AN INTEGRATED APPROACH TO CHLAMYDIA TRACHOMATIS INFECTION: THE ICTI CONSORTIUM, AN UPDATE

J.M. Lyons¹, S. Ouburg² and S.A. Morré²*

¹Integrated Disease Modeling, Claremont, California, USA; ²Laboratory of Immunogenetics, Department of Pathology, VU University Medical Center, Amsterdam, the Netherlands; *On behalf of the ICTI Consortium

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SUMMARY

The desire for an integrated approach to the study of Chlamydia trachomatis infection of the female genital tract resulted in the creation of the “ICTI Consortium” (Integrated approach to the study of Chlamydia Trachomatis Infection) in 2005. The ICTI consortium is based on tight 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 in order to develop new intervention strategies, including the vaccines and screening programs necessary to effectively diagnose, treat and prevent C. trachomatis infection. This article provides an update of ICTI Consortium activities carried out until September 2009.
Differences in the clinical course of infection
Clinical, demographic and environmental factors (coinfections, behavioral and biologic)

Host factors (genetic, immune mediator analysis)

Bacterial factors (omp, inc, pmp)

Clinical, demographic and environmental factors (coinfections, behavioral)

STD

Ocular

Differences in the clinical course of infection

Insights into risk factors: Susceptibility to disease, severity of subsequent disease

Main immunologic factors involved

Risk profiling, disease etiology, therapy, vaccination

Figure 1. Factors influencing the course of C. trachomatis infection.

MISSION
The ICTI Consortium’s mission is to promote the study of Chlamydia trachomatis infections using an integrated approach based on collaboration between basic scientists, clinicians, epidemiologists and health-care policy makers (1). This translational approach will help to further the valuable insight into the immunopathogenesis of this sexually transmitted infection in order to develop new intervention strategies, including the vaccines and screening programs necessary to effectively diagnose, treat and prevent C. trachomatis infection, and thereby prevent its long-term complications.

INTRODUCTION
Despite the availability of antibiotics that are clearly effective in eradicating infection (2-3) and following an apparent period of decline, the incidence of C. trachomatis genital tract infection (GTI) has been increasing 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 cases of reported sexually transmitted disease (STD) are estimated to be C. trachomatis infections. It is generally accepted that 70–80% of female C. trachomatis GTI are asymptomatic and without severe sequelae (6), and that repeated infection correlates with severe upper genital tract pathology, including, in decreasing order of occurrence, pelvic inflammatory disease, ectopic pregnancy and tubal infertility (7). The morbidity with these severe outcomes has driven attempts to develop not only screening programs but intervention strategies such as vaccines and vaginally applied prophylactic antimicrobials that might reduce susceptibility to and spread of infection with this agent.

CLINICAL COURSE OF INFECTION
Some striking between-individual differences are observed in the clinical course leading to infection with C. trachomatis, as listed below.

1. Transmission versus no transmission: Not all partners of a C. trachomatis-positive index patient are also 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 couples (8-10).

2. Symptomatic versus asymptomatic course of infection: The registered infections are mainly symptomatic and lead those affected to consult a physician due to clinical symptoms and complaints. However, it is known that C. trachomatis can also run an asymptomatic course. Although exact percentages are lacking, available data vary from 60–80% in women and 30–50% in men (11-13).

3. Persistence versus clearance of infection: Some people clear the infection spontaneously while others maintain a persistent infection for years. Some of the treated infections seem to reappear despite partners being co-treated (14-17).

4. Development of late complications (e.g., tubal infertility) 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 tubae 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 coinfections (Fig. 1).

The critical evaluation of host, bacterial, environmental, clinical and epidemiologic 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, 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 have been investigated with murine- and pig-based experimental models. For example, knockout mice have been used to assess the relevance of specific genes such as Toll-like receptor 4 (TLR4) or interferon-γ (IFN-γ) on the course of C. trachomatis. The findings have been extrapolated for primary infection to a human cohort with uncomplicated infections in an STD population, while for the translation of the murine findings after refections, a human cohort of women with subfertility was used. In these human cohorts, we have used candidate gene approaches to investigate whether or not 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 for either infection in general or for the development of late complication (Fig. 2).

The findings in humans have been confounded by potential differences in bacterial virulence factors and environmental factors such as coinfection. Fundamental studies have been undertaken to analyze bacterial factors in relation to the course of infection, as well as detailed analyses of coinfection status in the human cohorts. Eventually addressing the interaction among host, bacterial and environmental factors will be most valuable in determining those factors directing the course of infection. We aim for this approach to eventually contribute to the development of a vaccine. This will lead to the eradication of C. trachomatis, the most common sexually transmitted bacterial pathogen worldwide.

THE ICTI CONSORTIUM

The background of the ICTI Consortium participants (participants A to M) is clearly multidisciplinary: basic and translational researchers, clinicians, epidemiologists, STD experts and health-care policy makers (see Figures 3 and 4, Appendix I and the key references from the participants). Two animal models have been employed, a murine model (B) and a recently developed pig model (D). Bacterial factors are being studied by almost all participants. These factors include, among others, C. trachomatis serovars (omp1 gene), the inclusion protein IncA (A, G and H), and cytotoxicity variables and in vitro culture characteristics (B). Also, environmental factors (among other coinfections) are being studied in detail by different participants (A, I and H). Immunology and immunogenetics are mainly studied by participants A, B, F and H. Clinical and epidemiologic studies are undertaken by most of the participants. Screening and implementation are studied mainly by participants A, H, I, L and M. Innate and adaptive immune responses are being studied for vaccine approaches, mainly by participants B, D and F.

Description of collaboration and output

As shown in Figures 3 and 4, the collaboration between and output of the ICTI Consortium participants significantly increased after its initiation in February 2005 to September 2009: the number of participants increased from 10 to 13; the number of collaborations between the partners increased from 12 to 27; the range of C. trachomatis publications increased from 3 to 44 from to 4 to 73, with an increasing number of publications between partners (partners with 1–2 publications increased from 9 to 12, those with 3–5 publications increased from 2 to 8, and those with more than 5 publications between partners increased from 1 to 7).

Finally, the centers with the most publications have remained stable for the last 3 years and in 2009 were, in declining order, as follows: VU University Medical Center, Amsterdam (VUmc) (n = 73); Department of Medical Microbiology, Erasmus University (EUR/MZ) (n = 36); Public Health Laboratory, Municipal Health Service (GG&GD), Amsterdam (n = 29); and STI AIDS The Netherlands (Soa Aids Nederland) (n = 19).

EpiGenChlamydia Consortium

One of the major achievements has been the submission of grants by some of the ICTI Consortium participants. The year that the consortium was created, a Dutch NWO
Figure 3. ICTI consortium. Collaborations are based on publications from February 2005 until July 2006. See Appendix I for details on the consortium participants.
Figure 4. ICTI consortium. Collaborations are based on publications from December 2007 until September 2009. See Appendix I for details on the consortium participants.
grant was submitted and obtained funding to write a Sixth European Framework Programme grant (FP6), together with 20 groups in Europe, Africa and the United States. This FP6 Consortium started in July 2007 and ends December 31, 2009 (Fig. 5).

The EpiGenChlamydia Consortium, coordinated by ICTI partner A (VUmc), aims to structure transnational research to such a degree that comparative genomics and genetic epidemiology can be performed in large numbers of unrelated individuals. Biobanking and data-warehouse building are the most central deliverables of this Coordination Action in functional genomics research. In addition, the collective synergy acquired in this Coordination Action will allow for the generation of scientific knowledge on the C. trachomatis–host interaction, knowledge on the genetic predisposition to C. trachomatis infection, and the development of tools for early detection of a predisposition to C. trachomatis infection. This EpiGenChlamydia Consortium is described in detail elsewhere (19).

**CONCLUSIONS**

The ICTI Consortium has been and remains a very successful multidisciplinary collaboration between 11 Dutch Chlamydia groups, one group from Belgium and one group from California, USA. The many new collaborative efforts have resulted in coordination of research and a large increase in the number of publications within the Consortium and in the Netherlands. This Consortium will continue its work to integrate research performed by basic scientists, clinicians, epidemiologists and healthcare policy makers to further the valuable insight into the immunopathogenesis of C. trachomatis in order to develop new intervention strategies to effectively diagnose, treat and prevent this infection and its long-term complications.

**APPENDIX I: ICTI CONSORTIUM PARTICIPANTS**

A. Laboratory of Immunogenetics, Department of Pathology, VU University Medical Center (VUmc), Amsterdam, the Netherlands
   Servaas A. Morré (consortium coordinator) (samorretravel@yahoo.co.uk), J. Bart A. Crusius (b.crusius@vumc.nl), A. Salvador Peña (pena.as@gmail.com)
   Topic: Immunogenetics and C. trachomatis in general (19-21)

B. Integrated Disease Modeling (COH), Claremont, California, USA
   Joseph M. Lyons (jlyons001@msn.com)
   Topic: In vitro and murine modeling (22-24)

C. Department of Gynecology and Obstetrics, Westeinde Hospital, the Hague, the Netherlands
   Caroline J. Bax (grandeblu@grandeblu.nl), Paul M. Oostvogel (P.M.Oostvogel@lumc.nl), Joep Dörr (p.dorr@mchaaglanden.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 (VUmc-MM), Amsterdam, the Netherlands
   Paul H.M. Savelkoul (p.savelkoul@vumc.nl)
   Topic: Bacterial typing (31-33)

F. Department of Medical Microbiology, Erasmus University (EUR/MZ), Rotterdam, the Netherlands
   Jacobus M. Ossewaarde (OssewaardeJ@maasstadziekenhuis.nl)
   Topic: Innate immunity and C. trachomatis in general (34-36)

G. Academic Medical Center (AMC), Department of Medical Microbiology, University of Amsterdam, Amsterdam, the Netherlands

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**Figure 5.** Grants obtained by the ICTI Consortium which resulted in the EU Sixth Framework Programme (FP6) EpiGenChlamydia Consortium (www.EpiGenChlamydia.eu).
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Yvonne Pannekoek (y.pannekoek@amc.uva.nl)
Topic: Bacterial virulence (37-39)

H. Public Health Laboratory, Municipal Health Service (GGD Adam), Amsterdam, the Netherlands
Han S.A. Fennema (hfennema@ggd.amsterdam.nl), Henry J. de Vries (hj.devries@amc.uva.nl), Arjen Speksnijder (aspeksnijder@ggd.amsterdam.nl), Sylvia Bruisten (SBruisten@ggd.amsterdam.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@soaids.nl)
Topic: C. trachomatis screening (43-45)

J. Department of Obstetrics and Gynecology, University Medical Center Groningen, Groningen, the Netherlands
Jolande A. Land (j.a.land@og.umcg.nl)
Topic: Subfertility and tubal pathology (46-48)

K. Laboratory for Infectious Diseases (LvI Groningen), Groningen, the Netherlands
Antoine Beerens (a.beerens@infecctielab.nl) and Dirk Luijt (d.luijt@infecctielab.nl)
Topics: Diagnostics and quality control (49-51)

L. Department of Infectious Diseases, Public Health Service South Limburg (GGD Heerlen), Limburg, the Netherlands
Christian Hoebe (Christian.Hoebe@ggdzl.nl), Nicole Dukers (Nicole.Dukers@ggdzl.nl)
Topics: Screening, diagnostics, diagnosis (52-54)

M. Department of Infectious Diseases, Rotterdam Public Health Service (GGD Rotterdam), Rotterdam, the Netherlands
Hannelore Götz (gotzh@ggd.rotterdam.nl)
Topics: Epidemiology, C. trachomatis, screening (54-56)

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

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39. Pannekoek, Y., Spaargaren, J., Langerak, A., Merks, J., Morré, S.A., van der Ende, A. Interrelationship between poly-


