An integrated approach to the understanding of *Chlamydia trachomatis* infection
An integrated approach to the understanding of *Chlamydia trachomatis* infection

*Amsterdam, December 17, 2004*
DESCRIPTION OF THE ICTI CONSORTIUM:
AN INTEGRATED APPROACH TO THE STUDY OF CHLAMYDIA TRACHOMATIS INFECTION


1Laboratory of Immunogenetics, Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands, 2Public Health Laboratory, Municipal Health Service (GG&GD), Amsterdam, The Netherlands, 3Department of Medical Microbiology, Erasmus University, Rotterdam, The Netherlands, 4Department of Obstetrics and Gynecology, Research Institute Growth and Development (GROW), Academisch Ziekenhuis Maastricht, and Maastricht University, The Netherlands, 5Department of Gynecology and Obstetrics, Westeinde Hospital, The Hague, The Netherlands, 6Department of Medical Microbiology, Ghent University, Belgium, 7Department of Molecular Biotechnology, Ghent University, Belgium, 8Department of Medical Microbiology and Infection Prevention, VU University Medical Center, Amsterdam, The Netherlands, 9Academic Medical Center, Department of Medical Microbiology, University of Amsterdam, The Netherlands, 10STI AIDS The Netherlands (Soa Aids Nederland), Amsterdam, The Netherlands, 11Department of Infectious Diseases, City of Hope National Medical Center and Beckman Research Institute, Duarte, California, USA

CONTENTS
Summary ................................................................. 107
Mission ................................................................. 108
Introduction ......................................................... 108
Clinical course of infection ....................................... 108
The integrated approach ........................................... 109
The ICTI consortium ................................................. 109
Appendix I: ICTI consortium participants ..................... 111
References .............................................................. 112

Summary
The use of an integrated approach to the study of Chlamydia trachomatis infection of the female genital tract, presented at the mini-symposium "Chlamydia trachomatis infections" and described in the thesis of Joseph M. Lyons, has resulted in the creation of the ICTI consortium. The ICTI consortium is based on strong interaction and collaboration between basic scientists, clinicians, epidemiologists, and health care policy makers. This translational approach will...
help to further the valuable insight into the immunopathogenesis of this sexually transmitted infection (STI) and the development of new intervention strategies, including the vaccines and screening programs necessary to effectively diagnose, treat and prevent *C. trachomatis* infection. A background of the need for this integrated approach is presented and the goals and participants of the consortium are described. © 2005 Prous Science. All rights reserved.

**Mission**

The ICTI consortium will promote the study of *Chlamydia trachomatis* infections using an integrated approach based on collaboration between basic scientists, clinicians, epidemiologists and health care policy makers. This translational approach will help to provide valuable insight into the immunopathogenesis of this sexually transmitted infection (STI) and promote the development of new intervention strategies, including the vaccines and screening programs necessary to effectively diagnose, treat and prevent *C. trachomatis* infection and therefore contribute to the prevention of long-term complications.

**Introduction**

Despite the existence of antibiotics that are clearly effective at eradicating infection (1–3) and a period during which the incidence of *C. trachomatis* genital tract infection (GTI) appeared to decline, the incidence of this infection has been on the increase since the mid-1990s (4, 5), with an estimated 89 million new cases occurring worldwide each year (4). In the Netherlands, about 60,000 of the 110,000 STIs reported are estimated to be *C. trachomatis* infections. It is generally accepted that 70–80% of female *C. trachomatis* GTIs are asymptomatic and without severe sequelae (6), and that repeated infection is associated with severe upper genital tract pathology, which includes, in decreasing order of occurrence, pelvic inflammatory disease, ectopic pregnancy and tubal infertility (7). The morbidity associated with these pathologies has spurred attempts to develop screening programs, as well as intervention strategies such as vaccines and a vaginally applied prophylactic antimicrobial agent that could reduce the susceptibility to and spread of infection.

**Clinical course of infection**

There are striking interindividual differences in the clinical course of *C. trachomatis* infection.

*Transmission versus no transmission*

Not all partners of a *C. trachomatis*-positive index patient are *C. trachomatis* positive (confounding factors such as condom use were excluded). Transmission of the infection from the index patient to the partner is observed in 45–65% of cases (8–10).

*Symptomatic versus asymptomatic course of infection*

The infections reported are mainly symptomatic, since patients consult a physician due to clinical symptoms and complaints. However, while it is known that *C. trachomatis* can also run an asymptomatic course, exact percentages are lacking and data range from 60–80% of infections in women and 30–50% in men (11–13).

*Persistence versus clearance of infection*

Some patients clear the infection spontaneously, while in others the infection persists for years. Some of the treated infections seem to reappear despite treatment of partners (14–17).

*Development of complications versus no development of late complications*

*C. trachomatis* infection can ascend to the upper genital tract resulting in pelvic inflammatory disease, ectopic pregnancy and tubal infertility. Uncontrolled immune reactions in the fallopian tubes are believed to contribute to the disease pathogenesis. Repeated infections are associated with the development of these late complications. However, the infections result in secondary complications in only some women (16, 18).
These differences in the clinical course of infection can be explained by the interaction between the host (host factors) and the pathogen (virulence factors), an interaction which is influenced by environmental factors such as co-infections (Fig. 1).

The critical evaluation of host, bacterial, environmental, clinical and epidemiological data and the results of experimental studies conducted both in vitro and in vivo using animal models will lead to an understanding of the disease process, including both susceptibility to and severity of disease, and will contribute to the development of new intervention strategies that are necessary to effectively treat and prevent *C. trachomatis* infection of the female genital tract.

The integrated approach

Fundamental aspects of *C. trachomatis* infection have been investigated using murine and pig-based experimental models. For example, knockout mice have been used to assess the relevance of specific genes such as TLR4 or IFN-γ on the course of *C. trachomatis* infection. The findings for primary infection have been extrapolated to a human cohort with uncomplicated infections in a population with STIs, while for the translation of the murine findings after reinfection, a human cohort of women with subfertility has been used. In these human cohorts candidate gene approaches have been used to investigate whether the murine findings can be extrapolated to humans to identify important genes which regulate the susceptibility to and severity of infection, and thus potentially identify women at risk of either infection in general or the development of late complications (Fig. 2).

The findings in humans are confounded by potential differences in bacterial virulence factors and environmental factors such as co-infection. Studies have been undertaken to analyze bacterial factors in relation to the course of infection as well as detailed analyses of co-infection status in the human cohorts. Addressing the interaction among hosts, bacterial and environmental factors will be the most valuable in determining the factors directing the course of infection. It is anticipated that this approach will eventually contribute to the development of a vaccine, which in turn may lead to the eradication of *C. trachomatis* infection.

The ICTI consortium

The ICTI consortium participants (participants A to J) are from multidisciplinary backgrounds: basic and translational researchers, clinicians, epidemiologists and health care policy makers (see Fig. 3 and Appendix I for the participants and the letter assignation). Two animal models are in use: a murine model (B) and a recently developed pig model (D). Bacterial factors are being studied by almost all participants. These factors include *C. tra*-

---

**Fig. 1.** Factors influencing the course of *C. trachomatis* infection.
**C. trachomatis** serovars (*omp1* gene); the inclusion protein IncA (A, G, H); and cytotoxicity variables and *in vitro* culture characteristics (B). Also, detailed research on environmental factors (among other co-infections) is conducted by different participants (A, I, H). Immunology and immunogenetics are mainly studied by participants A, B, F and H. Clinical studies are mainly undertaken by participants A, C, G, H, I and J. Screening and implementation is researched mainly by participants A, H and I. Innate and adaptive immune responses are being investigated for vaccine development mainly by participants B, D and F. Finally, participants A, F, H, I and J are (partially) involved in health care policy.
Appendix I: ICTI Consortium participants

A. Laboratory of Immunogenetics, Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands
Servaas A. Morré, Consortium Coordinator (samorretravel@yahoo.co.uk)
J. Bart A. Crusius (b.crusius@vumc.nl), A. Salvador Peña (aspena@vumc.nl)
Topic: Immunogenetics and C. trachomatis in general (19–21)

B. Department of Infectious Diseases, City of Hope National Medical Center and Beckman Research Institute, Duarte, California, USA
Joseph M. Lyons (jlyons@coh.org), Jim I. Ito (jito@coh.org)
Topic: In vitro and murine modeling (22–24)

C. Department of Gynecology and Obstetrics, Department of Medical Microbiology, Westeinde Hospital, The Hague, The Netherlands
Caroline J. Bax (C.J.Bax@lumc.nl), P. Joep Dörr (p.dorr@mchaaglanden.nl),
Paul M. Oostvogel (P.M.Oostvogel@lumc.nl)
Topic: Subfertility and tubal pathology (25–27)

D. Department of Molecular Biotechnology, Ghent University, Ghent, Belgium
Daisy Vanrompay (daisy.vanrompay@UGent.be)
Topic: Pig modeling, vaccination (28–30)

E. Department of Medical Microbiology and Infection Prevention, VU University Medical Center, Amsterdam, The Netherlands
Paul H.M. Savelkoul (p.savelkoul@vumc.nl)
Topic: Bacterial typing (31–33)

F. Department of Medical Microbiology, Erasmus University, Rotterdam, The Netherlands
Jacobus M. Ossewaarde (j.ossewaarde@erasmusmc.nl)
Topic: Innate immunity and C. trachomatis in general (34–36)

G. Academic Medical Center, Department of Medical Microbiology, University of Amsterdam, Amsterdam, The Netherlands
Yvonne Pannekoek (y.pannekoek@amc.uva.nl)
Topic: Bacterial virulence (37–39)

H. Public Health Laboratory, Municipal Health Service (GG&GD), Amsterdam, The Netherlands
Joke Spaargaren (jspaargaren@ggda.amsterdam.nl), Han S.A. Fennema (h.fennema@ggda.amsterdam.nl), Henry J. de Vries (h.j.devries@amc.uva.nl)
Topic: Uncomplicated C. trachomatis infections and bacterial typing (40–42)

I. STI AIDS The Netherlands (Soa Aids Nederland), Amsterdam, The Netherlands
Jan E.A.M van Bergen (JvanBergen@soaaids.nl)
Topic: C. trachomatis screening (43–45)

J. Department of Obstetrics and Gynecology, Research Institute Growth and Development (GROW), Academisch Ziekenhuis Maastricht, and Maastricht University, Maastricht, The Netherlands
Jolande A. Land (Jian@sgyn.azm.nl)
Topic: Subfertility and tubal pathology (46–48)
References


