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The two-sided role of the vaginal microbiome in *Chlamydia trachomatis* and *Mycoplasma genitalium* pathogenesis

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ABSTRACT

Sexually transmitted infections (STI) can have major consequences for the reproductive health of women. *Mycoplasma genitalium* is a STI that is not as well studied but causes pelvic inflammatory disease (PID) among other complications. Another well-known STI is *Chlamydia trachomatis*, notorious for its capability to cause infertility. Both *C. trachomatis* and *M. genitalium* share some of the same clinical aspects. Parts of the pathogenesis of *C. trachomatis* and *M. genitalium* infections are unclear but potential factors are the microbiome and other STIs. The healthy vaginal microbiome is dominated by *Lactobacillus spp*; these bacteria protect the host against invading bacteria like *C. trachomatis* and *M. genitalium* by producing antibacterial compounds and providing a mechanical barrier. A dysbiosis of the vaginal microbiome is characterized by a non-*Lactobacillus spp.* dominated microbiome, also known as bacterial vaginosis (BV). BV and BV associated bacteria play a role in the pathogenesis of STIs such as *C. trachomatis* and *M. genitalium*. The different species of BV associated bacteria have distinct characteristics that could play a role in *C. trachomatis* and *M. genitalium* infections. Host factors should also be considered when analysing the interaction of *C. trachomatis* and *M. genitalium* and the microbiome. One important factor is the hormonal homeostasis. Oral hormonal contraception influences the vaginal milieu and could influence the infection process of STIs. Overall, this review attempts to give an overview of the pathogenesis of *C. trachomatis* and *M. genitalium* infections and the relationship between *M. genitalium*, *C. trachomatis*, and the vaginal microbiome.

INTRODUCTION

Sexually transmitted infections such as *Mycoplasma genitalium* and *Chlamydia trachomatis* are infections that are transmitted through sexual contact. When these bacteria try to invade the genital tract it will encounter a microbiome, which in women is the vaginal microbiome. The vaginal microbiome can be seen as a complementary part to our immune system that consists of bacteria. Humans and their microbiome live in a mutualistic relationship: the bacteria profit of the resources the host provides and in turn protect the host against invading pathogens(1). The typical healthy vaginal microbiome is dominated by *Lactobacillus spp.*(1-7). Different studies show that certain strains of the *Lactobacillus spp.* protect the host better against the colonisation of exogenous microorganisms than other strains *Lactobacillus*(1, 3, 8, 9). The *Lactobacilli* defend the host by producing a wide variety of antibacterial products, such as creation of an acidic environment by producing lactic acid(1, 3). These characteristics play a role in the barrier function of the microbiome.

The microbiome has a close interaction with the host. Not only is the host immune system essential for fighting off external threats, the barrier function of the microbiome is also essential. The first barrier in the host immune system is the epithelial barrier. This barrier is not only in constant contact with the microbiome but also under influence of the host hormonal cycle(10). The female sex hormones estradiol and progesterone influence the immune system indirectly through the epithelial layer. For example, the female sex hormones stimulate the immune system by triggering the epithelial cells to produce cytokines such as IL-8(10). This also applies to the production of antibacterial products and even the transport of immunoglobulins into the lumen(10). In short, the epithelial layer and the hormonal cycle strongly contribute to the host immune response, tying them to the susceptibility to diseases.

Susceptibility to various vaginal pathogens that invade the vagina forms a potential health risk. An important risk factor for infection by pathogens is the weakened barrier function of the vaginal microbiome. An example of this weakened barrier is when there is a dysbiosis as is the case with bacterial vaginosis (BV)(8). In BV the composition of the vaginal microbiome shifts from the dominant *Lactobacillus spp.* to a more diverse microbiome. Characteristic for BV is the rise in pH resulting in a more neutral pH environment(4). Studies showed that women that have BV are more prone to STIs such as *C. trachomatis* and *M. genitalium* infections(11-13). Pathogens like *C. trachomatis* and *M. genitalium* may utilise the failing defences

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to invade(3). There are various factors that play a role in the development of BV. Douching (extensive washing and rinsing of the vagina) for example has a big impact on the microbiome and could lead to BV in women with an already altered flora(14). Whether this impact is also seen in women with a normal *Lactobacillus spp.* dominated microbiome is currently unclear. Continuous condom use on the other hand protects against BV and other invading pathogens such as *Mycoplasma species*, however no lower incidence was seen in urogenital *C. trachomatis* infections(15). Overall this suggest that there may be an overlap in prevention of STIs and prevention of BV development.

C. trachomatis is a STI notorious for late complications like infertility(16). Other clinical consequences of *C. trachomatis* infections are PID and cervicitis(17). *C. trachomatis* has a characteristic infection process that consists of an infective form and a non-infective form, the latter of which is obligatory intracellular. The infectious form is known as elementary body (EB) that binds to the host cell and invades the cell(18). The EB resides in an inclusion in the cell, wherein the EB further differentiates. These inclusions are membrane bound vacuoles that help the bacteria to escape phago-lysosomal fusion. The EB differentiate into reticulate bodies(RB) that multiply various times, after which the RB can differentiate back to EBs. These EBs are released though lysis of the host cell and the cycle starts again(1, 8, 19). Important to note is that *C. trachomatis* is dependent on tryptophan for its growth. However, *C. trachomatis* is unable to synthesise tryptophan and utilises the environment for its tryptophan metabolism. If *C. trachomatis* resides in an environment that is tryptophan poor, it will differentiate into a persistent aberrant form which is not infectious(19).

A lesser known STI is *M. genitalium*, which poses a serious health risk because of clinical consequences like PID, cervicitis, and possible infertility(4, 6, 16). *M. genitalium* can also cause pregnancy complications such as preterm delivery and premature rupture of membranes(6, 20). Characteristic of *M. genitalium* is that it is a facultative anaerobe bacterium and lacks a cell wall. Interestingly, some studies associate *M. genitalium* with healthy individuals while other studies associate *M. genitalium* with BV or preterm delivery (2, 21). This leads to the hypothesis that the pathogenesis of *Mycoplasma spp.* is dependent on co-infection and/or the composition of the microbiome. Other species of *Mycoplasma* have been studied more extensively, certain characteristics also apply to the pathogenesis of *M. genitalium*(22). Because of the limited information there is on *M. genitalium*, we will use data that is available from other species *Mycoplasma* in this review.

Recently, Tamerelle *et al.*(2018) published a meta-analysis investigating the association between the vaginal microbiota and a number of STIs among which *C. trachomatis* and *M. genitalium*(23). This study concluded that for *M. genitalium* not enough studies were published that could be used for a meta-analyses. The aim of this study is to reveal the gaps of knowledge to provide guidance to future researchers with an interest in this topic. Interestingly, Tamerelle *et al.*(2018) showed that there is an association between vaginal microbiota with low *Lactobacillus* spp. and susceptibility for *C. trachomatis* infection(23). In the current study we outline the possible pathogenesis for this phenomena.

Few studies have addressed the exact relationship between *C. trachomatis* and *M. genitalium*. A London study found an unexpectedly high co-infection rate of *C. trachomatis* and *M. genitalium* of 0.5% under participants of a screening program and STI clinic patients(24). As infection rates expected through the even division of *M. genitalium* infections in all patient groups would be roughly 0.16%, this may suggest that these pathogens may occur more frequently in co-infections. Other studies have investigated co-infection in high risk groups that resulted in a rate of up to 39%(24-29). A possible explanation for the differences in prevalence is the composition of the microbiome, which could influence the susceptibility for STIs.

The aim of this paper is to evaluate two STIs *i.e.* *C. trachomatis* and *M. genitalium* and the interaction with the microbiome of the vagina based on available literature. The focus will be on the female genital tract because of the late complications these particular infections can have on women.

MATERIALS AND METHODS

The search terms used for this review are summarized in Table 1. The search was conducted in Web of Science, Cochrane Library, PubMed/MEDLINE, and Embase in January 2018. The results were limited to publications in English only; no publication date limitations were applied.

The articles were screened based on their relevance for answering the research question at hand. This means that the articles contained information about *Chlamydia trachomatis* and/or *Mycoplasma genitalium* and the interactions between these bacteria and the microbiome of the female reproductive tract. Additionally, any article found to be relevant by the authors was added.

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Table 1: Search terms used for this review.

Search term
Chlamydia
Immunology
Microbiome
Microflora
Microbiota
Mycoplasma
Vaginal microbiome

The inclusion and exclusion criteria used are stated in Table 2. The articles did not have to meet all the inclusion criteria to be included. Adult women and the vaginal microbiome are required for inclusion. Furthermore, the articles were manually curated to fall in the scope of this paper.

Not much is known about the pathogenesis of *M. genitalium*. To broaden the search results *in vivo* and/or *in vitro* studies concerning *M. genitalium* were included. To further widen the perspective of *Mycoplasma* pathogenesis, other *Mycoplasma spp.* were included such as *Mycoplasma hominis* and *Candidatus Mycoplasma giererdii*. In contrast, *C. trachomatis* is a well-known and extensively studied bacterium. Therefore, to narrow the results down and concentrate on the microbiome aspect we excluded the *in vitro* studies related to *C. trachomatis* unless no similar *in vivo* study was available.

Table 2: Inclusion and exclusion criteria used for the inclusion and exclusions of articles.

Inclusion	Exclusion
Adult woman (of reproductive age)	Animal studies
<i>In vitro M. genitalium</i>	Assessments of diagnostic methods
<i>In vivo C. trachomatis</i>	Genetic test analyses
<i>In vivo M. genitalium</i>	<i>In vitro C. trachomatis</i>
Vaginal microbiome	Reviews

RESULTS

The vaginal microbiome composition and its differences

Every woman is unique and so is every vaginal microbiome. There are a number of factors that cause differences between vaginal microbiomes. There are big differences between microbiomes in women of different ethnicities(30). One example is the difference between African and European women(31). Healthy African women are more likely to have a *L. iners* dominated microbiome and healthy European women are more likely to have a *L. crispatus* dominated microbiome(31, 32). This discrepancy could be attributed to the many factors that influence the vaginal microbiome. For example hygiene practises such as douching(33). Whether menses influences the microbiome composition is still unclear. There have been a number of studies that investigated the vaginal microbiome composition during menses, but the results contradict each other. One states that the microbiome stays stable(34) while the other reports small fluctuations(35). Lastly, Gajer *et al.*(2012) states that menses does influence the microbiome in some instances and the author suggest that this may be due to genomic heterogeneity in the dominating *Lactobacillus spp.*(36). Antibiotics are also known to influence the vaginal microbiome. When used, the microbiome shifts to a microbiome not dominated with *Lactobacilli*(34). Finally, it is clear that pregnancy impacts the microbiome(37). The microbiome does not undergo major composition changes during pregnancy compared to non-pregnant women. The microbiome of pregnant women is more stable and more often *Lactobacillus spp.* dominant than that of non-pregnant women(38). In general it seems that the microbiome is not static, but rather a dynamic system that is under the influence of menstrual cycle, antibiotics, ethnicity, pregnancy, and potentially many more factors.

The microbiome can fluctuate between different healthy bacterial compositions but it can also get out of balance and form a more permanent dysbiosis such as BV. BV is characterised by a diverse non-*Lactobacillus* dominated microbiome that is colonised by specific types of bacteria such as *G. vaginalis*(4). There are noticeable differences in vaginal microbiome composition between women with BV. *M. hominis* was associated with BV in European women in general(31), Belgian(2), and Greenlandish(39) women, while there was no clear correlation found in African women(31). *L. iners* shows a greater presence than *L. crispatus* in BV but neither were dominant. This was also seen in African sex workers(9).

Interestingly, *M. hominis* is one of the bacteria that are associated with BV but that also can occur in seemingly healthy women(31, 35). This shows that bacteria that are BV associated can be present in healthy women as well. BV is not static, but rather a dynamic process. There is evidence that the microbiome can fluctuate between composition and in some instances it can fluctuate between BV and healthy(40). Taken together, these findings emphasise that there is a wide range of possible healthy compositions of the vaginal microbiome, because bacteria such as *M. hominis* could be both BV associated in some women and associated with a healthy microbiome in others. Most important is that the dominance of *Lactobacillus spp.* is vital for the vaginal health.

The role of *Lactobacillus* in *Mycoplasma genitalium* and *Chlamydia trachomatis* pathogenesis

A homogeneous *Lactobacillus spp.* dominated vaginal microbiome is associated with healthy women(30). A distinct characteristic for *Lactobacillus spp.* is the production of H_2O_2 and lactic acid that are antimicrobial and inhibit invading bacteria(41). Lactic acid has been shown to be a competent inhibitor of *C. trachomatis*(3), while H_2O_2 inhibits BV associated bacteria such as *M. genitalium*(42). Some strains of *Lactobacillus spp.* are more capable of inhibiting pathogens due to the capacity of producing antibacterial components(43).

Multiple studies have been conducted to explore why *L. crispatus* is associated with the healthy microbiome, with the ability to produce high concentrations of lactic acid as most notable outcome. Due to the increased lactic acid production the pH of the vaginal tract is lowered, this lactic acid rich environment inhibits the spread of *C. trachomatis*(1, 3). Gong et al.(2014) suggested three possible mechanisms that are responsible for the effect lactic acid has on *Chlamydia* EBs: destruction of the surface molecule(s), destruction of the membrane, and disruption of the internal metabolism(3). Further research is needed to determine what the exact mechanisms are. Not all *Lactobacillus spp.* are competent in warding off potential invading bacteria, for example *L. iners* is frequently seen with BV associated bacteria(2, 13, 44). It has also been demonstrated that a vaginal microbiome dominated by *L. iners* does not protect against *C. trachomatis* infection(45). An explanation for this phenomenon is that *L. iners* produces less H_2O_2 and is associated with lower lactic acid production compared to other *Lactobacilli spp.*(46, 47). Genomic based identification showed that 9% of the *L. iners* were capable of H_2O_2 production compared to *L. crispatus* where 95% were capable of H_2O_2 production(46). These data show that a low pH, lactic acid, and high concentration

of H₂O₂ in the vaginal tract are important as protection against invading bacteria such as *C. trachomatis* and *M. genitalium*.

The epithelial layer of the vagina is an important factor in the interplay between *Lactobacilli* and invading bacteria, as it is in close contact with the microbiome. The glycogen produced by epithelial cells can be an energy source for *Lactobacillus spp.*(48). The epithelial layer also has a barrier function, and immune cells interact with the vaginal microbiota. The vaginal immune system does not attack *Lactobacillus spp.* but inhibits potential harmful bacteria(49). Furthermore, the available free glycogen that is produced by the epithelial layer plays a role in the abundance of *Lactobacillus spp.* especially *L. jensenii* and *L. crispatus*(50). The glycogen is released by the shedding of the epithelial cells and is then utilized by the *Lactobacillus spp.*(50). An important factor that influences the glycogen production is estrogen(41, 51). Estrogen stimulates the production of glycogen in the epithelial cells. Overall, glycogen production is beneficial for the host because more lactic acid producing *Lactobacillus spp.* means a lower pH which protects against invading bacteria. This organization of naturally occurring system is one example of how *Lactobacilli* live in symbiosis with the host and helps protect against invading pathogens such as *C. trachomatis* and *M. genitalium*.

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A factor that can disturb the relationship between the host and *Lactobacilli* is the use of hormonal contraceptives like the estradiol-progestin combined oral contraceptive pill (COCP) (52). The use of the COCP may have a beneficial effect on the microbiome by stimulating the *Lactobacillus spp.* because of the higher glycogen production. This is demonstrated in women who use COCP. They are found to be colonised more often with *L. crispatus* and *L. jensenii*, which are more beneficial to the host than most other *Lactobacilli*(52). This suggest that there is a benefit for women to take hormonal anticonception. There is a conflicting report that shows a higher *C. trachomatis* prevalence in risk groups that used contraception(53). However, this concerns a high risk group and the association could be caused by the risk behaviour of these women. In general it appears that the hormonal contraception is beneficial for women by promoting the beneficial strains of *Lactobacillus*.

Immunological reaction to Chlamydia trachomatis and the interaction with the microbiome

By bypassing the barriers such as those established by *Lactobacillus spp.* *C. trachomatis* can infect the human cells. Upon recognition of a *C. trachomatis* infection the immune system produces more IL-12, among other inflammatory cytokines(54). IL-12 is an inflammatory

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cytokine that stimulates the production of interferon- γ (IFN- γ). This is produced by macrophages, stimulates inflammation, and induces indoleamine-2,3-dioxygenase 1(IDO1). IDO1 inhibits *C. trachomatis* by limiting the available tryptophan that is necessary for *C. trachomatis* growth. Another source of tryptophan is the BV associated bacterium *Prevotella* spp.(19). It has been shown that tryptophan produced by *Prevotella* can be used by *Chlamydia* for survival when other sources of tryptophan are low or depleted. Prevention of large quantities of *Prevotella* aiding *C. trachomatis* is another positive aspect of healthy *Lactobacilli* dominated microbiota(3).

The relation between BV and *C. trachomatis* infection has been the subject of a number of studies. Dutch patients with *C. trachomatis* infection more often have a diverse vaginal microbiome, composed of species other than *Lactobacillus*(44). Some reports do show a higher incidence of *C. trachomatis* infection during BV(12), while another study shows no increased *C. trachomatis* incidence(55). The most notable difference between these studies is the study population. The study that showed lower *C. trachomatis* incidences during BV consisted of African women and the study that showed a higher *C. trachomatis* incidences during BV consisted of a mix of African American women and white American women. This may suggest that ethnicity may play a role in the infection process. This suggest that ethnicity may play a role in the infection process. As has been discussed previously, ethnicity plays a major role in vaginal microbiome composition. Healthy microbiomes but also BV compositions can have different composition for African women compared to European women(31). Not only BV-associated bacteria play a role in the susceptibility for *C. trachomatis* infection. *L. iners* dominated microbiomes increase the risk for *C. trachomatis* in infection as well(45). *L. iners* produces significantly less lactic acid which is an important inhibitor of *C. trachomatis*(3, 47). Overall, this suggests that the composition of the microbiome plays an important role in the infection process of *C. trachomatis*.

An important factor to consider in the interaction between host and microbiota is the polymorphisms in immune genes, as these may influence the immune response. For example, polymorphisms in the TNF- α gene (*TNFA*-208G>A) can influence the quantity of expression and thus the inflammatory response of the host. This is mainly seen in a disturbed microbiome, Nugent score >7, and could cause preterm birth(56). This is relevant for *C. trachomatis* infection because TNF- α plays a role in the innate immune response to *C. trachomatis* infections(57). The exact role of BV in *C. trachomatis* infection and its interaction

with the immune system is still unclear but it is interesting to further investigate how this influences the inflammatory reaction(56).

As explained earlier the relationship between the sex hormone estrogen and the vaginal microbiome is beneficial for the production of glycogen and thus beneficial for *Lactobacilli*. Also mentioned was the influence oral contraception could have on the microbiome. As these hormones influence the *Lactobacillus spp.* so does it also influence other bacteria. When looking at COCP use during a *C. trachomatis* infection there is a significant increase in inflammatory cytokines(55). It is clear that the hormones in COCP influence the microbiome and the inflammatory cytokines. Fichorova *et al.*(2015) suggest that this could be due to the differential regulation of inflammatory of the different combinations of hormones. Another explanation could be that the hormones that are used in the hormonal contraception are synthetic and not the natural occurring hormones and therefore could trigger a reaction.

Immunological reaction to *Mycoplasma genitalium* and the interaction with the microbiome

M. genitalium is, like *C. trachomatis*, an intracellular bacterium. Important for the survival of *M. genitalium* is the ability to adhere to the host cell and to invade the cell. *M. genitalium* uses MgPa adhesins for this process(58, 59). Before invading the host cell the *Mycoplasma spp.* need to survive in the H₂O₂ and lactic acid rich environment created by the *Lactobacillus spp.* that functions as a line of defence. It is evident that in a *Lactobacillus spp.* rich environment there is less *Mycoplasma spp.* infection such as *M. hominis*(60). Especially the H₂O₂ producing *Lactobacillus spp.* such as *L. jensenii* have this effect(61). Not much research has been conducted on how *Lactobacillus spp.* inhibits *Mycoplasma spp.* growth. Further research is needed to determine whether H₂O₂ or low pH by lactic acid is responsible for the effect against *Mycoplasma spp.*

The relationship between the vaginal composition and the pathogenesis of *Mycoplasma spp.* is double sided. *Mycoplasma spp.* does not only occur as a BV-associated bacterium but can also be part of a diverse microbiome(62). *Mycoplasma spp.* can be found in some healthy African women with a diverse microbiome, while there is a strong association with BV in European women(31, 60). *M. genitalium* is more frequently seen in patients with recent BV(63). The relationship between BV and *M. genitalium* can be explained by the fact that in BV there are lower quantities of lactic acid and thus higher pH which is beneficial for

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the survival of this bacteria. This is hypothetical and future studies have to investigate the relationship between BV and *M. genitalium*.

The immune system does not only play a part in the fight against infections, it will also limit the inflammatory reaction to reduce potential damage. An example is the 70-kDa heat shock protein (hsp70). This is an antagonist for the inflammatory IL-1. Hsp70 acts in stressful situations to inhibit the damage to the host cells. Hsp70 expression is increased during BV when *Mycoplasma spp.* is present(64). This is in response to an increased inflammatory reaction of the host during BV with *Mycoplasma spp.* This inflammatory reaction can further unbalance the vaginal microbiota and thus cause the host to be more susceptible to invading pathogens. We suggest that the reaction of the immune system to BV with *Mycoplasma spp.* may make the host susceptible for infections with *M. genitalium*.

Besides it's relation to dysbiosis, there is also a relationship between *Mycoplasma spp.* and other pathogens. One of these relationships is that with *Trichomonas vaginalis*(65). *T. vaginalis* is a protozoan parasite that causes an STI, called Trichomoniasis(16). Studies have shown a significant association between *M. genitalium* and *T. vaginalis*(66, 67). Other *Mycoplasma spp.* such as *Ca. M. giereridii* is also significant associated(65). *Ca. M. giereridii* is a newly found *Mycoplasma* species that is associated with higher pH and is more prevalent in African-American women than European women with a strong correlation with *T. vaginalis*(31). The exact nature of the relationship between *Mycoplasma spp.* with *T. vaginalis* is yet unclear. It is likely that *Mycoplasma spp.* and *T. vaginalis* have an overlap in favourable environment, especially microbiome compositions such as seen in BV. This could also mean that these pathogens do not interact with each other and only exist in the same environment. However, there is still much unclear about if *T. vaginalis* and *M. genitalium* interact with each other.

M. genitalium on its own has not been extensively researched. However, it is clear that there is a link between this pathogen and the vaginal microbiome. Especially in a microbiome with low amounts of *Lactobacillus spp.* and high amounts of BV associated bacteria. Not only BV associated bacteria are associated with *M. genitalium* but also *T. vaginalis*. However, no interactions between *M. genitalium* and *T. vaginalis* have been shown to occur. There may be other bacteria that reside in the vaginal microbiome that are associated with *M. genitalium* and could play a role in its pathogenesis. Further research should clarify these interactions.

DISCUSSION AND CONCLUSION

There are many factors that play a role in the interaction between the vaginal microbiome, the host immune system, and the STIs *C. trachomatis* and *M. genitalium*. It is a complex relationship with many aspects still to be uncovered. This review attempted to shed a light on the relationship between the microbiome and these pathogens. We established that there is an interaction between lactic acid levels and *C. trachomatis*, and between H₂O₂ levels and *M. genitalium*. We also discussed the association between *C. trachomatis* and *Prevotella*, in which *C. trachomatis* benefits of the tryptophan producing *Prevotella*. The association between *Mycoplasma spp.* and *T. vaginalis* and therefore possibly with *M. genitalium* suggest that an overlap in microbiome may be favourable for the pathogenesis of *T. vaginalis* and *Mycoplasma*. Taking this into account, there could be other pathogens that occur in the microbiome that are associated with *C. trachomatis* and/or *M. genitalium*. This could also mean that there is overlap in microbiome compositions that are beneficial for *C. trachomatis* and *M. genitalium*, which would be one explanation for the previously described co-infections(24).

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The vaginal microbiome is the first line of defence of the female genital tract and thus plays an important role in the infection process of bacteria. We found a common consensus that both *C. trachomatis* and *M. genitalium* thrive in a microbiome with less *Lactobacillus spp.* Especially less H₂O₂ and/or lactic acid producing *Lactobacillus spp.* *C. trachomatis* is also shown to more frequently infect hosts with a *L. iners* dominated microbiome. Due to other similarities this may also be the case for *M. genitalium*. Hormones have an effect on the microbiome. As has been discussed, estradiol stimulate the *Lactobacillus spp.*, which is beneficial for the host. However, contraception use with synthetic estradiol-progestin results in higher inflammation during *C. trachomatis* infection, suggesting that hormones influence the immune response and possibly impact symptoms and complications. A schematic depiction of the processes affecting *C. trachomatis* and *M. genitalium* can be seen in figure 1.

The immune response in reaction to *C. trachomatis* is largely mapped out, highlighting the role IFN- γ plays in the inhibition of *C. trachomatis* spread. However, the immune reaction in response to the *M. genitalium* infection is largely unknown. Hsp70 activity during BV is a clear sign the immune response to *M. genitalium* before there is an infection is notably different

from *C. trachomatis* infection. Overlapping in the pathogenesis is BV, this may increase susceptibility for both pathogens possibly through a higher immune reaction.

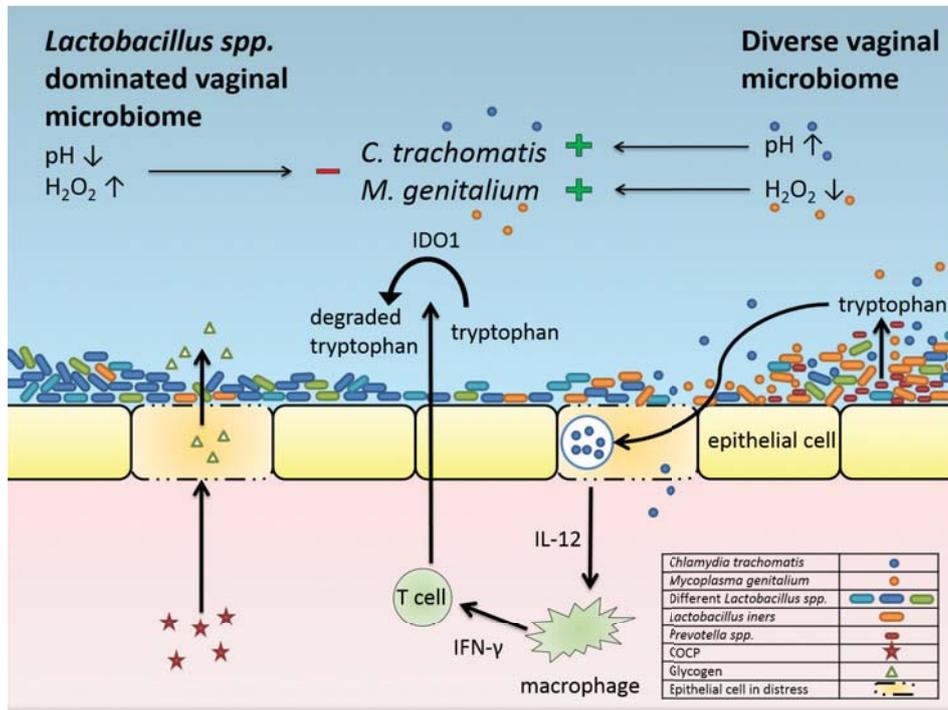


Figure 1: Depiction of the processes affecting *C. trachomatis* and *M. genitalium* in *Lactobacillus* dominated or diverse vaginal microbiota profiles.

The interaction between *C. trachomatis* and *M. genitalium* and the vaginal microbiome is not fully understood. Further studies that investigate the co-infection between *C. trachomatis* and *M. genitalium* may help us better understand how these pathogens cause infections and what role the vaginal microbiome plays in this infection process.

DECLARATIONS

Conflicts of interests

The authors declare no conflicts of interest

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