

How do orally administered probiotics have an effect on conditions outside of the gut?

Science and nature in balance

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Agenda

- About myself
- Gut microbiome
- Microbiotas outside the gut
- Evidence of orally ingested probiotics improving conditions outside of the gut
- Mechanisms of action allowing orally ingested probiotics to have systemic health benefits

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MailOnline HELLO! True Health EXPRESS prima

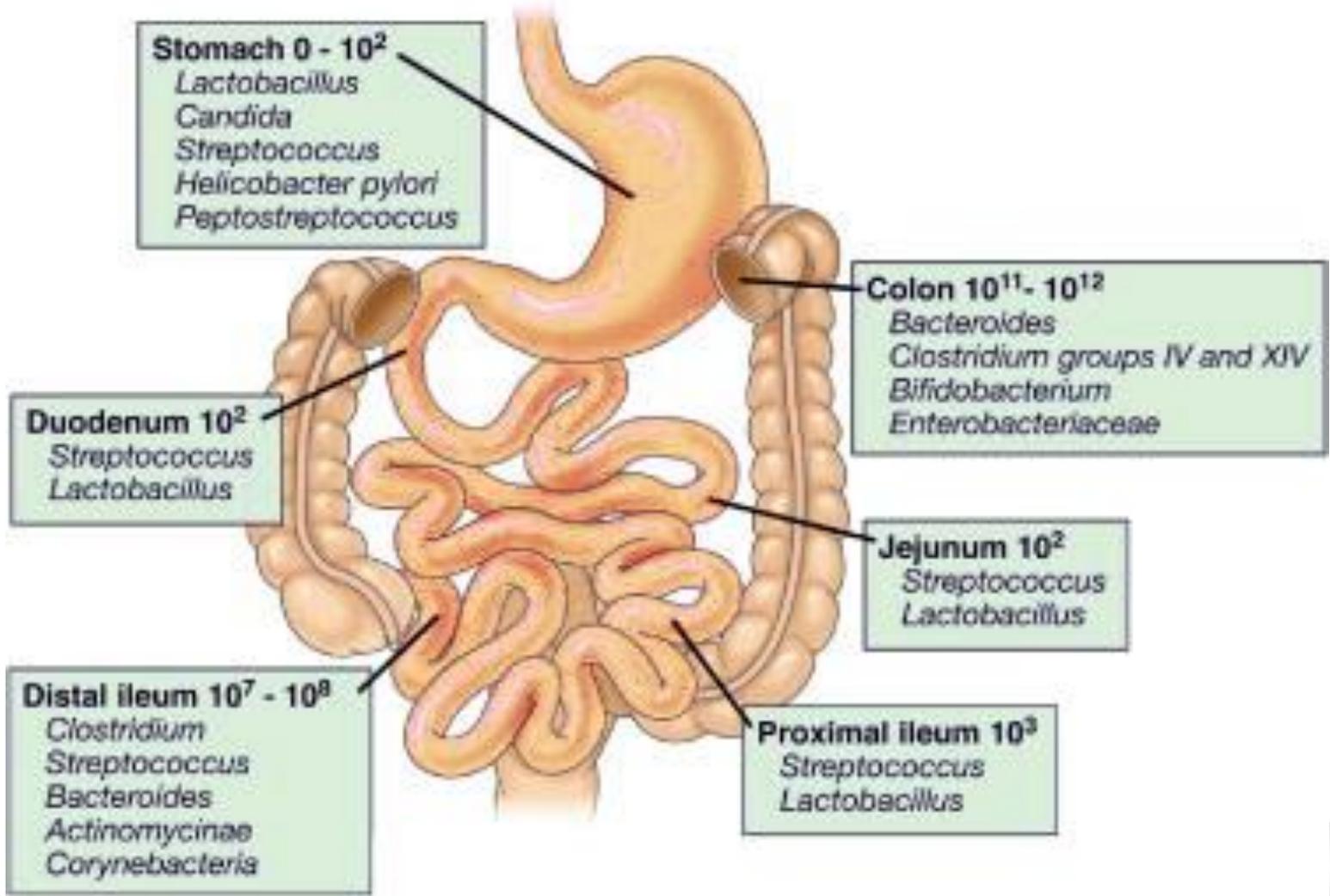
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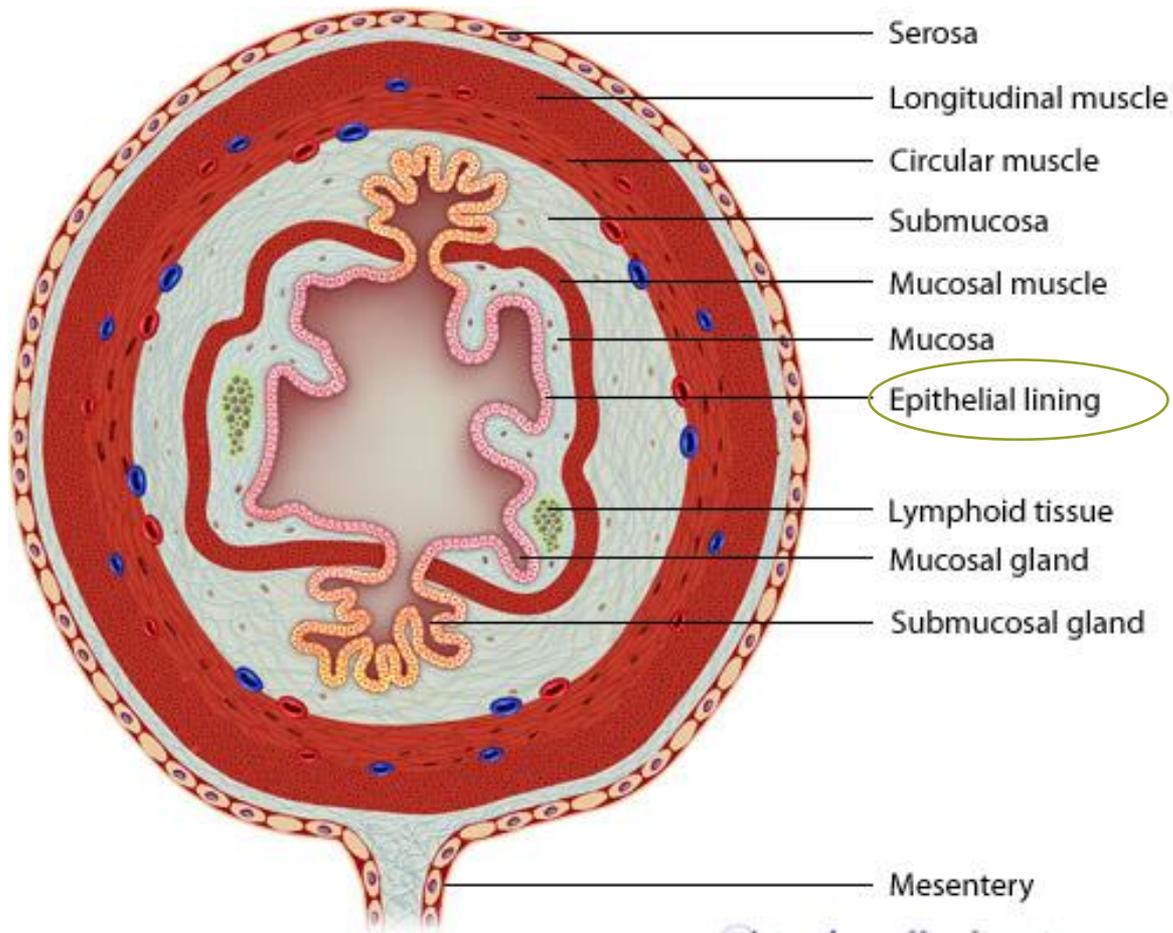


The Gut Microbiome



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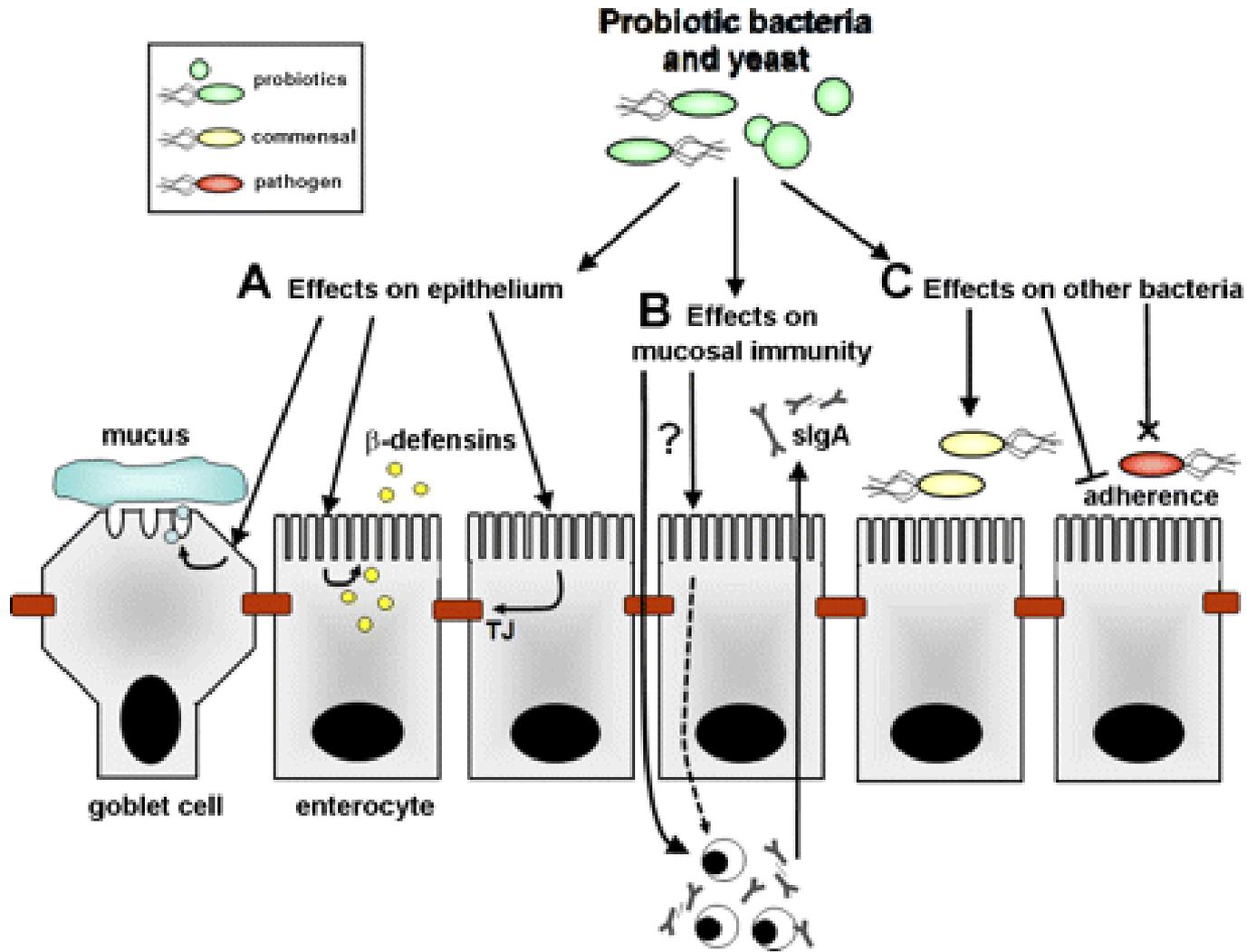




virtualmedicalcentre.com

<http://www.myvmc.com/anatomy/gastrointestinal-system/>

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https://www.researchgate.net/figure/42345184_fig1_Fig-1-Effects-of-probiotic-bacteria-and-yeast-on-intestinal-epithelial-barrier

Microbiotas outside
of the gut

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The Body's Microbiome Outside the Gut

Oral Microbiota

Lung Microbiota

Maternal Microbiota

Urogenital Microbiota

Skin Microbiota



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<http://www.the-scientist.com/?articles.view/articleNo/40600/title/The-Body-s-Ecosystem/>

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The Body's Microbiome Outside the Gut

- Oral microbiome: contains over 700 species of bacteria
- Lung microbiota: 1000 times less dense than the oral microbiota and about 1 million to 1 billion times sparser than the gut microbiota
- Genital and urinary microbiota: less species of bacteria, mainly lactobacilli species
- Skin microbiota: harbour many distinct groups of microbes depending on their physiological site (2)

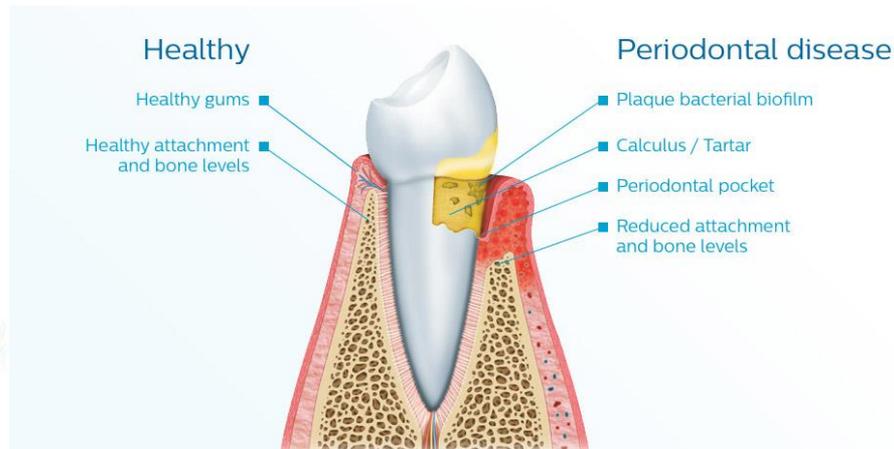
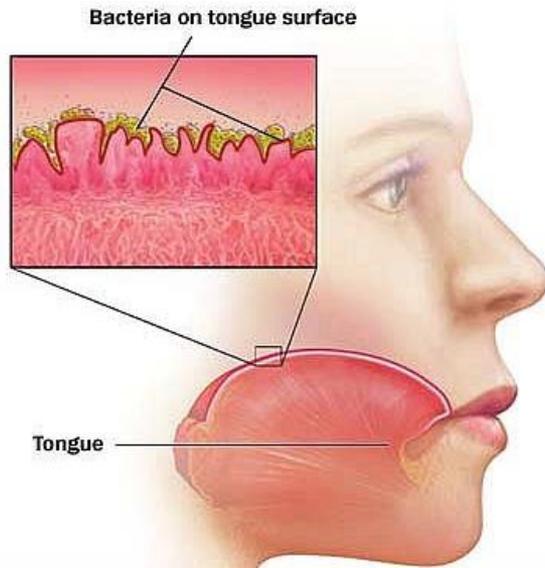


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Oral Microbiota

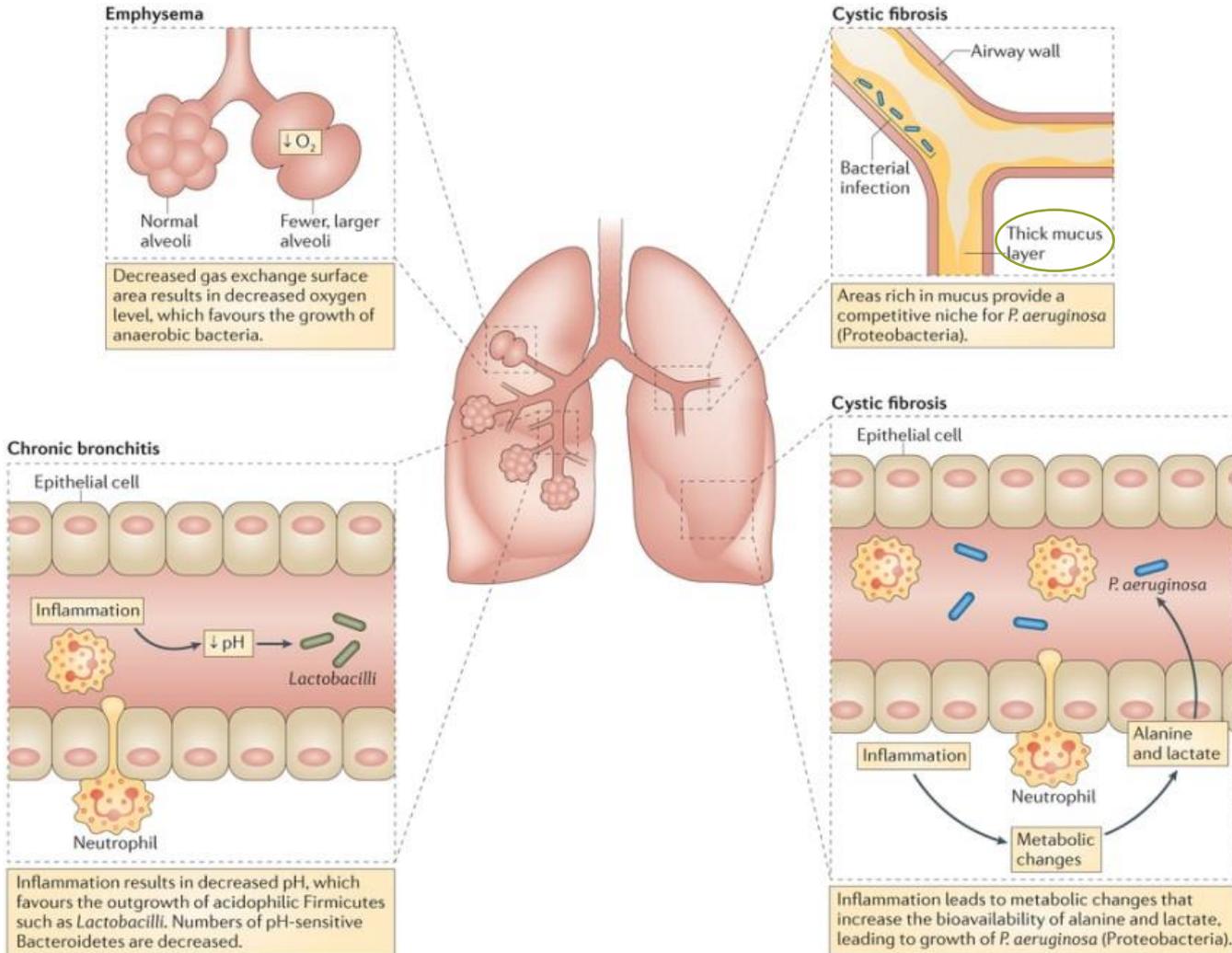
- Distinct communities on tongue, roof of mouth, biofilms on teeth and gums (3)
- The composition of this microbiota contributes to disease both within the oral cavity and systemically (1,2)
- Active immune system



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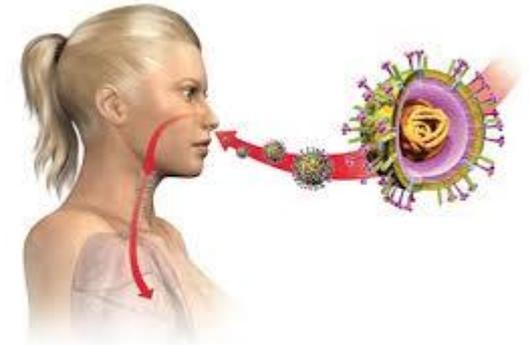
Lung Microbiota



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Lung Microbiota

- Children living on farms have lower prevalence of asthma and atopy and were exposed to a greater variety of environmental microorganisms (Ege *et al*, 2011)
- Healthy lung microbiotas were all characterised by more diverse profiles (de Steenhuijsen Piters, 2016)
- The lung microbiome of an individual with fatal influenza was dominated by gram-negative bacteria (Hu *et al*, 2016)



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Maternal Microbiota

Recent research suggests that a baby is sterile while in the womb?

- a) True
- b) False

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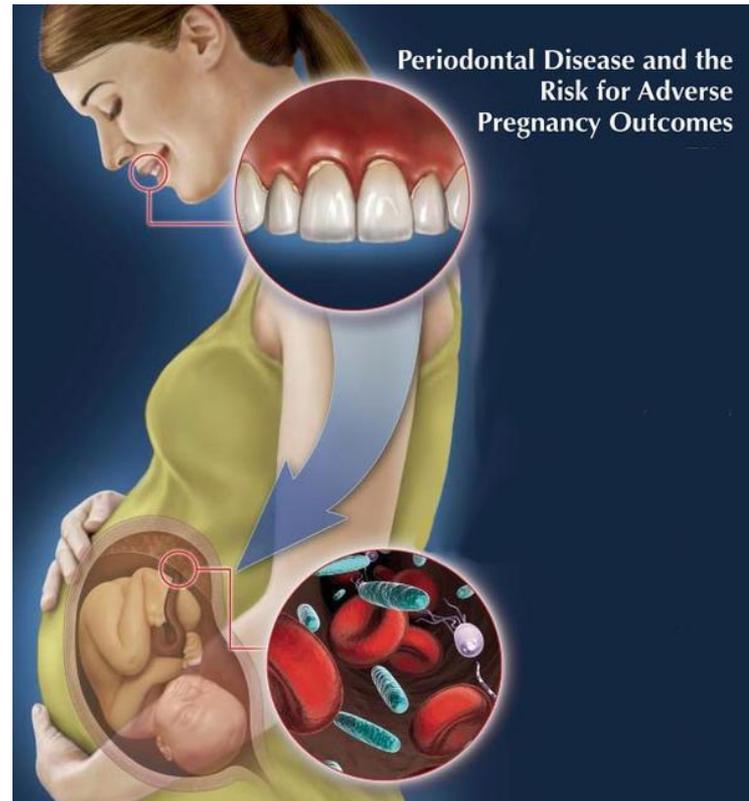
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Maternal Microbiota

Identified specific strains of bacteria given to pregnant mice in the meconium of pups delivered by C-section (Jimenez, 2008)

Microbes in placental tissue immediately after birth resembled mothers oral microbiota (Aagaard, 2012)

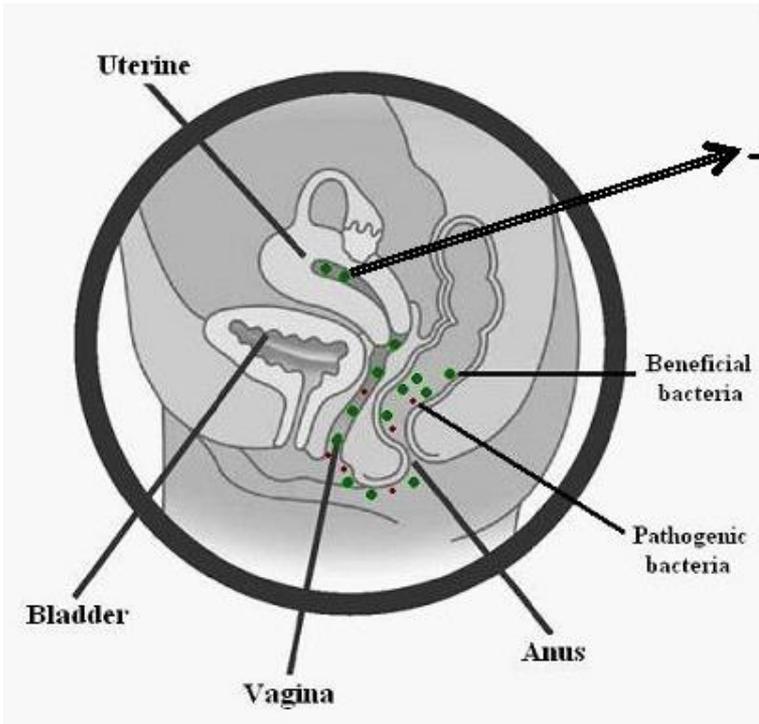
Fusobacterium nucleatum, a common oral species, is the most frequently isolated species from amniotic fluid of women with preterm labour whose babies were born in their sac (Hill, 1998)



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Vagina Microbiota



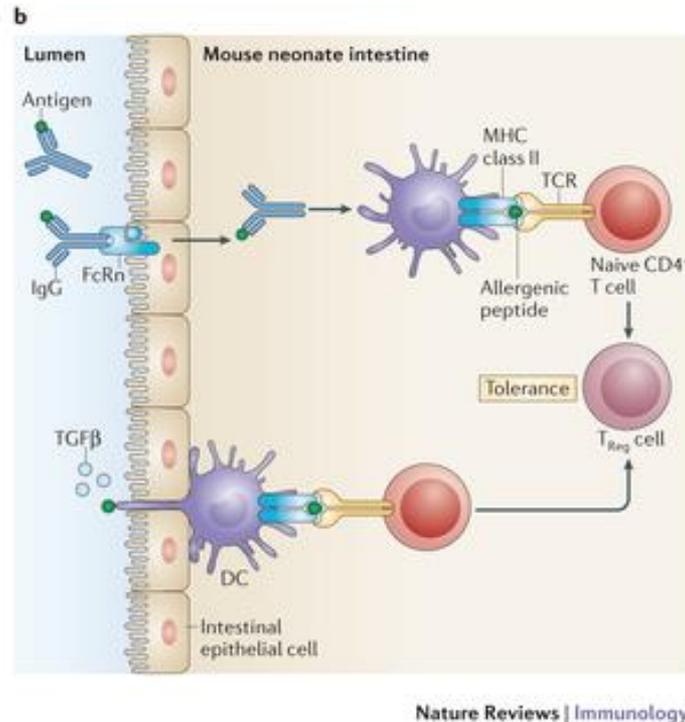
- Dominated by lactic acid bacteria (usually Lactobacilli)
 - Lower pH
- Many cases of bacterial vaginitis and UTI arise as a result of bacteria from the gut being excreted through the rectum and moving into the vagina or bladder (Reid et al, 2004)
- The vaginal microbiota changes significantly:
 - During pregnancy
 - After menopause

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Breast Milk

- Diverse communities of microbes in breast-milk which were **individual** to each woman (Hunt *et al*, 2011)
- Mastitis showed an overgrowth of a single strain pathogenic bacteria (Jimenez, 2015)
- Breast milk influences a switch in the infant from Th2 predominant to **Th1/Th2 balanced** immune response (Walker and Iyengar, 2015)



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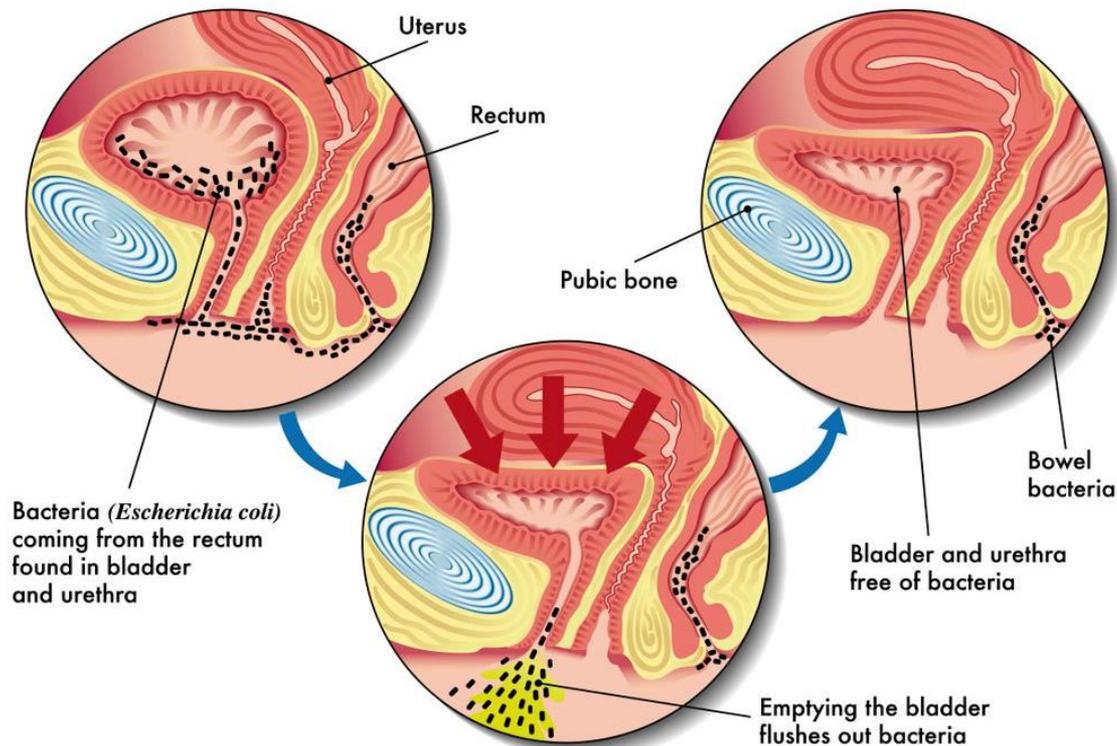
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Urinary Microbiota

The composition of bacteria found in the bladder could be a potentially important determinant in urologic disease (5,6)

Microorganisms at sites away from the urinary system are likely to have a profound effect on urinary health (1)

Significant differences between the microbiota in the lower urinary tract of individuals with urological symptoms (4)

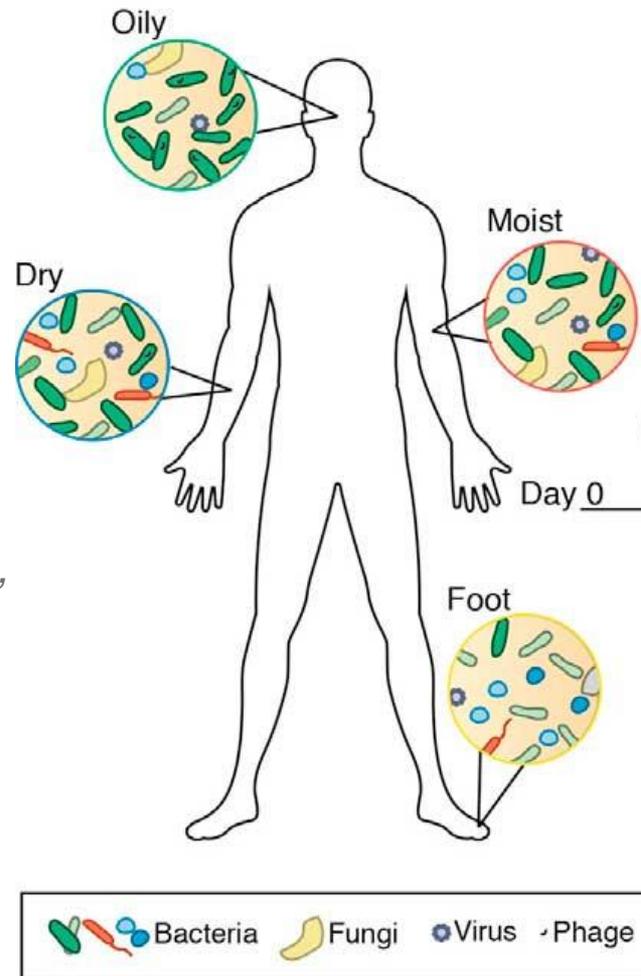


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Skin Microbiota

- *S. epidermis* to the skin of germ-free mice altered T-cell function (Naik *et al*, 2012)
- Immuno-deficient patients harbour more bacterial and fungal communities (Oh *et al*, 2013)
- Many common skin disorders have an underlying microbial dysbiosis:
 - Seborrheic dermatitis
 - Atopic dermatitis
 - Acne



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Evidence for probiotic
use outside of the gut

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Probiotics and Oral Health

- *Lactobacillus* species could reduce pathogenic bacteria (8)
- Ability to adhere to the tongue rather than to teeth (6)

- **Reduced dental caries** (Nase *et al*, 2001)
- **Lowered pathogenic bacteria** (Nase *et al*, 2001) (Nishihara *et al*, 2014)
- Inhibitory effects on VSC species and could have **potential benefits in halitosis** (Terai *et al*, 2015)
- **Reduced Candida** (Ishikawa, 2015)



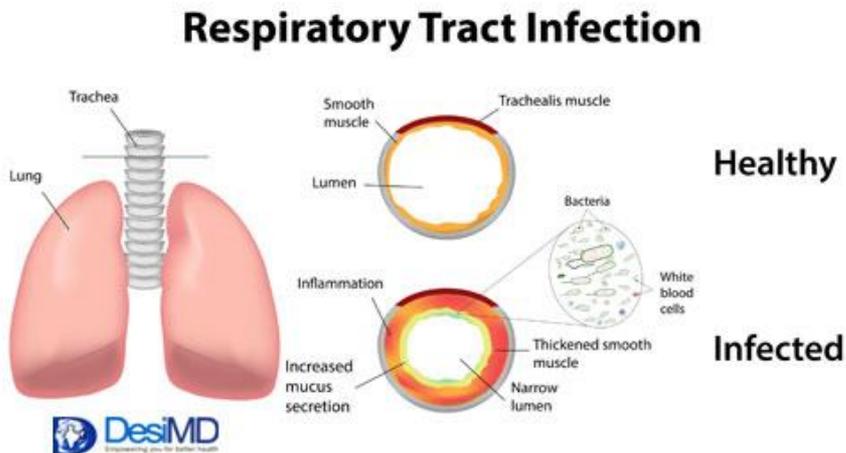
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Probiotics and Respiratory Health

- Reduce the number of episodes, duration and symptoms of URTI (3, 4, 5)
- Pneumonia is associated with dysbiosis of the URT microbiome (de Steenhuijsen Piters *et al*, 2016)
- Protexin strains have shown to be effective in infants with pneumonia improving rapid breathing and shortening hospital stays
- Protexin strains administered to children with cystic fibrosis significantly decreased intestinal inflammation (Fallahi *et al*, 2013)

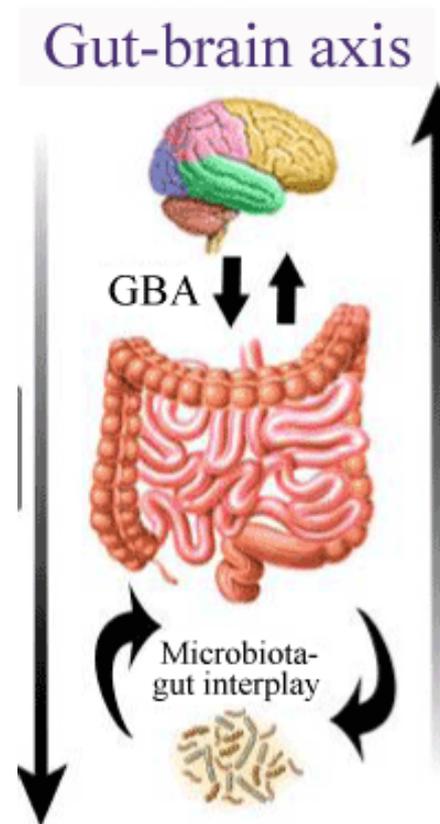
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Probiotics and Brain Conditions

- Multi-strain probiotics improved GI symptoms and improved ATEC scores and domains in autistic children (West *et al*, 2013)
- Infants receiving *L. rhamnosus* during their first 6 months may reduce the risk of neuropsychiatric disorder development later in childhood (Parrry *et al*, 2015)
- Probiotics significantly decreased anxiety symptoms in chronic fatigue patients (Rao *et al*, 2009)
- Decrease in stress-induced corticosterone and reduced anxiety- and depression-related behaviours in mice given *L.rhamnosus* (Bravo *et al*, 2011)



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Approximately how much of our immune system is located in the gut?

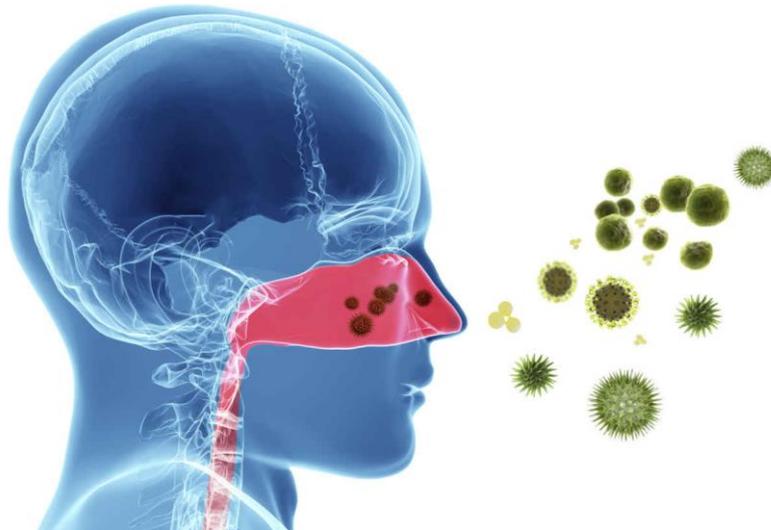
- a) 30%
- b) 50%
- c) 70%

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Probiotics and Immunity - Allergies

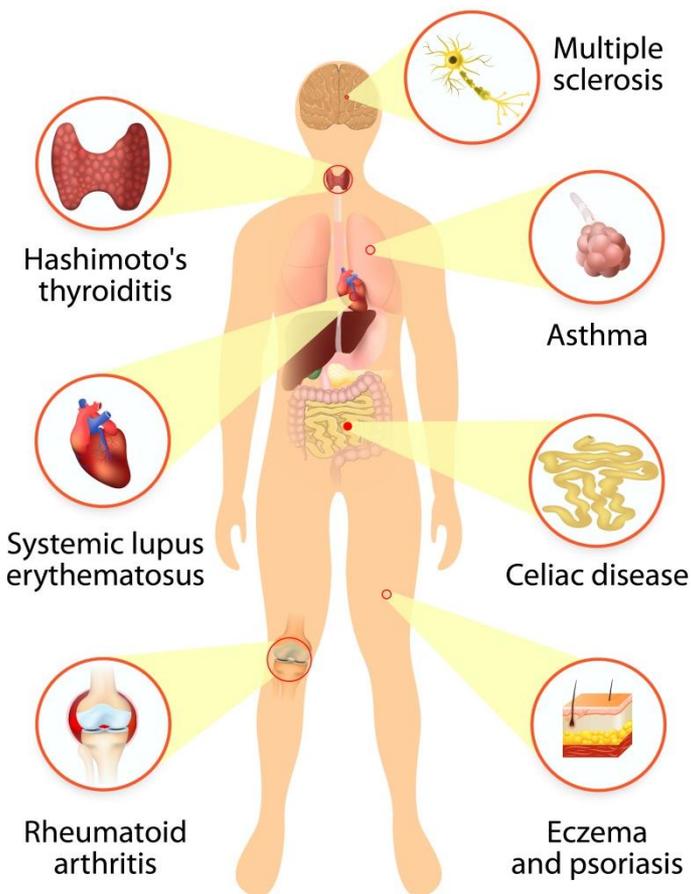
- Children who developed **allergies** at 5 years had significantly less diversity of bacteria as infants (Sjroger *et al*, 2009)
- Low total diversity of the gut microbiota during the first month of life was associated with **asthma** at 7 years old Abrahamsson *et al* (2014)
- Gut microbiota bacterial depletions and altered metabolic activity at 3 months are implicated in **childhood atopy and asthma** (Fujimura *et al*, 2016)
- Probiotics may be beneficial in improving symptoms and quality of life in patients with **allergic rhinitis** (Zajac *et al*, 2015)



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Probiotics and Immunity - Auto-immunity

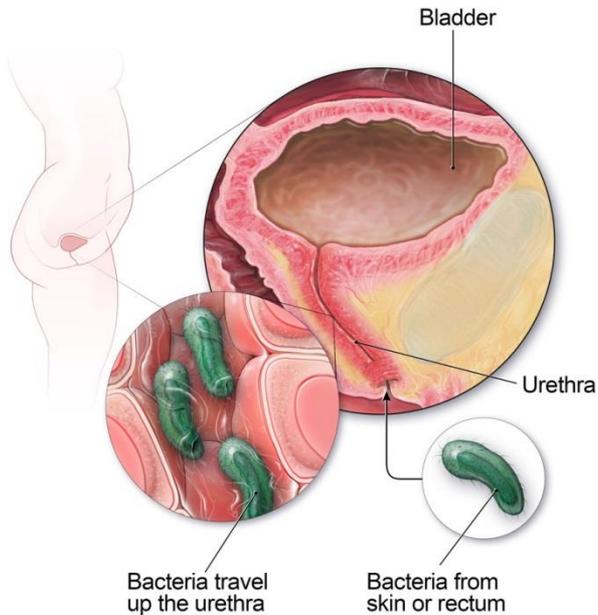


- Probiotics reduced inflammatory response, oxidative stress and reduced intestinal permeability therefore reducing autoimmunity response (Gomes *et al*, 2014)
- Multi-strain probiotic bacteria to mice which resulted in prevention from T1D (Calcinaro *et al*, 2005)
- Early probiotic supplementation (0-27 days) may reduce the risk of islet autoimmunity in children at the highest genetic risk of T1DM (Uusitalo *et al*, 2016)
- Probiotics suppresses immune responses in arthritic inflammation (So *et al*, 2008)

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Probiotics and Urogenital Health



- Subjects who developed UTIs had less diverse bladder microbiota (Horwitz *et al*, 2015)
- Probiotics intra-vaginally after treatment for cystitis with anti-microbials was associated with a reduction in recurrent UTI (Stapleton *et al*, 2011)
- Orally administered probiotics (Protexin strains) alongside conventional treatment for BV showed a higher rate of treatment success (Tafazzoli *et al*, 2014)

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Probiotics in Pregnancy and Breastfeeding

- Reduce the risk of **gestational diabetes** (lower blood glucose and insulin concentrations and improved glucose tolerance) (Laitenen *et al*, 2009)
- Prevention of **pre-term labour** by reducing risk of BV (Yang *et al*, 2005)
- Probiotics in pregnancy had been associated with reduced risk of **preeclampsia** (Brantsaeter *et al*, 2011)
- Probiotics in pregnancy may reduce late onset of **allergies** in the infant (Walker and Ivengar, 2015)
- *L. salivarius* during late pregnancy appears to be an efficient method to prevent **infectious mastitis** (Fernandez *et al*, 2016)



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What are the
mechanisms of
action?

Mechanisms of Action – Inside the gut

- Inhibition of pathogens
 - bacteriocin production
 - competitive exclusion
 - pH
- Extra nutrition and absorption
 - SCFA's
 - vitamins
 - enzymes
 - pH
- Immune stimulation
 - increase mucosal IgA
 - maintain epithelial barrier and tight junctions
 - reduced inflammation
 - regulate T-helper cells

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Inhibition of pathogens

Inhibition effect of Protexin strains on selected pathogens

	Pathogen strain													
	<i>S. typhimurium</i>			<i>S. aureus</i>			<i>E. coli</i>			<i>E. faecalis</i>			<i>C. difficile</i>	
	8h	24h	48h	8h	24h	48h	8h	24h	48h	8h	24h	48h	24h	48h
<i>L. acidophilus</i>	+++	+++	+++	+++	++	++	+++	++	++	+++	++	++	+++	+++
<i>L. rhamnosus</i>	+++	++	++	++	++	++	++	++	+	+++	+	++	++	++
<i>L. plantarum</i>	+++	+++	+++	+++	++	++	+++	++	++	+++	++	++	+++	++
<i>L. bulgaricus</i>	+++	++	++	++	++	+	+++	++	++	++	++	++	++	+
<i>L. casei</i>	+++	+++	+++	+++	++	++	+++	++	++	++	++	++	+++	++
<i>L. lactis</i>	+++	++	++	++	++	+	+++	++	++	++	+	+	++	+
<i>L. salivarius</i>	+++	+++	+++	+++	++	++	+++	+++	+++	+++	++	++	+++	+++
<i>L. fermentum</i>	+++	++	+	+++	+	-	+++	++	++	++	+	-	++	++
<i>L. helveticus</i>	+++	++	++	+++	++	++	+++	++	++	++	+	+	+++	++
<i>B. bifidum</i>	++	++	++	+++	++	++	++	++	++	++	++	++	-	-
<i>B. breve</i>	+++	++	++	++	+	+	++	++	++	++	+	+	+++	++
<i>B. infantis</i>	+	-	-	+	-	-	++	-	-	±	-	-	-	-
<i>B. longum</i>	++	++	++	++	++	++	++	++	++	++	++	++	-	-
<i>S. thermophilus</i>	++	±	±	++	±	±	++	±	±	++	-	-	-	-

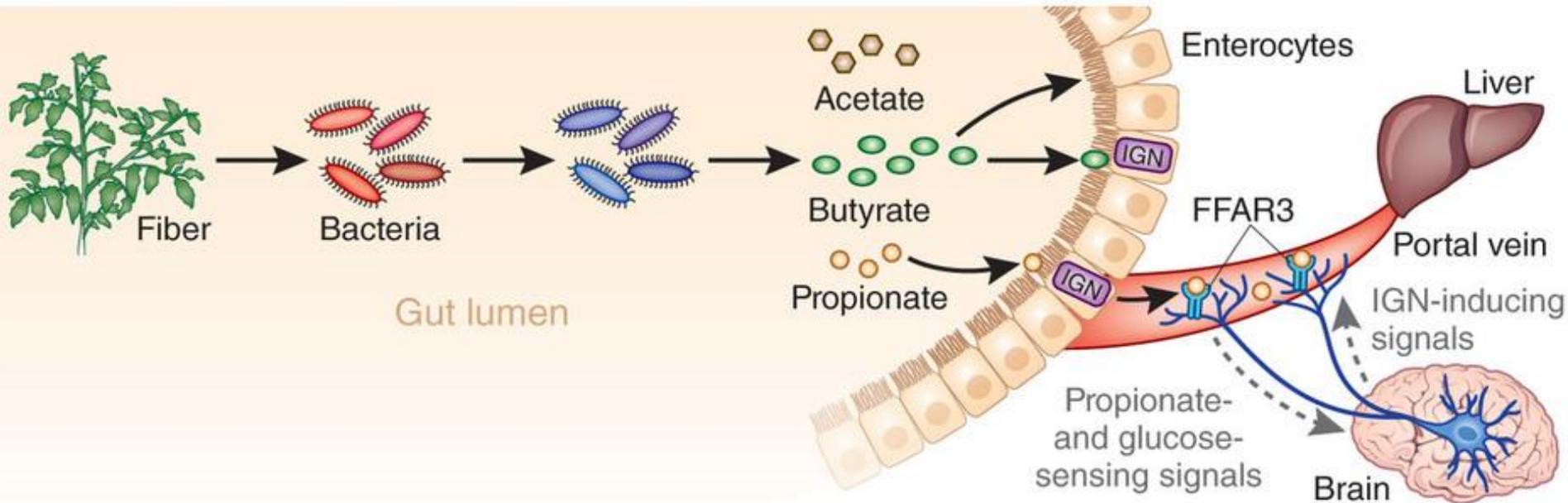
Key:

(±)	< 1 cm of inhibition but no clear halo	(++)	zone of inhibition between 1.1 - 1.7 cm
(-)	no inhibition	(+++)	zone of inhibition > 1.7 cm
(+)	zone of inhibition between 0.5 – 1 cm		

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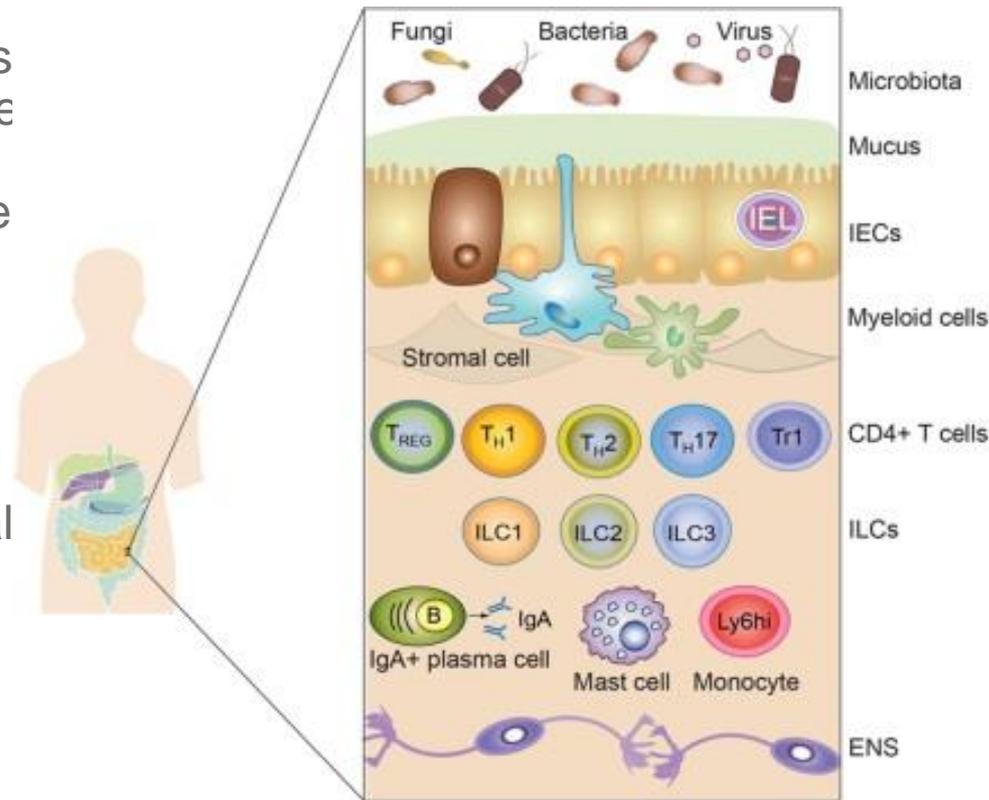
Extra Nutrition



- SCFA's and vitamins
- Enzymes
- Lower pH increases absorption of minerals

Immune stimulation

- Regulatory T cells are involved in the regulation of immune response
- Increase in sIgA
- Maintain epithelial barrier and tight junctions
- Reduce inflammation



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Can bacteria cross the epithelial layer of the gastrointestinal tract?

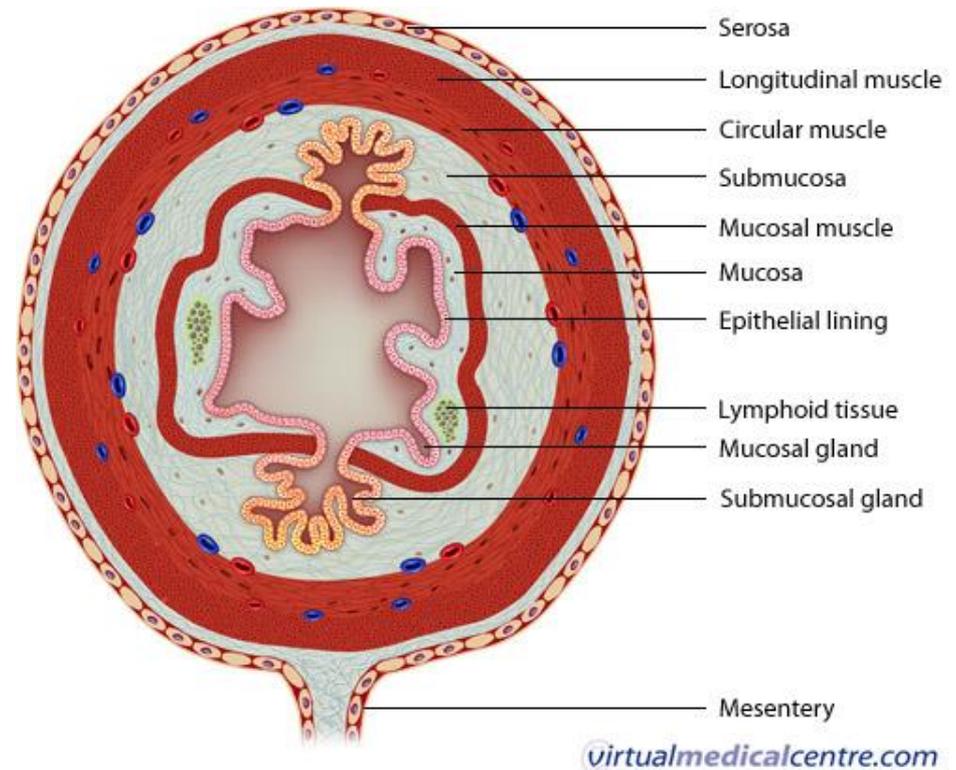
- a) Yes
- b) No

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Can bacteria cross the epithelial layer of the gastrointestinal tract?

- Bacteria can cross a damaged epithelial lining due to:
 - Bacterial overgrowth
 - Leaky gut
 - Reduced immune defences
- Bacteria can also travel intracellularly when there is no physical damage to the epithelial lining by travelling through the epithelial cells and then through the lymph to the mesenteric lymph node (1)
- Translocation of inflammatory compounds and toxic products across the epithelium could result in systemic symptoms.
- Bacterial translocation is described as the passage of **viable bacteria or their endotoxins or antigens from the intestinal lumen into the circulation** causing systemic inflammation and distant organ injury (Balzan et al, 2006)

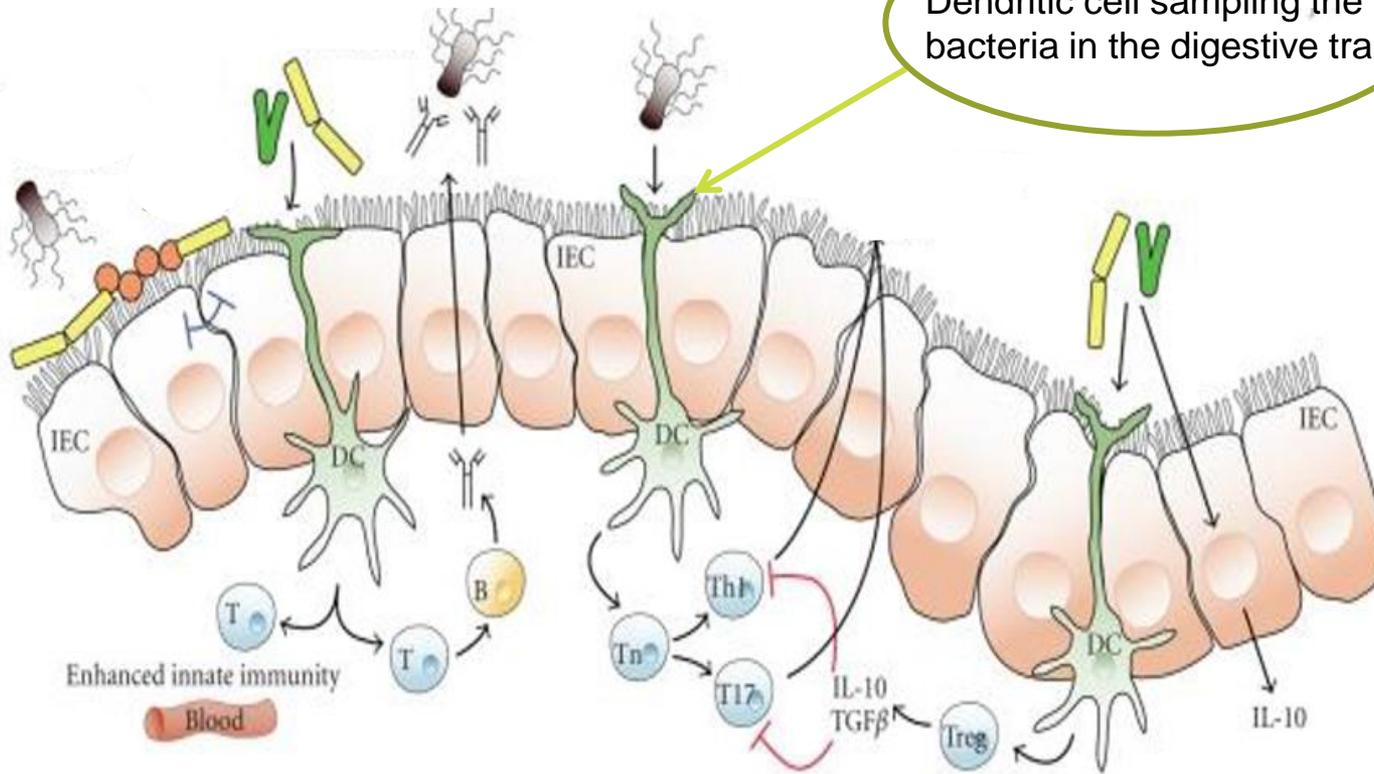


[virtualmedicalcentre.com](http://www.virtualmedicalcentre.com)

<http://www.myvmc.com/anatomy/gastrointestinal-system/>

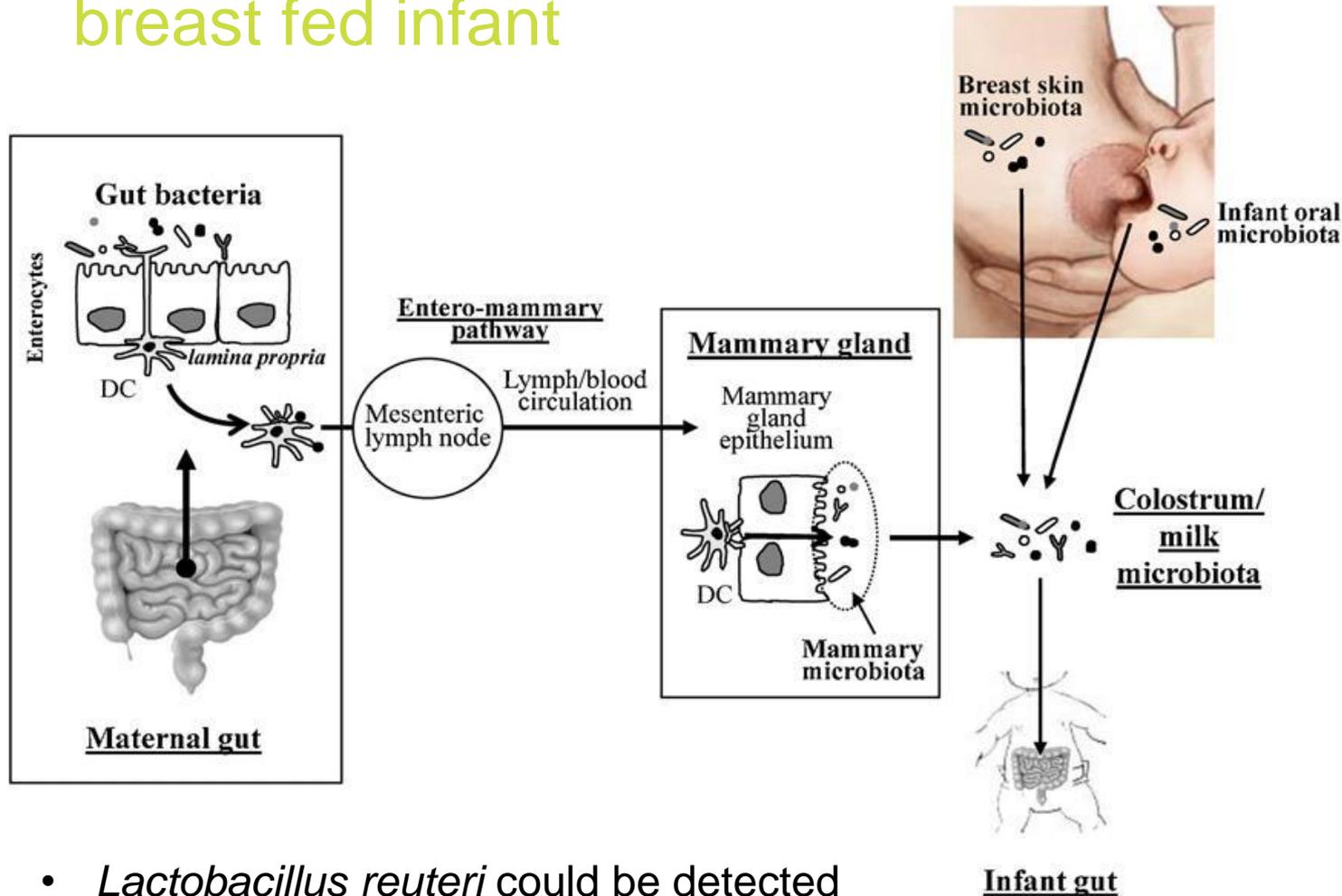
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Dendritic cell sampling the bacteria in the digestive tract



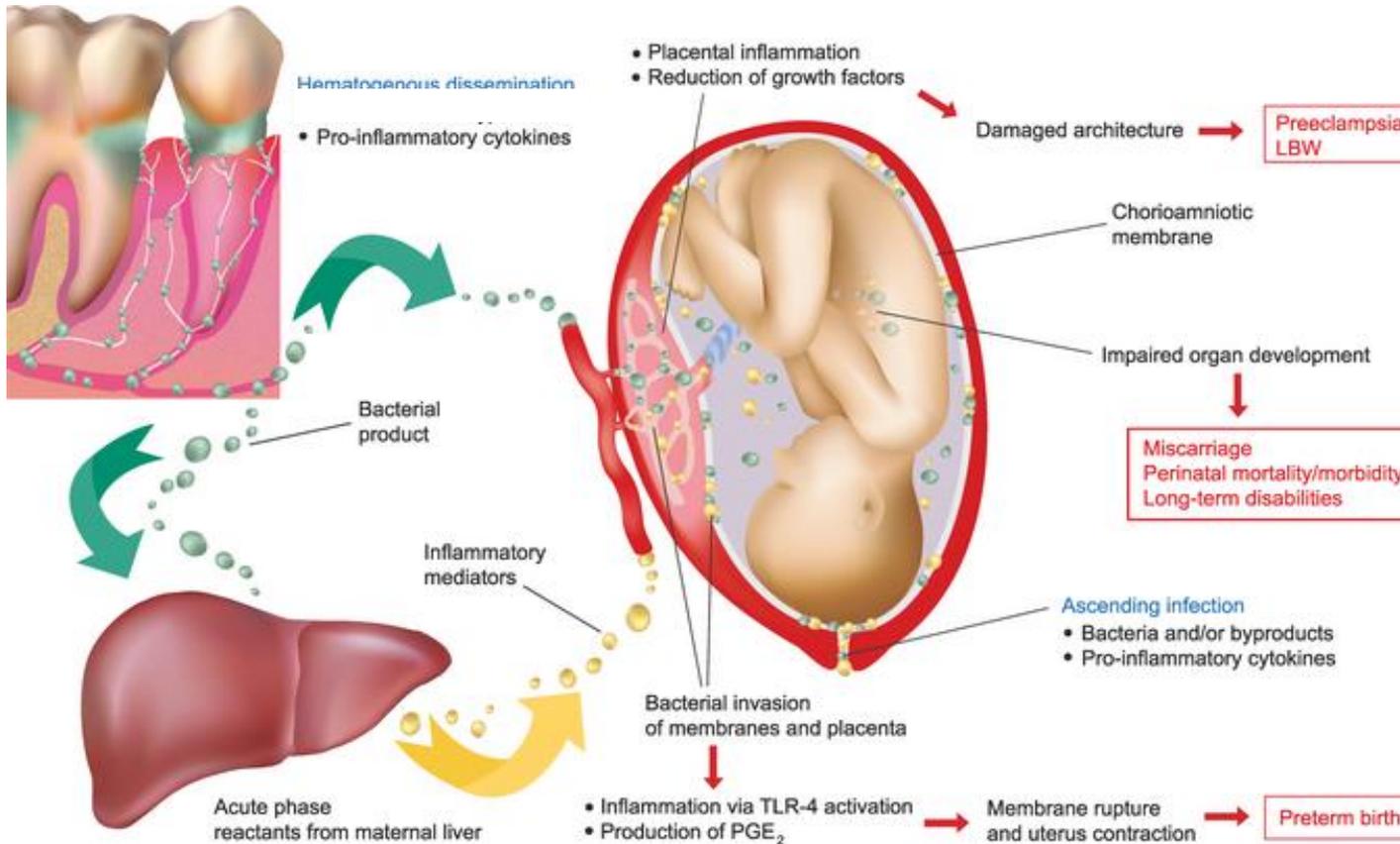
- Dendritic cells can sample the lumen of the digestive tract using their dendrites and communicate to other cells of the immune system. B cells can then produce antigens against pathogenic bacteria.
- DCs open the tight junctions between epithelial cells, send dendrites outside the epithelium and directly sample bacteria. DCs express tight-junction proteins, which preserves the integrity of the epithelial barrier (1)

Translocation of bacteria from mothers gut to breast fed infant



- *Lactobacillus reuteri* could be detected in breast milk after oral supplementation to the mother and in almost all infants (Abrahamsson *et al*, 2009)

Bacterial translocation of bacteria from oral cavity to placenta

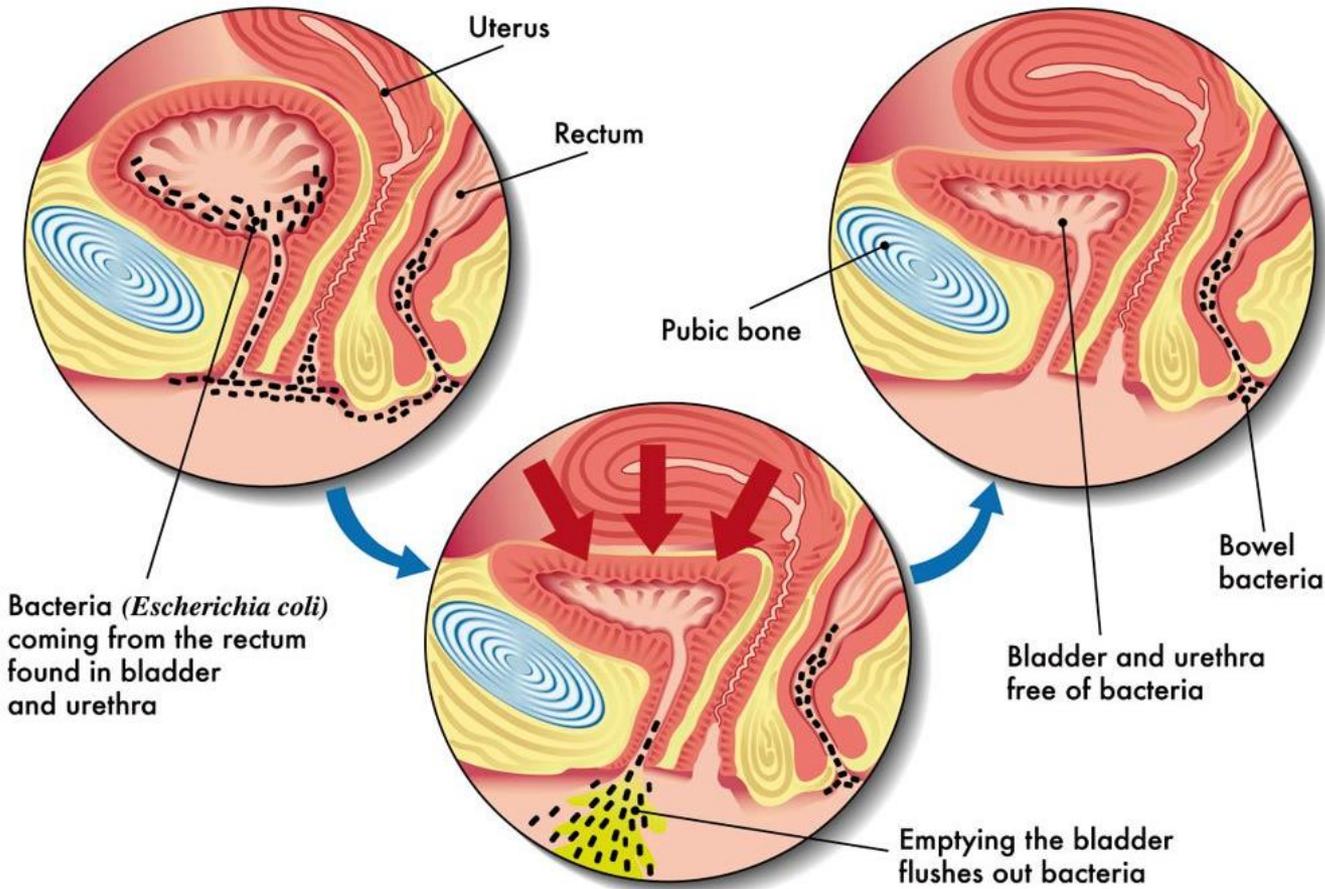


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Possible biological mechanisms/pathways associating periodontal disease and pregnancy complications.
<http://onlinelibrary.wiley.com/doi/10.1111/jcpe.12082/full> (1)

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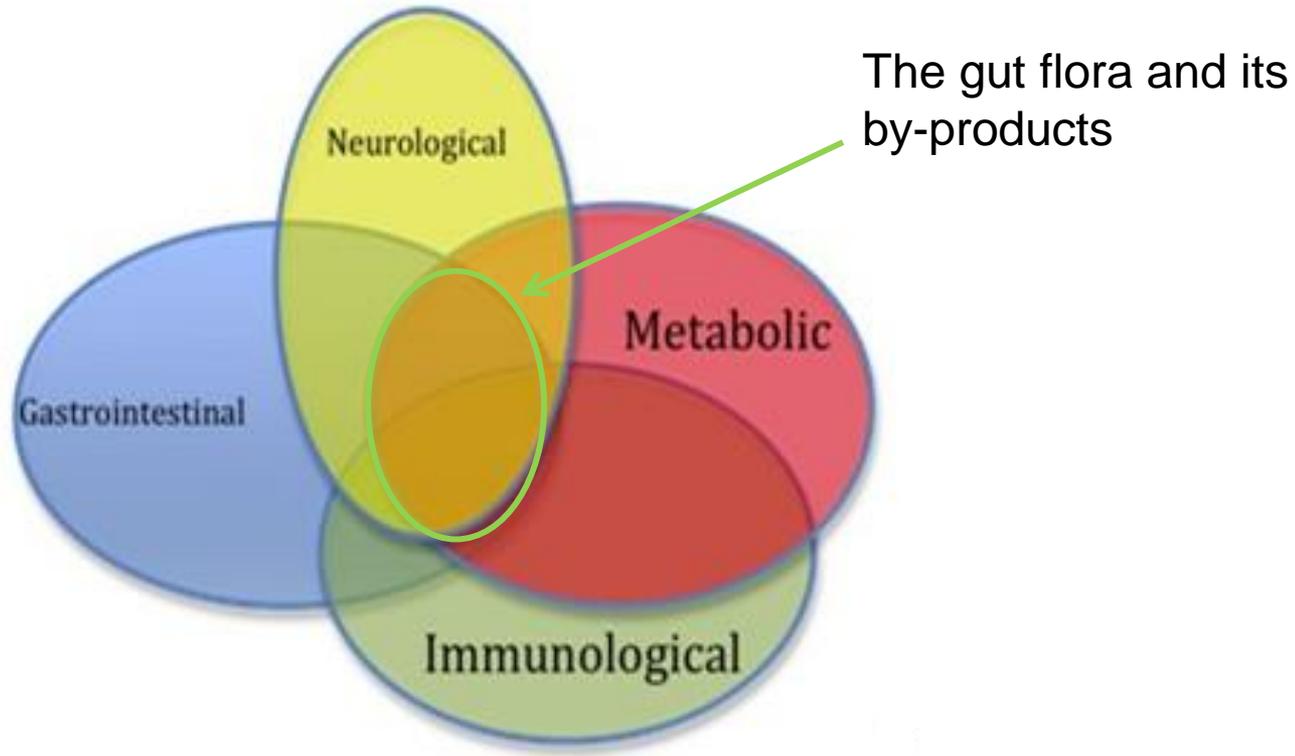
Bacterial translocation from the gut to the urogenital tracts



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Gut Microbiome and By-Products



Endotoxins in the GI tract: the triggering factor for inflammation and obesity (Cani et al, 2007)

Summary of the Evidence

- Improving the balance of the gut microbiome can have effects beyond the gut
 - Reducing endotoxins and inflammation
 - Increasing nutrient absorption and SCFAs
- Research suggests that a multi-strain probiotic may be more beneficial in improving the gut flora and therefore potentially more effective in conditions outside of the gut

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Any questions?



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Any further queries?

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References available on request

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