("mode of delivery" OR "delivery mode" OR "c-section" OR "caesarean section" OR "cesarean-section" OR "vaginal delivery" OR "normal delivery")))	-
Embase	July 18, 2018	(‘microbiota’ OR ‘microbiome’ OR ‘gut microbiota’) AND (‘delivery mode’ OR ‘mode of delivery’ OR ‘cesarean section’ OR ‘caesarean section’ OR ‘vaginal delivery’ OR ‘normal delivery’) AND (‘newborn’ OR ‘infant’)	Most congress and conference summaries.
Trip Medical Database	November 21, 2018	mode of delivery and microbiota e delivery mode and microbiota	Grey literature
Open Grey	February 18, 2020	mode of delivery and microbiota e delivery mode and microbiota	Grey literature

Supplementary Board 2. Tool to Assess Risk of Bias in Cohort Studies.

1. Was selection of exposed and non-exposed cohorts drawn from the same population?

Definitely yes (low risk of bias) Not clear Definitely no (high risk of bias)

2. Can we be confident in the assessment of exposure (Mode of delivery)?

Definitely yes (low risk of bias) Not clear Definitely no (high risk of bias)

3. Was there a difference in the evaluation of the outcome (stool collection methods or different laboratories) between exposed and unexposed?

Definitely yes (low risk of bias) Not clear Definitely no (high risk of bias)

4. There was control by confounders (stratification, adjustment), such as antibiotic use and breastfeeding? * check if any adjustments may have been used as eligibility criteria. Obs: Check "definitely yes", if at least antibiotic or breastfeeding is considered as adjustment or stratification

Definitely yes* (low risk of bias) Yes Not clear Definitely no (high risk of bias)

5. Can we be confident in the assessment of outcome (genetic sequencing or polymerase chain reaction (PCR) – denaturing gradient gel electrophoresis)?

Definitely yes (low risk of bias) Not clear Definitely no (high risk of bias)

6. Was the follow up of cohorts adequate?

Definitely yes (low risk of bias) Not clear Definitely no (high risk of bias)

Adapted from GRADE.

Supplementary Table 1. Data about antibiotic use.

Author, year	Antibiotic use (%)	
	Mother	**Child**
Gronlund et al., 1999	-	17.18
Yap et al., 2011	57.14 (P and PP)	-
Hesla et al., 2014	17.28 (P)	-
Jakobsson et al., 2014	29.17 (IP and PP)	-
Dogra et al., 2015	25.33	-
Bokulich et al., 2016	58.13 (P and IP)	58.13
Brumbaugh et al., 2016	60.87 (IP)	-
Pham et al., 2016	40 (PP)	10
Stokholm et al., 2016	31.86 (IP)	2.57
Yassour et al., 2016	-	28.21
Sakwinska et al., 2017	36 (P)	-
Stearns et al., 2017	100 (IP)	9.03
Akagawa et al., 2019	44.4 (IP)	-
Priputnevich et al., 2019	54.5 (IP and P)	-
Reyman et al., 2019	38.3 (IP)	30.0
Shao et al., 2019	51.2% (IP)	-
Yang et al., 2019	-	13.7

Note: P – pregnancy**; PP –** postpartum; **IP –** intrapartum.

Supplementary Table 2. Feeding mode data.

Author, year	Feeding (duration period: n)		
	Total	**VD**	**CS**
Gronlund et al., 1999	**EBF** - 2 mo: 41; **MBF** - 6 mo: 30	**EBF** - 2 mo: 19; **MBF** - 6 mo: 17	**EBF** - 2 mo: 22; **MBF** - 6 mo: 13
Adlerberth et al., 2006	**EBF**- 4 mo: 70 %; **MBF** – 6 mo: 74%	-	-
Chen et al., 2007	**EBF** – 7d: 40	**EBF**–7d: 20	**EBF**–7d: 20
Huurre et al., 2008	**EBF** – 2.3 mo: 141; **EBF** – 2.1 mo: 24	**EBF** – 2.3 mo: 141	**EBF** – 2.1 mo: 24
Mitsou et al., 2008	**EBF** – 4d 45; 30d: 26; 90d: 17; **MBF** – 4d: 35; 30d: 18; 90d: 4; **EFF** - 4d: 17; 30d: 15; 90d: 11	**EBF** - 4d: 22; 30d: 17; 90d: 10; **MBF** – 4d: 11; 30d: 5; 90d: 4; **EFF** – 4d: 4; 30d: 4; 90d: 4	**EBF** - 4d :23; 30d: 9; 90d: 7; **MBF** – 4d: 24; 30d: 13; 90d: MD; **EFF** – 4d: 13; 30d: 11; 90d: 11
Tanaka et al., 2009	**MBF**– 2 mo: 26	**MBF** – 2mo: 23	**MBF** – 2mo: 3
Yap et al., 2011	**EBF** - 6 mo: 6; **MBF** – 6 mo: 62; **EFF** – 6mo: 6	-	-
Tsuji et al., 2012	**EBF** – 1d: 151; 7d: 40; 1 mo: 42; 3 mo: 46; 6 mo: 20;**MBF** – 7d: 98; 1 mo: 10; 3 mo: 37; 6 mo: 12; **CBF** – 3 mo: 9; 6 mo: 37**; MBF + food**– 3 mo: 18; 6 mo: 36; **MD** – 7d: 7; 1 mo: 1; 3 mo: 2; 6 mo: **EFF** – 7d: 1; 1 mo: 3; 3 mo: 3; 6 mo: 3; **Formula + food** – 3 mo: 7; 6 mo: 15; **MD** – 7d: 7; 1 mo: 1; 3 mo: 2; 6 mo: 1	-	-
Kabeerdoss et al., 2013	**EBF** – 6 mo: 77; **MBF** - 1 w: 6; **CBF** - 4 mo: 8; 5 mo: 18	-	-
Hesla et al., 2014	**EBF** – 2 mo: 104; 6 mo: 31; **MBF** - 2 mo: 16; 6 mo: 77; **NBF** – 2 mo: 8; 6 mo: 20; **EFF** – 1w: 24	-	-
Jakobsson et al., 2014	**EFD** – 3 mo: 20; **MBF** – 3 mo: 3; 5 mo: 3; 6 mo: 20	**EBF** – 3 mo: 11; **MBF** – 3 mo: 3; 5 mo: 2; 6 mo: 12	**EFD** - 3 mo: 9; **MBF** – 3 mo: 0; 5 mo: 1; 6 mo: 8
Del Chierico et al., 2015	**Colostrum** – 1d: 31; 2d: 30; 3d: 28; **EBF** – 1d: 0; 2d: 0; 3d: 0; 7d: 7; 15d: 8; 30d: 5; **EFF** – 1d: 0; 2d: 0; 3d: 0; 7d: 1; 15d: 1; 30d: 2; **MBF** - 1d: 0; 2d: 0; 3d: 0; 7d: 1;15d: 1; 30d: 2	-	-
Dogra et al., 2015	**EBF** – 1 w: 15; 3 w: 14; 3 mo: 13; 6 mo: 7; **MBF** – 1 w: 50; 3 w: 52; 3 mo: 18; 6 mo: 13; **NBF** – 1 w: 10; 3 w: 9; 3 mo: 43; 6 mo: 51; **EFF** – 1 w: 10; 3 w – 9; 3 mo – 13; 6 mo: 51; NC - 4	-	-

Liu et al., 2015	**MBF** – 2d: 25; 4d: 16	**MBF** – 2d: 14; 4d: 6;	**MBF** – 2 d:11; 4d: 10
Bokulich et al., 2016	**MBF** – 3 mo: 31; **EFF** - 12	**MBF** – 3 mo: 20; **EFF** (dominant) – 3 mo: 4	**MBF** – 3 mo: 1; **EFF** (dominant) – 3 mo: 8
Brumbaugh et al., 2016	**MBF** – 2w: 21; 6 mo: 19	**MBF** – 2 w: 10; 6 w: 10	**MBF** - 2 w: 11; 6 w: 9
Lee et al., 2016	**MBF** - 6 mo: 6	**MBF** - 6 mo: 3	**MBF**- 6 mo: 3
Martin et al., 2016	**EFD** – meconium: 100; 2d: 76; 7d: 89; 30d: 79; 90d: 59; 180d: 10; **MBF** – Meconium: 2; 2d: 4; 7d: 11; 30d: 23; 90d: 30; 180d: 3; **EFF** – meconium: 3; 2d: 2; 7d: 3; 30d: 5; 90d: 15; 180d: 0; **CBF** - 30d: 3; 90d: 3; 180d: 88	-	-
Pham et al., 2016	**BF (NC)** - 2w: 38; 1 mo: 36; 3 mo: 33; 6 mo: 29 (72.5%); **Formula (NC)** – 2w: 16 (40%); 1 mo: 10; 3 mo: 12; 6 mo: 28	-	-
Stokholm et al., 2016	**EBF** - 103.1d	**EBF**- 105.4d	**EBF** – 88.4d (emergency CS); 102.5d (elective CS)
Yassour et al., 2016	**EBF** – 0.5 mo: 2; 2 mo:1; 3 mo: 2; 3.5 mo: 1; 4 mo: 2; 5 mo: 3; 5.5 mo: 1; BF **(final age of BF)** – 1.25 mo: 1; 1.48 mo: 1; 3.64 mo: 1; 4.1 mo: 1; 4.46 mo: 1; 5 mo: 1; **Formula (start)** – 0.5 mo: 3; 1.5 mo: 1; 2 mo: 1; 3 mo: 4; 3.5 mo: 2; 4 mo: 1; 5 mo: 3; 5.5 mo: 1; 6 mo: 1; **MD** - 5	**EBF** – 0.5 mo: 2; 2 mo: 1; 3 mo: 1; 3.5 mo: 1; 4 mo: 2; 5 mo: 3; 5.5 mo: 1; **BF (final age of BF)** – 1.25 mo: 1; 1.48 mo: 1; 3.64 mo: 1; 4.1 mo: 1; 4.46 mo: 1; 5 mo: 1; **Formula (start)** – 0.5 mo: 3; 1.5 mo: 1; 2 mo: 1; 3 mo: 4; 3.5 mo: 2; 4 mo: 1; 5 mo: 3; 5.5 mo: 1; 6 mo: 1; **MD** - 4	**EBF** – 0.5 months: 0; 2 months: 0; 3 mo: 1; 3.5 mo: 0; 4 mo: 0; 5 mo: 0; 5.5 mo: 0; **BF (final age of BF)** – 1.25 mo: 0; 3.64 mo: 0; 4.1 mo: 0; 4.6 mo: 0; 5 mo: 0; **Formula (start)** – 0.5 mo: 0; 1.5 mo: 0; 2 mo: 0; 3 mo: 0; 3.5 mo: 0; 4 mo: 0; 5 mo: 0; 5.5 mo: 0; 6 mo: 0; **MD** - 1
Brazier et., 2017	**EBF** – 9; **MBF** – 3; **EFF** - 2	**EBF**-5; **MBF**-2; **EFF** - 0	**EBF**- 2; **MBF**- 2; **EFF** - 2
Nagpal et al., 2017	**EBF** – 7d:42; 6 mo: 66; **EFF** – 7d: 47; 6 mo: 23	**EBF** – 7d: 36; 6 mo: 57; **EFF** – 7d: 40; 6 mo: 19	**EBF** – 7d: 6; 6 mo: 9; **EFF** – 7d: 7; 6 mo: 4
Sakwinska et al., 2017	**EBF** - 1w: 9; 3w: 10 - 10; **MBF** – 29; **EFF** – 2; **MD** - 1	**EBF** – 10; **MBF** – 21; **EFF** – 2; **MD** - 1	**EBF** - 0; **MBF** – 8; **EFF** - 0
Stearns et al., 2017	**MBF** (at least) – 12w: 74	**MBF** - 12w: 67	**MBF** - 12w: 7
Korpela et al., 2018	**EBF** - 1 w: 78; 6 mo: 72; **MBF** – 1 w: 21; 6 mo: 78; **MD** - 15; **EFF** – 6 mo: 15; **MD** - 2	**BFD** - 1 w: 70; 6 mo: 65; **MBF** – 1 w: 15; 6 mo: 65; **MD** – 12; EFF - 6 mo: 12; **MD** - 1	**EBF** - 1 w: 8; 6 mo: 7; **MBF** - 1 w: 6; 6 mo:13; **MD** - 3; **EFF** - 6 mo: 3; **MD** – 1
Akagawa et al., 2019	**BF** – 20; **FF** - 16	**BF** – 10; **FF** - 10	**BF** – 10; **FF** - 6
Priputnevich et al., 2019	**EBF** – NC; **MBF** - NC	-	-
Reyman et al., 2019	**BF** – NC; **EFF** – 22; **CBF**- NC	**BF** - 132.5d; **EFF** – 11; **CBF** – 130.5d	**BF** – 25d; **EFF** – 11; **CBF** – 128.0d
Shao et al., 2019	**BF**- 4d: 258; 7d: 449; 21d: 266	-	-
Yang et al., 2019	**MBF** – 1d: 75; 42d: 74; 3mo: 73; 6mo: 62; **FF** (dominant) – 1d: 27; 42d: 27; 3mo: 29; 6mo: 40	**MBF** – 1d: 37; 42d: 37; 3mo: 35; 6mo: 27; **FF** (dominant) – 1d: 9; 42d: 9; 3mo: 11; 6mo: 19	**MBF** – 1d: 38; 42d: 37; 3mo: 38; 6mo: 35; **FF** (dominant) – 1d: 18; 42d: 18; 3mo: 18; 6mo: 21

Note: VD – Vaginal delivery; **CS** – Cesarean section; **EBF**- Exclusive breastfeeding; **MBF** – mixed breastfeeding; **EFF** – Exclusive formula feeding; **CBF** – Complementary breastfeeding; **BF** – breastfeeding; **NBF** – no breastfeeding; d – day (s); w – week (s); mo – month(s); **NC**- Not clear.

Supplementary Table 3. Summary of findings for the mode of delivery on gut microbiota over six months.

Bacteria group	Period of collection	Total of studies	Effect on CS gut microbiota	Note
Actinobacteria	3, 10 d, 6 wk and 3 mo	1	1↑ (MD)	RA (%)
Bifidobacteriales	4 d	1	ND	RA (%)
	1 mo	1	ND	RA (%)
Bifidobacterium	Meconium	1	1 ↓	C (%)
	2 d	2	2↓	C [mean (SE)]; C (%)
	3 d	4	4 ↓	RA (%); C [mean (SE)]; C (%)
	4 d	2	2 ↓	C [mean (SE)]
	5 d	1	1↓*	C [mean (SE)]
	6 d	2	2↓	RA (%); RA [mean (%)]; C [mean (SE)]
	1 wk	7	5 ↓; 1 ↓ (MD); 1↓*	C (%); C [mean (SE)]
	2 wk	1	1↓	C (%)
	3 wk	1	1↓	RA [mean (%)]
	1 mo	7	6↓; 1↓ (MD)	C (mean/95 % CI); C [mean (SE)/n (%)]; C (%); C [mean (SE)]
	5 - 44 d	1	1↓	RA (%)
	3 mo	5	1↓; 2↓ (MD); 1↓*; 1↑	C (%); RA (%)
	Birth – 3 mo	1	1↓	C (%)
	1 d – 1 mo	1	1↓	RA (%)
	3d, 1 and 3 mo	1	1↓	RA (%)
	6 mo	2	1↓; 1↑	C (%)
Bifidobacterium catenulatum	Meconium	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	2	2↓	C (%); MD
	1 mo	1	1↓	C (%)
	3 mo	1	1↓	C (%)
	6 mo	1	1↓	C (%)
Bifidobacterium longum	Meconium	1	1↓	C (%)
	1 d	1	1↓	C (%)
	2 d	1	1↓	C (%)
	4 d	1	1↓	C (n)
	1 wk	1	1↓	C (%)
	1 mo	3	2↓; 1↓ (MD)	C [mean (SE)]; C (%)
	3 mo	1	1↓	C (%)
	6 mo	1	1↑	C (%)
Bifidobacterium longum subsp. longum	Birth – 3 mo	1	1↓	C (%)
Bifidobacterium longum + *Bifidobacterium breve* + *Bifidobacterium adolescentis*	1 w	1	1↓	RA (%)

Bifidobacterium longum + Bifidobacterium breve + Escherichia coli + Bacteroides vulgatus + Parabacteroides distasonis	4 d	1	1↓	C (%)
Bifidobacterium bifidum	Meconium	1	1↓	C (%)
	1 d	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	1	1↓	C (%)
	1 mo	2	1↓; 1↑ (MD)	C (%)
	3 mo	1	1↓	C (%)
	6 mo	1	1↓	C (%)
Bifidobacterium adolescentis	1 d	1	1↓	C (%)
	1 w	1	Absent in CS	MD
Micrococcus	1 d	1	1↑	C (%)
Bifidobacterium animalis	1 w	1	Higher in CS	MD
Bifidobacterium dentium	1 w	1	Higher in CS	MD
Bifidobacterium breve	1 wk	1	1↓	C (%)
Rothia	1 d	1	1↑	C (%)
Actinomycetales	4 d	1	ND	RA (%)
	1 mo	1	ND	RA (%)
Corynebacterium	1 d	1	1↑	C (%)
Collinsela	4 wk	1	1↓	RA (%)
Enterococcus	Meconium	1	1↓	C (%)
	1 d	1	1↑	C (%)
	2 d	1	1↓	C (%)
	4 d	1	1↑ (MD)	RA (%)
	1 wk	1	1↓	C (%)
	1 mo	1	1↑	RA [mean % (SE)]
	7 - 35 d	1	1↑	RA (%)
	3 mo	1	1↓	C (%)
	Birth – 3 mo	1	1↑	C (%)
	6 mo	1	1↑	C (%)
Enterococcus spp.	1 wk	1	1↑	C (%)
Enterococcus faecalis	1 wk	1	1↑	MD
	1 d	1	1↑	C (%)
	1 wk – 1 mo	1	Different between emergency CS	MD
Enterococcus faecalis + Enterococcus faecium + Staphylococcus epidermidis + Staphylococcus parasanguinis + Klebsiella oxytoca + Klebsiella pneumoniae + Enterobacter clocoae + Clostridium perfringens	4 d	1	1↑	C (%)

	4 - 21 d	1	1↑	C (%)
Enterococcus faecium	1 wk	1	1↑	RA (%)
Atopobium	Meconium	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	1	1↓	C (%)
	1 mo	1	1↓	C (%)
	3 mo	1	1↓	C (%)
	Birth – 3 mo	1	1↓	C (%)
	3d, 1 and 3 mo	1	1↓	RA (%)
	6 mo	1	1↓	C (%)
Bacteroides fragilis	Meconium	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	1	1↓	C (%)
	1 mo	2	1↓; 1↓ (MD)	C (%); MD
	3 mo	2	1↓; 1↑	C (%); controversial results within the same study (Martin et al., 2016)
	6 mo	3	3↓	C (%)
	Birth – 6 mo	1	1↓	C (%)
Bacteroides fragilis subgroup	Birth – 3 mo	1	1↓	C (%)
Bacteroides caccae	Meconium	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	1	1↓	C (%)
	1 mo	1	1↓	C (%)
	3 mo	1	1↓	C (%)
	6 mo	1	1↓	C (%)
	Birth – 6 mo	1	1↓	C (%)
Bacteroides vulgatus	Meconium	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	1	1↓	C (%)
	1 mo	2	1↓; 1↓ (MD)	C (%); MD
	3 mo	1	1↓	C (%)
	6 mo	1	1↓	C (%)
	Birth – 6 mo	1	1↓	C (%)
Bacteroides ovatus	Meconium	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	1	1↓	C (%)
	1 mo	1	1↓	C (%)
	3 mo	1	1↓	C (%)
	6 mo	1	1↓	C (%)
	Birth – 6 mo	1	1↓	C (%)
Bacteroides uniformis	2 d	1	1↓	C (%)
	1 wk	1	1↓	C (%)

	1 mo	2	1↓; 1↓ (MD)	C (%); MD
	3 mo	1	1↓	C (%)
	6 mo	1	1↓	C (%)
	Birth – 6 mo	1	1↓	C (%)
Bacteroides cellulositycus	1 mo	1	Absent in CS	MD
Bacteroides thetaiotaomicron	1 mo	1	Absent in CS	MD
Firmicutes	1 d	1	1↑ (MD)	RA (%)
	1 mo	1	1↑	C (%)
	3 mo	1	1↑	C (%)
	3, 10 d, 6 wk and 3 mo	1	1↑ (MD)	RA (%)
Selenomonadales	4 d	1	ND	RA (%)
	1 mo	1	ND	RA (%)
Lactobacillales	4 d	1	1↑	RA (%)
	1 mo	1	ND	RA (%)
Lactobacillus	1 d	1	1↓ (MD)	RA (%)
	2 d	1	1↓ (MD)	RA (%)
	3 d	1	1↓	C (%); *Lactobacillus* – like bacteria
	4 d	1	1↓	C [mean (SE)/n (%)]
	10 d	1	1↓	C (%)
	4 – 21d	1	ND	C (%); RA (%)
	1 mo	1	1↑ (MD)	C (%)
	3 mo	2	1↓; 1↓ (MD)	C (%)
	2 – 6 mo	1	1↑ (MD)	C (%); *Lactobacillus* – like bacteria
Lactobacillus gasseri	Meconium	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	1	1↓	C (%)
	1 mo	1	1↓	C (%)
	3 mo	1	1↑	C (%)
	6 mo	1	1↓	C (%)
Lactobacillus reuteri	Meconium	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	1	1↓	C (%)
	1 mo	1	1↑	C (%)
	3 mo	1	1↓	C (%)
	6 mo	1	1↓	C (%)
Bacillales	4 d	1	1↑	RA (%)
	1 mo	1	ND	RA (%)
Bacillus	1 d	1	1↑	C (%)
Gemella	1 d	1	1↑	C (%)
Globicatella	1 d	1	1↑	C (%)
Granulicatella	1 d	1	1↑	C (%)
Veillonella	6 d	1	1↑	RA [mean (%)]

	1 wk	1	1↑	RA [mean % (SE)]
	2 wk	1	1↓	C (%)
	3 wk	1	1↑	RA [mean (%)]
	1 mo	1	1↓	C (%)
Clostridiaceae	6 d	1	1↑	RA [mean (%)]
Clostridia	1 d	1	Absent in both	C (%)
	1 wk	1	1↑	C (%)
	2 wk	1	1↑	C (%)
	1 – 3 d, 1 and 6 mo	1	1↑	RA (mean %)
Clostridiales	4 d	1	ND	RA (%)
	1 mo	1	ND	RA (%)
	6 mo	1	1↑	RA (mean %)
Sarcina	Meconium, 2, 7 and 28 d	1	1↑	RA (%)
Clostridium sp	2 d	1	1↑	C (n)
	4 d	1	1↑	C (n)
	1 wk	1	1↑	MD
	1 wk – 1 mo	1	Different between emergency CS	MD
	1 mo	1	1↑	MD
Clostridium perfringens	Meconium	1	1↓	C (%)
	2 d	1	1↓	C (%)
	1 wk	2	1↓; 1 (ND)	C (%)
	1 mo	3	3↑	C (%)
	3 mo	1	1↓	C (%)
	Birth – 3 mo	1	1↑	C (%)
	6 mo	2	1↓; 1↑	C (%)
Clostridium butyricum	1 wk	1	ND	C (%)
	1 mo	1	1↑	C (%)
Clostridium innocuum	1 wk	1	ND	C (%)
Clostridium tertium	1 wk	1	ND	C (%)
	1 mo	1	1↑	C (%)
Clostridium ramosum	1 mo	1	1↑	C (%)
Clostridium paraputrificum	1 mo	1	1↑	C (%)
Clostridium difficille	1 mo	1	1↑	C (%)
Firmicutes/*Bacteroidetes* ratio	5 d	1	1↑	C (%)
	4 wk	1	1↑	C (%)
	5 mo	1	1↑	C (%)
Lactobacillus- Enterococcus	3 d, 1 and 3 mo	1	1↑	RA (%)
Bacteroides–Prevotella	1 – 3 mo	1	1↓ (MD)	RA (%)
	3 d, 1 and 3 mo	1	1↓	RA (%)
Bacteroidales	4 d	1	1↓	RA (%)
	1 mo	1	1↓	RA (%)
Bacteroidetes	25 h (VD); 40h (CS)	1	1↓	RA (%)

	Meconium/birth	1	1↓ (MD)	RA (%)
	1 – 3 d	1	1↓	C [mean (SE)]
	5 d	1	1↓	RA (%)
	1 wk	1	1↓	RA [mean % (SE)]
	2 wk	1	1↓	RA (%)
	42 d	1	1↓ (MD)	RA (%)
	3 mo	1	1↓ (MD)	RA (%)
	6 mo	1	1↓ (MD)	RA (%)
	4 wk	1	1↓	RA (%); D; R
	1 mo	1	1↓	D index (Shannon) [median (IQ)]
	1, 2, 3, 7, 17 and 30 d	1	1↓ (MD)	MD
	1wk – 1 mo	1	1↓ (MD)	RA (%)
	6 wk	1	1↓	RA (%)
	3 mo	1	1↓	RA [mean % (SE)]; D index (Shannon) [median (Q)]
	5 mo	1	1↓	RA (%); D; R
Bacteroidia	Birth, 1, 6 wk and 4 mo	1	1↓ (MD)	RA (%)
Bacteroides	1 d	1	1↓	C (%)
	3 d	1	1↓	C (%)
	6 d	1	1↓	RA [mean (%)]
	7 d	1	1↓	RA [mean % (SE)]
	1 wk	1	Absent in CS	C (%)
	2 wk	1	1↓	C (%)
	3 wk	1	1↓	RA [mean (%)]
	4 wk	1	1↓	RA (%)
	1 mo	2	1↓; 1↓ (MD)	C (%)
	2 mo	1	1↓	RA [mean (%)]
	2 wk, 1 and 3 mo	1	1↓	RA (%); compared between 4 CS and 12 VD
	3 mo	2	2↓	RA [mean % (SE)]; C (%)
	6 mo	2	2↓	C (%)
	2, 3, 4 and 6 mo	1	1↓ (MD)	RA (%)
Parabacteroides	1 mo	1	1↓	RA [mean % (SE)]
	3 mo	1	1↓	RA (%); compared between 4 CS and 12 VD
Parabacteroides diastasonis	1 mo	1	Absent in CS	MD
Bacteroides sp	2 d	1	1↓	C (n)
	4 d	1	1↓	C (n)
	2 wk	1	1↓	C (%)
	4 wk	1	1↑	C (%)
	2 mo	1	1↑*	C (%)
Proteobacteria	1 d	1	1↓ (MD)	RA (%)

	6 d	1	1↑	RA [mean (%)]
	3 wk	1	1↑	RA [mean (%)]
	42 d	1	1↑ (MD)	RA (%)
	2 mo	1	1↑	RA [mean (%)]
	3 mo	1	1↑	RA [mean % (SE)]
	3, 10 d, 6 wk and 3 mo	1	1↓ (MD)	RA (%)
	6 mo	1	1↑	RA [mean (%)]
Enterobacteriales	4 d	1	1↓	RA (%)
	1 mo	1	ND	RA (%)
Enterobacteriaceae	1 day	1	1↓ (MD)	RA (%)
	2 d	1	1↓ (MD)	RA (%)
	1 mo	2	1↓ (MD); 1 (ND)*	C (%); MD
Enterobacteria	1 d	1	1↓	C (%)
	3 d	1	1↑	C (%)
	1 mo	1	1↑*	C (%)
	6 mo	1	1↑	C (CFU/g feces)
Klebsiella	1 d	1	1↓	C (%)
	3 d	1	1↑	RA (%); OTU2
	10 - 20 d	1	1↑*	RA (%)
	Birth - 139 d	1	1↑	RA (%)
Klebsiella sp.	1 wk	1	1↑	C (%)
	2 wk	1	1↑	C (%)
Klebsiella oxytoca	1 wk	1	(ND)	RA (%)
	1 mo	1	1↑	MD
	1 wk – 1 mo	1	Different between VD	MD
Klebsiella pneumoniae	1 wk	1	1↑	MD
	1 mo	1	1↑	MD
	1 wk – 1 mo	1	Different between emergency CS	MD
Enterobacter	1 d	1	1↓	C (%)
Enterobacter sp	2 d	1	1↑	C (n)
	2 wk	1	1↑	C (%)
Enterobacter cloacae	1 wk	1	1↑	MD
	1 wk – 1 mo	1	Different between emergency CS	MD
Raoultella	1 d	1	1↓	C (%)
Kluyvera	1 d	1	1↓	C (%)
Morganella	1 d	1	1↓	C (%)
Citroabacter	1 d	1	1↓	C (%)
Pantoea	1 d	1	1↓	C (%)
Citrobacter freundii	1 wk – 1 mo	1	1↑*	MD
	1 wk - 1 mo	1	Different between emergency CS	MD
Escherichia	1 - 85 d	1	1↓	RA (%)
Escherichia coli	Meconium	1	1↓	C (%)

	1 d	1	1↓	C (%)
	2 d	1	1↓	C (n)
	3 d	1	1↓	C (%)
	1 wk	3	2↓; 1↓ (ND)	C (%); RA (%)
	2 wk	1	1↓	C (%)
	4 wk	1	1↓*	C (%)
	1 mo	1	1↓*	C (%)
	1 mo	1	1↓ (MD)	C (%)
	6 mo	1	1↓	C (%)
Staphylococcus	1 d	1	1↑	C (%)
	0 - 6 d	1	1↑	RA (%)
Staphylococcus sp	2 d	1	1↑	C (n)
Staphylococcus aureus	Meconium	1	1↑	C (%)
	1 d	1	1↑	C (%)
	1 wk	1	1↑	MD
	1 mo	1	1↑	C (%)
	1 wk - 1 mo	1	Different between emergency CS	MD
Staphylococcus epidermidis	1 wk	1	ND	RA (%)
	1 wk – 1 mo	1	Different between emergency CS	MD
Total bacterial	3 d	1	1↓	C (%)
	6 mo	1	1↓	C (%)
Bacillus	1 - 3 d	1	1↑	C [mean (SE)]
Streptococcus	1 d	1	1↑	C (%)
	4 d	1	1↓ (MD)	RA (%)
Streptococcus sp	4 d	1	1↑	C (n)
Bacteria (MD)	5 d	1	1↑	D; ↑ CS > VD (antibiotic) > VD (antibiotic)
	7 d	1	1↓ (MD)	D
Haemophilus	6 d	1	1↑	RA [mean (%)]
	3 wk	1	1↑	RA [mean (%)]
Verrucomicrobia	1 – 3, 7, 17 and 30 d	1	↑ (MD)	MD
Total anaerobes	2 wk	1	1↓	C (%)
	1 mo	1	1↓	C (%)
Strictly anaerobic bacteria	Meconium, 2, 7 and 28 d	1	1↑	RA (%)
NC	1 – 3 d and 1 mo	1	1↑ (MD)	D; R
Total bacteria cell number	1 mo	1	1↓	C (mean/95 % CI)

Note 1: d – days; **wk** – week (s); **mo** – month (s); **CS –** Cesarean section; ↓ **-** Lower; ↑- Higher; **RA** – Relative abundance; **C –** Colonization**; SE –** Standard error**; CI –** Confidence interval; **MD –** Missing data; **ND –** No difference; **NC** – Not clear; **D** – Diversity; **R** – richness; ***** - Not significant results (p- value ≥ 0.05). **Note 2:** Column "**Note"** shows the units in which the results were presented.

Supplementary Table 4. Gut microbiota according to mode of delivery.

Period of stool collection	Bacteria identified	Colonization/ relative abundance/ diversity/ richness		P - value	Interpretation	Author, year
		VD	CS			
Meconium/ at birth	*Bifidobacterium*	C (%) - 16.7	C (%) - 16.7	<0.05	Lower in CS	**Martin et al., 2016**
	Bifidobacterium catenulatum	C (%) - 2.8	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bifidobacterium longum	C (%) - 11.1	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bifidobacterium bifidum	C (%) - 12.5	C (%) - 4.2	<0.05	Lower in CS	**Martin et al., 2016**
	Enterococcus	C (%) - 21.3	C (%) - 12.0	<0.05	Lower in CS	**Martin et al., 2016**
	Atopobium	C (%) - 1.4	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bacteroidetes	RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Yang et al., 2019**
	Bacteroides fragilis	C (%) - 2.8	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
		C (%) - 12.5	C (%) - 4.2	<0.05	Lower in CS	**Martin et al., 2016**
	Bacteroides caccae	C (%) - 1.4	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bacteroides vulgatus	C (%) - 11.1	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bacteroides ovatus	C (%) - 1.4	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Firmicutes	RA (%) - MD	RA (%) - MD	MD	Higher in CS	**Yang et al., 2019**
	Lactobacillus gasseri	C (%) - 17.3	C (%) – 8.0	<0.05	Lower in CS	**Martin et al., 2016**
	Lactobacillus reuteri	C (%) - 20.0	C (%) - 4.0	<0.05	Lower in CS	**Martin et al., 2016**
	Clostridium perfringens	C (%) - 5.3	C (%) – 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Staphylococcus aureus	C (%) – 6.1	C (%) – 12.2	MD	Higher in CS	**Priputnevich et al., 2019**
	Proteobacteria	RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Yang et al., 2019**
	Escherichia coli	C (%) – 24.2	C (%) –9.1	>0.05	Lower in CS	**Priputnevich et al., 2019**
(25h – VD; 40h – CS)	*Bacteroidetes*	RA (%) – 8.5	RA (%) – 0.7	0.01	Lower in CS	**Brumbaugh et al., 2016**
1 day	*Lactobacillus*	RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Kabeerdoss et al., 2013**
		C (%) – 18.0	C (%) – 3.0	>0.05	Lower in CS	**Priputnevich et al., 2019**
	Enterobacteriaceae	RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Kabeerdoss et al., 2013**
	Klebsiella	C (%) – 27.0	C (%) –15.0	MD	Lower in CS	**Priputnevich et al., 2019**
	Raoultella	C (%) – 27.0	C (%) –15.0	MD	Lower in CS	**Priputnevich et al., 2019**
	Kluyvera	C (%) – 27.0	C (%) –15.0	MD	Lower in CS	**Priputnevich et al., 2019**
	Enterobacter	C (%) – 27.0	C (%) –15.0	MD	Lower in CS	**Priputnevich et al., 2019**
	Citrobacter	C (%) – 27.0	C (%) –15.0	MD	Lower in CS	**Priputnevich et al., 2019**
	Morganella	C (%) – 27.0	C (%) –15.0	MD	Lower in CS	**Priputnevich et al., 2019**

	Pantoea	C (%) – 27.0	C (%) –15.0	MD	Lower in CS	**Priputnevich et al., 2019**
	Bifidobacterium longum	C (%) – 9.0	C (%) – 3.0	>0.05	Lower in CS	**Priputnevich et al., 2019**
	Bifidobacterium bifidum	C (%) – 9.0	C (%) – 3.0	>0.05	Lower in CS	**Priputnevich et al., 2019**
	Bifidobacterium adolescentis	C (%) – 9.0	C (%) – 3.0	>0.05	Lower in CS	**Priputnevich et al., 2019**
	Bacteroides	C (%) – 3.0	C (%) – 0.0	MD	Lower in CS	**Priputnevich et al., 2019**
	Clostridia	C (%) – 0.0	C (%) – 0.0	MD	Absent in both	**Priputnevich et al., 2019**
	Staphylococcus aureus	C (%) – 44.0	C (%) – 55.6	MD	Higher in CS	**Priputnevich et al., 2019**
	Enterococcus faecalis	C (%) – 80.0	C (%) – 88.9	MD	Higher in CS	**Priputnevich et al., 2019**
	Escherichia coli	C (%) – 24.0	C (%) – 9.0	MD	Lower in CS	**Priputnevich et al., 2019**
	Enterobacteria	C (%) – 27.0	C (%) – 15.0	MD	Lower in CS	**Priputnevich et al., 2019**
	Staphylococcus	C (%) – 60.6	C (%) –70.0	MD	Higher in CS	**Priputnevich et al., 2019**
	Streptococcus	C (%) – 60.6	C (%) – 70.0	MD	Higher in CS	**Priputnevich et al., 2019**
	Enterococcus	C (%) – 60.6	C (%) – 70.0	MD	Higher in CS	**Priputnevich et al., 2019**
	Micrococcus	C (%) – 60.6	C (%) – 70.0	MD	Higher in CS	**Priputnevich et al., 2019**
	Gemella	C (%) – 60.6	C (%) – 70.0	MD	Higher in CS	**Priputnevich et al., 2019**
	Globicatella	C (%) – 60.6	C (%) – 70.0	MD	Higher in CS	**Priputnevich et al., 2019**
	Granulicatella	C (%) – 60.6	C (%) – 70.0	MD	Higher in CS	**Priputnevich et al., 2019**
	Rothia	C (%) – 60.6	C (%) – 70.0	MD	Higher in CS	**Priputnevich et al., 2019**
	Corynebacterium	C (%) – 60.6	C (%) – 70.0	MD	Higher in CS	**Priputnevich et al., 2019**
	Bacillus	C (%) – 60.6	C (%) – 70.0	MD	Higher in CS	**Priputnevich et al., 2019**
2 days	*Bifidobacterium*	C [mean (SE)] - 5.1 (4.7 – 5.9)	C [mean (SE)] - MD (<4.6 – 5.9)	0.01	Lower in CS	**Chen et al., 2007**
		C (%) - 82.3	C (%) - 22.2	<0.05	Lower in CS	**Martin et al., 2016**
	Bifidobacterium catenulatum	C (%) - 29.0	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bifidobacterium bifidum	C (%) - 51.6	C (%) - 11.1	<0.05	Lower in CS	**Martin et al., 2016**
	Bifidobacterium longum	C (%) - 62.9	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Lactobacillus	RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Kabeerdoss et al., 2013**
	Enterobacteriaceae	RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Kabeerdoss et al., 2013**
	Enterobacter sp	C (n) - 0	C (n) - 5	<0.01	Higher in CS	**Liu et al., 2015**
	Bacteroides sp	C (n) - 11	C (n) - 4	<0.05	Lower in CS	**Liu et al., 2015**
	Bacteroides fragilis	C (%) - 80.7	C (%) - 0	<0.05	Lower in CS	**Martin et al., 2016**
		C (%) - 20.9	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bacteroides caccae	C (%) - 17.7	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bacteroides vulgatus	C (%) - 67.7	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bacteroides ovatus	C (%) - 14.5	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Bacteroides uniformis	C (%) - 22.6	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Escherichia coli	C (n) - 13	C (n) - 5	<0.05	Lower in CS	**Liu et al., 2015**
	Staphylococcus sp	C (n) - 0	C (n) - 8	<0.00	Higher in CS	**Liu et al., 2015**

	Clostridium sp	C (n) - 0	C (n) - 5	<0.01	Higher in CS	**Liu et al., 2015**
	Clostridium perfringens	C (%) - 16.7	C (%) – 11.3	<0.05	Lower in CS	**Martin et al., 2016**
	Atopobium	C (%) - 29.0	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Enterococcus	C (%) - 62.9	C (%) - 61.1	<0.05	Lower in CS	**Martin et al., 2016**
	Lactobacillus gasseri	C (%) - 70.1	C (%) - 11.1	<0.05	Lower in CS	**Martin et al., 2016**
	Lactobacillus reuteri	C (%) - 20.9	C (%) - 5.5	<0.05	Lower in CS	**Martin et al., 2016**
3 days	*Enterobacteria*	C (%) - MD	C (%) - MD	0.07	Higher in CS	**Adlerberth et a., 2006**
	Escherichia coli	C (%) - MD	C (%) - MD	0.01	Lower in CS	**Adlerberth et a., 2006**
	Bifidobacterium	RA (%) - MD	RA (%) - MD	0.04	Lower in CS	**Dogra et al., 2015**
		C [mean (SE)] - 6.4 (4.9 – 7.8)	C [mean (SE)] - 5.6 (4.7 – 7.5)	0.01	Lower in CS	**Chen et al., 2007**
		C (%) - MD	C (%) - MD	0.03	Lower in CS MBF, compared to VD MBF	**Sakwinska et al., 2017**
		C (%) - MD	C (%) - MD	0.01	Lower in CS	**Gronlund et al., 1999**
	Klebsiella OTU2	RA (%) - MD	RA (%) - MD	<0.05	Higher in CS	**Dogra et al., 2015**
	Lactobacillus - like bacteria (LLB)	C (%) - MD	C (%) - MD	< 0.00	Lower in CS	**Gronlund et al., 1999**
	Total bacterial	C (%) - MD	C (%) - MD	0.01	Lower in CS	**Gronlund et al., 1999**
	Bacillus	C [mean (SE)] - 5.409 (4.564)	C [mean (SE)] - 99.441 (0.529)	<0.00	Higher in CS (1 – 3d)	**Lee et al., 2016**
	Bacteroidetes	C [mean (SE)] - 11.942 (19.186)	C [mean (SE)] - 0.003 (0.005)	0.05	Lower in CS (1 – 3d)	**Lee et al., 2016**
	Bacteroides	C (%) - MD	C (%) - MD	0.04	Lower in CS MBF (absent in CS MBF)	**Sakwinska et al., 2017**
	Klebsiella	C (%) - MD	C (%) - MD	0.04	Higher in CS MBF	**Sakwinska et al., 2017**
4 days	*Selenomonadales*	RA (%) – 0.9	RA (%) – 0.0	0.14	ND	**Akagawa et al., 2019**
	Enterobacteriales	RA (%) – 1.0	RA (%) – 0.1	0.01	Lower in CS	**Akagawa et al., 2019**
	Bacilales	RA (%) – 10.0	RA (%) – 23.0	0.01	Higher in CS	**Akagawa et al., 2019**
	Lactobacillales	RA (%) – 24.0	RA (%) – 61.0	<0.01	Higher in CS	**Akagawa et al., 2019**
	Lactobacillus	C [mean (SE)/n (%)] - 6.21 (2.07)/13 (59)	C [mean (SE)/n (%)] - 5.54 (MD)/ 1 (4)	0.00	Lower in CS (BF)	**Mitsou et al., 2008**
	Actinomycetales	RA (%) – 1.4	RA (%) – 4.7	0.17	ND	**Akagawa et al., 2019**
	Bifidobacteroidales	RA (%) – 12.0	RA (%) - 4.4	0.32	ND	**Akagawa et al., 2019**
	Bifidobacterium	C [mean (SE)/n (%)] - 7.06 (1.81)/ 9 (41)	C [mean (SE)/n (%)] - 5.62 (MD)/ 1 (4)	0.00	Lower in CS (BF)	**Mitsou et al., 2008**
		C [mean (SE)/n (%)] - 7.70 (0.59)/ 5 (23)	C [mean (SE)/n (%)] - 0 (0)/ 0 (0)	0.02	Lower in CS (BF)	**Mitsou et al., 2008**
		C [mean (SE)] - 7.1 (4.6 – 8.1)	C [mean (SE)] - 6.4 (4.9 – 7.8)	0.02	Lower in CS	**Chen et al., 2007**

	Bifidobacterium longum	C (n) - 5	C (n) - 0	<0.01	Lower in CS	**Liu et al., 2015**
	Bifidobacterium longum + *Bifidobacterium breve* + *Escherichia coli* + *Bacteroides vulgatus* + *Parabacteroides distasonis*	C (%) - 68.3	C (%) - MD	<0.05	Lower in CS	**Shao et al., 2019**
	Bacteroidales	RA (%) – 16.0	RA (%) - 2.4	<0.01	Lower in CS	**Akagawa et al., 2019**
	Bacteroides sp	C (n) - 4	C (n) - 1	<0.05	Lower in CS	**Liu et al., 2015**
	Streptococcus	RA (%) – 85.0	RA (%) – 81.0	MD	Lower in CS	**Akagawa et al., 2019**
	Streptococcus sp	C (n) - 0	C (n) - 7	<0.05	Higher in CS	**Liu et al., 2015**
	Clostridiales	RA (%) – 0.1	RA (%) – 0.1	0.83	ND	**Akagawa et al., 2019**
	Clostridium sp	C (n) - 0	C (n) - 7	<0.05	Higher in CS	**Liu et al., 2015**
	Enterococcus	RA (%) – 14.0	RA (%) – 18.0	MD	Higher in CS	**Akagawa et al., 2019**
	Enterococcus faecalis + *Enterococcus faecium* + *Staphylococcus epidermidis* + *Staphylococcus parasanguinis* + *Klebsiella oxytoca* + *Klebsiella pneumoniae* + *Enterobacter clocoae* + *Clostridium perfringens*	C (%) - MD	C (%) – 68.3	<0.05	Higher in CS	**Shao et al., 2019**
5 days	*Bifidobacterium*	C [mean (SE)] - 8.4 (6.5 – 10.8)	C [mean (SE)] - 7.7 (5.9 – 9.5)	0.05	Lower in CS	**Chen et al., 2007**
	Bacteria (MD)	D - MD	D - MD	0.02	Higher in CS > VD (antibiotic)> VD (no antibiotic)	**Tanaka et al., 2009**
6 days	*Bifidobacterium*	RA [mean (%)] – 34 (93)	RA [mean (%)] – 4 (56)	<0.05	Lower in CS	**Hesla et al., 2014**
		C [mean (SE)] - 9.1 (7.5 – 10.7)	C [mean (SE)] - 8.3 (6.0 – 9.9)	0.022	Lower in CS	**Chen et al., 2007**
	Bacteroides	RA [mean (%)] - 10 (67)	RA [mean (%)] - 0 (44)	<0.05	Lower in CS	**Hesla et al., 2014**
	Proteobacteria unclassified	RA [mean (%)] - 2 (16)	RA [mean (%)] - 12 (44)	<0.05	Higher in CS	**Hesla et al., 2014**
	Haemophilus	RA [mean (%)] - 1 (20)	RA [mean (%)] - 4 (56)	<0.05	Higher in CS	**Hesla et al., 2014**
	*Clostridiaceae*1	RA [mean (%)] - 1 (19)	RA [mean (%)] - 10 (50)	<0.05	Higher in CS	**Hesla et al., 2014**
	Veillonella	RA [mean (%)] - 2 (33)	RA [mean (%)] – 11 (75)	<0.05	Higher in CS	**Hesla et al., 2014**
	Staphylococcus	RA (%) - MD	RA (%) - MD	0.02	Higher in CS (0d – 6d)	**Reyman et al., 2019**
7 days/ 1 week	*Bifidobacterium*	C (%) - 69	C (%) - 44	0.08	Lower in CS	**Adlerberth et a., 2006**
		C [mean (SE)] - 9.3 (7.8 – 10.9)	C [mean (SE)] - 8.7 (6.0 – 10.7)	0.036	Lower in CS	**Chen et al., 2007**

	C (%) - MD	C (%) - MD	0.02	Lower in CS	**Nagpal et al., 2017**
	C (%) - 90.7	C (%) - 69.6	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - MD	C (%) - MD	MD	Lower in CS	**Tanaka et al., 2009**
	C (%) - MD	C (%) - MD	<0.01	Lower in CS	**Tsuji et al., 2012**
	C (%) – 84.0	C (%) -33.0	<0.05	Lower in CS	**Priputnevich et al., 2019**
Bifidobacterium catenulatum	C (%) - 28.0	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	MD	MD	<0.05	Absent in CS	**Priputnevich et al., 2019**
Bifidobacterium longum	C (%) - 69.3	C (%) - 8.7	<0.05	Lower in CS	**Martin et al., 2016**
Bifidobacterium longum + *Bifidobacterium breve* + *Bifidobacterium adolescentis*	RA (%) – 72.2	RA (%) – 0.07	0.0.2	Lower in CS	**Reyman et al., 2019**
Bifidobacterium bifidum	C (%) - 45.3	C (%) - 4.3	<0.05	Lower in CS	**Martin et al., 2016**
Bifidobacterium breve	C (%) – 84.0	C (%) -33.0	<0.05	Lower in CS	**Priputnevich et al., 2019**
Bifidobacterium adolescentis	MD	MD	<0.05	Absent in CS	**Priputnevich et al., 2019**
Bifidobacterium animalis	MD	MD	<0.05	Absent in VD	**Priputnevich et al., 2019**
Bifidobacterium dentium	MD	MD	<0.05	Absent in VD	**Priputnevich et al., 2019**
Bacteroidetes	RA [mean % (SE)] – 27 % (28)	RA [mean % (SE)] – 3% (8)	<0.05	Lower in CS	**Jakobsson et al., 2014**
Bacteroides	RA [mean % (SE)] - 24.1% (26.3)	RA [mean % (SE)] - 2.8% (8.4)	<0.05	Lower in CS	**Jakobsson et al., 2014**
	C (%) -32.0	C (%) – 0.0	< 0.05	Absent in CS	**Priputnevich et al., 2019**
Bacteroides fragilis	C (%) - 68.0	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - 12.5	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides caccae	C (%) - 5.3	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides vulgatus	C (%) - 56.0	C (%) - 17.30	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides ovatus	C (%) - 17.3	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides uniformis	C (%) - 14.7	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
Escherichia coli	C - MD	C - MD	0.04	Lower in CS	**Adlerberth et al., 2006**
	C - MD	C - MD	0.001	Lower in CS	**Adlerberth et al., 2006**
	C (%) - MD	C (%)- MD	0.001	Negatively associated with CS (aOR)/ different between VD (1w – 1 mo)	**Stokholm et al., 2016**
	C (%) – 64.0	C (%) – 44.4	>0.05	Lower in CS	**Priputnevich et al., 2019**
	C (%) – 71.6	C (%) – 36.4	<0.001	Lower in CS	**Reyman et al., 2019**
	RA (%) - MD	RA (%) - MD	>0.05	ND	**Reyman et al., 2019**
Klebsiella spp.	C (%) – 9.5	C (%) – 29.5	0.011	Higher in CS	**Reyman et al., 2019**

Klebsiella oxytoca	MD	MD	0.004	Positively associated with CS (aOR)/ different between VD (1w – 1 mo)	**Stokholm et al., 2016**
	RA (%) <0.001	RA (%) <0.006	0.153	ND	**Reyman et al., 2019**
Klebsiella pneumoniae	MD	MD	0.004	Positively associated with CS (aOR)/ different between VD (1w – 1 mo)	**Stokholm et al., 2016**
Citrobacter freundii	MD	MD	0.050	Positively associated with CS (aOR)/ different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
Clostridium sp	MD	MD	0.033	Positively associated with CS (aOR) / different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
Clostridium perfringens	C (%) - 21.9	C (%) - 50.0	<0.05	Higher in CS	**Martin et al., 2016**
	C (%) – 32.0	C (%) – 40.7	>0.05	ND	**Priputnevich et al., 2019**
Clostridium butyricum	C (%) – 32.0	C (%) – 40.7	>0.05	ND	**Priputnevich et al., 2019**
Clostridium innocuum	C (%) – 32.0	C (%) – 40.7	>0.05	ND	**Priputnevich et al., 2019**
Clostridium tertium	C (%) – 32.0	C (%) – 40.7	>0.05	ND	**Priputnevich et al., 2019**
Enterobacter cloacae	MD	MD	0.018	Positively associated with CS (aOR)/ different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
Enterococcus faecalis	MD	MD	< 0.001	Positively associated with CS (aOR)/ different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
Enterococcus faecium	RA (%) – 0.014	RA (%) – 0.035	0.023	Higher in CS	**Reyman et al., 2019**

	Staphylococcus aureus	MD	MD	0.019	Positively associated with CS (aOR)/ different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
	Staphylococcus epidermidis	RA (%) - MD	RA (%) - MD	>0.05	ND	**Reyman et al., 2019**
	Lactobacillus gasseri	C (%) - 39.7	C (%) - 33.3	<0.05	Lower in CS	**Martin et al., 2016**
	Lactobacillus reuteri	C (%) - 17.8	C (%) - 8.3	<0.05	Lower in CS	**Martin et al., 2016**
	Veillonella	RA [mean % (SE)] - 3.3% (4.3)	RA [mean % (SE)] - 11.2% (8.5)	<0.05	Higher in CS	**Jakobsson et al., 2014**
	Enterococcus	C (%) - 72.6	C (%) - 75.0	<0.05	Higher in CS	**Martin et al., 2016**
	Enterococcus spp.	C (%) – 54.1	C (%) – 81.8	0.004	Higher in CS	**Reyman et al., 2019**
	Atopobium	C (%) - 29.3	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
	Clostridia	C - MD	C - MD	0.01	Higher in CS	**Adlerberth et al., 2006**
	Bacteria (MD)	D - MD	D - MD	MD	Lower in CS	**Tanaka et al., 2009**
10 days	*Lactobacillus* - like bacteria (LLB)	C (%) - MD	C (%) - MD	< 0.001	Lower in CS	**Gronlund et al., 1999**
2 weeks	*Bacteroidetes*	RA (%) – 31.4	RA (%) – 0.3	0.001	Lower in CS	**Brumbaugh et al., 2016**
	Bacteroides	C (%) - MD	C (%) - MD	<0.01	Lower in CS (qPCR)	**Pham et al., 2016**
	Bacteroides spp.	C (%) - MD	C (%) - MD	0.003	Lower in CS	**Adlerberth et al., 2006**
	Escherichia coli	C (%) - MD	C (%) - MD	0.009	Lower in CS	**Adlerberth et al., 2006**
	Clostridia	C (%) - MD	C (%) - MD	0.003	Higher in CS	**Adlerberth et al., 2006**
	Enterobacteria (Klebsiella and Enterobacter spp.)	C (%) - MD	C (%) - MD	0.04	Higher in CS	**Adlerberth et al., 2006**
	Total bacteria	C (%) - MD	C (%) - MD	<0.05	Lower in CS (qPCR)	**Pham et al., 2016**
	Bifidobacterium	C (%) - MD	C (%) - MD	<0.05	Lower in CS (qPCR)	**Pham et al., 2016**
	Veillonella	C (%) - MD	C (%) - MD	<0.01	Lower in CS (qPCR)	**Pham et al., 2016**
	Total anaerobes	C (%) - MD	C (%) - MD	<0.01	Lower in CS (culture – based methods)	**Pham et al., 2016**
20 days	*Klebsiella*	RA (%) – MD	RA (%) - MD	0.02	Higher in CS (10d – 20d)	**Reyman et al., 2019**
3 weeks	*Bifidobacterium*	RA [mean (%)] – 40 (91)	RA [mean (%)] – 18 (79)	<0.05	Lower in CS	**Hesla et al., 2014**
	Bacteroides	RA [mean (%)] – 9 (53)	RA [mean (%)] – 0 (14)	<0.05	Lower in CS	**Hesla et al., 2014**
	Proteobacteria	RA [mean (%)] – 2 (31)	RA [mean (%)] – 11 (64)	<0.05	Higher in CS	**Hesla et al., 2014**
	Haemophilus	RA [mean (%)] – 1 (28)	RA [mean (%)] – 6 (64)	<0.05	Higher in CS	**Hesla et al., 2014**
	Clostridium	RA [mean (%)] – 1 (22)	RA [mean (%)] – 4 (36)	<0.05	Higher in CS	**Hesla et al., 2014**
	Veillonella	RA [mean (%)] – 4 (63)	RA [mean (%)] – 17 (71)	<0.05	Higher in CS	**Hesla et al., 2014**

21 days	*Enterococcus (faecalis + faecium + Staphylococcus (epidermidis + parasanguinis) + Klebsiella (oxytoca + pneumoniae + Enterobacter clocoae + Clostridium perfringens*	C (%) – 49.4	C (%) – 83.7	<0.05	Higher in CS (4 – 21d)	**Shao et al., 2019**
	Lactobacillus	C (%) – 11.9	C (%) – 15.7	>0.05	ND (4 – 21d)	**Shao et al., 2019**
		RA (%) – 1.2	RA (%) – 2.2	>0.05	ND (4 – 21d)	**Shao et al., 2019**
28 days/ 4 weeks	*Bacteroides*	RA – MD; D and R - ND	RA – MD; D and R - ND	0.0023	Lower in CS (RA) (meconium, 2, 7 and 28d)	**Brazier et., 2017**
	Collinsela	RA – MD; D and R - ND	RA – MD; D and R - ND	0.0042	Lower in CS (RA) (meconium, 2, 7 and 28d)	**Brazier et., 2017**
	Sarcina	RA – MD; D and R - ND	RA – MD; D and R - ND	0.0028	Higher in CS (RA) (meconium, 2, 7 and 28d)	**Brazier et., 2017**
	Klebsiella	RA – MD; D and R - ND	RA – MD; D and R - ND	0.0011	Higher in CS (RA) (meconium, 2, 7 and 28d)	**Brazier et., 2017**
	Strictly anaerobic bacteria	MD	MD	0.0230	The RA of strictly anaerobic bacteria was strongly associated with the delivery mode (meconium, 2, 7 and 28d)	**Brazier et., 2017**
	Escherichia coli	C (%) - MD	C (%) - MD	0.06	Lower in CS	**Adlerberth et a., 2006**
	Bacteroides spp.	C (%) - MD	C (%)- MD	0.01	Higher in CS	**Adlerberth et a., 2006**
30 days/ 1 month	*Actinomycetales*	RA (%) - 4.1 (BF)	RA (%) – 3.6 (BF)	0.06	ND	**Akagawa et al., 2019**
	Bifidobacteriales	RA (%) – 27.0 (BF)	RA (%) - 17.0 (BF)	0.42	ND	**Akagawa et al., 2019**
	Bifidobacterium	C (mean/95 % CI) - 20 x 10^8/1g faecal wet mass	C (mean/95 % CI) – 1.5 x 10^6/1g faecal wet mass	0.001	Lower in CS	**Huurre et al., 2008**
		C [mean (SE)/n (%)] - 8.11 (2.17)/ 9 (53)	C [mean (SE)/n (%)] - 0 (0)/ 0 (0)	0.007	Lower in CS (BF)	**Mitsou et al., 2008**

	C [mean (SE)/n (%)] - 7.47 (2.42)/ 6 (35)	C [mean (SE)/n (%)] - 0 (0)/ 0 (0)	0.042	Lower in CS (BF)	**Mitsou et al., 2008**
	C (%) - MD	C (%) - MD	<0.05	Lower in CS	**Tsuji et al., 2012**
	C (%) - MD	C (%) - MD	< 0.001	Lower in CS	**Gronlund et al., 1999**
	C [mean (SE)] - 0.038 (0.019)	C [mean (SE)] - 0.000 (0.000)	0.026	Lower in CS	**Lee et al., 2016**
	C (%) - 94.9	C (%) - 75.0	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) – 88.30	C (%) – 53.80	MD	Lower in CS	**Priputnevich et al., 2019**
	RA (%) - MD	RA (%) - MD	0.003	Lower in CS (1d – 1mo)	**Reyman et al., 2019**
Bifidobacterium longum	C [mean (SE)] - 48.739 (18.810)	C [mean (SE)] - 2.297 (2.297)	0.046	Lower in CS	**Lee et al., 2016**
	C (%) - 71.8	C (%) - 39.3	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) – 58.3	C (%) – 26.9	MD	Lower in CS	**Priputnevich et al., 2019**
Bacteroides uniformis	C (%) - 21.8	C (%) - 3.6	<0.05	Lower in CS	**Martin et al., 2016**
Bifidobacterium catenulatum	C (%) - 29.5	C (%) - 7.1	<0.05	Lower in CS	**Martin et al., 2016**
Bifidobacterium bifidum	C (%) - 50.0	C (%) - 21.4	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) – 33.3	C (%) – 34.6	MD	Higher in CS	**Priputnevich et al., 2019**
Enterobacteriaceae	MD	MD	MD	ND	**Bokulich et al., 2016**
Bacteroidales	RA (%) – 16.0 (BF)	RA (%) – 0.0 (BF)	<0.01	Lower in CS	**Akagawa et al., 2019**
Bacteroidetes	MD	MD	MD	Lower in CS with postponed C after the first days of life (1, 2, 3, 7, 17, 30d)	**Del Chierico et al., 2015**
	D index (Shannon) [median (IQ)] – 0.42 (0.00 – 0.81)	D index (Shannon) [median (IQ)] - 0.0 (0.00 – 0.00)	0.022	Lower in CS	**Jakobsson et al., 2014**
	RA (%) – MD	RA (%) – MD	MD	Absent in CS (1w – 1mo)	**Tanaka et al., 2009**
Bacteroides	C (%) - MD	C (%) - MD	<0.05	Lower in CS (qPCR)	**Pham et al., 2016**
	C (%) – 25.0	C (%) – 3.8	MD	Lower in CS	**Priputnevich et al., 2019**
Bacteroides fragilis	C (%) - 74.4	C (%) - 3.6	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - 12.8	C (%) - 3.6	<0.05	Lower in CS	**Martin et al., 2016**
	MD	MD	MD	Absent in CS	**Priputnevich et al., 2019**
Bacteroides caccae	C (%) - 10.3	C (%) - 3.6	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides vulgatus	C (%) - 58.9	C (%) - 3.6	<0.05	Lower in CS	**Martin et al., 2016**
	MD	MD	MD	Absent in CS	**Priputnevich et al., 2019**
Bacteroides ovatus	C (%) - 25.6	C (%) - 0.0	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides uniformis	MD	MD	MD	Absent in CS	**Priputnevich et al., 2019**
Bacteroides cellulositycus	MD	MD	MD	Absent in CS	**Priputnevich et al., 2019**

Bacteroides thetaiotaomicron	MD	MD	MD	Absent in CS	**Priputnevich et al., 2019**
Parabacteroides diastasonis	MD	MD	MD	Absent in CS	**Priputnevich et al., 2019**
Clostridiales	RA (%) – 1.1 (BF)	RA (%) – 9.1 (BF)	0.57	ND	**Akagawa et al., 2019**
Clostridium sp	MD	MD	MD	Positively associated with CS (aOR)	**Stokholm et al., 2016**
	MD	MD	MD	Different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
Clostridium perfringens	C (%) - 57	C (%) - 17	0.003	Higher in CS	**Gronlund et al., 1999**
	C (%) - 24.1	C (%) - 53.6	<0.05	Higher in CS	**Martin et al., 2016**
	C (%) - 35.5	C (%) - 61.5	0.12	Higher in CS	**Nagpal et al., 2017**
	C (%) – 33.3	C (%) – 65.4	<0.05	Higher in CS	**Priputnevich et al., 2019**
Clostridium butyricum	C (%) – 33.3	C (%) – 65.4	<0.05	Higher in CS	**Priputnevich et al., 2019**
Clostridium tertium	C (%) – 33.3	C (%) – 65.4	<0.05	Higher in CS	**Priputnevich et al., 2019**
Clostridium ramosum	C (%) – 33.3	C (%) – 65.4	<0.05	Higher in CS	**Priputnevich et al., 2019**
Clostridium paraputrificum	C (%) – 33.3	C (%) – 65.4	<0.05	Higher in CS	**Priputnevich et al., 2019**
Clostridium difficile	C (%) – 33.3	C (%) – 65.4	<0.05	Higher in CS	**Priputnevich et al., 2019**
Klebsiella oxytoca	MD	MD	MD	Positively associated with CS (aOR)	**Stokholm et al., 2016**
Klebsiella pneumoniae	MD	MD	MD	Positively associated with CS (aOR)	**Stokholm et al., 2016**
Escherichia coli	MD	MD	MD	Negatively associated with CS (aOR)	**Stokholm et al., 2016**
	C (%) – 70.8	C (%) – 61.5	>0.05	Lower in CS	**Priputnevich et al., 2019**
	MD	MD	MD	Different between emergency VD (1w – 1 mo)	**Stokholm et al., 2016**
Citrobacter freundii	MD	MD	MD	Different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
Staphylococcus aureus	MD	MD	MD	Different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
	C (%) – 58.3	C (%) – 76.9	MD	Higher in CS	**Priputnevich et al., 2019**

Staphylococcus epidermidis	MD	MD	MD	Different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
Enterobacteriales	RA (%) – 24.0 (BF)	RA (%) – 39.0 (BF)	0.58	ND	**Akagawa et al., 2019**
Enterobacteriaceae	C (%) - MD	C (%) - MD	MD	Lower in CS	**Tanaka et al., 2009**
Enterobacter cloacae	MD	MD	MD	Different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
Klebsiella oxytoca	MD	MD	MD	Different between VD (1w – 1 mo)	**Stokholm et al., 2016**
Klebsiella pneumoniae	MD	MD	MD	Different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
Parabacteroides	RA [mean % (SE)] - 3.3 (5.3)	RA [mean % (SE)] - 0 (0)	<0.05	Lower in CS	**Jakobsson et al., 2014**
Enterococcus	RA [mean % (SE)] - 0 (0.1)	RA [mean % (SE)] - 7.2 (9.5)	<0.01	Higher in CS	**Jakobsson et al., 2014**
	72.2	C (%) - 92.9	<0.05	Higher in CS	**Martin et al., 2016**
	C (%) - MD	C (%) - MD	MD	Lower in CS (1w – 1mo)	**Tanaka et al., 2009**
Enterococcus faecalis	MD	MD	MD	Different between emergency CS (1w – 1 mo)	**Stokholm et al., 2016**
NC	D index (Shannon) and R index (Chao1) - MD	D index (Shannon) and R index (Chao1) - MD	MD	Higher in CS (D and R) (1 – 3d, and 1 mo)	**Lee et al., 2016**
Atopobium	C (%) - 39.7	C (%) - 17.9	<0.05	Lower in CS	**Martin et al., 2016**
Enterobacteria	C (%) - 66.7	C (%) – 73.0	>0.05	Higher in CS	**Priputnevich et al., 2019**
Firmicutes	C (%) - MD	C (%) - MD	<0.01	Higher in CS (qPCR)	**Pham et al., 2016**
Selenomonadales	RA (%) – 4.5 (BF)	RA (%) – 4.8 (BF)	0.06	ND	**Akagawa et al., 2019**
Bacillales	RA (%) – 7.7 (BF)	RA (%) – 5.5 (BF)	0.06	ND	**Akagawa et al., 2019**
Lactobacillalles	RA (%) – 14.0 (BF)	RA (%) – 22.0 (BF)	0.64	ND	**Akagawa et al., 2019**
Lactobacillus	C (%) – 58.30	C (%) – 69.0	MD	Higher in CS	**Priputnevich et al., 2019**
Lactobacillus gasseri	C (%) - 49.3	C (%) - 46.4	<0.05	Lower in CS	**Martin et al., 2016**
Lactobacillus reuteri	C (%) - 18.9	C (%) - 21.4	<0.05	Higher in CS	**Martin et al., 2016**
Veillonella	C (%) - MD	C (%) - MD	<0.01	Lower in CS (qPCR)	**Pham et al., 2016**
Total anaerobes	C (%) - MD	C (%) - MD	<0.05	Lower in CS (culture – based methods)	**Pham et al., 2016**

	Verrucomicrobia	MD	MD	MD	Higher in CS in early days compared to later days (1, 2, 3, 7, 17, 30d)	**Del Chierico et al., 2015**
	Total bacteria cell number	C (mean/95 % CI) - 100 x 10^8/1g faecal wet mass	C (mean/95 % CI) - 30 x 10^8/1g faecal wet mass	0.001	Lower in CS	**Huurre et al., 2008**
6 weeks	*Bacteroidetes*	RA (%) – 22.7	RA (%) – 0.1	0.007	Lower in CS	**Brumbaugh et al., 2016**
35 days	*Enterococcus*	RA (%) - MD	RA (%) - MD	0.003	Higher in CS (7d – 35d)	**Reyman et al., 2019**
42 days	*Proteobacteria*	RA (%) - MD	RA (%) - MD	MD	Higher in CS	**Yang et al., 2019**
	Bacteroidetes	RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Yang et al., 2019**
44 days	*Bifidobacterium*	RA (%) – MD	RA (%) - MD	0.003	Lower in CS (5d – 44d	**Reyman et al., 2019**
2 months	*Bacteroides*	RA [mean (%)] – 10 (70)	RA [mean (%)] – 1 (28)	<0.05	Lower in CS	**Hesla et al., 2014**
	Bacteroides spp.	C - MD	C - MD	0.07	Higher in CS	**Adlerberth et a., 2006**
	Proteobacteria unclassified	RA [mean (%)] – 1 (30)	RA [mean (%)] – 5 (78)	<0.05	Higher in CS	**Hesla et al., 2014**
	Clostridium	RA [mean (%)] – 4 (25)	RA [mean (%)] – 16 (44)	<0.05	Higher in CS	**Hesla et al., 2014**
85 days	*Escherichia*	RA (%) - MD	RA (%) - MD	0.003	Lower in CS (1d – 85d)	**Reyman et al., 2019**
12 weeks/ 90 days/3 months	*Firmicutes*	C (%) – MD	C (%) – MD	<0.05	Higher in CS (qPCR)	**Pham et al., 2016**
		RA (%) - MD	RA (%) - MD	MD	Higher in CS (3 and 10d, 6 and 12w)	**Stearns et al., 2017**
	Lactobacillus	C - MD	C - MD	MD	Lower in CS	**Mitsou et al., 2008**
		C (%) - 31%	C (%) - 65%	0.03	Lower in CS	**Nagpal et al., 2017**
	Lactobacillus- Enterococcus	RA (%) - MD	RA (%) - MD	0.002	Higher in CS (3d, 1 and 3 mo)	**Yap et al., 2011**
	Lactobacillus gasseri	C (%) - 39.7	C (%) - 50.0	<0.05	Higher in CS	**Martin et al., 2016**
	Lactobacillus reuteri	C (%) - 23.1	C (%) - 21.4	<0.05	Lower in CS	**Martin et al., 2016**
	Bifidobacterium	C - MD	C - MD	MD	Lower in CS	**Mitsou et al., 2008**
		C (%) - MD	C (%) - MD	0.06	Lower in CS	**Nagpal et al., 2017**
		RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Kabeerdoss et al., 2013**
		C (%) - 97.4	C (%) - 100.0	<0.05	Higher in CS	**Martin et al., 2016**
		C (%) – MD	C (%) – MD	<0.001	Lower in CS (birth – 90d)	**Martin et al., 2016**
		C (%) – MD	C (%) – MD	<0.001	Lower in CS (qPCR)	**Pham et al., 2016**

	RA (%) - MD	RA (%) - MD	**0.003	Lower in CS 3d, 1 and 3 mo)	**Yap et al., 2011**
Bifidobacterium catenulatum	C (%) - 37.7	C (%) - 28.6	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) – MD	C (%) – MD	0.039	Lower in CS (birth – 90d)	**Martin et al., 2016**
Bifidobacterium longum	C (%) - 77.92	C (%) - 71.4	<0.05	Lower in CS	**Martin et al., 2016**
Bifidobacterium longum subsp. longum	C (%) – MD	C (%) – MD	<0.001	Lower in CS (birth – 90d)	**Martin et al., 2016**
Bifidobacterium bifidum	C (%) - 66.2	C (%) - 60.7	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides fragilis	C (%) - 30.8%	C (%) - 7.6%	0.001	Lower in CS	**Nagpal et al., 2017**
Bacteroidetes	RA [mean % (SE) - 19 (29)	RA [mean % (SE) - 4 (10)	<0.01	Lower in CS	**Jakobsson et al., 2014**
	RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Yang et al., 2019**
Bacteroidetes (Parabacteroides and Bacteroides)	RA (%) - MD	RA (%) - MD	MD	Lower in 4 infants (CS) compared to the 12 VD (2w, 1 and 3 mo)	**Pham et al., 2016**
Bacteroidetes	D index (Shannon) [median (Q)] - 0.64 (0.00 - 0.87)	D index (Shannon) [median (Q)] - 0.00 (0.00 – 0.00)	0.004	Lower in CS	**Jakobsson et al., 2014**
Bacteroides	RA [mean % (SE) - 14.6 (28.6)	RA [mean % (SE) - 3.6 (10.9)	<0.05	Lower in CS	**Jakobsson et al., 2014**
	C (%) – MD	C (%) – MD	<0.01	Lower in CS (qPCR)	**Pham et al., 2016**
Bacteroides–Prevotella	RA (%) - MD	RA (%) - MD	MD	Lower in CS (1 – 90d)	**Kabeerdoss et al., 2013**
	RA (%) - MD	RA (%) - MD	**0.014	Lower in CS (3d, 1 and 3 mo)	**Yap et al., 2011**
Bacteroides fragilis	C (%) - 77.9	C (%) - 32.1	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - 22.1	C (%) - 14.3	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides fragilis subgroup	C (%) – MD	C (%) – MD	0.036	Lower in CS (birth – 90d)	**Martin et al., 2016**
Bacteroides caccae	C (%) - 18.2	C (%) - 10.7	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides vulgatus	C (%) - 66.2	C (%) - 14.3	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides ovatus	C (%) - 24.7	C (%) - 7.1	<0.05	Lower in CS	**Martin et al., 2016**
Bacteroides uniformis	C (%) - 31.2	C (%) - 14.3	<0.05	Lower in CS	**Martin et al., 2016**
Enterococcus	C (%) - 89.7	C (%) - 96.5	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) – MD	C (%) – MD	0.008	Higher in CS (birth – 90d)	**Martin et al., 2016**
Clostridium perfringens	C (%) - 33.3	C (%) - 35.7	<0.05	Lower in CS	**Martin et al., 2016**
Atopobium	C (%) - 54.5	C (%) - 64.3	<0.05	Lower in CS	**Martin et al., 2016**

		C (%) – MD	C (%) – MD	<0.001	Lower in CS (birth – 90d)	**Martin et al., 2016**
		RA (%) - MD	RA (%) - MD	**0.017	Lower in CS (3d, 1 and 3 mo)	**Yap et al., 2011**
	Proteobacteria	RA [mean % (SE)] - 7 (8)	RA [mean % (SE)] - 15 (14)	<0.05	Higher in CS	**Jakobsson et al., 2014**
		RA (%) - MD	RA (%) - MD	MD	Lower in CS (3 and 10d, 6 and 12w)	**Stearns et al., 2017**
	Clostridium perfringens	C (%) – MD	C (%) – MD	0.013	Higher in CS (birth – 90d)	**Martin et al., 2016**
	Actinobacteria	RA (%) - MD	RA (%) - MD	MD	Higher in CS (3 and 10d, 6 and 12w)	**Stearns et al., 2017**
4 months	*Bacteroidia*	RA (%) - MD	RA (%) - MD	MD	Lower in CS (at birth, 1w, 6w and 4 mo)	**Korpela et al., 2018**
139 days	*Klebsiella*	RA (%) – MD	RA (%) – MD	0.003	Higher in CS (birth – 139d)	**Reyman et al., 2019**
180 days/6 months	*Bifidobacterium*	C (%) - 97.4	C (%) - 100.0	<0.05	Higher in CS	**Martin et al., 2016**
		C (%) - MD	C (%) - MD	<0.05	Lower in CS (qPCR)	**Pham et al., 2016**
	Bifidobacterium sp.	RA (%) - MD	RA (%) - MD	MD	Lower in CS (2, 3, 4, 6 mo)	**Yassour et al., 2016**
	Bifidobacterium longum	C (%) - 78.9	C (%) - 96.2	<0.05	Higher in CS	**Martin et al., 2016**
	Bifidobacterium bifidum	C (%) - 77.6	C (%) - 69.2	<0.05	Lower in CS	**Martin et al., 2016**
	Proteobacteria	RA [mean (%)] – 0 (24)	RA [mean (%)] – 2 (61)	<0.05	Higher in CS	**Hesla et al., 2014**
	Clostridiales	RA [mean (%)] – 11 (78)	RA [mean (%)] – 20 (89)	<0.05	Higher in CS	**Hesla et al., 2014**
	Bacteroides	C (%) – 76	C (%) - 36	0.009	Lower in CS	**Gronlund et al., 1999**
	Total bacterial	C (%) - MD	C (%) - MD	0.03	Lower in CS	**Gronlund et al., 1999**
	Firmicutes	RA (mean %) - 48.07	RA (mean %) - 78.96	0.005	Higher in CS (1 – 3d, 1 and 6 mo)	**Lee et al., 2016**
	Lactobacillus - like bacteria (LLB)	C (%) - MD	C (%) - MD	MD	Higher in CS (2 – 6 mo)	**Gronlund et al., 1999**
	Lactobacillus gasseri	C (%) - 35.1	C (%) - 26.9	<0.05	Lower in CS	**Martin et al., 2016**
	Lactobacillus reuteri	C (%) - 22.1	C (%) - 19.2	<0.05	Lower in CS	**Martin et al., 2016**
	Clostridia	RA (mean %) - 28.30	RA (mean %) - 48.52	0.627	Higher in CS (1 – 3d, 1 and 6 mo)	**Lee et al., 2016**
	Clostridium	C [mean (SE)] - 0.121 (0.139)	C [mean (SE)] - 43.2236 (16.409)	0.045	Higher in CS	**Lee et al., 2016**
	Clostridium perfringens	C (%) - MD	C (%) - MD	MD	Higher in CS	**Nagpal et al., 2017**

	C (%) - 36.4	C (%) - 34.6	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - 33	C (%) - 69	0.02	Higher in CS	**Nagpal et al., 2017**
Bacteroidetes	RA (%) - MD	RA (%) - MD	MD	Lower in CS	**Yang et al., 2019**
Bacteroides	C (%) - MD	C (%) - MD	<0.01	Lower in CS (qPCR)	**Pham et al., 2016**
	RA (%) - MD	RA (%) - MD	MD	Absent in CS and low in 7 VD (2, 3, 4, 6 mo)	**Yassour et al., 2016**
Bacteroides fragilis	C (%) - MD	C (%) - MD	<0.05	Lower in CS	**Tsuji et al., 2012**
	C (%) – 38.5	C (%) – 73.7	0.02	Lower in CS	**Nagpal et al., 2017**
	C (%) - 82.9	C (%) - 57.7	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - 34.2	C (%) - 26.9	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - MD	C (%) - MD	0.003	Lower in CS (birth – 180d)	**Martin et al., 2016**
Bacteroides caccae	C (%) - 23.7	C (%) - 11.5	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - MD	C (%) - MD	0.028	Lower in CS (birth – 180d)	**Martin et al., 2016**
Bacteroides vulgatus	C (%) - 65.8	C (%) - 38.5	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - MD	C (%) - MD	<0.001	Lower in CS (birth – 180d)	**Martin et al., 2016**
Bacteroides ovatus	C (%) - 30.3	C (%) - 7.7	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - MD	C (%) - MD	0.006	Lower in CS (birth – 180d)	**Martin et al., 2016**
Bacteroides uniformis	C (%) - 40.8	C (%) - 15.4	<0.05	Lower in CS	**Martin et al., 2016**
	C (%) - MD	C (%) - MD	0.001	Lower in CS (birth – 180d)	**Martin et al., 2016**
Bifidobacterium catenulatum	C (%) - 55.3	C (%) - 53.9	<0.05	Lower in CS	**Martin et al., 2016**
Enterococcus	C (%) - 97.4	C (%) - 100.0	<0.05	Higher in CS	**Martin et al., 2016**
Atopobium	C (%) - 71.4	C (%) - 69.2	<0.05	Lower in CS	**Martin et al., 2016**
Escherichia coli	C (%) - MD	C (%) - MD	0.03	Lower in CS	**Adlerberth et al., 2006**
Enterobacteria	C (CFU/g feces) - $10^{7.7}$	C (CFU/g feces) - $10^{8.6}$	0.0006	Higher in CS	**Adlerberth et al., 2006**

Note: VD – Vaginal delivery; **CS** – Cesarean section; **ND** – No difference between the groups; **C** – colonization; **RA** – Relative abundance; **D** – Diversity; **R** – Richness; * - Adjusted odd ratio (aOR) gestational age, parity, hospitalization and duration of EBF; **MD** – Missing data; **NC** – not clear; ** Linear mixed model analysis adjusted for location, weaning age, sibling, breastfeeding up to 6 months, eczema and prenatal anitibiotics.

7. Conclusão

Os resultados dessa dissertação confirmam o encontrado na literatura, ou seja, que o tipo de parto influencia a composição da microbiota intestinal infantil. No entanto, com base nas evidências disponíveis, ainda é prematuro concluir que o parto cesáreo modifica a composição da microbiota.

Alguns táxons bacterianos específicos vêm sendo estudados em associação ao tipo de parto, porém os estudos são concentrados em determinados grupos de bactérias, e em especial nos gêneros *Bifidobacterium*, *Bacteroides*, *Lactobacillus* e nas espécies *Escherichia coli* e *Clostridium perfringens*. Diante disso, essa dissertação observou que essas bactérias, com exceção de *C. perfringens*, são encontradas em menores concentrações no intestino de crianças nascidas por parto cesáreo.

Os dados apresentados na RSL são coerentes com o descrito na literatura para os gêneros *Bifidobacterium* e *Bacteroides* (e espécie *Bacteroides fragilis*). A colonização intestinal de ambos foi potencialmente menor em crianças nascidas por parto cesáreo. Os resultados para as espécies *Bifidobacterium longum, Bifidobacterium catenulatum, Bacteroides vulgatus* e *Bacteroides uniformis* foram semelhantes aos gêneros *(Bifidobacterium* e *Bacteroides*, respectivamente), no entanto, poucos estudos foram realizados. Os resultados para o gênero *Lactobacillus* e a espécie *E. coli* corroboram o encontrado na literatura, de que crianças nascidas por parto cesáreo apresentam menores concentrações dessas bactérias. Apesar de ser descrita como uma bactéria patogênica encontrada em condições de doenças, a colonização da espécie *C. perfringens* foi potencialmente aumentada em crianças nascidas por parto cesáreo, no entanto são necessários mais estudos que associem as espécies *B. longum, B. catenulatum, B. uniformis, B. ovatus, E. coli, C. perfringens* e o gênero *Lactobacillus* com o tipo de parto.

Os resultados para os gêneros *Bifidobacterium*, *Bacteroides* e *Lactobacillus* estão de acordo com o descrito na RSL anterior (Rutayisire et al., 2016). Adicionalmente a esse estudo, resultados para as espécies *B. longum*, *E. coli* e *C. perfringens* foram descritos nessa dissertação. Em nossos dados, no geral, os grupos de bactérias que apresentam papel benéfico descrito na literatura foram encontrados em menor concentração no intestino de crianças nascidas por parto cesáreo. Nesse sentido, os achados da RSL corroboram com o potencial fator negativo do parto cesáreo na microbiota infantil.

Os resultados que diferiram entre si para a avaliação de bactérias específicas no mesmo período, foram possíveis de serem observados pela diferença do uso de antibióticos. Ainda que avaliar o efeito do uso de antibiótico não tenha sido nosso objetivo, os resultados corroboram com o papel modificador do mesmo.

O aleitamento materno foi considerado um modificador de efeito na composição da microbiota. Essa variável foi considerada como um modificador de efeito na associação entre o tipo de parto e microbiota infantil. O leite materno influencia beneficamente a microbiota de nascidos por parto cesáreo. No entanto, apesar de todos os estudos informarem dados sobre amamentação, somente onze deles controlaram por essa variável, o que impossibilitou que a RSL sintetizasse os resultados de acordo com a amamentação. Ainda assim, ao comparar a microbiota de crianças nascidas por parto cesáreo que foram amamentadas, foi possível observar maior similaridade com a microbiota de crianças nascidas por parto vaginal. Os resultados corroboram com o encontrado na associação inversa (aleitamento materno presente ou ausente categorizados por tipo de parto) na meta-análise de Ho et al. (2018).

A localização geográfica é outro fator importante que pode interferir na microbiota e que foi considerada nessa dissertação. Observou-se que resultados para o gênero *Bifidobacterium* aparentemente são mais frequentes em crianças asiáticas, enquanto o gênero *Bacteroides* em crianças da Europa Central. Ainda que seja um tema pouco explorado, esses resultados corroboram com o encontrado na literatura.

A qualidade metodológica dos estudos também pode influenciar os resultados. Observamos uma alta prevalência de estudos classificados como alto risco de viés, e diante disso nossos achados supõem que os vieses dentro desses estudos podem influenciar a qualidade geral da evidência. Nosso estudo, por ser uma RSL, não tem como objetivo avaliar a qualidade geral da evidência, no entanto nossos achados sugerem que sejam realizados mais estudos com a presença mínima de vieses.

Os pontos fortes dessa dissertação envolvem a apresentação inédita de resultados para a sistematização da associação entre o tipo de parto e microbiota, considerando o papel da amamentação, descritos para a localização geográfica, com a avaliação da qualidade dos estudos. Como limitações desse trabalho, não foi possível sintetizar os resultados da associação entre o tipo de parto e microbiota com o papel da amamentação. A ausência de dados (em números) para os resultados da microbiota disponíveis nos estudos dificultou a realização de uma meta-análise. No entanto, como forma de facilitar a condução desse tipo de estudo sugerimos que todos os dados sejam disponibilizados em

materiais suplementares ou adicionados ao *software* desenvolvido por Gonzales et al. (2018), que tem como objetivo concentrar dados de microbiota.

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9. Anexos

Anexo 1. Modelo de carta enviada ao primeiro autor

(DATE)
Dear **(Author name)**,

I am a Professor of nutritional epidemiology from Rio de Janeiro Federal University, Brazil.

As you know systematic reviews and meta-analysis are very important to synthesize the available evidence, point out where there is need for more research and assist for better decisions in clinical practice. As one may expect, the contribution of other authors providing the information is essential.

I am currently undertaking a systematic review and Meta-analysis (MA) that has as a preliminary title '*Association of mode of delivery and changes in the composition of infant gut microbiota up to 6 months: a systematic review of literature and meta-analysis, considering the role of breastfeeding'*.

The main objective intends to evaluate the association between mode of delivery and changes in infant gut microbiota. To ensure the results are valid, it is essential that all relevant studies are included.

The study described your abstracts **(Abstract title)** is eligible for inclusion in our review and MA. To determine if the study meets the appropriate criteria, I would be very grateful if you could initially confirm some basic details, because I found your abstract in Embase and I need to know more information (spreadsheet attached).

I would like to know if the article of this abstract has been published, and if there is could you please send me the PDF or the link?

Later it may become necessary to receive the raw data. If your study ends being included in the review, it will be cited in our paper, to be published in a high impact factor journal. I would be very glad if you could complete the accompanying form (attached), and return it to me on the email (gkac@nutricao.ufrj.br) copying Luciana Princisval my master on science student (lucianaprincisvals@gmail.com).

Yours sincerely,
Professor Gilberto Kac

Observatory of Nutritional Epidemiology
Rio de Janeiro Federal University
Av. Carlos Chagas Filho, 373
CCS, Bloco J, 2º andar
21941-902
Rio de Janeiro, RJ - Brasil
phone: (+55) 21 25626595

Anexo 2. Modelo de carta enviada ao orientador/correspondente

(DATE)

Dear **(Author name)**,

I am a Professor of nutritional epidemiology from Rio de Janeiro Federal University, Brazil.

As you know systematic reviews and meta-analysis are very important to synthesize the available evidence, point out where there is need for more research and assist for better decisions in clinical practice. As one may expect, the contribution of other authors providing the information is essential.

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The study described in your student's abstracts (First author name) (Abstract title) is eligible for inclusion in our review and MA. To determine if the study meets the appropriate criteria, I would be very grateful if you could initially confirm some basic details, because I found your abstract in Embase and I need to know more information (spreadsheet attached).

I could not find her/his email but would like to know if the article in this summary has been published, and if so could you send me the PDF or link? Or, if you'd prefer, could you send me her email?

Later it may become necessary to receive the raw data. If your study ends being included in the review, it will be cited in our paper, to be published in a high impact factor journal. I would be very glad if you could complete the accompanying form (attached), and return it to me on the email (gkac@nutricao.ufrj.br) copying Luciana Princisval my master on science student (lucianaprincisvals@gmail.com).

Yours sincerely,

Professor Gilberto Kac

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Anexo 3. Formulário de extração de dados

Data extraction form
Y (**Yes**), N (**No)** or Unknow **(UK)**

Identification	
Study ID	Reviewer
Title	
Author	Year
Settings	
Location	Language
Study name	
Study design	Study Duration and study data

Comments:
_____
_____

Participants			
Sample			
Number of repeated measures of stool			
Time (months) of each stool collection ( ) < 1 mo specify: _____ days ( ) 1 mo ( ) 2 mo ( ) 3 mo ( ) 4 mo ( ) 5 mo ( ) 6 mo			
Characteristics			
Ethnicity ( ) Y ( ) N Specify: _____			
Sociodemographic			
Income ($) Specify: _____	Schooling (years) Specify: _____		
Siblings/ child contact ( ) Y ( ) N ( ) Uk	BMI pre-pregnancy Specify: _____kg/m² ( ) Low weight ( ) Normal weight ( )Overweight ( )Obesity		
Gestational age ( ) Y ( ) N ( ) Uk Specify: _____	Use antibiotic (mother) ( ) Y ( ) N ( ) Uk Specify: _____ During: ( ) Prenatal ( ) Breastfeeding ( ) Uk Duration:_____ days		
Use antibiotic (child) ( ) Y ( ) N ( ) Uk			
Considered breastfeeding the analysis? ( ) Y ( ) N ( ) Uk Duration: _____months			
% breastfed:	% not breastfed:	% mixed breastfed:	% formula fed:

<table>
<tr><td colspan="2">Other foods
( ) Y ( ) N ( ) Uk
Age: _____
Still breastfed?
( ) Y ( ) N ( ) Uk</td></tr>
<tr><td>% breastfed:</td><td>% not breastfed:</td></tr>
<tr><td colspan="2">Exposure</td></tr>
<tr><td colspan="2">Mode of delivery</td></tr>
<tr><td>Vaginal (n/percentage (%)):</td><td>C-section (n/percentage (%)):</td></tr>
<tr><td colspan="2">Outcomes</td></tr>
<tr><td colspan="2">Bacterial detection techniques
( ) DNA extraction and 16S rRNA gene sequencing
( ) DNA extraction and 16S rRNA gene amplification
( ) Culture-dependent and molecular methods
( ) Fluorescence in situ hybridization of bacterial cells
( ) Other _____</td></tr>
</table>

Relative abundance? ( ) Y ( ) N ( ) Uk					
Colonization frequency? ( ) Y ( ) N ( ) Uk					
Statistical analysis					
Used statistical method ( ) Y ( ) N ( ) Uk					
OTUs ( ) Y ( ) N ( ) Uk		Richness estimators ( ) Y ( ) N ( ) Uk		Diversity indice ( ) Y ( ) N ( ) Uk	
Vaginal delivery			**C- section**		
Bacteria	**(26)** Relative abundance (%)	**(27)** Colonization frequency (%)	Bacteria	**(26)** Relative abundance (%)	**(27)** Colonization frequency (%)

Vaginal delivery							**C-section**						
Sample (Time of collection)	Number of sequences	**(29)** OTUs	**(30)** Richness		**(31)** Diversity		Sample (Time of collection)	Number of sequences	**(29)** OTUs	**(30)** Richness		**(31)** Diversity	
			Ace	Chao 1	Simpson	Shannon				Ace	Chao 1	Simpson	Shannon

Principal components analysis (PCoA)? ( ) Y ( ) N

Comments: _____

_____

Unifrac distance

Statistically different? ( ) Y ( ) N ( ) Uk

Libshuff (hypothesis test)
Statistically different? ( ) Y ( ) N ( ) Uk

Venn Diagram? ( ) Y ( ) N ( ) Uk

Results:

Comments:

_____
_____