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The epidemiological aspects associated with *Chlamydia trachomatis* infection

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Abstract--The widespread bacteria causing sexually transmitted infection (STI) worldwide is *Chlamydia trachomatis*. The prevalence of chlamydial diseases that are spread via sexual contact is relatively high throughout the world. Urethritis and cervicitis are often caused by *C. trachomatis*, and its aftereffects include ectopic pregnancy, reactive arthritis, epididymitis, tubal factor infertility, proctitis, and pelvic inflammatory disease (PID). In addition, chlamydial infections may cause severe ocular or reproductive illness, resulting in infertility or blindness, depending on the bacterial strain. There have been many ways to calculate transmission probability, but each has drawbacks. It is linked to a broad spectrum of short- and long-term health repercussions and sequelae. In low- and middle-income nations like India, where the majority of the burden goes unreported and where there is a lack of systematic data to assess the situation, improved urogenital *C. trachomatis* infection management is especially crucial. This study's goal was to highlight the current state of the significant epidemiological factors related to chlamydial infections.

Keywords---Chlamydia trachomatis, Epidemiology, Infection, Sexually transmitted disease.

1. Introduction

A gram-negative sexually transmitted bacteria that infect people around the globe is *C. trachomatis* (Ct). It is a very often reported bacterial infection in the US and frequently causes cervicitis in women and urethritis in men [1]. It is the most prevalent sexually transmitted illness in the whole world. In addition, it produces "trachoma," the most common infectious cause of blindness globally.

The reservoir of infections, typically asymptomatic, provide a constant supply for effective disease transmission and permits quiet sickness. In addition, scarring of the ovaries, fallopian tubes, endometrial lining, and sometimes the nearby perineum from *C. trachomatis* infection raises the likelihood of subsequent ectopic pregnancies and tubal infertility [2]. The fundamental cause of these effects is that *C. trachomatis* is thought to be the most expensive nonviral STD [3]. Considering this, screening initiatives to prevent pelvic inflammatory disease (PID) in women started in the US in the late 1980s. By the mid-1990s, the US Preventive Screening Task Force and other significant organizations had publicly approved these initiatives [4]. National chlamydia screening programs exist in other nations as well [5].

C. trachomatis is the species with the highest epidemiological and clinical significance; it is the most prevalent bacterial STI (sexually transmitted illness) and infects the human urinary and genital system [6]. In addition, the WHO estimated that there were 131 million new Chlamydia infections in 2012; 60% of these cases were reported in affluent nations, although most of these infections went undiagnosed and untreated. Due to its effect on human health, Ct has, up till now, been the species generating the most attention (mainly on reproductive and sexual health) [7-10].

C. trachomatis possesses a single circular chromosome with over a million base pairs and a 7.5 kb highly stored plasmid in numerous copies in each cell [11]. Its defining traits are the minimal genetic variation among variants (2% of the genome) and conserved genomes of this species. However, it shows certain areas with strong recombination and nucleotide diversity events [12]. Genetically distinct strains affect diverse groups, including MSM (men having sex with men), bisexuals, and heterosexuals [13]. It has been shown that molecular distinctions between strains relate to their tropism and geographical dispersion. These qualities have led to the usage of several typing methods, allowing for the determination of a strain's tissue tropism, the identification and distinction of new or persistent infections, a dynamic transmission understanding, and the observing of the evolution of particular clones [14].

C. trachomatis has historically been typed via serotyping, which employs antibodies directed against the OMP (outer membrane protein). Unfortunately, this method is considered tedious, time-consuming, and insensitive [15]. Polymerase chain reaction (PCR), DNA hybridization-based methods, RFLP

(restriction fragment length polymorphism), and DNA microarrays based on analysis of the *ompA* gene are among molecular approaches that have been utilized to *C. trachomatis* [16, 17]. These have resulted in the identification of 19 variations, which have been divided into three clusters: the variants L1-L3 and L2a, linked to LGV (Lymphogranuloma venereum); the variants A, B, Ba, and C, attached to trachoma; and the variants Da, Ga, D-K, Ja, and Ia, linked to genital-urinary diseases [18, 19].

Every year, there are about 200 million new sexually transmitted infections (STIs) brought on by bacteria like *Chlamydia trachomatis* and *Treponema pallidum*, and 350 million individuals affected by chronic hepatitis B (HBV) and C (HCV) infections [9]. The quality of life of infected and ill patients is negatively impacted by the expensive and significant financial burden of treating these diseases [20, 21]. There are 19 distinct *C. trachomatis* serotypes, each exhibiting a unique tropism and causing a range of severe repercussions in humans, including urethritis, trachoma, and venereal lymphogranuloma. Antibiotics may be used to treat infections, but poor treatment compliance and the widespread presence of the bacteria make frequent screenings even more necessary [22]. The Americas (25.2 million cases) and the Western Pacific (37.2 million cases) have the most significant infection rates [23]. Chlamydia infection is widespread in rural and urban Brazilian Amazon populations, and sexual transmission has been documented, especially in native Indian tribes [24].

In the field of public health, India has introduced STI syndromic case management. This implies that those who exhibit sure signs are empirically cured with an antibiotics mix [25]. Azithromycin and cefixime are used to treat the primary clinical manifestations of *C. trachomatis* infection and vaginal and urethral discharge. Over 80% of illnesses are untreated because they are asymptomatic, which is a significant drawback of the syndromic method, particularly in the case of *C. trachomatis*. This increases the danger of long-term consequences of this illness for many people. Untreated *C. trachomatis* infections may affect a person's health in various ways, whether they appear with symptoms or not (Figure 1). Chlamydial conditions that are left untreated may develop into RTIs (reproductive tract infections), which may cause pelvic inflammatory illness, tubal factor infertility, and a higher risk of ectopic pregnancy in women (with associated morbidity and death) [26]. By resulting in spontaneous miscarriage and stillbirth, *Chlamydia trachomatis* may directly affect pregnancy outcomes. It may also cause pre-term labour, which is linked to poor neonatal outcomes [27, 28]. Infection with HIV and perhaps the HPV (human papillomavirus) may spread and be acquired more efficiently when the genital tract is inflamed.

Last but not least, STIs in general, including *C. trachomatis*, carry a considerable psychological impact. For example, the impact on sexual pleasure may have a detrimental effect on a person's relationships and sexual health. In addition, general welfare is impacted by perceived prejudice and stigma, particularly in traditional countries like India [29]. The problem with this is that, in the lack of diagnostic testing, these STI-associated symptoms might just as well be brought on by any other illness that is not sexually transmitted.

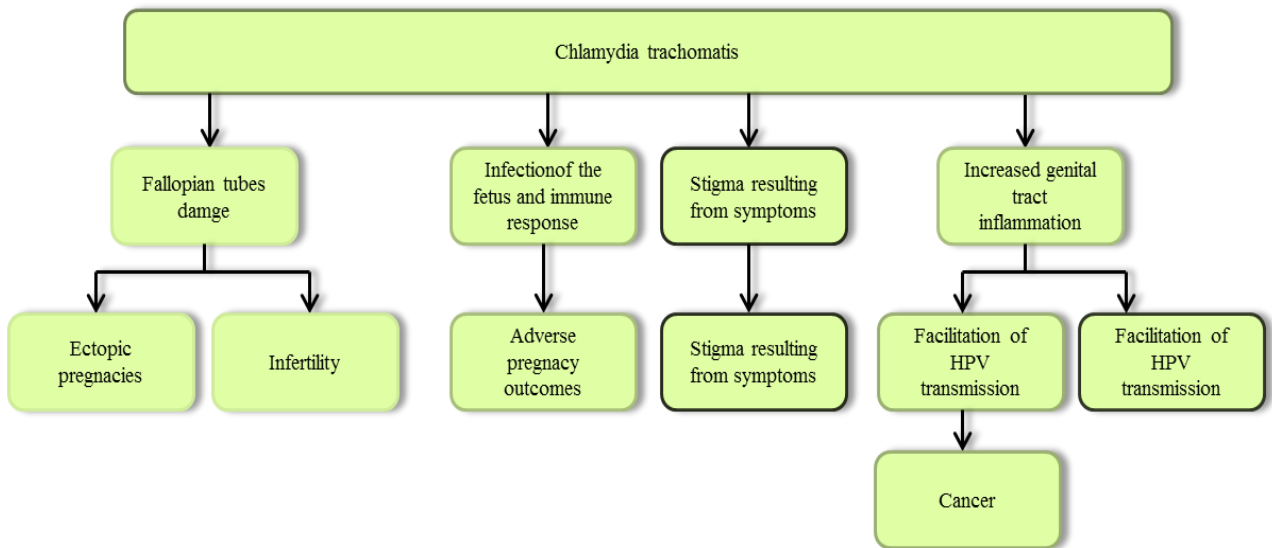


Figure 1. Untreated *Chlamydia trachomatis* effect on individual's health [30]

2. Clinical Manifestations of *C. trachomatis* infection

Both cervicitis in women and urethritis in males may result from chlamydial infection. However, these infections only cause little or no symptoms in around 50% of men and 70% of women, going unnoticed. The ATP and nutrients of host cells are necessary for the Gram-negative bacteria *C. trachomatis* to maintain its biphasic, intracellular developmental cycle *in vivo*. The bacterium often exists in 2 highly specialized morphologic forms in this cycle: the external, infectious, and metabolically active intracellular RB (reticulate body) and metabolically in-active EB (elementary body), which splits by binary fission inside the inclusion [31]. After interacting with several potential ligands on Chlamydia, now recognized as having a route independent of the host cell's surface heparin sulfate glycosaminoglycans, the infectious elementary body enters the mucosal host cells. The EB may then rearrange into the more prominent, replicative form of the RB because, once inside, the endosome seems to be prevented from merging with the lysosomes by the epithelial cell-surface antigens of the EB. Binary fission is used by RBs to effectively divide the endosome, which has now become a chlamydial cytoplasmic inclusion, with the material. After 2-3 days, multiplication stops, and nucleoid condensation takes place, allowing the reticulate body to develop into a contagious elementary body. The elementary body is expelled from the cell and infects other host cells [32].

Chlamydiae may lead to a protracted and often asymptomatic infection. It has been shown *in vitro* that Chlamydia may enter a latent state when exposed to stressful circumstances such as penicillin exposure, IFN (interferon)-exposure (it exhausts the tryptophan that is accessible), growth in iron depletion, [33] or non-permissive cells. This 3rd phase referred to as the "permanent form," has been described as a development stage that is viable but uncultivated and establishes a long-term bond with the infected host. Because of persistence, *Ct* may stay inactive in the host cell, but once the stressful circumstances are gone, it can be

retrieved from the culture. Additionally, there is mounting evidence that chlamydial persistence in vivo exists [34]. All researchers in the field do not accept chlamydial persistence; however, many think that both viabilities of the organism and the nucleic acid detection must be proven to show that chlamydial persistence occurs in vivo. This is because direct identification of Chlamydiae is contested in the diagnosis of latent Chlamydia infection. Because even extremely low levels of specific antibodies may be directly linked to a long-term infection [35], serum tests have long been used to identify patients with long-term, persistent illness; because of the low detectable levels of specific antibodies, the latent infection might be difficult to diagnose. Though it is uncertain how often persistence happens in vivo, persistence may serve as an adaptive survival strategy for the organism [36].

***Trachomatis* infection in Female**

The most contaminated anatomic location in females is the cervix. This can manifest as proctitis, pelvic inflammatory disease, perihepatitis, cervicitis, or urethritis. Untreated chlamydial infections in women increase the risk of ectopic pregnancy and infertility, increasing medical expenses. Additionally, conjunctivitis and pneumonia may occur in children delivered vaginally to moms who have genital *C. trachomatis* infection. The polarized superficial columnar epithelial cells that line the upper reproductive tract and endocervix are the targets of Chlamydia on their apical surface. This connection is enhanced in endometrial epithelial cells with high estrogen levels [37].

Women with cervicitis may not have any symptoms at all, or they may complain of post-coital bleeding or mucopurulent vaginal discharge. Cervical haemorrhage, oedema, and congestion have all been reported. Cervicitis may be accompanied by urethral infection. Leucocyturia with a culture-negative result is indicative of *C. trachomatis* infection. Cervicitis may lead to ascending infections. This commonly occurs with endometritis, which may result in erratic uterine bleeding. PID or salpingitis is often a subclinical condition. It is plausible that *C. trachomatis* represents the root of at least 60% of acute PID cases in Europe. Salpingitis may cause significant reproductive problems, including tubal scarring. Chlamydial infection may cause 2/3 of all instances of tubal factor infertility and 1/3 of all cases of ectopic pregnancy. More than 15% of women with a history of PID may have chronic pelvic discomfort associated with peritoneal adhesions [38].

***Trachomatis* infection in Male**

Chlamydia trachomatis infection in males may result in epididymitis, urethritis, proctitis, prostatitis, or reactive arthritis. Conjunctivitis, pharyngitis, and lymphogranuloma venereum are also the symptoms of *C. trachomatis* infection in both men and women. A less prevalent condition known as LGV (lymphogranuloma venereum), brought on by specific serovars of Chlamydia trachomatis, is exemplified by swollen lymph nodes or severe proctocolitis [39]. Post-gonococcal urethritis and non-gonococcal urethritis are caused mainly by *C. trachomatis*. In young men, acute epididymitis may exacerbate urethritis. Dysuria and a mild clear or white urethral discharge are among the symptoms after 7–21 days of incubation [40]. Oculo-genital serovars may be linked to acute proctitis;

however, this condition is often less severe than LGV serovars. Chlamydial infection does not substantially contribute to male infertility, and there is little indication that *C. trachomatis* plays a role in prostatitis [41, 42]. Conditions with genital *C. trachomatis* have also been linked to reactive arthritis or Reiter's syndrome, including urethritis, arthritis, conjunctivitis, and mucocutaneous lesions with a high male-to-female ratio.

3. Risk factors and demographic factors for *Chlamydia trachomatis* infection

Young age (20 yr) is the most prevalent demographic factor associated with chlamydial infection in women. The squamocolumnar junction, a critical host target for *Ct*, is everted and hence more exposed in the cervix of the younger women, which may account for the anatomical changes. Unmarried status, nulliparity, race as a member of the black community, and low socioeconomic level are additional risk factors for chlamydial infection [43]. Additionally recognized risk factors for the chlamydial disease include concurrent gonococcal infection, having many sexual partners, finding a new partner, not using barrier contraceptives, and having many sexual partners. Additionally, it has been shown that using oral contraceptives is linked to cervical chlamydial infections [44].

4. *Chlamydia trachomatis* Cell biology

Chlamydial species are intracellular microorganisms that need live cells to reproduce. The chlamydial chromosome has a base pair count of around one million and can encode up to 600 proteins. There are now 18 different *C. trachomatis* serotypes known. Neonatal infections and sexually transmitted genital infections are caused by serotypes D through K. Specific genital disorders or clinical presentations, including PID, are not serotype-specific, according to the available research. Chlamydia has a cell cycle that is unique from all other bacteria. Membrane-bound intracellular inclusions are produced as a result of endocytosis. Chlamydia may transform from a dormant state to infectious forms that can reproduce inside host cells, making it harder and harder to get rid of this organism. The mechanisms underlying specific membrane events, attachment and endocytosis, organism multiplication within the cell, conversion from the metabolically inactive EB to the metabolically active replicative RB, and various chlamydial antigens expression throughout the cell cycle are still poorly understood. However, a tremendous amount of new material has just been available on the Chlamydia infection cell biology. The intricate biology of Chlamydia has been revealed by the 1 042 519 base pair. The chlamydial genes phylogenetic mosaic suggests an extremely complicated evolutionary process for adaptation to obligatory intracellular living. Because molecular mimicry between endogenous molecules and microbial proteins has been linked to various autoimmune illnesses, it is now possible to provide more extensive in-vitro and in-vivo confirmation of a causal association between *C. trachomatis* infection and particular disease syndromes. This molecular knowledge has already changed the methods for studying these obligatory intracellular infections [45].

5. Epidemiology of *Chlamydia trachomatis*

Public health initiatives to lower infections of *Chlamydia trachomatis* are based on the findings that Ct is a substantial cause of PID (pelvic inflammatory disease), and reproductive sequelae include chronic pelvic pain, infertility, and ectopic pregnancy [46]. Controlled studies have shown that *C. trachomatis* diagnosis decreased pelvic inflammatory disease, and improvements in nucleic acid amplification assays, single-dose therapy, and modern public health technologies made it possible to execute population-wide initiatives to prevent infertility and control infection [4]. Most infections in women appear to have been clinically visible in the early days of Ct study since 20 (91%) of 22 Ct-infected women in that analysis had mucopurulent cervicitis. MPC (mucopurulent cervicitis) significantly decreased in prevalence as control initiatives developed, and now, most infections in women are asymptomatic [47]. Although many elements influence how disease manifests clinically, the length of the infection that led to the emergence of an immune response is probably crucial. Case discovery is supported by screening since most *C. trachomatis* infections are now asymptomatic. The now-famous mathematical model may be used to explain the management of sexually transmitted infections (STDs), such as *C. trachomatis* = $R_0 \frac{1}{4} \beta cD$.

Sexually transmitted disease control affects the three factors that govern the reproduction rate. Condoms and vaccinations target parameter, behavioural interventions target parameter c , and D , the target parameter for screening and therapy; the primary goals of the screening and treatment-based *C. trachomatis* control program are to reduce the length of infection. Evaluation of *Chlamydia trachomatis* control measures in the "Canadian province of British Columbia" has shown the efficacy of treatment and screening in lowering pelvic inflammatory disease incidence by more than 80% [48]. This finding demonstrates the program's effectiveness and raises the possibility that *C. trachomatis* infection duration has a significant role in predicting the risk of pelvic inflammatory disease. However, when the same population's response to screening and treatment was examined, infection cases decreased and then sharply increased [49]. Growing rates of reinfection were linked to the rising rates. Understanding the natural history of *C. trachomatis* infection was necessary to resolve these perplexing results.

Geisler et al. discovered that 44 of 200 affected women spontaneously cleared the illness before returning to the clinic for treatment. Even though all the women got treatment, the risk of reinfection was four times lower in women who spontaneously cleared the infection than in women who did not. These findings suggest that the acquired immune response linked to infection clearance and resistance to reinfection, as well as the inflammatory pathology linked to pelvic inflammatory disease (PID) and mucopurulent cervicitis (MPC), are related to the duration-dependent host responses to infection [50].

Molano et al. saw up eighty-two asymptotically infected but untreated women for five years before reporting the crucial finding. About half of the women under surveillance after a year were still sick, and even after five years, only about ten per cent of the women had the infection. *C. trachomatis* causes long-lasting

infections, requiring months or even years to achieve immune-mediated clearance [51].

6. The burden of *Chlamydia trachomatis* infection in India

Over one billion people live in India, a nation with a varied ethnic population and one of the world's worst burdens of infectious illnesses. The healthcare system is divided into two parts: the public sector, which serves lower-income individuals, and the commercial sector, which primarily serves high-income inhabitants [52, 53]. According to estimates from 2005–to 2006, the private healthcare industry serves as the primary care provider for 63 per cent of rural and 70 per cent of urban families. Healthcare quality varies greatly, with rural public healthcare facilities often offering the lowest-quality treatment [54]. High maternal and infant mortality rates highlight this wide gap [55].

Table 1. The WHO's STI strategy's strategic directions

Basic components	Strategic action
The basic package of high-impact interventions is the first direction of universal health coverage.	Interventions for impact
Address the barriers and the most effective methods for providing the continuum of care to various groups identified by the second dimension of universal health coverage.	Delivering for equity
Need for comprehensive data collection and monitoring to better understand the STI epidemic.	Information for focused action
The third aspect of universal healthcare is accessed. Find creative and sustainable financial strategies for the STI control response. Methods for cutting expenses.	Financing for sustainability

7. Previous studies on *Chlamydia trachomatis*

Table 2.

Author	Study or statement	References
Thomas et al., 2018	Proposes an integrated care strategy to improve the control and treatment of <i>C. trachomatis</i> in India, considering the WHO framework. The model takes into consideration the obstacles to efficient <i>C. trachomatis</i> control. The barriers are examined and organized into many groups.	[30]
Moore et al., 2003	Findings provide a molecular foundation for the need for both humoral immune responses and T-cell protective immunity against chlamydial reinfection. The activation of rate Th1 by FcR + / + but not FcR / antigen-presenting cells enhance by in-vitro anti-chlamydial antibodies.	[56]
Kari et al., 2011	Created an attenuated, plasmid-free strain of <i>C. trachomatis</i> for the eyes and showed that it could guard against trachoma in a nonhuman monkey model. These	[57]

	plasmid-free strains may represent the greatest hope at developing a vaccine that can produce sufficient protection, including both B and T cell responses, in the absence of harmful disease. Naturally, it will be crucial to thoroughly understand the molecular processes behind these plasmid-free "vaccine" strains, given the regulatory restrictions associated with live attenuated vaccines.	
Dominika et al., 2002	Reported that most nations do not permit reporting chlamydial infections, and those that do so have subpar reporting systems. Direct immunofluorescence testing is still the most widely utilized diagnostic procedure; however, nucleic acid amplification tendencies are visible. The reporting process and the diagnosis of Ct infections are still insufficient, making it impossible to manage the epidemiological situation or provide patients with the best care possible. The professionals and the public education are now the essential tasks.	[58]
Patino et al., 2018	Examined the pattern of each molecular marker and its role in describing the population structure and intra-specific genetic variation, as well as assessing the utility of the four MLST schemes accessible for Ct. Additionally, they discovered that whole-genome data, especially from cgMLST (core genome MLST), enable high-resolution grouping for <i>C. trachomatis</i> isolates.	[59]
Ferreira et al., 2019	In four towns of the Marajó Archipelago, the dynamics of hepatitis C, hepatitis B, <i>C. trachomatis</i> and <i>Treponema pallidum</i> infections were examined. They found that consistent implementation of interventions including health education, regular examination, prompt treatment, and awareness of infection risk factors would stop the spread of illnesses. However, in remote places with limited access to healthcare practitioners where people live, dangerous infectious pathogens are present.	[60]

Conclusion

It is commonly acknowledged that *C. trachomatis* may cause major genitourinary problems in both men and women. Cell biology, bacterial-host cell interactions, disease-producing processes, host defense evasion components, transmission sources, and antimicrobials utilized for therapy are all now the subject of information. Therefore, promoting the control and treatment of Ct infection is essential to enhance health outcomes in countries with low- and middle-income and achieve sustainable development. The underlying healthcare and sickness burden and traditional and cultural obstacles call for audacious measures. There is no vaccination available for *C. trachomatis* related STIs in humans. There are still numerous gaps that need to be filled despite these advancements. The

creation of an efficient vaccination, the ultimate intervention, is still a long way off, and more study is needed.

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