Chlamydia trachomatis, a Hidden Epidemic: Effects on Female Reproduction and Options for Treatment

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報告：R2 關貝如

Introduction

- Chlamydia trachomatis
  - Gram-negative bacterium
  - unique biphasic developmental cycle
  - Serovars D-K

Introduction

- 70% of infected women and 50% of infected men are asymptomatic
- Risk factor
  - Age: 15-24
  - Gender: woman > man
  - Race

Introduction

- increase in infections
  - 7.5% from 2006 to 2007 in U.S.
  - independent 5% per year increase in C. trachomatis positivity between 1997 and 2004

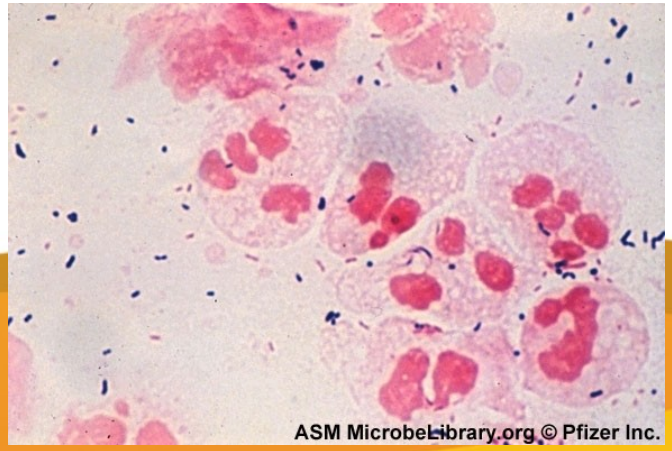
Cost effective

- Screening is cost effective, because of the reduction in long-term health costs.

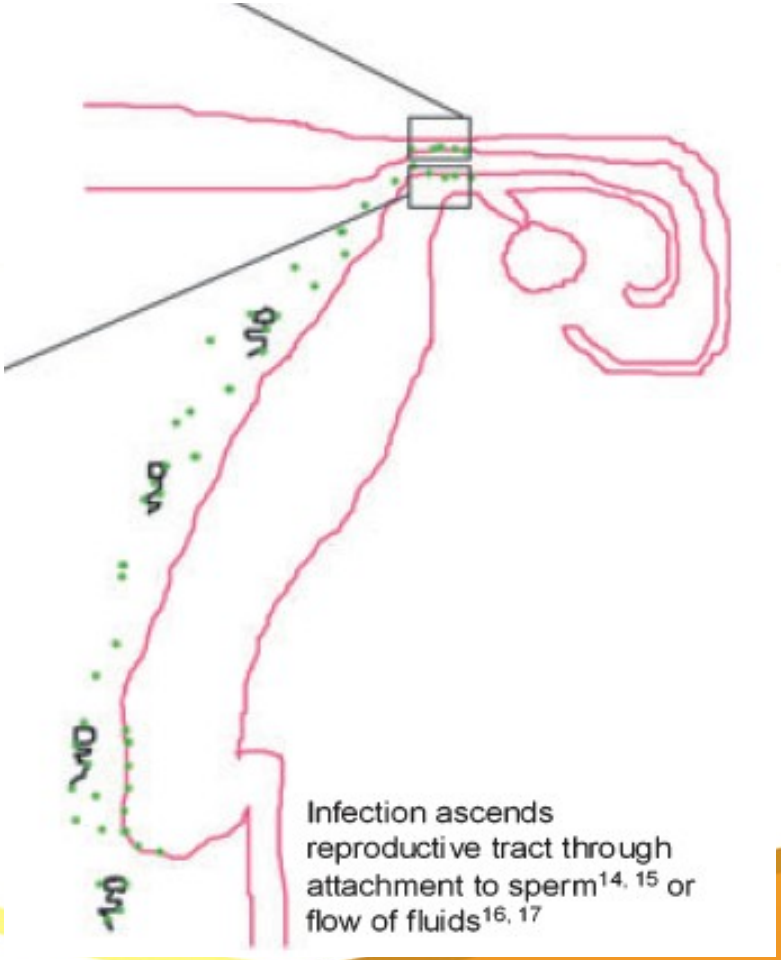
Chlamydia infection and immunity

Infection

- primary site
  - Woman: columnar epithelial cells of the endocervix
    - pelvic inflammatory disease (PID): (4.5~6.4X)
    - ectopic pregnancies: (2~2.5X)
    - tubal infertility
  - Men: urogenital epithelia
    - prostatitis
    - epididymitis



Infection ascends reproductive tract



Infection ascends reproductive tract through attachment to sperm[14, 15] or flow of fluids[16, 17]

- Attachment to sperm
- Flow of fluids
  - Particles approximately the same size of sperm, or radio-labeled sperm

infection kinetics

- Chlamydia muridarum
  - the differential cell infiltration between the lower and upper genital tract
  - the rate at which this occurs
  - the rate of infection ascension.

Infection

- The infectious dose of Chlamydia is known to modulate the innate immune response, with greater inoculating doses causing a greater innate immune response.

Infection

- Because of the greater immune responses elicited by high infectious challenge doses, the infection does not cause as great a degree of hydrosalpinx.

- The development of pathological sequelae may not be affected by the sexual transmission dose.

- the number of Chlamydia caviae transmitted by an infected male guinea pig during mating is known

Immunity

- Natural immunity to a single infection is known to be short lived and serovar specific

- Multiple infections with different serovars induces longer term, cross-serovar immunity

Immunity

- Women have spontaneously cleared a genital infection without medical intervention

- Antibiotic intervention increases the longer term rates of re-infection because of the inability of the person to develop protective immunity against Chlamydia

Immunity

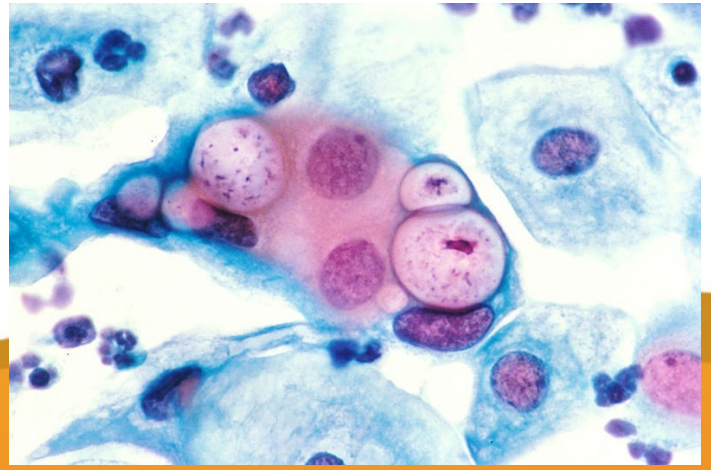
- Primary infection:
  - both a Th1 and Th2 response needs to be mounted
    - CD4+ Th1 cells
    - CD8+ T cells,
    - B cells,
    - Neutrophils
    - Dendritic cells39 (DCs)

Immunity

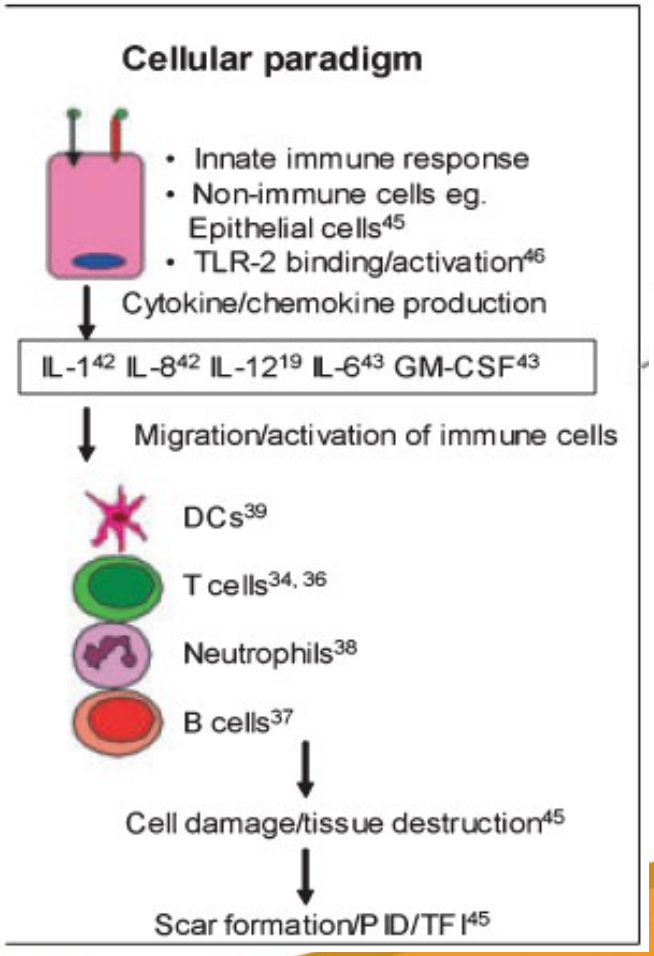
- clearance
  - primary infection is dependent on the development of cell-mediated immunity
  - Secondary infection requires the presence and production of antibodies

Immunity-cytobrush samples

- women infected with C. trachomatis had an increase in CD3+, CD4+ and CD8+ cells, and neutrophils, and an increase in recruitment of myeloid and plasmacytoid DCs

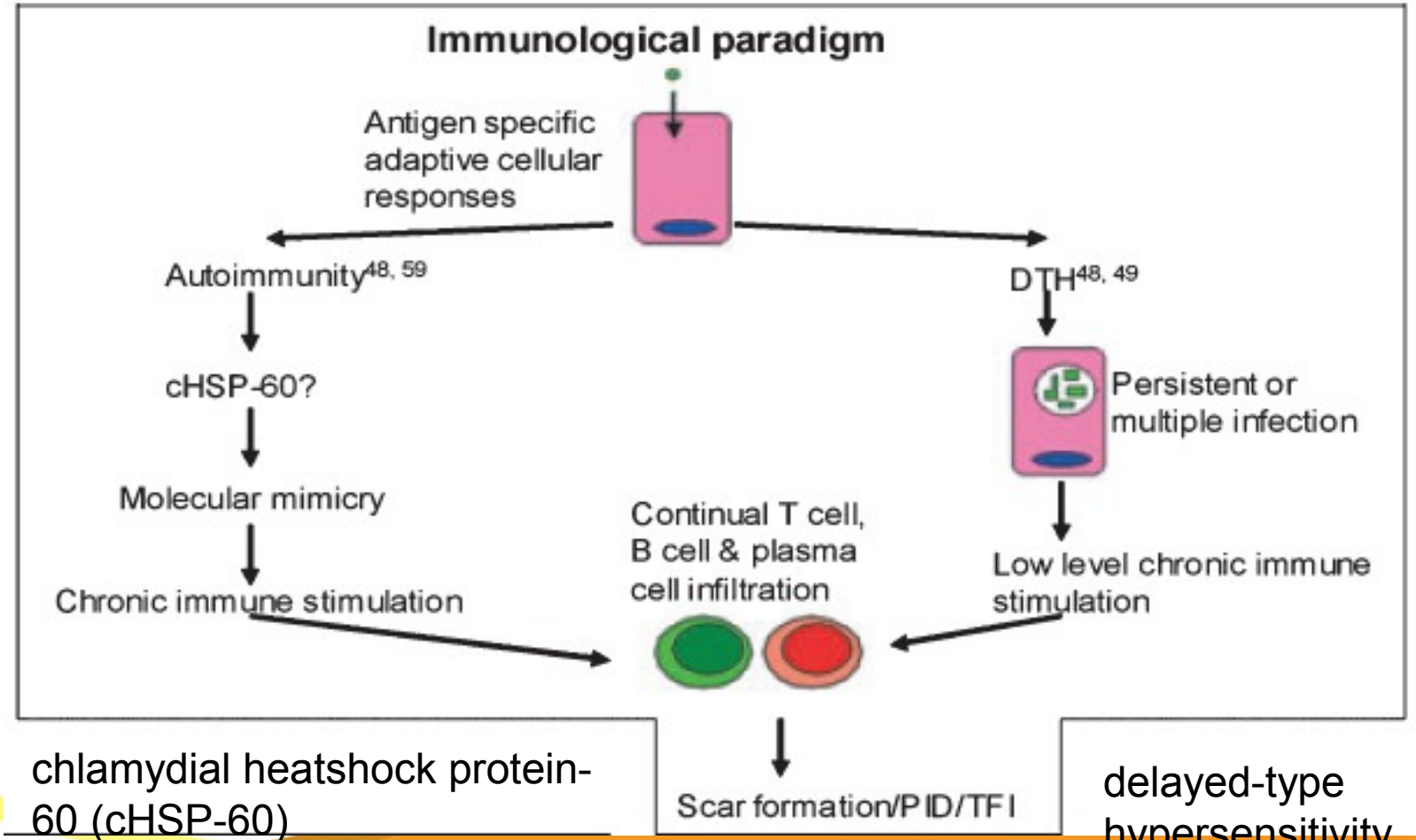


Cellular paradigm



- It is the host's immune response to infection that is responsible for the damage rather than the infection itself.

Immunological paradigm



chlamydial heatshock protein-60 (cHSP-60)

delayed-type hypersensitivity (DTH)

Immunity-DTH

- Guinea pigs sensitized with Triton-X-100 soluble chlamydial EBs had greater ocular delayed hypersensitivity when re-exposed to infection at other sites, including vaginal and intestinal infections

- Monkeys immunized against C. trachomatis developed a greater follicular response in the eye upon re-exposure than non-immune controls

Treatment or Prevention?

Treatment

- Azithromycin or doxycycline
  - a single 1-g dose v.s. 7-day course

- Resistance
  - tetracyclines,
  - macrolides,
  - fluoroquinolones,
  - doxycycline,
  - azithromycin,
  - ofloxacin.

Re-infected

- Infected women, who completed antibiotic treatment,
  - 10% within 1 month
  - 13% by 3 months
  - even though abstinence or 100% condom use

Arrested immunity hypothesis

- Early intervention with antibiotics interferes with the development of protective immune responses

Prevention-vaccine

- A partially protective vaccine will dramatically decrease the rate of spread of infections and reduce economic burden.

- An efficacious vaccine will need to induce both a strong Th1-cell-mediated response and a humoral response.

Vaccine candidate

- Major outer membrane protein (MOMP)
- Chlamydial protease-like activity factor (CPAF)
  - adjuvants : IL-12 and CpG-ODN

Problems with Vaccine Development

- How efficacious?
- Therapeutic effect?
- Protection against re-exposure?
- The effects of vaccine administration during an acute chlamydial genital infection?

Conclusions

- Chlamydia trachomatis genital infections are continually increasing, with women at the greatest risk of infection and inflammatory sequelae.

Conclusions

- Because of
  - the asymptomatic nature of most infections,
  - the increased incidence of development of severe reproductive impairment with re-infection
  - the fact that antibiotic treatment has been unable to halt the increased incidence of infection,

- There is an urgent need for the development of a vaccine that prevents further spread of infection and pathological damage to the female reproductive tract.

Conclusions

- Progesterone and estradiol can affect many components of the immune response, including antigen presentation by DCs and macrophages, production and transport of antibody into the female reproductive tract (FRT)

Conclusions

- Nasal route induced the greatest IgA antibody secretion in vaginal secretions

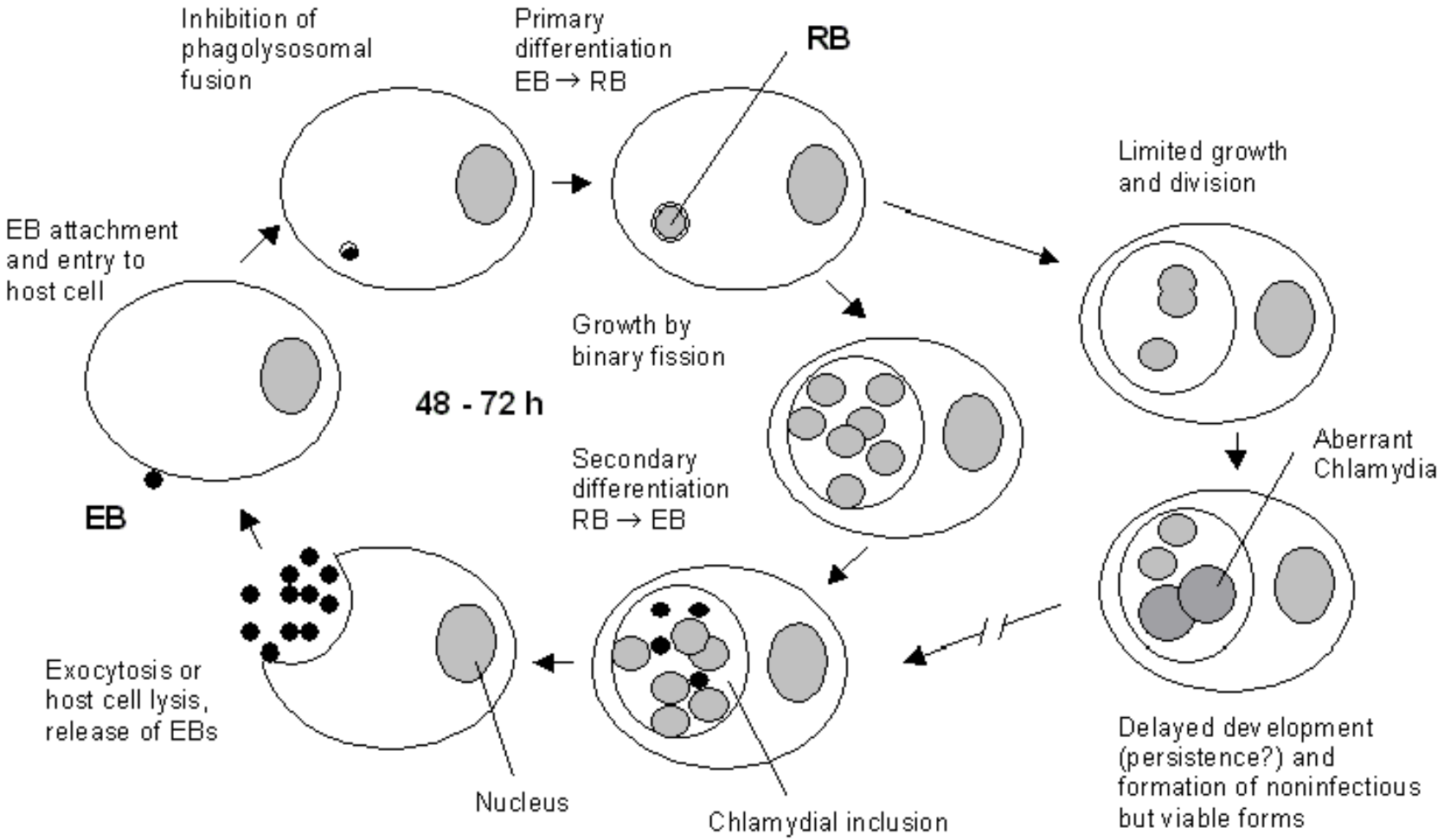
- Immunized vaginally on days 10 and 24 of their menstrual cycle had the greatest amounts of IgG and IgA in cervical secretions

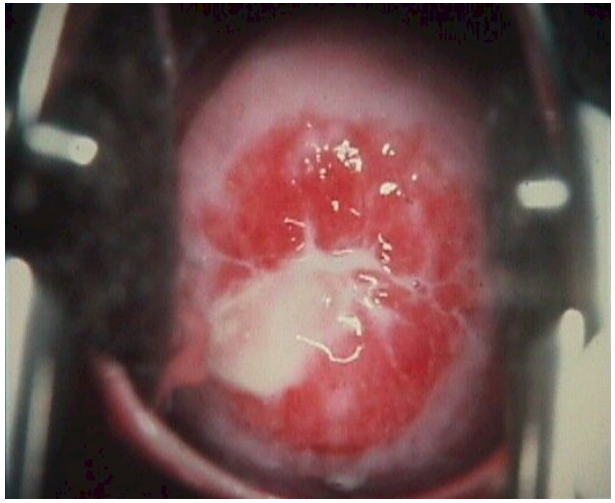
Conclusions

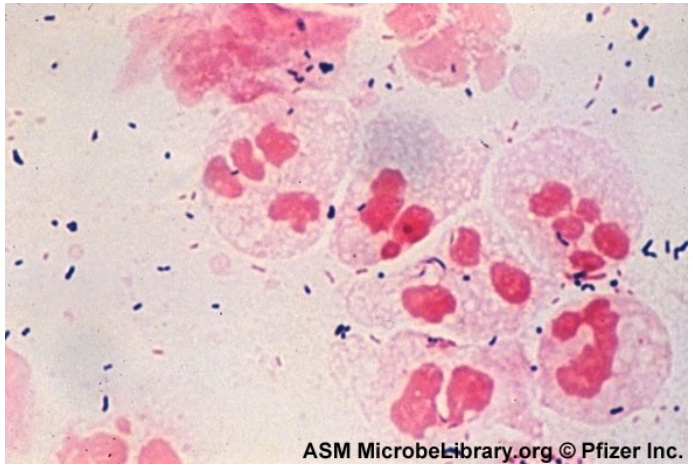
- Factors that should be considered when developing any potential vaccine include
  - targeting the protective immune response to the reproductive tract
  - the infection status of vaccines
  - potentially the influence of hormonal status on protection

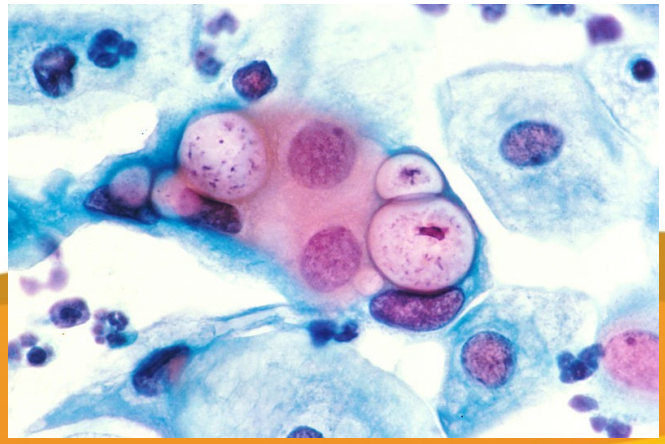
Thanks for listening!

Life cycle









Chlamydia species and biovars

- Chlamydia species
  - Chlamydia trachomatis (a human pathogen),
  - Chlamydia suis (affects only swine)
  - Chlamydia muridarum (affects only mice and hamsters)
- C. trachomatis includes three human biovars:
  - serovars Ab, B, Ba, or C
    - trachoma: infection of the eyes which can lead to blindness and is prevalent in Africa
  - serovars D-K
    - urethritis, pelvic inflammatory disease, ectopic pregnancy, neonatal pneumonia, and neonatal conjunctivitis
  - serovars L1, L2 and L3
    - lymphogranuloma venereum (LGV)