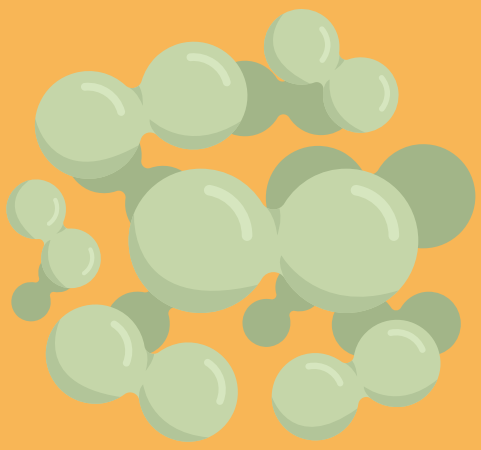
RESEARCH & DEVELOPMENT LANDSCAPE FOR MATERNAL ENTERIC MICROBIOME MEDICINES (2000-2023)

JANUARY 2024

AIM
ACCELERATING
INNOVATION FOR MOTHERS

Maternal environmental enteric dysfunction (EED) can have significant direct and indirect impacts on pregnancy and neonatal outcomes



TARGETING THE MATERNAL ENTERIC MICROBIOME

A new frontier in improving maternal and neonatal health outcomes

The gut microbiota plays a critical role in human health and is implicated in the pathogenesis of several diseases, including type 2 diabetes, inflammatory bowel disease, and Alzheimer's disease.[1,2] With ever-increasing evidence on the gut microbiota's importance, there has been mounting interest in the maternal gut microbiome and its influence on pregnancy and neonatal outcomes.

Changes in the composition of the maternal gut microbiome during pregnancy are normal and are driven by physiological immune and inflammatory changes.[3,4] However, as can happen at any stage in life, the maternal gut microbiome is susceptible to imbalance. Maternal environmental enteric dysfunction (EED) describes this imbalance and the associated inflammation in the gut, which may lead to altered maternal metabolism, decreased nutrient absorption and impaired barrier function.[5–7] The exact pathogenesis of EED is unclear, however the condition is in part thought to develop from chronic exposure to enteric pathogens, such as Shigella and Campylobacter, as a result of poor water, sanitation and hygiene conditions, rendering people in low- and middle-income countries (LMICs) more susceptible.[5–7]

Maternal EED can have significant direct and indirect impacts on pregnancy and neonatal outcomes. Intestinal inflammation can lead to low birth weight, and reduced nutrient absorption can also impact fetal growth.[8] Interventions targeting the maternal enteric microbiome have been shown to reduce childhood undernutrition more effectively than maternal nutrition supplementation alone.[9] Growing evidence also suggests that aberrations in the maternal gut microbiome are associated with – and may contribute to – the pathogenesis of various obstetric conditions, such as preeclampsia, preterm birth, and gestational diabetes mellitus.[4,8,10,11]

While some medicines can effectively prevent and treat pregnancy-related conditions such as preeclampsia and preterm birth, nearly all are off-label. Many have undesirable side effects, limited efficacy, or target only the isolated, downstream effects of the condition. Additionally, while there are candidates under development for these conditions in the research and development (R&D) pipeline, new and transformative medicines continue to be a distant prospect.[12,13] With increasing evidence on the key role that maternal EED plays in the development and progression of major pregnancy-related conditions, as well as in determining neonatal outcomes, attention is slowly turning to upstream interventions that target the maternal enteric microbiome. Incorporating these interventions during pregnancy and lactation presents a promising opportunity to impact and improve maternal and infant health outcomes, particularly in LMICs.

THE ACCELERATING INNOVATION FOR MOTHERS (AIM) PROJECT

The Accelerating Innovation for Mothers (AIM) project was established in 2020, spearheaded by the Concept Foundation and delivered in partnership with Policy Cures Research and the Burnet Institute. The goal of this project is to reinvigorate investment and spur R&D of products for significant pregnancy-specific conditions where biomedical product gaps exist. As part of this project, a comprehensive pipeline database of maternal health medicines, diagnostics and devices has been developed for a range of pregnancy-related conditions, including preterm birth/labour, preeclampsia/eclampsia, intrauterine growth restriction, postpartum haemorrhage, fetal distress, iron deficiency maternal anaemia and maternal environmental enteric dysfunction. This report covers insights into the R&D landscape for medicines targeting the maternal enteric microbiome, with specific focus on maternal EED as it relates to pregnancy and neonatal health outcomes.

To be included in the maternal enteric microbiome medicines pipeline database, medicines had to be:

- used to prevent or treat maternal environmental enteric dysfunction;
- specifically tested in, indicated for or targeted for use in pregnant women and/or lactating people within the postpartum period (up to 42 days after birth);
- indicated for improvement of maternal outcomes (during pregnancy and up to 42 days after birth) or neonatal outcomes (within the first 28 days of life);
- either in active discovery/preclinical or clinical development now, or have been in development at one point between 2000 and 2023, or approved and registered for clinical use and/or used currently in clinical treatment (off-label); and
- either entirely new entities, existing/repurposed/label extensions, or new formulations or dosing of existing/registered products.

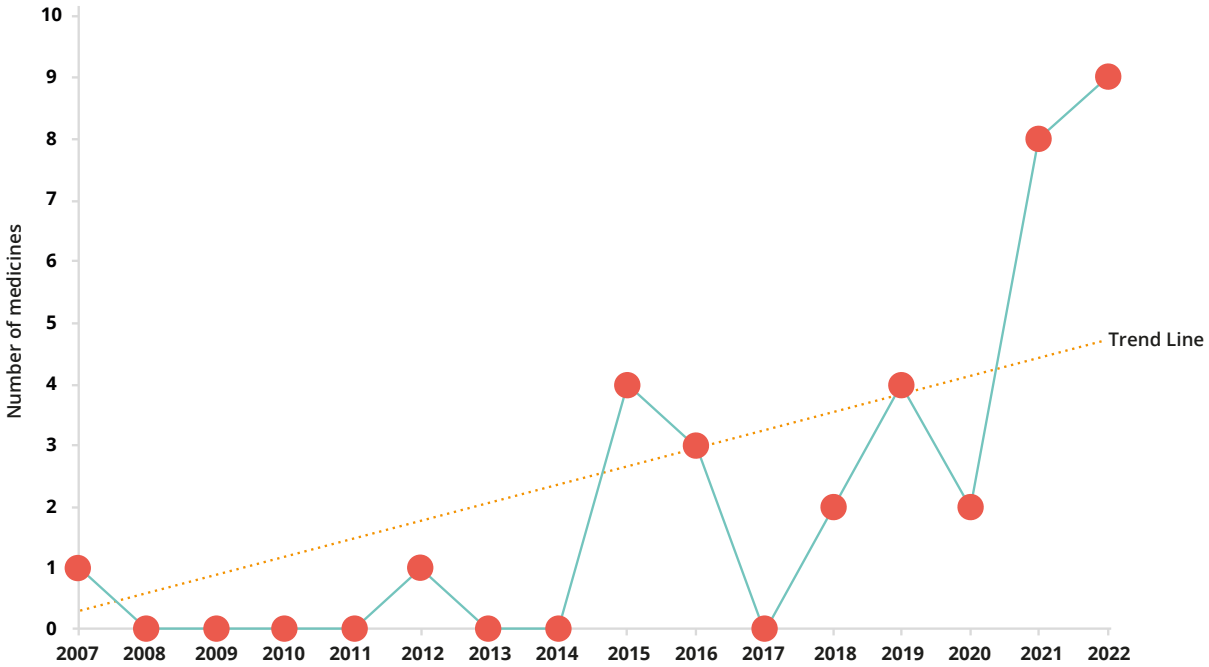
We searched a variety of sources in a stepwise fashion to identify and validate candidates or products. More details on our methodology can be found here.

OVERVIEW OF THE PIPELINE

Over 80% of candidates (28 candidates) were in active development, with evidence of R&D activity within the last three years (2020-2023). Just six candidates (18%) were inactive, all due to a lack of recent activity as opposed to product terminations. While the overall number of candidates under investigation is low, the number of active candidates is proportionately high in comparison to other pregnancy-related conditions, such as preeclampsia/eclampsia and preterm labour/birth. This reflects increasing interest in the maternal gut microbiome in recent years. In fact, over the entire 23-year period from 2000 to 2023, two-thirds of the R&D of candidates targeting the maternal enteric microbiome began in the last five years, and just under 95% of R&D began in the last decade. Only two candidates were studied prior to this time, in 2007 and 2012, both of which are no longer in active development.

Over half of the candidates identified were microbial interventions (18 candidates, 53%), which are designed to modify the maternal enteric microbiome by introducing and replacing enteric bacteria (for example via probiotics, fermented foods, and faecal microbiota transplants). The next largest share of candidates were bioactive compounds (13 candidates, 38%), which modulate the maternal enteric microbiome by providing different food substrates for the bacteria within it, thereby supporting the growth of beneficial microflora (for example, prebiotic glycans, microbial metabolites, or plant polyphenols). The remaining three candidates (8.8%) were small-molecule drugs, which aim to alter the maternal microbiome in various ways, including killing certain bacteria or preventing their growth.

Figure 1: Maternal enteric microbiome medicines by earliest start date of R&D

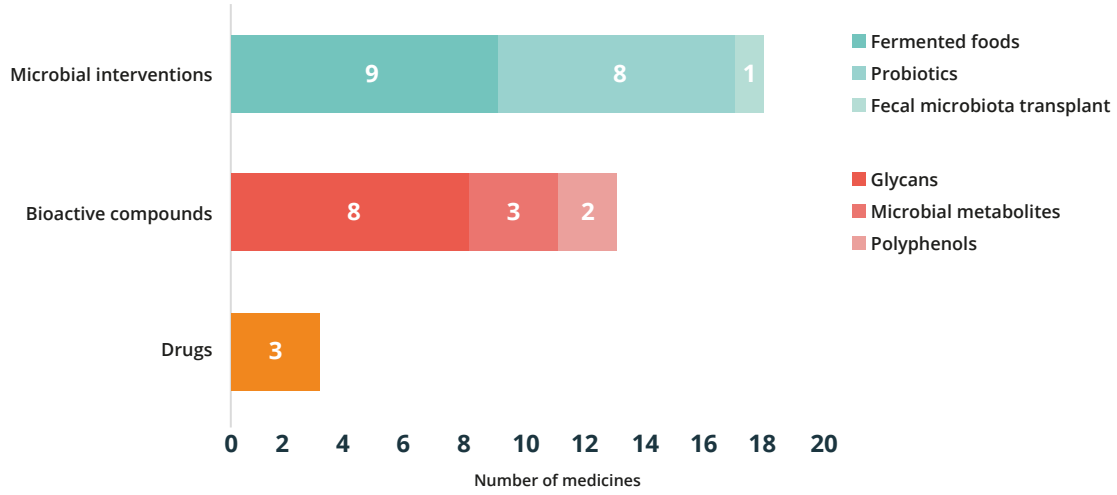


*For three candidates in discovery and preclinical stages, the earliest start date of R&D could not be accurately identified. In these cases, the publication date of the study was used instead (refers to candidates which have their earliest year of R&D listed as 2015, 2022 and 2022).

Just 34 candidates have been investigated that target the maternal enteric microbiome to improve pregnancy and neonatal outcomes.

Half of the 18 microbial interventions were fermented foods (nine candidates). Almost all of these were traditional region-specific fermented foods from Africa and Asia, including fermented rice water, fermented porridges, pickles and other fermented soy and dairy products. The only fermented food which was neither traditional nor region-specific was Bifidobacterium fermented milk; as the name suggests, this refers to milk fermented by Bifidobacteria, which are naturally occurring bacteria in the human gastrointestinal tract and are commonly used in commercial probiotics.

Figure 2: Maternal enteric microbiome medicines by product type and subtype



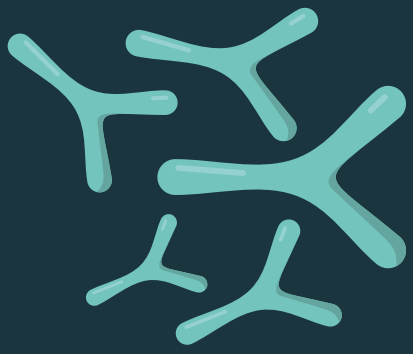
Probiotics – non-fermented food probiotic supplements included under the banner of microbial interventions – encompassed eight candidates (44% of microbial interventions). These eight entailed a variety of probiotic products containing different combinations of probiotic bacterial strains, including those with Bifidobacteria and Lactobacillus. One of the probiotics, Vivomixx, is a marketed probiotic containing a specific mix of eight probiotic strains, known as the 'De Simone' formulation. Vivomixx has been studied in a Phase II clinical trial for its influence on infant birth weight and its ability to prevent excessive gestational weight gain and gestational diabetes mellitus in obese pregnant women via modulation of the maternal gut microbiome. However, results demonstrated that there was no significant difference in outcomes between the control and intervention group, though faecal microbiota analyses showed an overall increase in gut microbiota diversity in the probiotic group.[14]

The final microbial intervention was faecal microbiota transplant (FMT), which involves the transfer of gut flora from the faeces of a healthy individual into a recipient's gastrointestinal tract to reestablish a new intestinal microbiota. In the past year, the US FDA has approved two FMT products from Ferring Pharmaceuticals and Seres Therapeutics, respectively administered rectally and orally, both for the prevention of recurrent Clostridium difficile infection (CDI) in adult individuals following antibacterial treatment for recurrent CDI.[15],[16] (REF). While FMT is clearly gaining significant traction in the broader field of enteric microbiome research, exploration of its use during pregnancy is still in its infancy. One case report published in 2022 described the use of FMT in a pregnant patient with CDI.

The bacterial strains from the FMT donor were transmitted to the pregnant woman, and then to the infant born 26 weeks after the FMT, suggesting that FMT treatment of pregnant women could be used as a potential strategy for neonatal seeding.[17]

The 13 bioactive compounds consisted of prebiotic glycans (eight candidates, 62% of bioactive compounds), microbial metabolites (three candidates, 23%) and polyphenols (two candidates, 15%). Glycans are carbohydrates which function as prebiotics, feeding and stimulating the growth of beneficial gut microbes.[18] Polyphenols are also prebiotics, being natural compounds synthesised exclusively by plants, while microbial metabolites refer to the variety of metabolites produced by gut microbiota, which likely play a key role in modulating the microbiome composition and exert effects on the host by acting as signalling molecules and as substrates for metabolic reactions.[17],[20],[21]

Many maternal enteric microbiome interventions under investigation are available food products, probiotics, or other products already proven safe for humans, which could help accelerate progress through the R&D pathway.



The glycans studied for their effect on the maternal enteric microbiome included the oligosaccharides galactosaccharide ("GOS") and fructosaccharide ("FOS"), which were researched both individually and in combination. There were also biochemically diverse plant polysaccharides and plant-derived oligosacchardies in discovery and preclinical stages of research, as well as a prebiotic-containing dairy product and a prebiotic banana yogurt, both designed to feed the gut microbiota, in Phase II clinical trials.

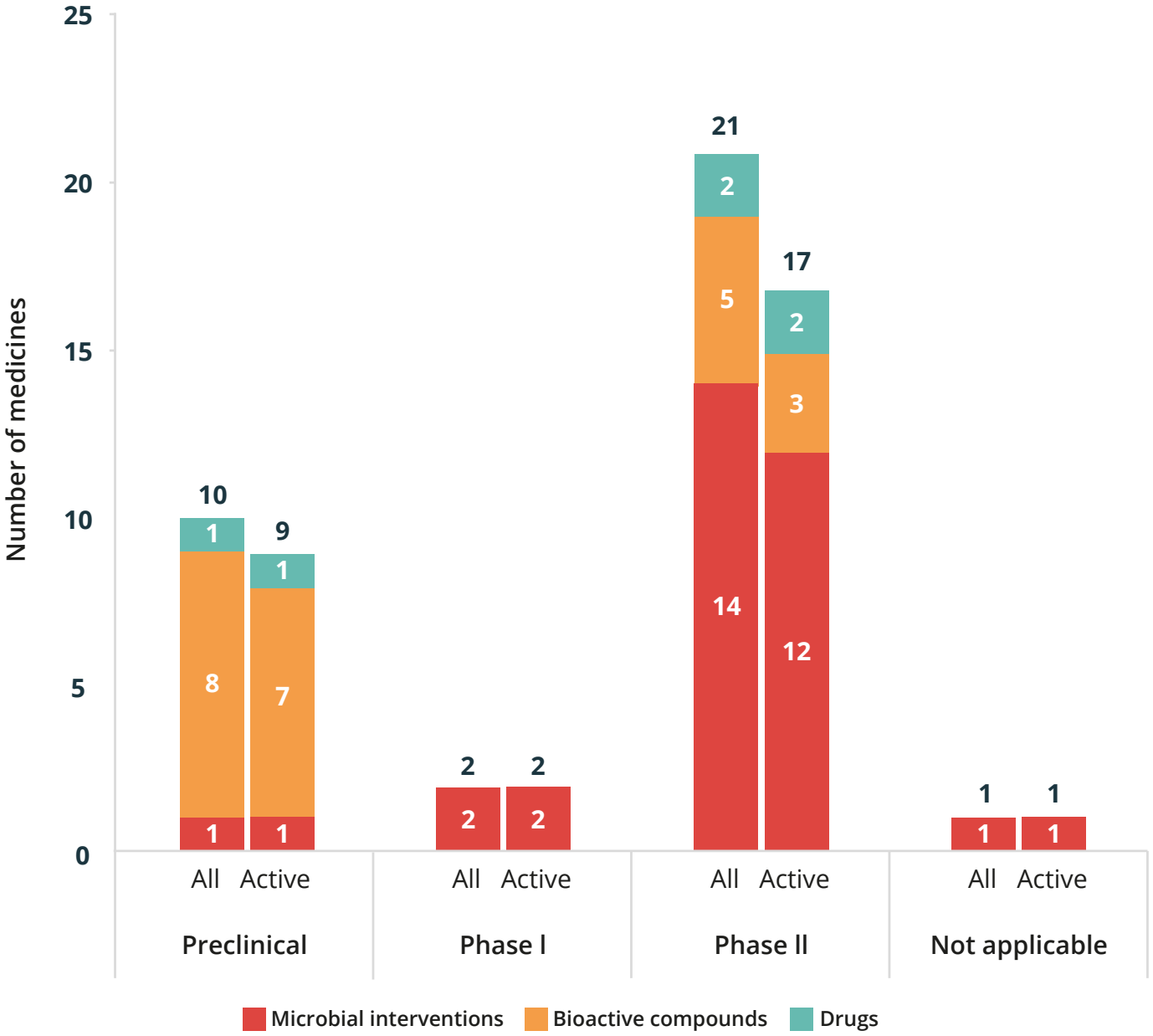
The three microbial metabolite candidates were all short-chain fatty-acids: acetate, butyrate and propionate. The latter two candidates were studied together, alongside the bacteria responsible for their production, Akkermansia muciniphila, in a preclinical rat study which evaluated their ability to treat preeclampsia via modulation of the maternal gut microbiome.

Polyphenols under investigation were garlic oil and puerariae lobatae radix (Asian ginseng). These candidates were studied for their efficacy in modulating the maternal gut microbiota to prevent maternal chronic kidney disease-induced offspring hypertension and preeclampsia, respectively.

The three remaining maternal enteric microbiome candidates were small-molecule drugs (8.8%), including melatonin, the antibiotic combination sulfamethoxazole & trimethoprim, and the anti-malarial combination sulfadoxine & pyrimethamine. Melatonin was tested for its ability to prevent cadmium-induced intrauterine growth restriction, partly via its effects on the gut microbiota and intestinal barrier. Previously, melatonin has been demonstrated to alter the gut microbiota, promoting a decrease in the ratio of Firmicutes to Bacteroidetes, and increasing the relative abundance of Akkermansia.[22] The fixed-dose combination of sulfamethoxazole & trimethoprim is being studied in rural Zimbabwe to see whether it can reduce inflammation or infection or change the microbiome during pregnancy, thereby reducing the risk of small-for-gestational age infants and preterm birth. Finally, sulfadoxine & pyrimethamine, normally administered as intermittent preventive treatment for malaria control during pregnancy, are being tested to determine whether they exert a malaria-independent protective effect against poor birth outcomes, including low birth weight, via effects on the gut or vaginal microbiome.

Of the 34 candidates under investigation, the largest proportion (21 candidates, 62%) were in Phase II clinical trials. This partially reflects the fact that most maternal enteric microbiome interventions are available food products or probiotics, or other products already proven safe for humans – including some during pregnancy – and as such candidates are largely progressing straight to Phase II trials to test efficacy in small cohorts. This is especially true of microbial interventions, where almost 80% of candidates (14) are in Phase II clinical trials. Indeed, almost all microbial interventions are already-available food products or probiotics, the latter of which is most often treated as a dietary supplement and more loosely regulated. Of the microbial interventions, only FMT is subject to stricter regulation, with the FDA designating that human stool is a biological agent and should be regulated as such to ensure patient safety.

Figure 3: Maternal enteric microbiome medicines by R&D stage, product type and development status (active vs inactive)



Beyond Phase II clinical trials, most of the remaining candidates were in discovery and preclinical stages (10 candidates, 29%), including more than 60% of the bioactive compounds (eight candidates). There were two candidates in Phase I clinical trials, including FMT and a probiotic combination with four unspecified strains developed by Denmark's Chr. Hansen, for which the purpose of the early-stage clinical trial was to determine whether the probiotic constituents could be recovered from the maternal and infant faeces. An R&D stage designation was not applicable for the fermented soy & dairy based candidate, since it was only evaluated in a prospective cohort study using data from the broader Japan Environment and Children's study to investigate whether intake of fermented foods was associated with a reduced risk of preterm birth.[23]

Most of the candidates identified were repurposed having already been approved and marketed for another condition (28 candidates, 82%). Just six candidates (18%) were new products not marketed for any other conditions, including acetate, propionate, prebiotic plant-derived oligosaccharides (phytochemical combination) and biochemically diverse plant polysaccharides in discovery and preclinical R&D stages, as well as a prebiotic and a probiotic yogurt both made specifically for Phase II clinical trials targeting the maternal enteric microbiome.

Research for the 34 candidates was conducted in 20 different countries. The largest amount of research was conducted in China, with nine candidates under investigation.

There were nine candidates which originated from and were particular to a specific country or geographical region ('region-specific'), of which the overwhelming majority were traditional fermented foods. These included achars (pickles) from Pakistan, dadiah (fermented milk) from Indonesia, mageu (fermented grain porridge) from South Africa, soymilk-burkina (fermented milk and millet beverage) from Ghana, torani (fermented rice water) from India, fermented millet porridge from Burkina Faso and fermented soy & dairy from Japan. The remaining region-specific candidates included moringa and lactobacillus rhamnosus GR-1 probiotic yoghurt, which was made specifically for a study conducted in Tanzania and modified from a pre-existing yogurt already produced in Tanzania as part of the Western Heads East network of microenterprise community-run kitchens. It also included the prebiotic yogurt, Native Yogurt Banana (NaYOBA) – a yogurt also made specifically for a study in India.

Figure 4: Regional specificity of maternal enteric microbiome medicines

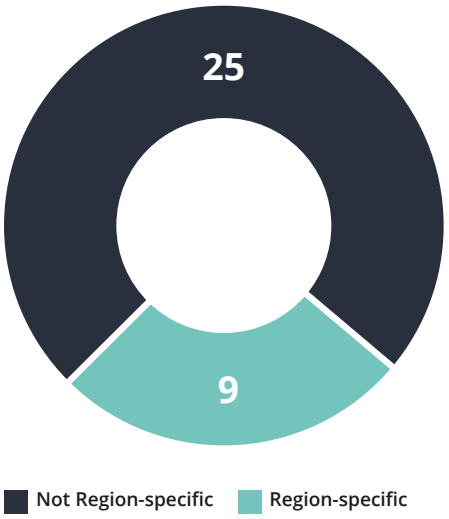
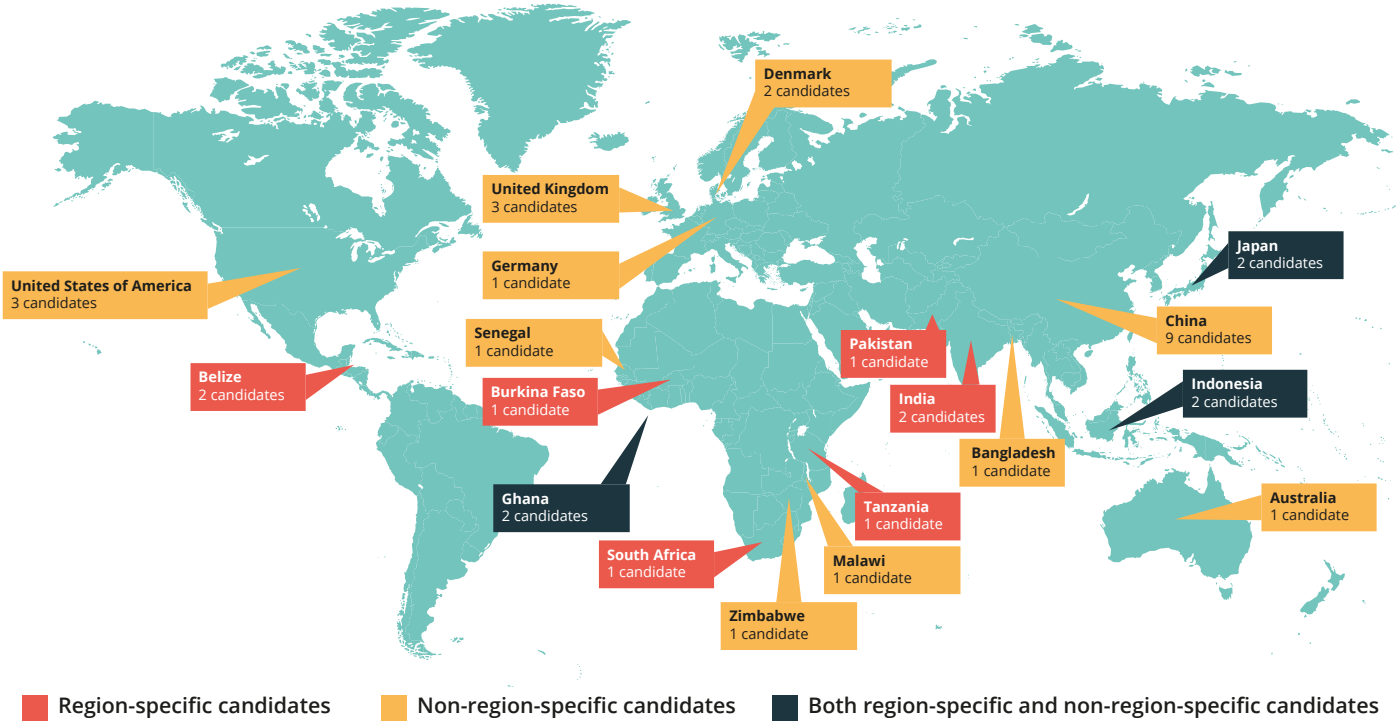


Figure 5: Number of maternal enteric microbiome medicines by country of R&D*

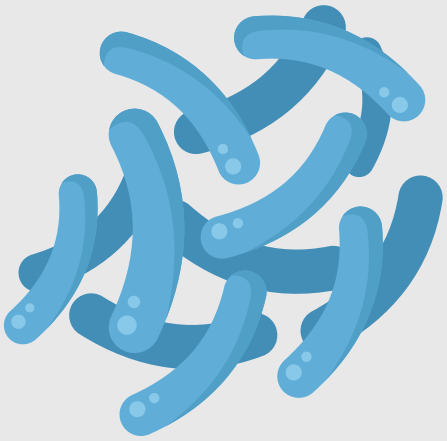


*If candidates were under development in more than one country, the candidate was listed in each country of development. Therefore, the number of candidates on this map will be more than the total number of candidates.

Almost all investigators and developers of maternal enteric microbiome medicines were academic or government research institutions. The only identified industry developer was Denmark's Chr. Hansen, which completed a Phase I clinical trial for a probiotic combination of four unspecified strains in 2022.

Funders of R&D were not able to be identified for every candidate, however there are some funders which are evidently active in this space. In particular, the Bill & Melinda Gates Foundation contributed funding for the research of seven candidates. Five of these were traditional region-specific fermented foods funded through the Global Grand Challenges award commencing in 2021, titled 'Integrating Tradition and Technology for Fermented Foods for Maternal Nutrition'. The US NIH also funded the R&D of two candidates, including biochemically diverse plant polysaccharides and the anti-malarial combination, sulfadoxine & pyrimethamine.

The landscape of candidates targeting the maternal enteric microbiome is diverse, but the majority of products have at most been evaluated in single small-scale clinical trials with insufficient power to prove efficacy



GROWING PROMISE, BUT TOO EARLY TO CALL

At present, the field of research into maternal enteric microbiome medicines remains nascent. There are no approved products that target the maternal enteric microbiome to improve pregnancy and neonatal outcomes, and only a small number of candidates have been studied for this indication. The majority of candidates under investigation have at most been evaluated in one small-scale clinical trial with insufficient power to prove efficacy, and no large Phase III clinical trials have been identified. Furthermore, the preclinical pipeline is relatively bare – in and of itself offering limited scope for a robust future pipeline – and few novel compounds are under investigation. Clearly, it will be some time before medicines targeting the maternal enteric microbiome are available and utilised for this specific purpose, with their desired and anticipated impact on maternal and infant health outcomes being more likely a fairly distant possibility than an imminent reality.

Encouragingly, however, the landscape does give a clear indication of growing activity in this area. Ten years ago, just two candidates had been studied for this indication. Five years ago, this figure jumped to nine. In the following five years, this number climbed again, sitting at a total of 34 candidates studied for their ability to target the maternal enteric microbiome as of 2023. Hopefully, interest and investment in this area will continue to rise, buoyed by advances in the broader field of microbiome research. Indeed, while research into the maternal gut microbiome is only now coming into its own, the broader field of microbiome research has seen an explosion of interest in the past decade, with Forbes labelling the 2010s the 'Decade of the Microbiome'.[24] According to McKinsey, US$7.4bn has been invested into microbiome research in the two decades leading to 2020, with another paper estimating that, as of 2019, more than US$3bn has been invested in gut-microbiome innovation companies.[25],[26] This investment is starting to bear some fruit, with the FDA recently approving the first two microbiome-based therapeutics: both FMT products for the treatment of recurrent C. difficile infection. Hopefully, the maternal enteric microbiome field will follow the same trajectory of growth and breakthrough, and with significant global health funders – such as the Bill & Melinda Gates Foundation – placing increasing strategic emphasis in this area, it remains a tangible possibility.

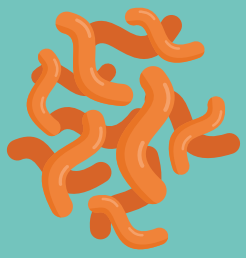
Even in its current embryonic state, the landscape of candidates targeting the maternal enteric microbiome is diverse, with significant variation in the types of products that are under investigation. This diversity is set to continue, for example with the Bill & Melinda Gates Foundation recently investing in BrightSeed's AI Forager platform to discover new plant bioactives that improve maternal EED, as well as a broad sweep of other products, including microbial metabolites and therapeutic foods.[27],[28] This diversity is encouraging at an early stage. However, there may be benefits in focusing on food products and dietary supplements over small-molecule therapies and other more complex drugs. Food products and dietary supplements may be more acceptable to users, especially if the intention is for them to be taken during pregnancy due to a perceived lower risk of teratogenicity. Additionally, these types of products may be easier to roll out, facing fewer regulatory hurdles. Alongside tighter regulations for medicines taken during pregnancy, the FDA's rigorous approach to microbiome therapy has led to a number of holds on clinical trials in this space.[29] If progress is to accelerate, food products and dietary supplements may present the path of least resistance, and the better option for women if proven effective.

Alongside the diversity in product types, there is also significant variation in the maternal or neonatal outcomes that the medicines are targeting. Of the candidates under development, studies are evaluating their ability to prevent and treat preeclampsia, intrauterine growth restriction, preterm birth, low birth weight, gestational diabetes mellitus, and more. Optimistically, targeting the maternal enteric microbiome could offer improvements to a wide range of pregnancy-related conditions and neonatal outcomes. However, greater understanding on the contributions of the maternal gut microbiome to the pathogenesis of each of these conditions is required to focus the research in this field, and ultimately improve the impact of interventions.

Additionally, it is currently unclear whether region-specific products will have broader applicability in the global setting, due to both geographic diversity in gut microbiota composition and to potential challenges with their roll out, particularly for traditional fermented foods. It also remains to be seen whether the global scale-up of products should even be pursued over a more regional approach. These uncertainties are not surprising given the infancy of this field. However, at this stage the portfolio may benefit from a unified agenda that identifies and addresses these questions and outlines specific priorities for the development of maternal enteric microbiome medicines. In the past, medicines development for other global health diseases has benefited considerably from cohesive sector-wide approaches. The same may be required for maternal enteric microbiome medicines if progress in this field is to accelerate.

ACKNOWLEDGEMENTS

We would like to thank Ina Schuppe Koistinen, PhD, Associate Professor and Alliance Director at the Center for Translational Microbiome Research (CTMR) for her review and input into the maternal enteric microbiome medicines pipeline database.



REFERENCES

1. Hills RD, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR. Gut Microbiome: Profound Implications for Diet and Disease. Nutrients. 2019 Jul 16;11(7):1613.
2. Varesi A, Pierella E, Romeo M, Piccini GB, Alfano C, Bjørklund G, et al. The Potential Role of Gut Microbiota in Alzheimer's Disease: From Diagnosis to Treatment. Nutrients. 2022 Feb 5;14(3):668.
3. Edwards SM, Cunningham SA, Dunlop AL, Corwin EJ. The Maternal Gut Microbiome during Pregnancy. MCN Am J Matern Child Nurs. 2017;42(6):310–7.
4. Gorczyca K, Obuchowska A, Kimber-Trojnar Ż, Wierzchowska-Opoka M, Leszczyńska-Gorzelak B. Changes in the Gut Microbiome and Pathologies in Pregnancy. Int J Environ Res Public Health. 2022 Aug 12;19(16):9961.
5. Crane RJ, Jones KDJ, Berkley JA. Environmental Enteric Dysfunction: An Overview. Food Nutr Bull. 2015 Mar 1;36(1_suppl1):S76–87.
6. Moya-Alvarez V, Sansonetti PJ. Understanding the pathways leading to gut dysbiosis and enteric environmental dysfunction in infants: the influence of maternal dysbiosis and other microbiota determinants during early life. FEMS Microbiol Rev. 2022 May 1;46(3):fuac004.
7. Lauer JM, Duggan CP, Ausman LM, Griffiths JK, Webb P, Agaba E, et al. Biomarkers of maternal environmental enteric dysfunction are associated with shorter gestation and reduced length in newborn infants in Uganda. Am J Clin Nutr. 2018 Oct;108(4):889–96.
8. EBioMedicine. The maternal microbiome: another bridge linking mothers and infants. eBioMedicine [Internet]. 2021 Sep 1 [cited 2023 Oct 30];71. Available from: https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00395-9/fulltext
9. Valentine G, Chu DM, Stewart CJ, Aagaard KM. Relationships Between Perinatal Interventions, Maternal-Infant Microbiomes, and Neonatal Outcomes. Clin Perinatol. 2018 Jun 1;45(2):339–55.
10. Ishimwe JA. Maternal microbiome in preeclampsia pathophysiology and implications on offspring health. Physiol Rep. 2021 May;9(10):e14875.
11. Hasain Z, Mokhtar NM, Kamaruddin NA, Mohamed Ismail NA, Razalli NH, Gnanou JV, et al. Gut Microbiota and Gestational Diabetes Mellitus: A Review of Host-Gut Microbiota Interactions and Their Therapeutic Potential. Front Cell Infect Microbiol [Internet]. 2020 [cited 2023 Oct 30];10. Available from: https://www.frontiersin.org/articles/10.3389/fcimb.2020.00188
12. McDougall ARA, Hastie R, Goldstein M, Tuttle A, Ammerdorffer A, Gülmezoglu AM, et al. New medicines for spontaneous preterm birth prevention and preterm labour management: landscape analysis of the medicine development pipeline. BMC Pregnancy Childbirth [Internet]. 2023 [cited 2023 Oct 30];23(1). Available from: https://link.springer.com/epdf/10.1186/s12884-023-05842-9
13. McDougall ARA, Hastie R, Goldstein M, Tuttle A, Tong S, Ammerdorffer A, et al. Systematic evaluation of the pre-eclampsia drugs, dietary supplements and biologicals pipeline using target product profiles. BMC Med. 2022 Nov 4;20:393.
14. Halkjær SI, de Knegt VE, Lo B, Nilas L, Cortes D, Pedersen AE, et al. Multistrain Probiotic Increases the Gut Microbiota Diversity in Obese Pregnant Women: Results from a Randomized, Double-Blind Placebo-Controlled Study. Curr Dev Nutr. 2020 Jul;4(7):nzaa095.
15. Research C for BE and. VOWST. FDA [Internet]. 2023 May 18 [cited 2023 Nov 20]; Available from: https://www.fda.gov/vaccines-blood-biologics/vowst
16. Research C for BE and. REBYOTA. FDA [Internet]. 2022 Dec 19 [cited 2023 Nov 20]; Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/rebyota
17. Wei S, Jespersen ML, Baunwall SMD, Myers PN, Smith EM, Dahlerup JF, et al. Cross-generational bacterial strain transfer to an infant after fecal microbiota transplantation to a pregnant patient: a case report. Microbiome. 2022 Nov 10;10(1):193.
18. Koropatkin NM, Cameron EA, Martens EC. How glycan metabolism shapes the human gut microbiota. Nat Rev Microbiol. 2012 Apr 11;10(5):323–35.
19. Bertelli A, Biagi M, Corsini M, Baini G, Cappellucci G, Miraldi E. Polyphenols: From Theory to Practice. Foods. 2021 Oct 27;10(11):2595.
20. Krautkramer KA, Fan J, Bäckhed F. Gut microbial metabolites as multi-kingdom intermediates. Nat Rev Microbiol. 2021 Feb;19(2):77–94.
21. Fobofou SA, Savidge T. Microbial metabolites: cause or consequence in gastrointestinal disease? Am J Physiol-Gastrointest Liver Physiol. 2022 Jun;322(6):G535–52.
22. Melatonin prevents obesity through modulation of gut microbiota in mice - Xu - 2017 - Journal of Pineal Research - Wiley Online Library [Internet]. [cited 2023 Oct 30]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jpi.12399
23. Ito M, Takamori A, Yoneda S, Shiozaki A, Tsuchida A, Matsumura K, et al. Fermented foods and preterm birth risk from a prospective large cohort study: the Japan Environment and Children's study. Environ Health Prev Med. 2019 May 1;24(1):25.
24. The Decade Of The Microbiome [Internet]. [cited 2023 Oct 30]. Available from: https://www.forbes.com/sites/linhanhcat/2019/12/31/decade-of-the-microbiome/?sh=7838928b9961
25. Microbiome R&D: gut conviction that microbes can help humanity. Financial Times [Internet]. 2021 May 24 [cited 2023 Oct 30]; Available from: https://www.ft.com/content/8aea7a0a-3de1-4312-9b3c-86799b94a1d9
26. Li D, Gao C, Zhang F, Yang R, Lan C, Ma Y, et al. Seven facts and five initiatives for gut microbiome research. Protein Cell. 2020 Jun;11(6):391–400.
27. nutraingredients-usa.com. Gates Foundation funds Brightseed to discover plant-based bioactives to improve birth outcomes [Internet]. nutraingredients-usa.com. 2021 [cited 2023 Nov 20]. Available from: https://www.nutraingredients-usa.com/Article/2021/11/04/Gates-Foundation-funds-Brightseed-to-discover-plant-based-bioactives-to-improve-birth-outcomes
28. INV-051043 [Internet]. Bill & Melinda Gates Foundation. [cited 2023 Nov 20]. Available from: https://www.gatesfoundation.org/about/committed-grants/2023/05/inv-051043
29. Zamecnik A. Is the microbiome therapy hype up for a reckoning? [Internet]. Pharmaceutical Technology. 2023 [cited 2023 Oct 30]. Available from: https://www.pharmaceutical-technology.com/features/is-the-microbiome-therapy-hype-up-for-a-reckoning/

ANNEXE: Included maternal enteric microbiome medicines by product type and subtype

Name	Product type	Product subtype
Fermented soy & dairy – unspecified	Microbial interventions	Fermented foods
Bifidobacterium fermented milk	Microbial interventions	Fermented foods
Soymilk-Burkina (fermented milk and millet beverage)	Microbial interventions	Fermented foods
Moringa and Lactobacillus rhamnosus GR-1 probiotic yogurt	Microbial interventions	Fermented foods
Fermented millet porridge	Microbial interventions	Fermented foods
Dadiah (fermented milk)	Microbial interventions	Fermented foods
Torani (fermented rice water)	Microbial interventions	Fermented foods
Mageu (fermented grain porridge)	Microbial interventions	Fermented foods
Achars (pickles)	Microbial interventions	Fermented foods
Akkermansia muciniphila	Microbial interventions	Fermented foods
Probiotic combination – four unspecified strains	Microbial interventions	Probiotics
Vivomixx	Microbial interventions	Probiotics
Probiotic combination – unspecified strains	Microbial interventions	Probiotics
Probiotics and LC-PUFA – combined, unspecified strains	Microbial interventions	Probiotics
Lactobacillus and bifidobacterium – combined	Microbial interventions	Probiotics
Lactobacillus spp	Microbial interventions	Probiotics
Bifidobacterium spp	Microbial interventions	Probiotics
Faecal microbiota transplant	Microbial interventions	FMT
Biochemically diverse plant polysaccharides – unspecified	Bioactive compounds	Glycans
Plant-derived oligosaccharides (prebiotic phytochemical combination)	Bioactive compounds	Glycans
Galactooligosaccharide	Bioactive compounds	Glycans
Prebiotic banana extract + Iron: Native Yogurt Banana (NaYOBA)	Bioactive compounds	Glycans
Prebiotic-containing dairy – unspecified	Bioactive compounds	Glycans
Oligosaccharide-sialic acid	Bioactive compounds	Glycans
Fructooligosaccharide	Bioactive compounds	Glycans
GOS/lcFOS – combined	Bioactive compounds	Glycans
Acetate	Bioactive compounds	Microbial metabolites
Butyrate	Bioactive compounds	Microbial metabolites
Propionate	Bioactive compounds	Microbial metabolites
Puerariae Lobatae Radix	Bioactive compounds	Polyphenols
Garlic oil	Bioactive compounds	Polyphenols
Melatonin	Drugs	
Sulfamethoxazole and trimethoprim – combined	Drugs	
Sulfadoxine and pyrimethamine – combined	Drugs	

This work has been funded by
the Bill & Melinda Gates Foundation

BILL & MELINDA GATES *foundation*

Concept Foundation

POLICY CURES RESEARCH.

Burnet

Concept Foundation

Concept Foundation
2024

Bâtiment F2F3 Avenue
de Sécheron 15

1202 Geneva
SWITZERLAND

www.theaimproject.org
info@conceptfoundation.org