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# ***Chlamydia trachomatis* Infection and Reproductive Health Outcomes in Women**

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## **1. Introduction**

*Chlamydia trachomatis* infection is a major and increasing public health problem worldwide and is currently the main cause of sexually-transmitted infections (STI). The incidence of this infection is highest in young women and is especially important in this population group due to the potential consequences in the female reproductive tract, such as pelvic inflammatory disease, tubal damage, and infertility. During pregnancy, *C. trachomatis* infection has been associated with adverse outcomes, including spontaneous abortion, ectopic pregnancy, premature rupture of membranes, preterm birth. Moreover, the infection can be transmitted perinatally to women's offspring causing neonatal conjunctivitis, nasopharyngitis and pneumonia.

Because of the particular characteristics of this intracellular microorganism (unique biphasic division cycle, slow metabolism) and its interaction with the host's immune response, *C. trachomatis* infection may often pass unnoticed and be under-diagnosed, facilitating its spread, which is mainly associated with sexual risk behaviour. *C. trachomatis* is currently classified in 18 genotypes, or serovars, based on the genetic variation of the major outer membrane protein (MOMP). The genotypes most frequently producing genitourinary tract infection are genotypes D, E, F, G, H, I, J and K. In the last decade, the microbiological diagnosis of *C. trachomatis* infection has improved due to the development of nucleic acid amplification techniques (NAATs) and their progressive introduction in laboratories. Contact tracing is essential in the management of this infection to avoid reinfections. Due to the high and growing impact of *C. trachomatis* infection in public health, the main international agencies involved in STI surveillance (Centers for Disease Control and Prevention [CDC], European Centre for Disease Prevention and Control [ECDC]...) have proposed various prevention measures and levels of intervention to improve its control.

This chapter discusses the transmission and epidemiological data of *C. trachomatis* infection in women of reproductive age, especially pregnant women, and the etiopathogenic mechanisms causing its symptoms and sequelae on fertility and pregnancy. The management of this infection in pregnancy will be analysed in detail, focusing on diagnosis and appropriate treatment, information on the possible effects of this infection, and partner management, which may raise particularly delicate issues. Finally, the screening strategies established in several countries for the population groups with the highest prevalence of this infection will be described and their effectiveness in controlling its spread and in

preventing its adverse effects on fertility, pregnancy and vertical transmission, will be analysed.

## 2. Epidemiology

### 2.1 Transmission

Transmission of *C. trachomatis* infection is through direct contact between the mucous membranes of two individuals during sexual activity or through an infected birth canal. Because of the anatomical characteristics of the female genital tract, the risk of contracting an STI is higher in women than in men.

As with other STI, the risk of *C. trachomatis* transmission is directly related to certain sexual activities, such as starting sexual relations at an early age, their frequency, and a recent change of partner, and especially to risk behaviours, such as sexual activity without protection or incorrect condom use, multiple sexual partners and promiscuity. Other risk factors are a history of contact with *C. trachomatis* or other STI, a previous STI, etc. Pregnant women are not free of these risks.

In the last few years, the incidence of this infection has increased, partly due to a false sense of security created by antiviral HIV therapy in some sectors of the population, leading to carelessness in the use of preventive methods during sexual relations, thus facilitating STI. A higher risk of infection has been described in persons with a low socioeconomic position and in substance abusers, due to lower awareness of and compliance with preventive measures in these population groups. Adolescents are the group most likely to engage in high-risk behaviours, such as unprotected sex, especially when they are under the influence of drugs or alcohol.

A major feature of the epidemiology of *C. trachomatis* infection is the high percentage of the infected population that may be asymptomatic, often for several months. While the percentage of asymptomatic infected men is estimated to be up to 50%, in women this percentage may be as high as 70-75% (18). Asymptomatic infected individuals may spread undiagnosed infection among the sexually active population. Consequently, to improve *C. trachomatis* infection control, in many countries screening strategies have been recommended in the population with the highest prevalence, in addition to treatment of cases and partner management to prevent reinfections.

Transmission of *C. trachomatis* infection among the population can also be facilitated by the emergence of mutated strains, as occurred in Sweden in 2006 with the new variant of *C. trachomatis* (nvCT), which was not detected with the molecular techniques used in some regions due to a 377 bp deletion in the cryptic plasmid (74). The nvCT caused many false-negative diagnoses, allowing this variant to spread to other northern European countries (91). Fortunately, spread beyond these countries has been limited (70).

Another important issue is that other microorganisms causing an STI, including HIV, hepatitis B virus, herpes simplex viruses, *Neisseria gonorrhoeae*, *Treponema pallidum*, can be transmitted in the same episode as that leading to *C. trachomatis* infection. Moreover, in *C. trachomatis*-infected individuals, there is a greater risk of acquiring and, in the case of coinfection, of transmitting other STI due to the inflammatory alterations produced in affected genital mucous membranes (28).

## 2.2 Incidence rate

*C. trachomatis* affects over 600 million people worldwide with more than 90 million new cases occurring globally each year (98). In the USA, more than 1.2 million new cases were reported in 2009, a rate of 409/100,000 people, the most frequently affected being young black women aged 15-24 years (22). In Europe, an incidence rate of 150/100,000 inhabitants has been reported, with an incidence of 1,200/100,000 among women aged between 15 and 24 years (35). The real figures are probably higher since cases are under-reported due to the marked differences in national surveillance and reporting systems. Indeed, some European countries do not provide data, others report very low incidence rates (<1/100,000 inhabitants), and some regions, such as Nordic countries or the UK, report incidence rates of >250/100,000 inhabitants. Consequently, the reported data should be interpreted with caution: a low rate could underestimate the real incidence if the diagnostic measures and reporting systems are inadequate; however an increasing rate may not reflect greater transmission of the infection in countries implementing screening programs that allow detection of asymptomatic cases. Nevertheless, the tendencies in data from several countries show that the reported incidence of *C. trachomatis* infection has increased considerably in the last few years (Figure 1). This increase may be due to the sum of multiple factors: the rise in sexual risk behaviours, decreased compliance with preventive measures, greater knowledge and awareness of *C. trachomatis* infection - leading to more frequent diagnosis -, increased sensitivity of diagnostic methods, and improvement in reporting systems, among other factors.

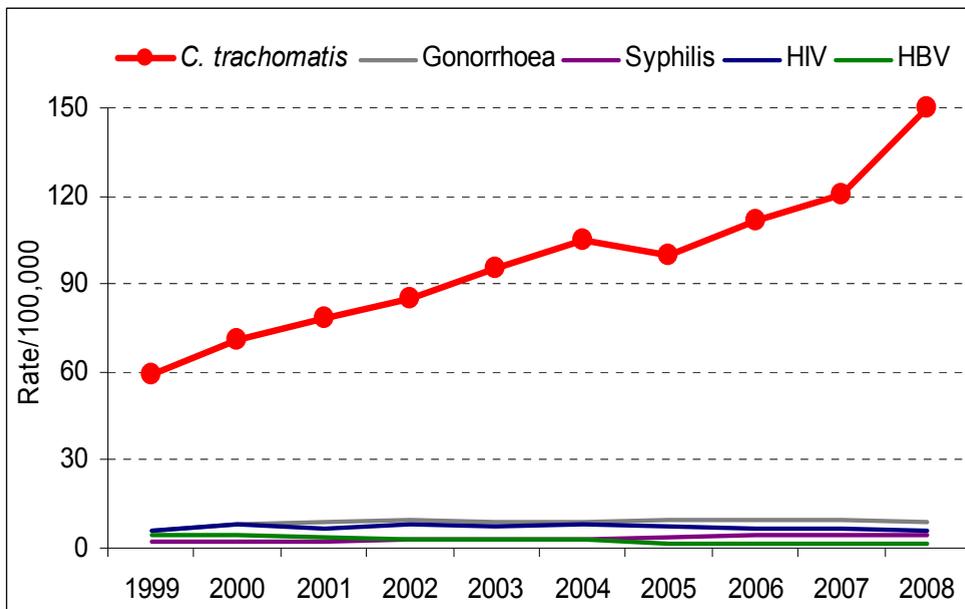


Fig. 1. Incidence rate of *C. trachomatis* and other sexually transmitted infections in the EU per 100,000 inhabitants (ECDC data). (HBV: hepatitis B virus).

Author, country, study period, (reference)	Samples	Population	Women analysed (prevalence)	Factors associated with higher prevalence
X.S. Chen et al, China (Fuzhou, Fujian), Jul-Sep/02 (25)	Cervix	Antenatal care attendees (first prenatal visit)	504 (10.1%)	Younger (18% in $\leq 25$ years), higher monthly income
Pinto et al, Brazil (national study), Mar-Nov/09 (67)	Urine	Parturient women 15-24 years	2071 (9.8%)	Younger (13% in $< 20$ years), first sexual intercourse $< 15$ years, $> 1$ partners/yr.
Romoren et al, Bostwana (Gaberone), Oct/00-Feb/01 (76)	Cervix	Antenatal care attendees	703 (8%)	Younger ( $< 20$ years), unmarried, $< 1$ year in relationship
Kilmarx et al, Thailand (Bangkok and Chiang Rai), Jun-Dec/96 (51)	Urine	Antenatal care attendees (first prenatal visit)	1021 (5.7%)	Younger (13% in $< 20$ years), higher gestational age
Silveira et al, USA (Baltimore, Maryland), Jul/05-Feb/08 (RS) (85)	Not provided	Parturient women with antenatal care information available	2127 (4.7%)	Younger (12% in $< 20$ years), ethnicity (black), single, smoking, NG during pregnancy
Roberts et al, USA (Dallas, Texas), May-Sep/09 (75)	Cervix and urine	Pregnant women at 35-37 weeks' gestation	2018 (cervix: 4.3%) (urine: 4.1%)	Not provided
Rours et al, The Netherlands (Rotterdam), Feb/03-Jan/05 (77)	Urine	Pregnant women attending midwifery practice or antenatal clinic	4055 (3.9%)	Younger (13% in $< 21$ years), ethnicity (16% in Antillean), single (12%)
McMillan et al, Ireland (Dublin), Jun/03-May/04 (60)	Urine	Asymptomatic pregnant women	783 (3.8%)	Younger and single
M.Y. Chen et al., Australia (Melbourne), Oct/06-Jul/07 (24)	Urine	Pregnant women 16-25 years	987 (3.2%)	$> 1$ sexual partner in the past year (12%)
Böhm et al., Germany (national study), Apr-Dec/08 (RS) (14)	Cervix (group1), urine (group 2)	Asymptomatic (g1 and 2) or symptomatic (g 3) pregnant women	51164 (3.1%) g1: 31856 (3.3%) g2: 18169 (2.9%) g3: 1139 (2.0%)	Younger (10% in $\leq 20$ years)

Author, country, study period, (reference)	Samples	Population	Women analysed (prevalence)	Factors associated with higher prevalence
Oakeshott et al, United Kingdom (south London), Jun/98-Jul/00 (63)	Vaginal (self taken), urine	Pregnant women <10 weeks' gestation (general practice and family planning clinic)	1216 (2.4%)	Younger (9% in <25 years, 14% in teenagers), ethnicity (9% in blacks)
Hospital Donostia, Spain (Data not yet published, Oct/10-May/11)	Urine	Pregnant women with complications and unselected parturient women	551 (1.5%)	Younger (5.2% in <30 years)

Abbreviations: NG: *Neisseria gonorrhoeae*; RS: retrospective study

Table 1. Prevalence of *C. trachomatis* infection determined by nucleic acid amplification techniques in studies performed in pregnant women (attending antenatal services) or parturient women throughout the world (if not otherwise specified, prospective, cross-sectional, observational studies).

In the last few years, numerous epidemiological studies have aimed to determine the prevalence of *C. trachomatis* infection in pregnant women, an essential step for the design of appropriate infection control programs in distinct geographical regions (Table 1). The results of these studies are influenced by the sociodemographic characteristics of the population studied, such as age, setting of the population tested, and risk factors, etc., as well as by the type of sample and the diagnostic method used. Currently, the methods of choice in these studies are based on NAATs, generally indicating a prevalence of between 1 and 10%, the highest prevalence being found among young pregnant women and single pregnant women. Specifically, the prevalence in women aged less than 20-22 years was >10% in studies performed in countries as far apart as Botswana, Brasil, Germany, the USA and Ireland.

### 3. Symptoms, etiopathogenesis, and sequelae

The main target of *C. trachomatis* are columnar epithelial cells, particularly in the cervix and urethra, as well as in the rectum, throat, and conjunctiva; in adult women, the squamous epithelium of the vagina is unreceptive to infection. Most infections in women start in the endocervix and the main clinical manifestation in symptomatic infections is cervicitis, sometimes with intermenstrual or postcoital bleeding or dyspareunia. Symptoms usually begin 2 to 6 weeks after infection. Vaginal discharge is present in 50% and is usually mucous and less abundant and purulent than in *Neisseria gonorrhoeae* infections. Dysuria and pollakiuria are infrequent, but urethritis can be associated with cervicitis. In women with hypogastric pain, pelvic inflammatory disease (PID) should be suspected. Depending on sexual practices, other local symptoms (pharyngeal, rectal) may be present. Without an accurate and rapid diagnosis, untreated infections (symptomatic or asymptomatic), may spread among the sexually active population and give rise to complications and sequelae.

The consequences of *C. trachomatis* infection for women's reproductive health can be severe. This pathogen may spread upward from the endocervix, possibly due to binding to

spermatozooids or the passive transport mechanisms of the genital tract, causing endometritis, salpingitis or PID, which can lead to sequelae in 10-20% of patients, mainly infertility and ectopic pregnancy (19). The risk of PID is increased in women with *C. trachomatis* infection who undergo uterine instrumentation, which can reactivate the bacteria or provoke upward spread (4). In addition, *C. trachomatis* can occasionally cause HLA-B27-associated reactive arthritis, Reiter's syndrome, perihepatitis, and Fitz-Hugh-Curtis syndrome. Another complication of *C. trachomatis* infection is its possible role as a carcinogenic co-factor in the development of cervical neoplasms caused by high-risk human papillomavirus (HPV) types (66).

During pregnancy, these infections have been associated with premature rupture of membranes, premature delivery, low birth weight neonates, and miscarriage. Women can infect their neonates through the birth canal, causing conjunctivitis, nasopharyngitis and pneumonia. The risk of perinatal transmission has been estimated to be 20-50% for conjunctivitis (manifesting at 5-12 days after birth), frequently associated with nasopharyngeal infection, and 10-20% for pneumonia (at 1-3 months) (16). Postpartum endometritis can also be associated with *C. trachomatis* infection.

### 3.1 Factors involved in etiopathogenesis

Knowledge of the etiopathogenesis and mechanisms of interaction among microorganisms and their hosts is important to adopt the most appropriate prevention and control strategies, such as screening of high-risk populations, optimal screening intervals, etc., and will help in the development of future vaccines. Paradoxically, in some patients, the defense mechanisms against *C. trachomatis* infection - mainly the inflammatory and adaptive immune responses - could be harmful to tissues. Tissue lesions giving rise to sequelae could be of immunopathological origin rather than due to the direct action of chlamydia.

Epithelial cells are the first defense against *C. trachomatis* infection. On becoming infected, these cells secrete chemokines and cytokines, which stimulate the cellular inflammatory response (leucocytes, natural killer cells, dendritic cells...). The continuous release of some of these cytokines (interleukin [IL]-1, IL-8...), especially during chronic or repeated infections, can cause direct tissue damage and scarring (17,87).

In addition, shortly after *C. trachomatis* infection, an innate cellular immune response is produced, mediated mainly by CD4<sup>+</sup> T cells, with production of Th1-type cytokines, such as tumor necrosis factor (TNF)- $\alpha$  and interferon (INF)- $\gamma$ , which inhibit intracellular chlamydial replication (39). If the infection is not eradicated and persists, or in repeat infections, adaptive T cell immune responses against *C. trachomatis* antigens can be produced, which could collaterally contribute to the development of inflammatory sequelae through autoimmune or delayed hypersensitivity mechanisms, which are still not well understood (17). In experimental animal models, in repeat infections, the enhanced inflammatory response may be mediated by cytotoxic CD8<sup>+</sup> T cells primed against chlamydial heat shock protein 60 (cHSP60), producing greater tissue destruction and fibrosis than in the initial infection, this risk increasing with each additional reinfection (56,71). Serum and genital mucosal IgA and IgG antibodies to specific *C. trachomatis* proteins such as cHSP and to chlamydial elementary bodies (EBs) are usually detected during active infection in women (37), but their precise role in the resolution of infection remains unclear.

*In vitro* studies have revealed that the peculiar metabolic cycle of *C. trachomatis* can be altered by INF- $\gamma$  and other inducers. In a normal cycle, the infectious but metabolically inactive extracellular EBs infect cells, and once inside, they differentiate to non-infectious but metabolically active intracellular reticulate bodies (RBs) that multiply by binary fission within vacuoles. In turn, these RBs reorganize back to EBs that are released to the extracellular medium. In the altered cycle, morphologically enlarged, aberrant, and nondividing RBs are found in a viable but noncultivable state (100). This mechanism may contribute to persistent *C. trachomatis* infection in humans, avoiding the immune system and inducing an immunopathogenic response. However, the question of whether these altered RBs appear *in vivo* and are involved in the development of sequelae remains to be elucidated.

Other determining factors in the development of PID and sequelae may be the natural duration of untreated *C. trachomatis* infection in the host and the number of infections acquired. Approximately half of infections resolve spontaneously in the first year after initial chlamydia testing, but in some women infections may persist for several years. The duration of infection and the chlamydial load in repeat infections seem to be lower than in the first infection, suggesting the existence of some degree of partial immunity (37). However, repeat infections are common and are associated with a higher risk of PID and sequels (41). The sooner an infection is detected, the lower the microorganism's opportunity to ascend the upper genital tract and the lesser the time of action of the immunopathological mechanisms involved in the development of sequelae.

Only a minority of infected women develop reproductive disorders, due to differences in numerous factors including the type of dendritic cell, co-stimulatory molecule expression, the cytokine secretion pattern and hormone levels (1). Therefore, there may be a greater genetic predisposition linked to expression of specific *C. trachomatis* cell receptors, as well as differentiated mechanisms in the immunological response (HLA class I and II variants and functional polymorphisms in cytokine) that determines the result of infection in the host and its potential consequences (3,88).

Although the *ompA* gene of *C. trachomatis* evolves more rapidly than the remaining genome, and its product (MOMP) is exposed on the surface of EBs, there is no evidence that any genotypic *C. trachomatis* variant (MOMP serovars) has a greater capacity than other variants to spread or avoid the immune response and produce greater clinical severity (30,92). The possible roles of other *C. trachomatis* biomarkers, such as the polymorphic outer membrane autotransporter family of proteins (89), type III secretion system effectors (29), and the putative large cytotoxin (9) are currently being studied. These biomarkers could help to identify strain-specific variants with distinct pathogenic characteristics. Further studies that analyse the phenotypic behaviour of this microorganism together with the clinical and epidemiological features of the population studied are required. Furthermore, new studies should attempt to gain greater insight into the molecular epidemiology of the strains involved through techniques allowing high genotypic discrimination, such as multilocus sequence typing (MLST), variable number tandem repeat (VNTR)...

## 3.2 Main reproductive health sequelae in women

### 3.2.1 PID

PID includes several genital tract disorders among women, such as endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis. For PID to occur, *C. trachomatis*, *N. gonorrhoeae*,

or other microorganisms must spread upward from the lower genital tract, infecting and causing inflammation of the uterus, fallopian tubes, and ovaries. The most frequent cause of PID is *C. trachomatis* genital infection, and studies in women with laparoscopically proven PID have described a prevalence of 10-60% (86). However, the risk of developing PID among *C. trachomatis*-infected women is not well known since few prospective studies have been performed and the number of cases included has generally been small. Despite these limitations, the risk seems to be high: the results of a recent randomised controlled trial performed in the UK that included 75 women with untreated, asymptomatic *C. trachomatis* infection found that 9.5% (95% CI 4.7%-18.3%) developed PID over 1 year (63). Although current data are limited, the risk of developing PID seems to be higher in the first few weeks of infection (41).

The main clinical manifestation of PID is abdominal pain. However, particularly in the initial stages, the symptoms may be non-specific, consisting of abnormal discharge, intermenstrual or postcoital bleeding, fever, urinary frequency, low back pain, nausea/vomiting, etc., and several consultations are required to reach a diagnosis. After a PID - which can be symptomatic or subclinical - gynecological and reproductive sequelae may appear, such as infertility (15-20%), ectopic pregnancy (an increased risk of 6-10-fold) and chronic pelvic pain, as a result of alterations in the cilia lining the fallopian tubes, destruction of ciliated cells, tubal occlusion, scarring, or adhesion formation among pelvic organs. However, the risk of developing sequelae after PID caused by *C. trachomatis* and that caused by other etiologies seems to be similar (41). Genetic studies of individual immunopathogenetic factors have suggested that a single nucleotide polymorphism in inflammasome-associated NLRP3 is related to the severity of *C. trachomatis* infection (95). Screening for chlamydia infection and treatment can prevent PID, although, as mentioned in the section on prevention, some authors have questioned the cost-effectiveness of screening in the prevention of sequelae.

### 3.2.2 Tubal factor infertility

An estimated 5-15% of women of reproductive age are infertile, representing a major problem for more than 70 million women worldwide (15). According to the WHO, *C. trachomatis* postinfection damage of the fallopian tubes may cause 30-40% of cases of female infertility (99), the most common cause being PID.

Multiple mechanisms can contribute to the development of this severe repercussion of *C. trachomatis* infection. Studies in the murine model have demonstrated that interstitial cells of Cajal (ICC), which form a dense network associated with the smooth muscle cells of the oviduct, are the source of the electrical pacemaker activity responsible for oviduct motility and egg transport, and that these cells are damaged by the inflammatory responses released by chlamydia infection. The destruction of the oviduct ICC networks might contribute to oviduct stasis and pseudo-obstruction, functional block of oocyte transport and retention of secretions, which could progress to fibrosis, tubal occlusion and finally infertility (32). Hydrosalpinx, a result of tubal obstruction, is present in about 30% of women with tubal factor infertility (TFI), and the fluid can reflux into the uterine cavity, inhibiting implantation of embryos in the endometrium. In addition, cystic fibrosis transmembrane conductance regulator (CFTR), an AMP-activated chloride channel that regulates epithelial electrolyte and fluid secretion and whose expression is elevated in the reproductive tract of

*C. trachomatis*-infected women, has been implicated in the pathogenesis of hydrosalpinx formation (2). Moreover, CFTR expression has another effect on fertility in the uterus, given that this substance plays a role in the regulation of the balance between the fluid volume in the endometrial mucous membrane during the estrous cycle, which is involved in blastocyst implantation. In the murine model, CFTR overexpression induced by cytokine release during *C. trachomatis* infection leads to abnormal fluid accumulation in uterus at diestrus and to a reduced implantation rate (43).

In addition, individual genetic variations may play a major role in the immune response to *C. trachomatis* and in the pathogenesis of complications and sequelae. More specifically, functional polymorphisms in specific cytokine genes and other components of the host's immune and proinflammatory response (IL-10, IL-12, TNF- $\alpha$ , NLRP3...) are involved in the regulation of the immune response and contribute to the distinct manifestations of the disease and its outcomes (66). Lastly, the sequence identity shared between cHSP60 and human HSP60 (48.5%) has traditionally been considered to cause cross-reactivity and consequently autoimmunity, which could play a role in the pathogenesis of TFI. However, TFI has recently been associated with antibodies against cHSP60, but not against human HSP60, pointing to an infectious rather than an autoimmune inflammation and suggesting antibody testing as a supplement in TFI diagnosis (44).

### 3.2.3 Ectopic pregnancy

Approximately 1-2% of pregnancies are ectopic, and 97-98% occur in the Fallopian tubes, representing the main cause of maternal death in the first trimester of pregnancy (94). The risk of ectopic pregnancy is higher in women with Fallopian tube damage due to pelvic infections mainly by *C. trachomatis* or pelvic surgery, previous ectopic pregnancy, smoking and *in vitro* fertilization. Therefore, most of the above-mentioned etiopathogenic mechanisms of TFI can also cause an ectopic pregnancy.

Tubal ectopic pregnancy is caused by a combination of factors that allow embryo retention in the Fallopian tube due to limitations in tubal transport and/or alterations in the tubal environment that favour early egg implantation. The Fallopian tubes in women with ectopic pregnancies show altered expression of prokineticin receptors (PROKRs), a molecule involved in the control of smooth muscle contractility. Through ligation of tubal Toll-like receptor 2 and activation of NF $\kappa$ B (nuclear factor kappa-light-chain enhancer of activated B cells), *C. trachomatis* infection leads to increased tubal PROKR2, probably predisposing the tubal microenvironment to ectopic implantation (84). In addition, an increase in the expression of activins and inducible nitric oxide synthase (iNOS) within the human Fallopian tube of patients with an ectopic pregnancy and antibodies against *C. trachomatis* has been observed, suggesting that these proteins may be involved in the microbial-mediated immune response that contributes to tubal damage and ectopic pregnancy (72). Nitric oxide production is considered to be part of the innate immune response (being bactericidal for intracellular pathogens, including *C. trachomatis*), but chronic chlamydia infections can lead to an excess of iNOS-derived nitric oxide, damaging tubal epithelial cells and possibly leading to an ectopic pregnancy (83). Lastly, the elafin molecule has anti-protease, anti-microbial, innate immune defence and anti-inflammatory properties and is found in various human mucosal membranes such as those of the female genital tract, and whose expression is increased in the Fallopian tubes of women with ectopic pregnancy. Elafin is also up-regulated in an *in-vitro* model in response to *C. trachomatis* infection (52).

### 3.2.4 Pregnancy outcomes

*C. trachomatis* infection during pregnancy has been associated with adverse outcomes such as premature rupture of membranes (PRM), premature delivery, low birth-weight and miscarriage. However, the results of studies on this topic have often been distinct and even contradictory. Many of these publications included a small number of women and used inappropriate serological methods to distinguish between current and past infection.

Recently, two large population-based studies (each with about 4000 women) have shed new light on the potential role of *C. trachomatis* in this context. A population-based retrospective cohort study carried out in Washington State (USA) using birth certificate data found that chlamydia-infected women had a higher risk of preterm delivery and PRM than a non-infected control group (13). Premature delivery (<37 weeks) occurs in 9.6% of all births worldwide and can be due to multiple factors, with 30% being related to PRM (8). The mechanism through which chlamydia causes PRM is not well known, but could be produced through choriodecidual inflammation and chorioamnionitis generated through some of the above-mentioned etiopathogenetic mechanisms. Interestingly, this risk has been reported to decrease in successfully treated patients, given that the frequency of PRM was lower than in patients who were treated but who had either persistent or recurrent chlamydia infection at the end of pregnancy; furthermore, the risk was not significantly different to the risk in those without *C. trachomatis* detection in pregnancy (27). In the second population-based cohort study, a prospective and non-interventional analysis during pregnancy performed in Holland, *C. trachomatis* infection detected with NAATs was significantly associated with prematurity before 35 weeks of pregnancy, this risk being higher before 32 weeks (78). Of deliveries before 32 and 35 weeks of pregnancy, 14.9% and 7.4%, respectively, were associated with *C. trachomatis* infection, suggesting that chlamydia contributes more to early than to late prematurity. In this study, pregnancy was shorter in chlamydia-positive women. Neither of these two population-based studies found that low birth weight (<2,500 g) or small-for-gestational-age neonates, or miscarriage were associated with maternal *C. trachomatis* infection.

A recent Polish study found that the prevalence of *C. trachomatis* detected by NAATs and serology was higher in women who miscarried than in other pregnant women, suggesting that chlamydial infection can cause spontaneous pregnancy loss (97). However, studies designed to analyse the possible role of *C. trachomatis* in miscarriage are lacking and this issue continues to be controversial. Finally, postpartum endometritis is a common complication in *C. trachomatis*-infected women.

### 3.2.5 Cervical neoplasia

Cervical neoplasia is the second most common cancer in women worldwide, the main cause being persistent infection with high-risk HPV. However, only a small proportion of HPV infections are persistent and progress to cervical cancer, suggesting that co-factors may also be involved in its carcinogenesis. Some seroepidemiological studies have associated *C. trachomatis* with the development of cervical squamous cell carcinoma, and it has even been suggested that this association could be greater with specific serotypes (G, I, D and B) (6,65). The results of two large (8441 women), multinational, clinical trials that evaluated the safety and efficacy of an HPV vaccine suggested that *C. trachomatis* is an independent, but

moderate, co-factor for the development of cervical neoplasia. In addition, *C. trachomatis* seems to be involved only in the early stages of cervical carcinogenesis, as no increased risk associated with *C. trachomatis* was found for CIN-3 (55).

The mechanisms causing this association are unknown. *C. trachomatis* modulates the host immune response and inhibits apoptosis, which could encourage the persistence of infected HPV cells. Moreover, *C. trachomatis* induces inflammation and cervical metaplasia, favouring the access and propagation of HPV, given that metaplastic cells are potential targets for HPV. Chlamydia infection may increase the access of HPV to the basal epithelium and increases HPV viral load (66). Therefore, some authors argue that associations between *C. trachomatis* and cervical premalignancy could be caused, in part, by an increased susceptibility to HPV infection (79). In contrast, new molecular evidence now suggests that chlamydial protease-like activity factor induces centrosome amplification, which may help to explain the role of chlamydia in cervical carcinogenesis (49).

#### 4. Microbiological diagnosis

This section aims to outline the microbiological diagnostic methods most commonly used in *C. trachomatis* infection and to define the most appropriate samples for diagnosis in women. Diagnostic techniques, which are discussed in another chapter, will not be described in detail. A general consideration when approaching the diagnosis of an STI in the clinical setting is that other microorganisms that could cause coinfection should always be investigated. Consequently, other bacterial causes, such as *N. gonorrhoeae* and *Trichomonas vaginalis*, among others, must be excluded and a serum sample must be requested to investigate HIV, hepatitis B and C viruses and syphilis infection. Obviously, this practice is not applied in most screening programmes.

Appropriate samples for *C. trachomatis* detection are cervical exudates, vaginal swabs and urine samples. Depending on the symptoms, conjunctival, pharyngeal and rectal exudates can also be obtained, as well as other samples in specific cases. Cervical exudates should be obtained by a gynecologist. Vaginal swabs can be self-collected or collected by a physician, with no differences in sensitivity or specificity (81). With urine sampling, it is essential to collect first-void urine, defined as the first 10-30mL of the urine, and for the patient not to have urinated for at least 2 hours previously. Self-collected vaginal swabs and first-void urine are samples that are widely accepted by women (12), and can be collected in-house and mailed to laboratories, thus facilitating epidemiological studies and screening programmes in asymptomatic women. In addition, urine allows samples to be grouped into pools and increases the cost-effectiveness of studies, with little reduction in sensitivity (77). A large German study, using 5 urine pools, obtained a negative predictive value of 98.1% for the pooling system (14).

A wide variety of techniques are available for *C. trachomatis* detection. Cell culture, antigen-based detection methods, such as direct fluorescent assay, immunochromatography and enzyme immunoassay, and nucleic acid hybridization tests have been widely used in clinical laboratories. Due to their lower sensitivity, all these techniques are being substituted by NAATs, which increase detection by 20-40% and are the currently recommended techniques. However, NAATs are expensive and their introduction for *C. trachomatis* detection may be difficult in some laboratories. The chlamydial load is lower in urine than in

vaginal swabs and is lower in the latter than in endocervical swabs (61). Therefore, vaginal swabs and urine should only be analysed through molecular amplification methods. These distinct chlamydial loads probably explain the lower sensitivity found by some authors when using first-void urine rather than vaginal or endocervical swabs (14), although this difference has not been found in all studies (75). The most recent NAATs use specific primers and probes that target two cryptic plasmid fragments or a fragment of the cryptic plasmid and another fragment of the *ompA* gene. These new NAATs are able to detect variants with deletions in the cryptic plasmid such as the new Swedish *C. trachomatis* variant (nvCT), first detected in 2006. The nvCT variant contains a 377-bp deletion in the cryptic plasmid that covers the single targets originally utilized in some commercial NAATs (74). The use of modern automatic nucleic acid extraction devices also helps to improve the sensitivity of techniques that perform manual extraction through lysis (69).

Numerous point-of-care tests, based on immunological methods and providing rapid diagnosis have been designed for *C. trachomatis* detection. The sensitivity of these tests is currently considered to be inadequate, at around <50%, as is their specificity, given that most are based on lipopolysaccharide detection, which often presents cross-reaction with the lipopolysaccharide of Gram-negative bacteria, leading to the possibility of false-positive results. Given this possibility, the development of a point-of-care tests that detects *C. trachomatis* with sufficient sensitivity (>90%) is currently a pressing need (48). Recently, new tests based on signal amplification systems have shown a higher sensitivity of around 80% (59).

Serological methods are not useful in the diagnosis of uncomplicated *C. trachomatis* infection. The antibody profile generated in acute and chronic infection is not well known. Moreover, the serological response can be inconsistent or weak, since the infection is usually limited to the mucosal surface. Nevertheless, antibody detection is considered important in women with TFI, as serological evidence of past infection is associated with a significantly increased risk of women suffering TFI (4). Likewise, serological methods are useful in epidemiological studies (53).

*C. trachomatis* typing can be performed through serotyping with monoclonal antibodies against the MOMP protein or genotyping of the *ompA* gene, whether through restriction fragment length polymorphism analysis or sequencing. Genotyping through sequencing is easier to implement in clinical laboratories and can be performed directly in the clinical sample, which explains its increasing use. This technique is allowing the worldwide distribution of distinct genotypes of *C. trachomatis* to be determined and its possible geographical features and temporal evolution to be compared (68). Other techniques allowing greater discrimination and differentiation among strains, such as MLST and VNTR, have been developed; these techniques will help to generate further insight into the natural history of the infection, thus enabling detailed clinical-epidemiological studies and aiding vaccine design.

## 5. Treatment

In addition to accurate diagnosis and appropriate antibiotic therapy, the management of uncomplicated *C. trachomatis* infection also requires counseling and treatment of the sexual partner(s), which reduces the possibility of reinfection of the original partner and infection of possible other partners, thus decreasing transmission within the community.

*C. trachomatis* is usually susceptible to tetracyclines, macrolides, fluoroquinolones, amoxicillin, rifampin and sulfonamides, among other antibiotics. With rare exceptions, such as rifampin, chlamydiae do not easily develop resistances to antibiotics and, because these microorganisms are obligate intracellular bacteria they are unlikely to acquire resistance genes from other bacteria through horizontal transmission (45). Although there are few studies of antimicrobial susceptibility in *C. trachomatis*, reports of isolates in patients with resistance strains are scarce, and in most of these reports, the isolates screened displayed characteristics of heterotypic resistance, affecting only a small part of the bacterial population. This type of resistance often disappears with the spread of the bacteria (80). However, heterotypic resistance could cause treatment failure in patients with high chlamydial load (46). A recent European study that included *C. trachomatis* isolates from all the urogenital serovars (D through K, n=45) found that all the isolates were susceptible to the antimicrobials tested: levofloxacin, erythromycin, doxycycline, clarithromycin, and azithromycin (33). Nevertheless, in India, decreased antibiotic susceptibility to azithromycin and doxycycline has been reported in 38% – a significant proportion – of the strains isolated in patients with recurrent infections (10). The advisability of monitoring the development of *C. trachomatis* resistance is hampered by the lack of standardized antimicrobial susceptibility tests, which currently require cell cultures.

The standard treatment regimens for uncomplicated lower genital tract infections are one dose of azithromycin or two doses/day of doxycycline for 7 days (Table 2). Both regimens have shown an efficacy of >95% in the microbial cure of *C. trachomatis* (54), although compliance is lower with doxycycline. A single dose of azithromycin should be the treatment of choice in persons who may not be able to comply with longer treatment regimens. Other alternatives are erythromycin, which is associated with a higher rate of adverse effects, and ofloxacin and levofloxacin, which are more expensive. The treatment of HIV-infected women is similar. Treatment should be started as soon as possible, especially in women with urethritis/cervicitis with clear secretion and/or more than 5 leukocytes per field in the Gram stain, even when an etiologic diagnosis is unavailable. In these patients, the recommended empirical treatment includes an oral dose of azithromycin and an intramuscular dose of ceftriaxone to cover possible infection by – or coinfection with – *N. gonorrhoeae*. After starting treatment, patients should abstain from sexual contact for 7 days.

Infection	Antibiotic treatment
Urethritis/cervicitis	Azithromycin 1 g po 1 dose Doxycycline 100 mg/12h po 7 days
Lymphogranuloma venereum	Doxycycline 100 mg/12h po 21 days
PID	Cefoxitin 2 g/6h IV + doxycycline 100 mg/12h po Clindamycin 900 mg/8h IV + gentamicin 1.5 mg/kg/8h IM/IV
Pregnancy	Azithromycin 1 g po 1 dose Amoxicillin 500 mg/8h po 7 days
Ophthalmia neonatorum	Erythromycin base or ethylsuccinate 50 mg/kg/day (4 doses) po 14 days
Infant pneumonia	Erythromycin base or ethylsuccinate 50 mg/kg/day (4 doses) po 14 days

Table 2. Recommended regimens of antibiotic treatment in *C. trachomatis* infections

An indispensable component of treatment is partner management. This strategy is often difficult but it is essential to strongly advise patients to inform their sexual partners of their infection and for their partners to be examined. All sexual partners in the 60 days prior to symptom onset in the index case – or the last contact, if more than 60 days previously – must be diagnosed and treated. When attendance by sexual partners is highly unlikely, the index patient may be given the partner's treatment and instructed in its use, a practice known as expedited partner therapy, which is easier if azithromycin is used. Lack of partner management is usually the most frequent cause of reinfection, and expedited partner therapy has been shown to be useful in ensuring partner treatment among men and in reducing repeat infections among women (20).

A cure test is not routinely recommended if treatment of the index case has been adequate. This test is recommended in pregnancy (see below) and when there is doubt about treatment compliance, suspected reinfection or persistent symptoms. When a cure test is performed, NAATs should be used 3-5 weeks after the end of treatment. *C. trachomatis* nucleic acids can persist in cells for up to 3 weeks (23). Nevertheless, since reinfection is frequent in persons with previous *C. trachomatis* infection (47), a new test of *C. trachomatis* detection is recommended approximately 3 months after the end of treatment (23).

In pregnancy, tetracyclines and fluoroquinolones are contraindicated. The recommended antibiotics are azithromycin, amoxicillin and erythromycin and the current first-line choice is a single oral dose of 1 g of azithromycin. Erythromycin produces a higher frequency of gastrointestinal adverse effects, requiring treatment withdrawal; moreover, in pregnant women, liver clearance of this drug is increased, which could reduce its plasma concentration, thus increasing the risk of treatment failure (66). Due to the lower effectiveness of antimicrobials in pregnancy, as well as the possible adverse effects on pregnancy course and the possibility of neonatal transmission, a cure test is recommended 3-5 weeks after the end of treatment, as well as a further test at 3 months to exclude reinfection. In pregnant women with risk factors, such as those aged  $\leq 25$  years or with several sexual partners or a new sexual partner, an additional test should be performed in the third trimester of pregnancy (23).

The treatments recommended in other situations are shown in table 2. Treatment of PID falls beyond the scope of this chapter. However, since *C. trachomatis* is one of the most common causes of PID, the etiology of PID is often polymicrobial and *C. trachomatis* detection in cases of PID is far from easy – especially without samples from the upper-genital tract – treatment of *C. trachomatis* should be covered in all patients with PID.

Lastly, prophylaxis or specific treatment in the neonates of mothers with genital *C. trachomatis* infection is not recommended. These neonates should be monitored clinically to allow microbiological diagnosis and treatment if symptoms develop: up to one month should be allowed for the development of conjunctivitis, and up to 3 months for pneumonia.

## 6. Prevention

In addition to being easily treated with antibiotics, *C. trachomatis* infection is preventable. Because of the increasing incidence rates of this infection, the high percentage of the population that may have asymptomatic infection, and the severity of its potential sequelae, various control programs have been developed. The CDC in the USA recommend annual

chlamydia screening in all sexually active women aged  $\leq 25$  years and in older women with risk factors. Screening of all pregnant women is also recommended (23). In Europe, the ECDC have described four levels of intervention in *C. trachomatis* infection control (34): A) primary prevention: sexual health promotion and information; B) case management: guidelines for clinical and microbiological diagnosis, as well as for patient treatment, which includes contact tracing, and a system for case reporting; C) "opportunistic" testing: screening in asymptomatic persons from specified groups considered at risk to detect new cases, mainly in young persons and/or those with several sexual partners when attending health services for other reasons; and D) proactive systematic population-based screening, aimed at covering a substantial portion of a defined population to reduce the prevalence of infection. Although most European countries carry out the first two levels, fewer have experience and knowledge of the third and fourth levels. In this context, no consistent association between the economic resources of a country and the intensity of chlamydia control activities has been found (57). In their guidelines, the ECDC recognizes that there is insufficient epidemiological information for decision making and aims to obtain sufficient data between 2010-11.

The increase in the last few years in the incidence rates of several STI such as *C. trachomatis* infection highlights the need to maintain and, if possible, intensify primary prevention through health education and safe sex campaigns, such as correct and consistent condom use. Information campaigns are essential to raise awareness of STI not only among young people but also among their parents and even the physicians involved in the management of these infections (96), since the stigma commonly associated with STI is usually a handicap to their management and to adherence to prevention programmes. Primary prevention of *C. trachomatis* infection through vaccination is not yet feasible. The complex antigen structure of this pathogen and still insufficient knowledge of the protective *C. trachomatis* antigens involved in the immune response have proven to be a barrier to the development of effective vaccines.

Secondary prevention through opportunistic or systematic screening is still the most important intervention to limit the adverse effects of *C. trachomatis* infection on reproductive health (66). Screening for chlamydia in females aged  $< 25$  years has been described as one of the most beneficial and cost-effective preventive services that can be offered in medical practice (58), and has been considered as an A-rated recommended preventive service (strongest recommendation) (93). Screening of men has not been shown to be cost-efficient and, although this practice could prevent many infections in women, its impact on the burden of disease in women by testing young men or specific risk groups is controversial (38,50).

Preventive strategies should focus especially on the young, because the incidence rates of infection are much higher in this population group and the increase observed in the last decade has affected mainly this age group, with little variation in other age groups (73). To comply with the objectives of public health programmes and reduce transmission among the population as far as possible, both wide acceptance among the target population and high coverage and regular uptake are essential (53). Unfortunately, screening coverage rates do not usually exceed 60%, partly due to lack of knowledge among some young women about the need for screening and the social stigma attached to STI (21,58). Publicity campaigns and strategies such as "Get Yourself Tested" (available at

<http://www.gytnow.org>) aim to improve these results and avoid the formation of core groups with high reinfection rates, such as sexually active adolescent girls or young men with a previous history of STI (7,36,66). The various screening modalities have contributed to the increase in the number of detected cases, without this increase representing a real rise in incidence, given that it essentially reveals previously undetected asymptomatic infections. Moreover, recent studies using mathematical models suggest that screening reduces the prevalence of infection (50,90).

Opportunistic screenings aim to halt spread of infection and avoid its sequelae through detection of new cases in asymptomatically infected risk groups. The most common target groups are usually sexually active young persons, especially those with frequent changes of partner, pregnant women, women seeking pregnancy termination, and those undergoing instrumentation of the uterus. Partly due to differences in the local epidemiology and burden of disease, various policies and practices are underway in several countries such as the USA, England, Denmark, Estonia, Iceland, Latvia, Norway, and Sweden, although not all of these policies are nationwide and some are implemented in specific regions only (19,34,50,57). Women are usually more willing than men to undergo diagnostic tests for STI. For example, in Sweden, less than 30% of all persons tested for chlamydia are men (42). Since 2003 in Stockholm and currently in other Swedish counties, there is an opportunistic screening called "Chlamydia Monday", because the campaign takes place annually one Monday in September. Every year, the number of chlamydia cases reported in Sweden is higher in September and October, since the opportunities of finding a new sexual partner and becoming infected increase in summer. During the campaign, massive media activity provides information and promotes condom use to prevent STI, and encourages people to get tested for chlamydia with the aim of recruiting young men in particular, who request testing less than women. "Chlamydia Monday" helps to raise awareness of the importance of STI among the public and is a cost-effective intervention to decrease the prevalence of chlamydia and its complications in Sweden, encouraging both men and women to seek testing (31).

Systematic screening for chlamydia using the internet and self-sampling kits has been implemented in certain regions of The Netherlands among 16 to 29 year-olds and its results in terms of the impact on population prevalence and cost-effectiveness evaluation will allow the advisability of implementing a nationwide chlamydia screening programme to be assessed and the optimal strategy to be designed. The acceptability of this home-based screening was high, the response rate being 63% (40); however, increasing this response remains difficult. Innovative strategies such as those used in this programme that combine confidentiality, simplicity and perception of the benefit of screening could increase the participation achieved in opportunistic screenings.

Knowledge of the impact of chlamydia screening on individuals and public health is limited (39,53). The health gains and cost-savings obtained by *C. trachomatis* screening programmes may have been overestimated, especially in epidemiological studies using serological techniques. The effect of screenings on reducing the risk of developing complications and sequelae has been analysed in some studies that have reached distinct conclusions; furthermore, comparison of these studies is difficult due to their various limitations, such as the study type and duration, the age groups analysed, and the multifactorial causes of the sequelae, among other factors. A large nonrandomized cohort study in female US Army

recruits found no differences in hospitalizations for PID among women who were screened compared with those who were not (26). Equally, a randomised study with 9-year follow-up in women aged 21-23 years performed in Denmark found no differences between screened and non-screened women in the rates of PID and long-term risk of reproductive complications as the outcome (5). In contrast, two randomized trials comparing chlamydia screening in young women with a control group not invited for testing found a 50% reduction in PID over the subsequent year (64,82). Finally, in another randomised trial, limited evidence was observed suggesting that screening for chlamydia reduces PID rates: 10% of asymptomatic infected women not treated developed PID within a year, versus 2% of screened and treated women (63). Further studies evaluating the effectiveness of chlamydia screening are clearly needed.

The risk of longer-term reproductive health consequences, such as infertility and ectopic pregnancy, is low after treatment of a single episode (62,66); however, as previously mentioned, the development of sequelae is influenced by the immunopathological changes produced after successive reinfections and by the length of the infection (39). Therefore, the optimal frequency for testing is currently estimated to be once a year or with each change of partner. In this context, tertiary prevention - i.e. accurate diagnosis and appropriate treatment - shortens the duration of infection, and, if partner management is included, prevents transmission chains and reinfections.

In countries with a high prevalence of *C. trachomatis* infection, screening in pregnant or puerperal women increases infection control by including a substantial proportion of the target population. There is evidence of improved pregnancy and birth outcomes for pregnant women aged <25 years treated for chlamydia, and screening has been recommended (93). No studies have evaluated the effectiveness of screening in pregnant women aged >25 years old, but this practice could prevent adverse pregnancy outcomes and vertical infection. For these reasons, universal screening in pregnancy should be considered unless selective criteria can be validated (85). If the screening is performed at the beginning of pregnancy, there is a risk of not preventing possible reinfections, and if performed at the end, some of the complications of infection during pregnancy cannot be avoided. The CDC has recommended screening in all women at the first antenatal visit with rescreening in the third trimester in women aged  $\leq 25$  years and those who have a new or more than one sexual partner, as these are the women at highest risk. Women usually have little awareness of the transmission and effects of chlamydia before being tested, and the high acceptance of screening demonstrated in young women who have previously been informed of the sequels of this infection and its possible consequences on the health of their neonates will be essential to the uptake of chlamydia screening in future antenatal screening strategies (11).

In summary, most chlamydia infections are undetected and therefore the potential complications and sequels that can arise are not prevented. In the next few years, improvement in screening programs due to the knowledge currently being gained will probably enhance not only individual benefit, but also the impact on public health.

## 7. Conclusion

*C. trachomatis* genital infection is an increasing public health problem worldwide and has major adverse effects on women's reproductive health and in pregnancy. This infection may

go unnoticed in up to 75% of infected women. The development of molecular amplification techniques in the last few years has increased the sensitivity and specificity of the detection of this intracellular bacterium. Infection is easily treated with antibiotics, while single-dose therapy improves adherence. An essential part of treatment is contact management. However, the most effective weapon is prevention. The adoption of the optimal preventive measures for each country is helped by better knowledge of the incidence, prevalence and impact of this infection. National health systems should make every effort to improve surveillance and to provide information on this infection, its potential consequences and the possibilities of prevention to the public. Special emphasis should be placed on young persons and on the core groups that are least likely to follow these preventive measures. Prevention can be enhanced through screening, which is especially important in pregnant women to reduce complications in both the pregnancy and the neonate. Despite the progress made in the last few years in the knowledge of etiopathogenesis, diagnosis, treatment and prevention of *C. trachomatis*, further research is required to reduce the burden of this infection.

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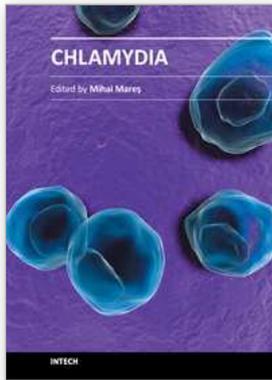
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## **Chlamydia**

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Nowadays, Chlamydia still represents a redoubtable pathogen. Among its consequences, the blindness in children and severe impairment of reproductive health in adults are the most mutilating. Worldwide, it is estimated that six million of people suffer from post-trachoma blindness and almost 90 million become sexually infected each year. Due to its silent evolution and sexually transmission, the chlamydial infection can occur in anyone. The book "Chlamydia - A Multifaceted Pathogen" contains an updated review of all-important issues concerning the chlamydial infection. It comprises 18 chapters grouped in four major parts dealing with etiology and pathogenicity, clinical aspects, diagnosis and prevention. The new molecular data about the pathogenicity and the exhaustive presentation of clinical findings bring novelty to the book and improve our knowledge about Chlamydia induced diseases.

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