REVIEW

Moms, babies, and bugs in immune development [version 1; peer review: 2 approved]

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Abstract

Bacteria and mammals have co-evolved with one another over millennia, and it has become impossible to interpret mucosal immunity without taking the microbiota into consideration. In fact, the primary role of the mucosal immune system is regulating homeostasis and the host relationship with the microbiota. Bacteria are no longer seen as simply invading pathogens, but rather a necessary component to one's own immune response. On the one hand, the microbiota is a vital educator of immune cells and initiator of beneficial responses; but, on the other, dysbiosis of microbiota constituents are associated with inflammation and autoimmune disorders. In this review, we will consider recent advances in the understanding of how the microbiota influences host mucosal immunity, particularly the initial development of the immune response and its implications.

Keywords

mucosal immunity, microbiota, immune development

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Introduction

The significant impact of the microbiota in terms of host immunity has become increasingly clear in the past decade as researchers have begun to unravel the complex relationship between bacteria and the human host. Previous research has demonstrated the integral role that microbiota bacteria have on immune cell development, particularly T lymphocytes. In mice, multiple bacteria, including various species from the class Clostridia, have been shown to favor the differentiation of anti-inflammatory, regulatory T cells (Tregs)¹⁻⁴, while another member of the Clostridium family, Segmented Filamentous Bacteria (SFB), along with the human commensal *Bifidobacterium adolescentis*, have been shown to promote the effector T helper 17 cells⁵⁻⁸ that produce the cytokines interleukin (IL)-17 and IL-22. Interestingly, immunomodulatory molecules derived from bacteria have been shown to influence T cell differentiation. Polysaccharide A (PSA), a component of *Bacteroides fragilis*, directly interacts with CD4⁺ T cells in a Toll-like receptor 2 (TLR2)-dependent manner to induce IL-10-producing Foxp3⁺ Tregs as well as shape colonization of the microbiota^{9,10}. Dysregulation of the immune cell interaction with the microbiota can lead to aberrant T cell responses to commensal constituents of the microbiota and is characteristic of multiple immune disorders¹¹⁻¹³. While it is clear that the microbiota influences immune reactivity, there still remains the question as to whether the balance between them is imprinted in the genome, or whether the composition of the microbiota, and thus its effects on immune cells, shifts with environmental influence. Evidence for the latter has been demonstrated in mice from diverse environments, including barn (feral) and pet store mice, which have elevated antigen-experienced CD8⁺ T cells, cells which control immune reactivity to intracellular pathogens and tumors, compared to laboratory mice housed in clean, specific pathogen-free (SPF) conditions¹⁴. The difference in these immune reactive cells is most likely shaped by the environmental antigen exposure, and therefore the microbiota of the mice, as SPF laboratory mice co-housed with feral mice developed a more robust immune system such that they were better able to respond to the pathogen *Listeria monocytogenes* compared to SPF mice that had not been co-housed and had an unaltered microbiota¹⁴. The post-birth colonization of the intestine with bacteria is largely thought to influence future immune development¹⁵, and there have been multiple recent studies expanding this principle¹⁶⁻¹⁹. In this review, we will discuss recent advances on the impact of the microbiota on the development of the immune response, consequences of the transmission of the maternal microbiota, and the plasticity of interactions between the microbiota and host immunity.

Maternal microbiome and mode of delivery

The microbiome has significant impacts on the development of lymphoid structures and immunity, as witnessed by germ-free (GF) mice who lack isolated lymphoid follicles in the small intestine and are deficient in secretory IgA (SIgA)²⁰. In order to examine the impact of the maternal microbiome on fetal development, Gomez de Agüero and colleagues transiently infected GF pregnant dams with a non-replicating strain of *Escherichia coli* (E.coli HA107) and surveyed the impact on neonate immunity¹⁷. Mice born to colonized dams had increased levels

of small intestinal innate lymphoid cells (ILCs), most notably the NKp46⁺RORγt⁺ subset, compared to those born to GF dams, a difference that was sustained after the pups were weaned. Transiently colonized dams were able to passively transfer microbial molecules to offspring in utero, providing a stimulus for immune development. Functionally, only mice born to dams transiently colonized with HA107 or treated with an aryl hydrocarbon receptor (AhR) ligand, and not GF mothers, were able to curb the translocation of a replicating strain of E.coli (JM83) to the mesenteric lymph nodes, demonstrating a critical role for the maternal microbiota in neonate immune development during pregnancy¹⁷.

The health of the maternal microbiome also has a significant impact on the developing neonate, as the human placenta has been shown to harbor commensal microbes that may alter development^{21,22}. Malnutrition of neonates, either the excess or lack of adequate food, leads to poor health outcomes and is associated with a more immature microbiota²³. Lack of sufficient nutrients in breast milk, due to a suboptimal diet of the mother, may contribute to malnutrition and subsequent stunting, wasting or other development disorders²⁴.

The maternal microbiome has significant effects on the resulting bacterial colonization of the neonate in the context of modes of delivery. Human newborns delivered via Cesarean section (C-section) have microbiomes that more closely resemble that of the skin microbiota of the mother while vaginally delivered infants have microbiomes that more closely mimic that of the vaginal flora, though it is possible to partially restore a microbiome characteristic of a vaginal delivery in C-section infants by swabbing the newborn with constituents of the mother's vaginal flora shortly after birth^{25,26}. Whether the vaginal flora, which encourages expansion of *Lactobacillus* followed by upregulation of members of *Bacteroides*, is more protective in infancy or early childhood illness is a matter that has yet to be determined²⁶. A diverse microbiota is typically associated with better health outcomes²⁷, and recent data has shown that newborns delivered via C-section have lower bacterial diversity, particularly in the *Bacteroidetes* phylum, coupled with lower circulating levels of T helper cell type 1 chemokines, during the first 24 months of life compared to vaginally delivered newborns^{28,29}.

Secretory antibodies and breast milk

In addition to mode of delivery, maternal breast milk plays a role in shaping mucosal responses in neonates. In mice, it has been demonstrated that maternal transfer of broadly reactive IgA and IgM antibodies through the breast milk aids in preventing the attachment of luminal bacteria to the mucosal surface in neonates³⁰. Antigen-specific IgG antibodies from the mother delivered to the neonate through the breast milk or retro-transported via neonatal Fc receptor (FcRn) to the mucosa from the neonatal plasma also contribute to the protection against pathogens in early life. While SIgA has long been established as mediator of intestinal homeostasis³¹, helping to mold the gut microbiota and its interactions with the host, recent advances have demonstrated the long-term benefits of breastfeeding, particularly in the context of the delivery of SIgA^{16,30}. Rogier and colleagues demonstrated

that the passive transfer of SIgA in breast milk was necessary in establishing intestinal homeostasis and protecting suckling mice from opportunistic pathogens by restricting the translocation of bacteria from the intestinal lumen to the draining lymph nodes. Additionally, mice that received maternal SIgA via breast milk had elevated expression of colonic epithelial cell genes associated with barrier protection, establishing an additional protective mechanism for maternal SIgA delivery in mucosal pathogen exclusion during the critical time point in development in which the neonate gut is being colonized¹⁶.

While the majority of IgG antibody responses are T cell-dependent and antigen-specific, maternally-derived T cell-independent IgG responses to microbiota commensal species have recently been identified¹⁹. These IgG antibodies were primarily derived from the breast milk and were largely of the IgG2b and IgG3 isotypes¹⁹. These responses were largely dependent on Toll-like receptor (TLR) signaling, specifically TLR2 and TLR4, and prevented translocation of bacteria to the mesenteric lymph nodes in mice. Mice lacking these maternal antibodies developed T cell-dependent antibodies to the microbiota as a compensatory mechanism to achieve mucosal homeostasis. The long-term effect of such compensatory adaptive immune responses on future health are not clear¹⁹. The T cell independent IgG antibodies, in conjunction with IgA, were important in shaping the immune response to the microbiota, expanding the function of IgG from the previous dogma of only facilitating responses to pathogens^{19,32}.

In addition to antibody delivery, breast milk also provides lactoferrin, α -lactalbumin, complex lipids, short chain fatty acids (SCFAs) and free oligosaccharides to the neonate^{22,24}. Free oligosaccharides available in breast milk during early lactation aid in colonizing the infant microbiota by acting as a food source for beneficial *Bifidobacterium longum* subsp. *infantis* strains³³ as well as serving as decoy receptors for epithelial binding sites^{24,34}. Lactoferrin functions as an anti-microbial after cleavage, providing protection against pathogens for the neonate^{24,35}. SCFAs have been shown to have a myriad of beneficial effects on the host commensal flora, including the induction of protective Tregs, “competitive exclusion” of non-beneficial bacteria, enhancement of the growth of stable butyrate consumers, promotion of mucus and barrier integrity, and anti-inflammatory effects²².

The effect of antibiotics and probiotics on the microbiota and immunity

The infant gut experiences profound changes, including multiple blooms and attritions of specific species within the first 2–3 years

of life before normalizing to a more adult-like state that is better able to withstand perturbations, such as treatment with antibiotics or significant illness^{24,36–38}. Early life use of antibiotics has been recently associated with delayed maturity of the microbiota³⁷, as well as enhanced risk of obesity, allergies, inflammatory bowel disease, and asthma^{39–43}. Additionally, antibiotic manipulation of the microbiota in adult mice leads to impaired innate and adaptive antiviral responses to both systemic and respiratory viruses, demonstrating an important role for commensal bacteria in regulating antiviral response^{44,45}.

A recent human study found that supplementation with the probiotic *Lactobacillus rhamnosus* during early pregnancy decreases the risk of developing gestational diabetes mellitus (GDM), particularly in mothers over 35 years of age or those with prior elevated risk of GDM, compared to expectant mothers without probiotic intervention⁴⁶. Additionally, antibiotic treatment of mothers during labor or delivery significantly alters the oral microbiome of offspring, with some neonates expressing antibiotic-resistant genes days after birth, a consequence that could lead to bacterial dysbiosis later in development¹⁸.

Conclusions

Nascent studies in the differentiation and development of the neonate microbiota have set the stage for understanding how bacteria, particularly the gut microbiota, shape immunity. While contributing factors, such as maternal antibiotic treatment, mode of infant delivery and whether or not the neonate is breastfed, help to shape the microbiota constituents, longitudinal studies are necessary to determine how these factors might influence infection resistance and overall health. Studies in mice have revealed a role for bacteria in immune cell differentiation, most notably in the generation of T helper 17 cells by SFB and Tregs by select members of the class Clostridia. Applying this knowledge to the treatment of human disorders will be an important next step of this research. As antibiotic usage increases worldwide, it has become increasingly necessary to consider the beneficial gut bacteria with which we have co-evolved as potential modulators of our immune system to maintain health.

Competing interests

The authors declare that they have no competing interests.

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References

1. **F** Atarashi K, Tanoue T, Shima T, *et al.*: **Induction of colonic regulatory T cells by indigenous *Clostridium* species.** *Science*. 2011; **331**(6015): 337–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
2. **F** Atarashi K, Tanoue T, Oshima K, *et al.*: **T_H17 induction by a rationally selected mixture of *Clostridia* strains from the human microbiota.** *Nature*. 2013; **500**(7461): 232–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
3. Narushima S, Sugiura Y, Oshima K, *et al.*: **Characterization of the 17 strains of regulatory T cell-inducing human-derived *Clostridia*.** *Gut Microbes*. 2014; **5**(3): 333–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. **F** Sefik E, Geva-Zatorsky N, Oh S, *et al.*: **MUCOSAL IMMUNOLOGY. Individual intestinal symbionts induce a distinct population of ROR γ^t regulatory T cells.** *Science*. 2015; **349**(6251): 993–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
5. **F** Ivanov II, Frutos Rde L, Manel N, *et al.*: **Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine.** *Cell Host Microbe*. 2008; **4**(4): 337–49.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
6. **F** Atarashi K, Nishimura J, Shima T, *et al.*: **ATP drives lamina propria T_H17 cell differentiation.** *Nature*. 2008; **455**(7214): 808–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
7. **F** Ivanov II, Atarashi K, Manel N, *et al.*: **Induction of intestinal Th17 cells by segmented filamentous bacteria.** *Cell*. 2009; **139**(3): 485–98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
8. **F** Tan TG, Sefik E, Geva-Zatorsky N, *et al.*: **Identifying species of symbiont bacteria from the human gut that, alone, can induce intestinal Th17 cells in mice.** *Proc Natl Acad Sci U S A*. 2016; **113**(50): E8141–E8150.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
9. **F** Round JL, Mazmanian SK: **Inducible Foxp3⁺ regulatory T-cell development by a commensal bacterium of the intestinal microbiota.** *Proc Natl Acad Sci U S A*. 2010; **107**(27): 12204–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
10. **F** Round JL, Lee SM, Li J, *et al.*: **The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota.** *Science*. 2011; **332**(6032): 974–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
11. **F** Hand TW, Dos Santos LM, Bouladoux N, *et al.*: **Acute gastrointestinal infection induces long-lived microbiota-specific T cell responses.** *Science*. 2012; **337**(6101): 1553–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
12. Alexander KL, Targan SR, Elson CO 3rd: **Microbiota activation and regulation of innate and adaptive immunity.** *Immunol Rev*. 2014; **260**(1): 206–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. **F** Calderón-Gómez E, Bassolas-Molina H, Mora-Buch R, *et al.*: **Commensal-Specific CD4⁺ Cells From Patients With Crohn's Disease Have a T-Helper 17 Inflammatory Profile.** *Gastroenterology*. 2016; **151**(3): 489–500.e3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
14. **F** Beura LK, Hamilton SE, Bi K, *et al.*: **Normalizing the environment recapitulates adult human immune traits in laboratory mice.** *Nature*. 2016; **532**(7600): 512–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
15. Renz H, Brandtzaeg P, Hørfelt M: **The impact of perinatal immune development on mucosal homeostasis and chronic inflammation.** *Nat Rev Immunol*. 2011; **12**(1): 9–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. **F** Rogier EW, Frantz AL, Bruno ME, *et al.*: **Secretory antibodies in breast milk promote long-term intestinal homeostasis by regulating the gut microbiota and host gene expression.** *Proc Natl Acad Sci U S A*. 2014; **111**(8): 3074–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
17. **F** Gomez de Agüero M, Ganai-Vonarburg SC, Fuhrer T, *et al.*: **The maternal microbiota drives early postnatal innate immune development.** *Science*. 2016; **351**(6279): 1296–302.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
18. **F** Gomez-Arango LF, Barrett HL, McIntyre HD, *et al.*: **Antibiotic treatment at delivery shapes the initial oral microbiome in neonates.** *Sci Rep*. 2017; **7**: 43481.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
19. **F** Koch MA, Reiner GL, Lugo KA, *et al.*: **Maternal IgG and IgA Antibodies Dampen Mucosal T Helper Cell Responses in Early Life.** *Cell*. 2016; **165**(4): 827–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
20. Hooper LV, Littman DR, Macpherson AJ: **Interactions between the microbiota and the immune system.** *Science*. 2012; **336**(4420145): 1268–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. **F** Aagaard K, Ma J, Antony KM, *et al.*: **The placenta harbors a unique microbiome.** *Sci Transl Med*. 2014; **6**(237): 237ra65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
22. Thorburn AN, Macia L, Mackay CR: **Diet, metabolites, and “western-lifestyle” inflammatory diseases.** *Immunity*. 2014; **40**(6): 833–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. **F** Subramanian S, Huq S, Yatsunenkov T, *et al.*: **Persistent gut microbiota immaturity in malnourished Bangladeshi children.** *Nature*. 2014; **510**(7505): 417–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
24. Gordon JL, Dewey KG, Mills DA, *et al.*: **The human gut microbiota and undernutrition.** *Sci Transl Med*. 2012; **4**(137): 137ps12.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. **F** Dominguez-Bello MG, Costello EK, Contreras M, *et al.*: **Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns.** *Proc Natl Acad Sci U S A*. 2010; **107**(26): 11971–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
26. **F** Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, *et al.*: **Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer.** *Nat Med*. 2016; **22**(3): 250–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
27. Dicksved J, Halfvarson J, Rosenquist M, *et al.*: **Molecular analysis of the gut microbiota of identical twins with Crohn's disease.** *ISME J*. 2008; **2**(7): 716–27.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. **F** Jakobsson HE, Abrahamsson TR, Jenmalm MC, *et al.*: **Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section.** *Gut*. 2014; **63**(4): 559–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
29. Romano-Keeler J, Weitkamp JH: **Maternal influences on fetal microbial colonization and immune development.** *Pediatr Res*. 2015; **77**(1–2): 189–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Harris NL, Spoerri I, Schopfer JF, *et al.*: **Mechanisms of neonatal mucosal antibody protection.** *J Immunol*. 2006; **177**(9): 6256–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Macpherson AJ, McCoy KD, Johansen FE, *et al.*: **The immune geography of IgA induction and function.** *Mucosal Immunol*. 2008; **1**(1): 11–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Niewiesk S: **Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies.** *Front Immunol*. 2014; **5**: 446.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
33. Zivkovic AM, German JB, Lebrilla CB, *et al.*: **Human milk glycobiome and its impact on the infant gastrointestinal microbiota.** *Proc Natl Acad Sci U S A*. 2011; **108**(Suppl 1): 4653–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Martín-Sosa S, Martín MJ, García-Pardo LA, *et al.*: **Sialyloligosaccharides in human and bovine milk and in infant formulas: variations with the progression of lactation.** *J Dairy Sci*. 2003; **86**(1): 52–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Jones EM, Smart A, Bloomberg G, *et al.*: **Lactoferricin, a new antimicrobial peptide.** *J Appl Bacteriol*. 1994; **77**(2): 208–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. **F** Yatsunenkov T, Rey FE, Manary MJ, *et al.*: **Human gut microbiome viewed across age and geography.** *Nature*. 2012; **486**(7402): 222–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
37. **F** Bokulich NA, Chung J, Battaglia T, *et al.*: **Antibiotics, birth mode, and diet shape microbiome maturation during early life.** *Sci Transl Med*. 2016; **8**(343): 343ra82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
38. Christmann BS, Abrahamsson TR, Bernstein CN, *et al.*: **Human seroreactivity to gut microbiota antigens.** *J Allergy Clin Immunol*. 2015; **136**(5): 1378–86.e1–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
39. **F** Azad MB, Bridgman SL, Becker AB, *et al.*: **Infant antibiotic exposure and the development of childhood overweight and central adiposity.** *Int J Obes (Lond)*. 2014; **38**(10): 1290–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
40. **F** Cho I, Yamanishi S, Cox L, *et al.*: **Antibiotics in early life alter the murine**

- colonic microbiome and adiposity. *Nature*. 2012; **488**(7413): 621–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
41. Metsälä J, Lundqvist A, Virta LJ, *et al.*: **Mother's and offspring's use of antibiotics and infant allergy to cow's milk.** *Epidemiology*. 2013; **24**(2): 303–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
42. Hviid A, Svanström H, Frisch M: **Antibiotic use and inflammatory bowel diseases in childhood.** *Gut*. 2011; **60**(1): 49–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Arrieta MC, Stiemsma LT, Dimitriu PA, *et al.*: **Early infancy microbial and metabolic alterations affect risk of childhood asthma.** *Sci Transl Med*. 2015; **7**(307): 307ra152.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
44. Clarke TB, Davis KM, Lysenko ES, *et al.*: **Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity.** *Nat Med*. 2010; **16**(2): 228–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
45. Abt MC, Osborne LC, Monticelli LA, *et al.*: **Commensal bacteria calibrate the activation threshold of innate antiviral immunity.** *Immunity*. 2012; **37**(1): 158–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
46. Wickens KL, Barthow CA, Murphy R, *et al.*: **Early pregnancy probiotic supplementation with *Lactobacillus rhamnosus* HN001 may reduce the prevalence of gestational diabetes mellitus: a randomised controlled trial.** *Br J Nutr*. 2017; **117**(6): 804–13.
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