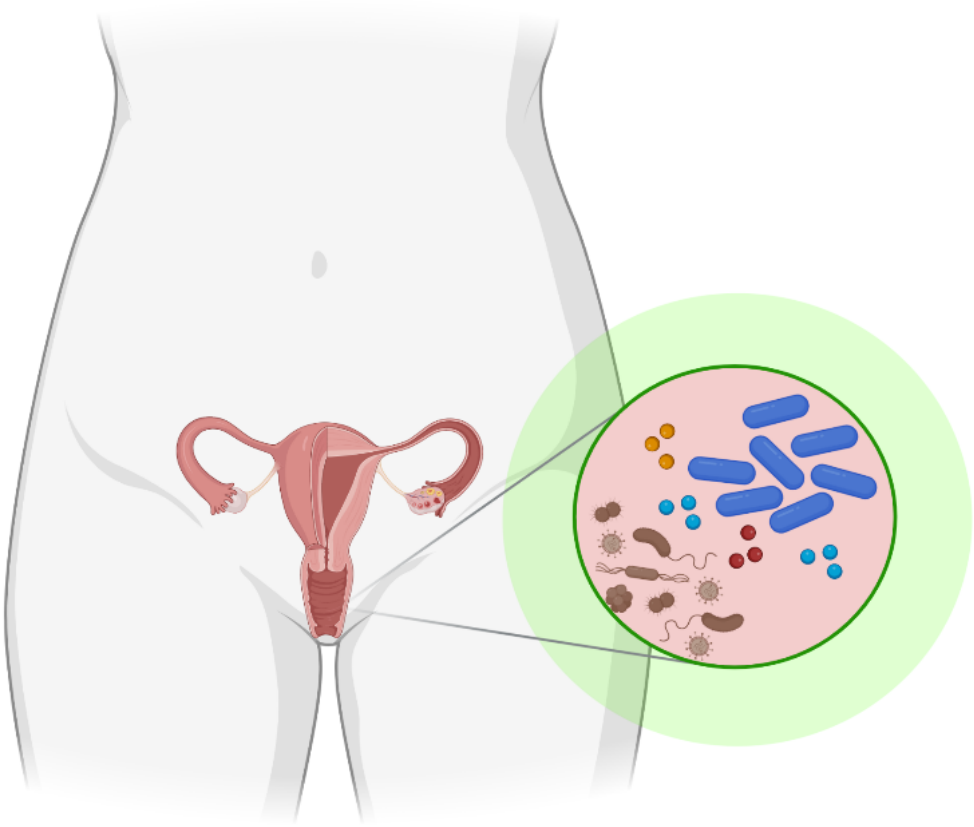
The reproductive tract microbiome and health

Mummy: my vagina has bacteria growing in it?



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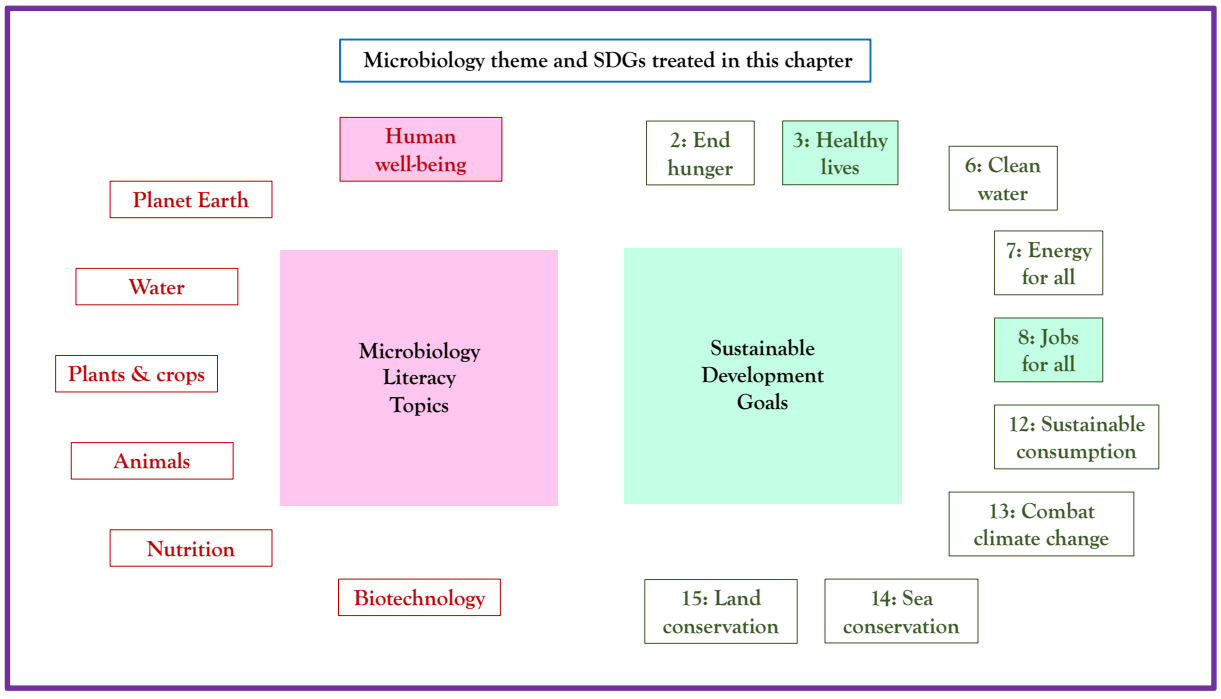
The reproductive tract microbiome and health

Storyline

The female reproductive tract is colonised by a complex and unique community of microorganisms that are collectively referred to as the microbiota. These microbes play an important role in shaping health and disease states at different stages of a women's life. At birth, microbes seeded during or shortly after delivery begin to colonise the infant gut and lower reproductive tract, including the vagina and cervix. Gradual dominance of the lower reproductive tract microbiome by *Lactobacillus* species associates with good health and is influenced by hormonal changes (e.g. during puberty and after the onset of menopause). During the reproductive years, the composition of the vaginal microbiome can fluctuate during the menstrual cycle or in response to other external factors, such as antibiotics or certain hygiene practices. A loss of *Lactobacillus* species and increased microbial diversity can increase susceptibility to pathogen infection, including sexually transmitted infections. During pregnancy, changes in the microbiome can lead to untimely activation of inflammation in the gestational tissues leading to premature labour and birth. The reproductive tract microbiome therefore has multiple consequences for Sustainable Development Goals.

The microbiology and societal context

The microbiology: reproductive tract microbiota origin and development; temporal evolution of the vaginal microbiome; exogenous factors that impact microbiota composition (e.g. antibiotics, hygiene practices, live biotherapeutics); women's health; the pregnancy vaginal microbiome, microbial seeding of the neonate and immune system development in infants. *Sustainability issues*: health; economy and employment.



The reproductive tract microbiome and health: the Microbiology

1. ***The reproductive tract microbiome is different and unique from other body sites.*** The female reproductive tract can be divided into lower and upper components. The lower reproductive tract includes the vagina and the cervix, the upper reproductive tract includes the uterus, fallopian tubes, and ovaries (cover image). Like other mucosal surfaces of the human body, the vagina and cervix harbour a complex microbial community that has a homeostatic and mutualistic relationship with the host. This means that both microbes and the host receive benefit through their interactions. The reproductive tract supports microbial growth by providing nutrients and a humid and warm habitat. In return, resident commensal microbes produce antimicrobial compounds and anti-inflammatory factors that contribute to the first line of defence against potential pathogen invasion.

Despite the term 'microbiota' referring to the collection of bacteria, viruses, fungi and archaea in a specific microbial community, study of the reproductive tract microbiota has overwhelmingly been limited to investigation of bacteria, which will therefore be the focus of this topic. It is estimated that between 10^{10}-10^{11} bacteria colonise the lower reproductive tract. This is significantly higher than the upper reproductive tract, which until recently was widely considered to be sterile.

In addition, the bacterial composition of the lower and upper reproductive tract can differ within the same women. This may reflect the ability of certain microbes to traverse the cervix more readily, which acts as a physical, biochemical and immunological barrier to any microbes trying to enter the uterus. Different selection pressures (e.g. energy sources, pH, immune factors) and frequent shedding of the endometrium help maintain low levels of microbes in the upper reproductive tract.

High-throughput molecular-based techniques, such as next-generation sequencing, which allows for the large scale comparison of genetic information of different microbes, have revolutionised our understanding of the types and relative abundances of bacteria that colonise the reproductive tract. Bacterial profiles can be statistically clustered based on their similarity into so-called community state types (CSTs). Over the last decade, five major vaginal CSTs have been observed consistently in studies throughout the world. Four of these have low bacterial diversity and richness and are dominated by just one main *Lactobacillus* species: *L. crispatus* (CST I), *L. gasseri* (CST II), *L. iners* (CST III), or *L. jensenii* (CST V). Women with CST IV communities are depleted of *Lactobacillus* species and instead have higher bacterial diversity, often enriched for strict anaerobic bacteria including *Prevotella, Gardnerella, Megasphera, Sneathia* and *Atopobium* species.

In contrast to the gut, where high bacterial diversity often associates with states of good health, an optimal vaginal microbiome is generally low in diversity and dominated by only one or a few *Lactobacillus* species. As will be discussed later in this topic, high diversity vaginal microbiomes are often associated with disease and pathology. However, the relationship between health and the vaginal microbiome is influenced also by host ethnicity. About 10% of asymptomatic, healthy White women of reproductive age carry high diversity CST IV bacterial profiles, compared to around 40% of asymptomatic, healthy Black or Hispanic women.

2. ***The origin of the reproductive tract microbiota and how it changes over a woman's lifespan.*** During gestation, the fetus develops in the uterine cavity in a largely microbe-free environment. The first major exposure of the neonate to microbes occurs in the birth canal, during delivery. If born vaginally, different body sites of the neonate, including the lower reproductive tract, are therefore initially colonised by microbes from the maternal reproductive

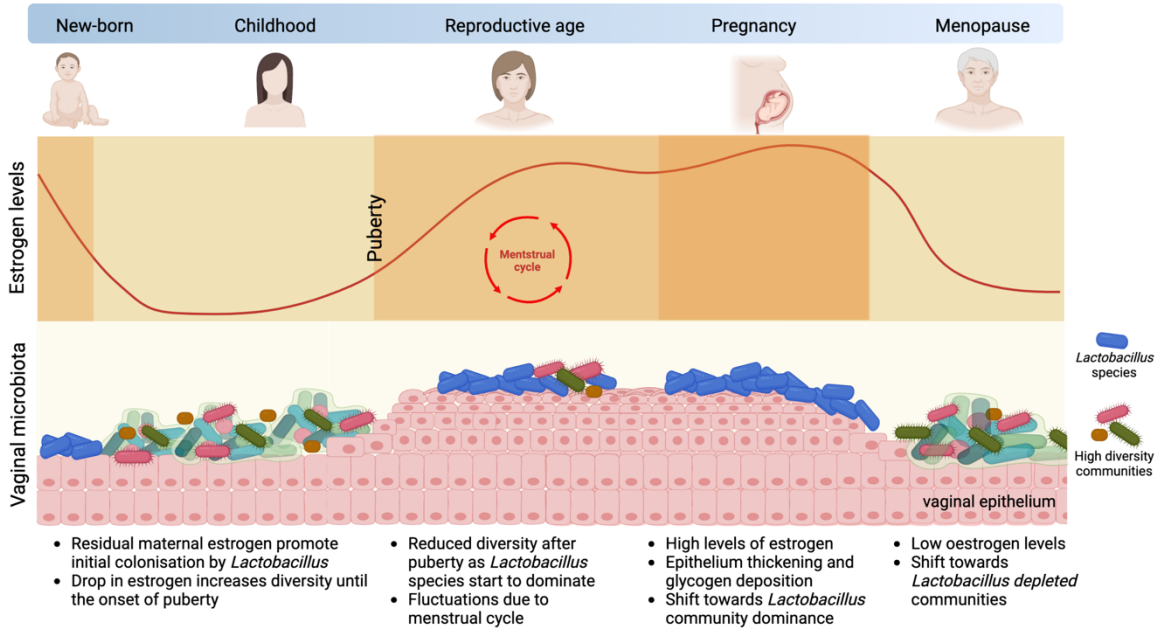
tract. These microbes are homogeneously distributed across the new-born and include *Lactobacillus, Bifidobacteria, Prevotella, Atopobium* and *Sneathia* species.

A baby born via Casearean section, will be colonised initially by skin bacteria, including *Streptococcus* species, seeded shortly after birth during skin-to-skin contact and breast feeding.

After delivery, residual maternally derived estrogen circulating in the female new-born promotes storage of glycogen, the storage form of glucose, in the vaginal epithelium, which is a major carbon source for lactic acid-producing bacteria, including *Lactobacillus* species. As maternal estrogen depletes, the prevalence of lactic acid-producing bacteria decreases leading to an increase in pH and shift towards *Lactobacillus* depleted, high-diversity communities. During puberty, increasing levels of estrogen help to re-establish a mucosal environment favourable to *Lactobacillus* colonisation.

Cyclical hormonal patterns and menstruation during reproductive age leads to natural fluctuation in the relative levels of *Lactobacillus* in the lower reproductive tract. Following menopause, reduced estrogen is associated with decreased glycogen deposition in the vaginal epithelium, vaginal dryness, atrophy and *Lactobacillus* depletion.

The most dramatic change in circulating hormonal levels that can be experienced by women occurs during pregnancy. The placenta produces high concentrations of estrogen which is accompanied by an increased relative abundance of *Lactobacillus* species and reduced bacterial diversity. This supports the development of an optimal reproductive tract microbiome during pregnancy that helps to prevent colonisation of the infant and placenta by potentially pathogenic bacteria. However, after delivery, maternal estrogen levels rapidly decline causing a decrease in *Lactobacillus* species dominance and a shift towards high-diversity communities. In this way, pregnancy has a lasting impact on the vaginal microbiome. These high-diversity communities can persist in some women for more than 1 year after delivery before *Lactobacillus* species dominance is restored.



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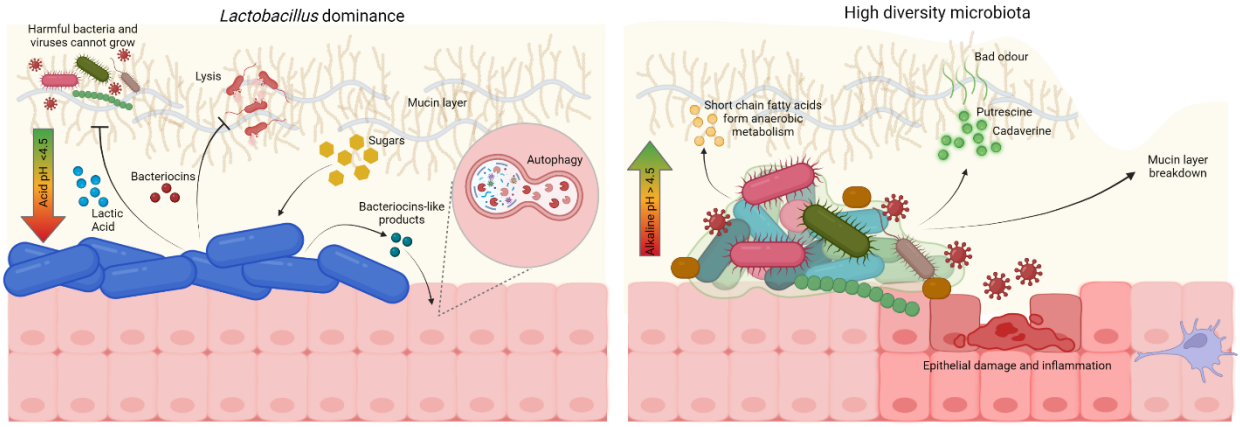
Overview of the relationship between vaginal microbiome composition and estrogen levels during a woman's lifespan.

3. ***Lactobacillus species help defend the reproductive tract from infection.*** *Lactobacillus* species utilise glycogen and other complex sugars in the epithelial mucosa as energy sources. The end-product of the metabolism of these sugars is lactic acid, which accumulates and acidifies the vaginal mucosa to a pH of between 3.8 – 4.5. While *Lactobacillus* species have evolved to survive in such acidic conditions, many potentially pathogenic vaginal microbes are unable to do so. Lactic acid also has an important anti-inflammatory role in the lower reproductive tract, and can help maintain the epithelial barrier, which can otherwise be degraded by inflammation. *Lactobacillus* species also prevent pathogen colonisation through the production of antimicrobial compounds called bacteriocins that inhibit growth of other bacteria, viruses, and fungi.

Defence against infection of the reproductive tract is particularly important during pregnancy where activation of inflammation in response to infection can lead to remodelling and breakdown of the cervix and fetal membranes. This can trigger the untimely onset of labour and eventual activation of pathways leading to preterm delivery and birth. However, the degree of protection conferred on the vaginal niche by *Lactobacillus* is species-dependant. For example, *L. iners* is often observed to co-colonise the vagina with potentially pathogenic bacteria. This is likely due to the fact that its genome (the complete set of genetic material) is substantially smaller than other vaginal *Lactobacillus* species such as *L. crispatus*, and its survival may be more reliant upon co-factors, enzymes and other energy sources produced by other community members in the niche, including potential pathogens. When *Lactobacillus* species are displaced from the reproductive tract, high diversity bacterial communities often include microbes that produce high levels of short-chain fatty acids that can cause inflammation and breakdown of the vaginal epithelium.



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Mechanisms of protection against infection provided by *Lactobacillus* species.

4. ***Endogenous and exogenous factors alter the composition of the lower reproductive tract microbiota.*** In some women, bleeding (e.g., during menstruation) causes instability in the vaginal microbiome. Some vaginal species such *Gardnerella vaginalis* require iron for growth, which can be acquired through lysing erythrocytes (red blood cells) in the menstrual blood.

Personal hygiene practices such as vaginal douching or the use of antimicrobial soaps can have a negative impact on the vaginal microbiota composition. Sexual intercourse also introduces a disturbance in the vaginal microbiota through exposure to exogenous bacteria. The use of oral contraceptives that affect hormone levels can also impact on microbial composition. Antibiotics used to treat reproductive tract infections cause major reshaping

of the vaginal microbiome. Additionally, unintended vaginal microbiome dybiosis can be caused through off-target effects of antibiotics used to treat other types of infections.

Visual overviews of vaginal microbiota composition and its alterations in the context of health and disease can been seen in Videos 1 and 2 as well as Infographic 1.

5. ***A suboptimal vaginal microbiome increases risk of infection.*** A loss of healthy *Lactobacillus* species from the lower reproductive tract and an overgrowth of anaerobic bacteria leading to symptoms such as itching, inflammation and discharge is called Bacterial Vaginosis (BV). This is a common condition that is associated with an increased risk of acquiring sexually transmitted infections (STIs) and adverse reproductive health outcomes. For example, BV is a major risk factor for HIV infection. Bacterial species that cause BV produce compounds and metabolites that can break down the protective mucosal layer of the vaginal epithelium, disrupting its integrity and increasing the chance of viral particles entering the bloodstream. Moreover, rapid metabolism of the drug tenofovir by BV-associated bacteria inhibits its ability to prevent HIV infection.

Genital tract infection by human papillomavirus (HPV), which contributes to the development of cervical cancer, is influenced by the lower reproductive tract microbiome. In women with high diversity CST IV microbial profiles, there is a higher risk for persistent HPV infection compared to women with *Lactobacillus* dominance of the lower reproductive tract. Similarly, BV is associated with decreased HPV clearance.

Find an example about secondary pathologies associated with suboptimal vaginal bacterial communities in Video 3.

6. ***The reproductive tract microbiome is a risk factor for adverse pregnancy outcomes.*** Preterm birth is the leading cause of neonatal and childhood mortality. Survivors of preterm birth can be faced with several long-term health consequences including neurodevelopmental, behavioural, respiratory, visual, and hearing disabilities. Around 40% of all preterm births are associated with infection. A major route of infection is thought to be via vaginal pathogen ascension.

Maternal immune response to infection can lead to the activation of proinflammatory and tissue remodelling pathways in the reproductive tract and gestational tissues that leads to premature onset of cervical ripening (softening and dilation), rupture of the fetal membranes (amniotic sac), and uterine contractions. Recent studies have shown that *Lactobacillus* dominance of the vaginal microbiome, particularly by *L. crispatus*, is protective against adverse pregnancy outcomes, including miscarriage and preterm birth.

7. ***The maternal reproductive tract microbiome also influences short and long-term health of the new-born.*** The maternal reproductive tract plays an important role in shaping the development of the early neonatal gut microbiome, which in turn is a critical determinant of immune development and metabolic programming. Perturbation of the early life gut microbiome is associated with delivery mode, antibiotic exposure and formula feeding. It has been long recognised that exposure to pathogenic bacteria present in the maternal reproductive tract during delivery can cause sepsis and other complications shortly after delivery. However, recent studies also indicate that vaginal bacteria transferred from mother to child during delivery can influence, both positively and negatively, immune development and therefore clinical outcomes in early childhood (e.g. development of allergic sensitisation, asthma).

Find more information on this topic in Podcast 1 and Video 4.

8. ***Interventions to modulate the reproductive tract microbiota.*** A commonly-used strategy to treat infections or imbalances of the reproductive tract microbiome is the use of antibiotics such as metronidazole and clindamycin. However, these treatments are largely non-selective and lead to eradication of healthy vaginal microbes, contributing to high rates of BV recurrence. Re-establishment of an optimal reproductive tract microbiome may be improved through the use of live biotherapeutics or probiotics. However, the effectiveness of this approach is dependent on several factors, including the route of administration and the strains of bacteria used. An alternative strategy that is currently being explored is vaginal microbiome transplantation, whereby the entire microbial community of a healthy donor is transferred into a patient.

Find a summary on probiotics in Infographic 2.

Relevance for Sustainable Development Goals and Grand Challenges

The reproductive tract microbiome relates to the following SDGs:

- **Goal 3. Ensure healthy lives and promote well-being for all at all ages** (improve health, reduce preventable disease and premature deaths). An optimal reproductive tract microbiome helps to prevent infection and associated disease pathogenesis (e.g. cervical cancer development) and improves reproductive outcomes for women. A healthy microbiome during pregnancy associates with reduced risk of miscarriage and premature birth. In addition, during childbirth, exposure of the new-born infant to a healthy reproductive tract microbiome will optimise the development of the early neonatal gut microbiome which has important implications for later life health (e.g. immune development and metabolic programming). These effects have major economic consequences for health budgets in developed and developing nations.
- **Goal 8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all** (promote economic growth, productivity and innovation, enterprise and employment creation). Dysbiosis of the female reproductive tract is a global problem and BV is the most common vaginal infection among women of reproductive age. The consequences of this issue are not limited to health and well-being, but include high economic burden often marked by clear racial disparities. The direct economic cost of BV includes costs per test and per case treated, the costs resulting from increased risk of contracting other diseases and the costs of related to adverse outcomes in pregnancy (e.g., preterm birth). Other indirect costs include time burden and costs of transportation and childcare necessary to attend clinics for recurrent BV treatment etc. This can also negatively impact productive employment and black communities are more like to suffer this burden. This is the result of both socioeconomic status, and biological factors, such as lower vaginal concentrations of protective *Lactobacillus* species among black women. Better knowledge of vaginal microbiota could help overcome these costs and disparities.

Potential Implications for Decisions

1. ***Individual***
   a. Are there likely to be any negative impact of external factors such as hygiene practices (e.g., vaginal douching) or antibiotic use on the reproductive tract microbiome and what the implication of this might be for reproductive health outcomes?
   b. Could these factors also influence the early colonisation of the neonatal gut microbiome and therefore longer-term health outcomes of newborn babies?
   c. Non-microbial parameters: the final costs of testing for and treatment of vaginal infections, BV, etc.

2. ***Community policies***
   a. Health costs associated with treatment for reproductive tract infections and recurrent BV
   b. Implementation of campaigns for BV awareness.
   c. Initiatives for overcoming cultural shame around vaginal health topics in minority communities.

3. ***National policies related to the reproductive tract microbiome***
   a. Healthcare economics of vaginal dysbiosis and how it mediates risk of related disease pathologies.
   b. Implementation of nation-wide screening policies (with focus towards minority and disadvantaged communities).

Pupil participation

1. ***Class discussion of the issues associated with maternal reproductive tract microbiome***

2. ***Pupil stakeholder awareness***
   a. Maternal health is generally important for successful pregnancy. In recent years we have become aware that the microbiome affects almost all aspects of our health. Which part of the microbiome is most important for human pregnancy?
   b. Preterm birth has major negative personal implications for families, and financial implications for healthcare providers. Can you think how these impacts could be decreased?
   c. What are the implications of a series of pregnancies on the lower genital tract microbiome?

3. ***Exercises***
   a. Can you think of a simple way to monitor the health or otherwise of a women's vaginal microbiome? [measure pH]
   b. What are some factors that can lead to changes in the reproductive tract microbiome composition? [hormonal changes, antibiotics, bleeding, sexual intercourse, hygiene practices, ethnicity]
   c. What are the implications of birth control on the lower genital tract microbiome? How might different approaches to birth control have different effects? [physical methods – increased diversity; hormonal methods (estrogen) – less diversity]

The Evidence Base, Further Reading and Teaching Aids

Vaginal microbiome composition in health and disease

Video 1: TEDx Talk describing the microbiome in women's health: https://www.youtube.com/watch?v=CqasLvlSWGU

Infographic 1: Infographic summarising information about vaginal microbiota and factors that can influence composition: https://www.biocodexmicrobiotainstitute.com/en/pro/infographics-share-your-patients#5-things-to-know-about-the-vaginal-microbiota

France M, Alizadeh M, Brown S, Ma B, Ravel J. Towards a deeper understanding of the vaginal microbiota. Nat Microbiol. 2022 Mar;7(3):367-378. doi: 10.1038/s41564-022-01083-2. Epub 2022 Mar 4. PMID: 35246662; PMCID: PMC8910585.

MacIntyre DA, Sykes L, Bennett PR. The human female urogenital microbiome: complexity in normality. Emerg Top Life Sci. 2017 Nov 30;1(4):363-372. doi: 10.1042/ETLS20170042. PMID: 33525775.

Martin DH, Marrazzo JM. The Vaginal Microbiome: Current Understanding and Future Directions. J Infect Dis. 2016 Aug 15;214 Suppl 1(Suppl 1):S36-41. doi: 10.1093/infdis/jiw184. PMID: 27449871; PMCID: PMC4957511.

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Vaginal microbiome across a woman's lifespan

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Muhleisen AL, Herbst-Kralovetz MM. Menopause and the vaginal microbiome. Maturitas. 2016 Sep;91:42-50. doi: 10.1016/j.maturitas.2016.05.015. Epub 2016 Jun 1. PMID: 27451320.

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Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SS, McCulle SL, Karlebach S, Gorle R, Russell J, Tacket CO, Brotman RM, Davis CC, Ault K, Peralta L, Forney LJ. Vaginal microbiome of reproductive-age women. Proc Natl Acad Sci U S A. 2011 Mar 15;108 Suppl 1(Suppl 1):4680-7. doi: 10.1073/pnas.1002611107. Epub 2010 Jun 3. PMID: 20534435; PMCID: PMC3063603.

Lactobacillus species and vaginal health

Video 2: Microbiota city, brief introductory video to vaginal microbiota https://www.youtube.com/watch?v=1SSPUDpYGRk

Amabebe E, Anumba DOC. The Vaginal Microenvironment: The Physiologic Role of Lactobacilli. Front Med (Lausanne). 2018 Jun 13;5:181. doi: 10.3389/fmed.2018.00181. PMID: 29951482; PMCID: PMC6008313.

Petrova MI, Lievens E, Malik S, Imholz N, Lebeer S. Lactobacillus species as biomarkers and agents that can promote various aspects of vaginal health. Front Physiol. 2015 Mar 25;6:81. doi: 10.3389/fphys.2015.00081. PMID: 25859220; PMCID: PMC4373506.

Tachedjian G, Aldunate M, Bradshaw CS, Cone RA. The role of lactic acid production by probiotic Lactobacillus species in vaginal health. Res Microbiol. 2017 Nov-Dec;168(9-10):782-792. doi: 10.1016/j.resmic.2017.04.001. Epub 2017 Apr 20. PMID: 28435139.

Vaginal microbiome, bacterial vaginosis and other infections

Video 3: TED-Ed video exploring yeast infections in vagina and how bacteria help fighting it: https://www.youtube.com/watch?v=Bgc1C1xI2dA&t=166s

Chehoud C, Stieh DJ, Bailey AG, Laughlin AL, Allen SA, McCotter KL, Sherrill-Mix SA, Hope TJ, Bushman FD. Associations of the vaginal microbiota with HIV infection, bacterial vaginosis, and demographic factors. AIDS. 2017 Apr 24;31(7):895-904. doi: 10.1097/QAD.0000000000001421. PMID: 28121709; PMCID: PMC5370567.

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Mitra A, MacIntyre DA, Marchesi JR, Lee YS, Bennett PR, Kyrgiou M. The vaginal microbiota, human papillomavirus infection and cervical intraepithelial neoplasia: what do we know and where are we going next? Microbiome. 2016 Nov 1;4(1):58. doi: 10.1186/s40168-016-0203-0. PMID: 27802830; PMCID: PMC5088670.

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Vaginal microbiome in pregnancy and preterm birth

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Gudnadottir U, Debelius JW, Du J, Hugerth LW, Danielsson H, Schuppe-Koistinen I, Fransson E, Brusselaers N. The vaginal microbiome and the risk of preterm birth: a systematic review and network meta-analysis. Sci Rep. 2022 May 13;12(1):7926. doi: 10.1038/s41598-022-12007-9. PMID: 35562576; PMCID: PMC9106729.

Vaginal microbiome in seeding of the neonatal gut

Podcast 1: Podcast and interview with experts about vaginal seeding at birth: https://www.bmj.com/content/352/bmj.i227

Video 4: Microbes from Mom: Vaginal Birth vs. C-Section: https://www.youtube.com/watch?v=YB0WDp-Stys

Website on vaginal seeding: https://my.clevelandclinic.org/health/treatments/22096-vaginal-seeding

Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. 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 Jun 29;107(26):11971-5. doi: 10.1073/pnas.1002601107. Epub 2010 Jun 21. PMID: 20566857; PMCID: PMC2900693.

Modulation of the vaginal microbiome

Infographic 2: visual summary of probiotics definition, use and production https://www.biocodexmicrobiotainstitute.com/sites/default/files/2021-10/%5Binfography%5D%20What%20are%20probiotics_en.pdf

López-Moreno A, Aguilera M. Vaginal Probiotics for Reproductive Health and Related Dysbiosis: Systematic Review and Meta-Analysis. J Clin Med. 2021 Apr 2;10(7):1461. doi: 10.3390/jcm10071461. PMID: 33918150; PMCID: PMC8037567.

Mei Z, Li D. The role of probiotics in vaginal health. Front Cell Infect Microbiol. 2022 Jul 28;12:963868. doi: 10.3389/fcimb.2022.963868. PMID: 35967876; PMCID: PMC9366906.

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Glossary

Archaea: microorganisms that are evolutionary related to bacteria but have several key differences in their composition, e.g., while bacterial cell walls are generally composed of a combination of protein and sugars called peptidoglycan, archaeal cell walls are composed of complex sugars called polysaccharides.

Atrophy: Vaginal atrophy describes the thinning, drying and inflammation of the vaginal walls caused by a decrease of estrogens in the body. It most often occurs after menopause.

Bacteriocins: Small antibacterial molecules produced by many commensal bacteria. These compounds have the capacity to eliminate specific colonizing pathogens. Bacteriocins are typically composed of peptides or proteins of variable biochemical properties, molecular weight and have many different mechanisms of action and spectrums of activity.

Cervical ripening: A normal process of softening and opening of the cervix before labour starts. During most of pregnancy, the cervix is rigid and closed as to hold the baby inside the uterus. During labour, cervical dilation allows the baby to pass through the birth canal.

Commensal microbes: Types of microbes that reside at different body sites without causing any harm to the host.

Diversity: Describes the number of different species of microbes present in a defined environment and their relative abundance.

Dysbiosis: Refers to disruption of the microbiome that results in changes in functional composition, metabolic activities, or a shift in the local distribution of microbes. In the vaginal context in coincides with the depletion of *Lactobacillus* species and increase of microbial diversity.

Epithelium: The vaginal epithelium is the inner lining of the vagina consisting of multiple layers of squamous epithelial cells.

Erythrocytes: Also known as red blood cells, are cells present in the blood that do not have a nucleus. The have a biconcave shape and transport oxygen and carbon dioxide between the lungs and tissues.

Estrogen: A sex hormone responsible for the development and regulation of the female reproductive system.

Genome: All the genetic material in an organism. It is made up of DNA (or RNA in some viruses) and includes genes and other elements that control the activity of those genes within a living cell.

Gestational tissues: Tissues produced and developed during pregnancy. These tissues include the decidua, myometrium, cervix and maternal blood originating from the mother and villous placenta, fetal membranes (chorion and amnion), umbilical cord, and fetal blood originating from the fetus.

Glycogen: A multibranched polysaccharide that serves as a form of energy storage of glucose in animals, fungi, and bacteria. Glycogen is accumulated in the vaginal epithelium cells and used by commensal bacteria as energy source.

High-throughput: Techniques that use automated equipment to rapidly test thousands to millions of samples. In the context of sequencing they are technologies capable of sequencing many fragments of DNA in parallel. This enables scientists to read hundreds of millions of DNA fragments and generate great amount of data in less time and using less resources.

Homeostatic: Of the state of homeostasis. In biology, homeostasis is any self-regulating process in which systems adjust to optimal conditions to maintain stability and survive.

Inflammation: A key component of the body's defence mechanism whereby the immune system identifies and removes harmful and foreign stimuli and begins the healing process. However, inflammation can be detrimental if activated during early stages of pregnancy or against self-antigens.

Lactobacillus species: bacterial species commonly found in the human mouth, gastrointestinal tract, and female genital tract, where they produce lactic acid and competitively inhibit pathogens. *Lactobacilli* appearance is rod-like, small, slender, and they are nonmotile. *Lactobacilli* are gram-positive bacilli usually disposed in chains.

Live biotherapeutics: sometimes also called Live Biotherapeutic Product (LBP). These are biological products that contains live organisms. They are applicable to the prevention, treatment or cure of a disease or condition of humans. Similar to probiotics but more specific. See definition below.

Menopause: A period in a woman's life where her menstrual cycle stops permanently marking the end of the reproductive years. Menopause is caused by the loss of ovarian follicular function and a decline in circulating blood estrogen levels.

Menstrual cycle: A cyclic series of hormonal changes that contribute to alter the status of the female reproductive tract. A cycle lasts in average 28 days and involves both an ovarian and a uterine cycle. The ovarian cycle controls the production and release of eggs and the production of estrogen and progesterone. The uterine cycle alters the structure of the uterus lining to receive an embryo. Bleeding occurs when fertilisation does not occur, and the lining is shed.

Metabolites: Small chemical compounds such as amino acids, lipids, sugars, organic acids, etc., which are routinely formed as intermediate or terminal products of cellular metabolism.

Microbiome: the entire habitat, including the microorganisms (bacteria, archaea, and viruses), their genomes (i.e., genes), and the surrounding environmental conditions.

Microbiota: the collection of all microorganisms present in a defined environment. Differs from microbiome for not including the host environment.

Mutualism: an ecological relationship between two or more species that results in a beneficial effect for each of the organisms involved.

Next-generation sequencing: also known as NGS, it is a parallel DNA sequencing technique. NGS allows the sequencing of millions of fragments simultaneously per run.

Pathogen: A microbe that causes disease to its host.

pH: a numerical scale expressing the acidity or alkalinity of a solution on a logarithmic scale on which 7 is neutral, lower values are more acidic and higher values more alkaline.

Probiotics: A live microorganisms that, when administered in adequate amounts, confers a health benefit to the host.

Puberty: the transition from childhood into adulthood marked by a child's physical and hormonal changes. Children develop secondary sexual characteristics and become able to have children. Secondary sexual characteristics include growth of pubic, armpit, and leg hair, breast enlargement and increased hip width in girls.

Richness: The number of species in a defined microbial community.

Seeded: Seeding refers to the transfer of bacteria from one site to another. More specifically vaginal seeding refers to the process of transferring maternal vaginal microbes to the newborn. This can happen either naturally through vaginal birth or inoculating a cotton swab with vaginal fluids to transfer the vaginal flora to the mouth, nose, or skin of the infant.

Sepsis: A strong systemic reaction to infection that is associated with high morbidity and mortality. Usually requires urgent interventions in order to improve outcomes.

Sterile: Being in a state completely absent of microorganisms.

Sustainable Development Goals: Goals that were formulated and adopted by all United Nation Member States in 2015 as a universal call to action to end poverty, protect the planet and ensure that all people enjoy peace and prosperity by 2030.