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

*J.M. Lyons[1], S. Ouburg[2] and S.A. Morré[2*]*

[1]Integrated Disease Modeling, Claremont, California, USA; [2]Laboratory 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.*

**Correspondence:** Dr. S.A. Morré, Laboratory of Immunogenetics, Department of Pathology, VU University Medical Center, P.O. Box 7057, 1007 MB, Amsterdam, the Netherlands. E-mail: samorretravel@yahoo.co.uk

## 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.

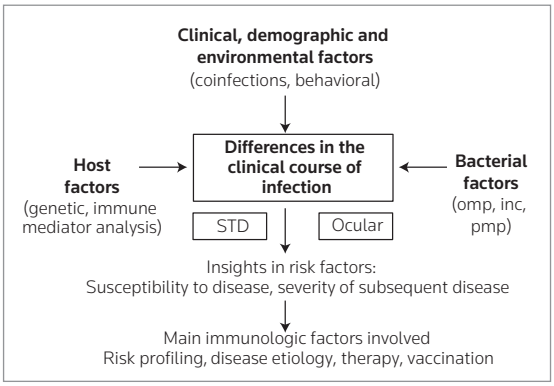


**Figure 1.** Factors influencing the course of *C. trachomatis* infection.

## 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 reinfections, 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.

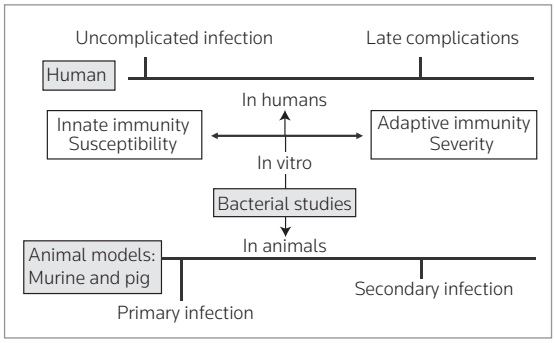


**Figure 2.** Integrated approach to *C. trachomatis* infections based on animal models and human cohorts generating translational data relevant to fighting infection.

### 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 participants 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

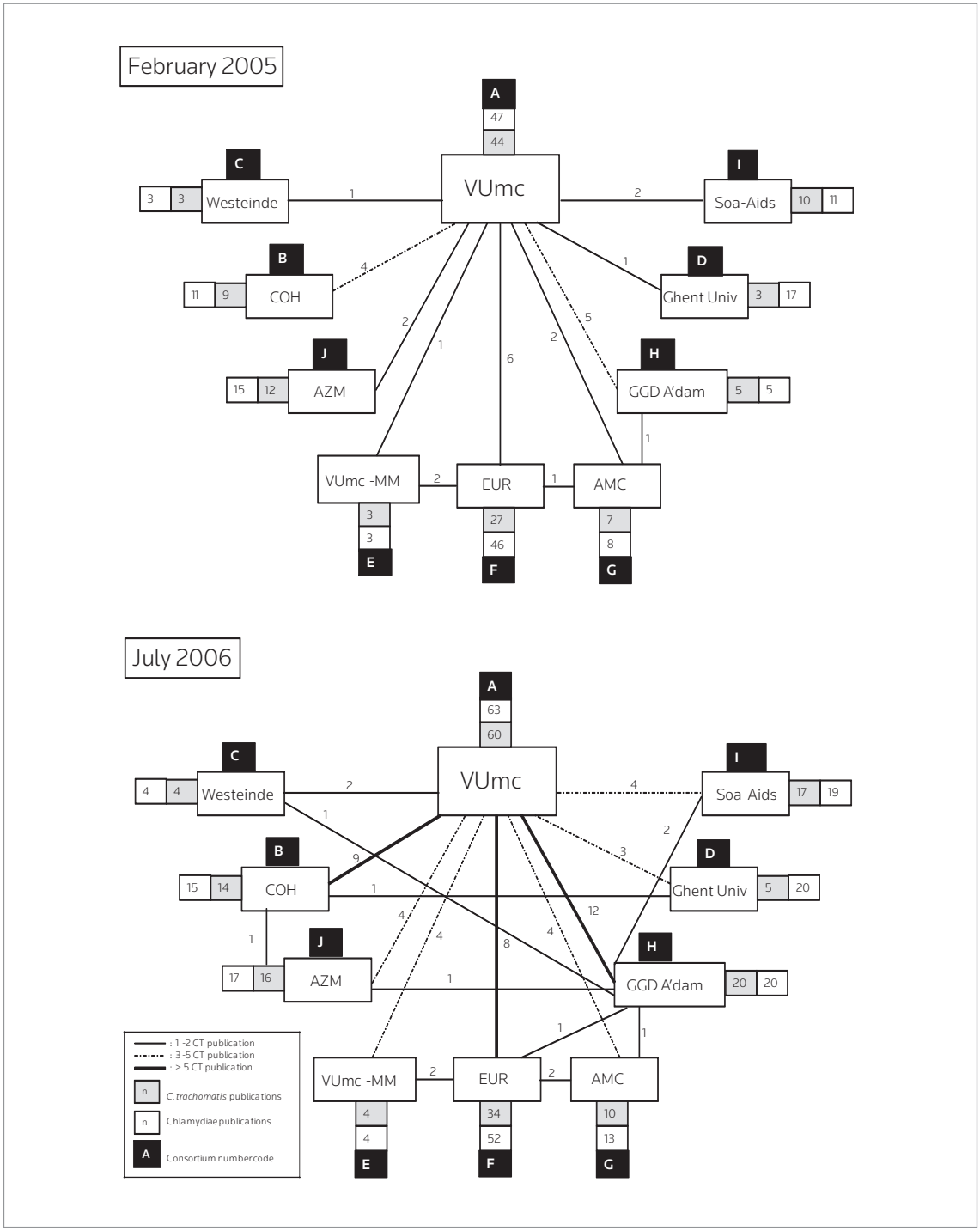


**Figure 3.** ICTI consortium. Collaborations are based on publications from February 2005 until July 2006. See Appendix I for details on the consortium participants.

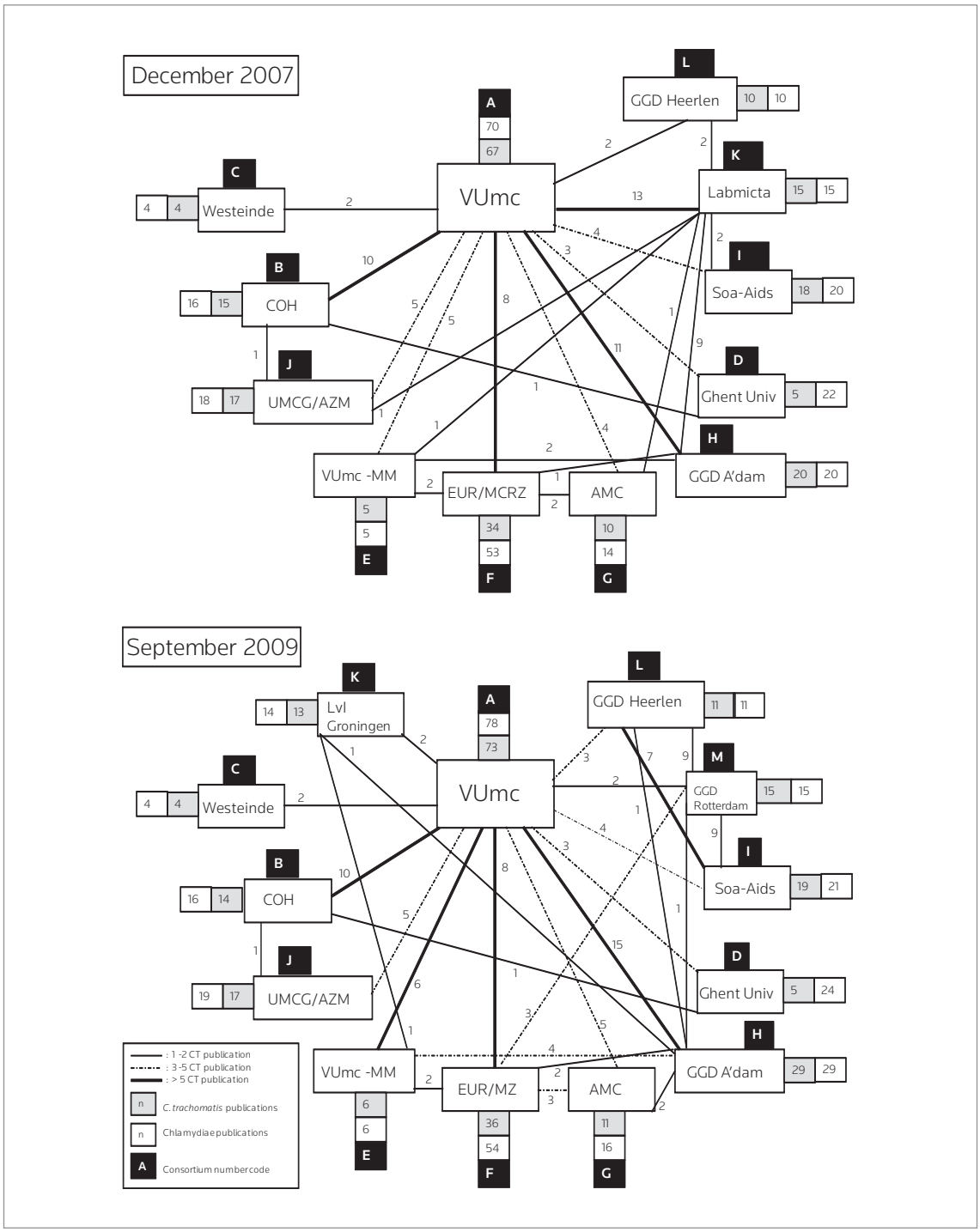


**Figure 4.** ICTI consortium. Collaborations are based on publications from December 2007 until September 2009. See Appendix I for details on the consortium participants.

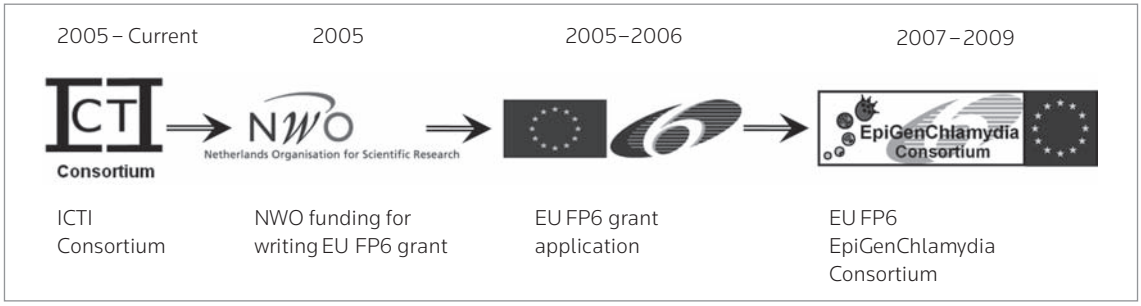


**Figure 5.** Grants obtained by the ICTI Consortium which resulted in the EU Sixth Framework Programme (FP6) EpiGenChlamydia Consortium (www.EpiGenChlamydia.eu).

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

Yvonne Pannekoek (y.pannekoek@amc.uva.nl)

Topic: Bacterial virulence (37-39)

H. Public Health Laboratory, Municipal Health Service (GGD A'dam), Amsterdam, the Netherlands

Han S.A. Fennema (hfennema@gggd.amsterdam.nl), Henry J. de Vries (h.j.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@soaaids.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@infectielab.nl) and Dirk Luijt (d.luijt@infectielab.nl)

Topics: Diagnostics and quality control (49-51)

L. Department of Infectious Diseases, Public Health Service South Limburg (GGD Heerlen), Limburg, the Netherlands

Christan 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

1. Morré, S.A., Spaargaren, J., Ossewaarde, J.M. et al. *Description of the ICTI consortium: An integrated approach to the study of chlamydia trachomatis infection*. Drugs Today (Barc) 2006, 42(Suppl. A): 107-14.
2. Scholes, D., Stergachis, A., Heidrich, F.E., Andrilla, H., Holmes, K.K., Stamm, W.E. *Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection.* N Engl J Med 1996, 334: 1362-6.
3. van Valkengoed, I.G., Morré, S.A., van den Brule, A.J. et al. *Follow-up, treatment, and reinfection rates among asymptomatic Chlamydia trachomatis cases in general practice*. Br J Gen Pract 2002, 52(481): 623-7.
4. Gerbase, A.C., Rowley, J.T., Heymann, D.H., Berkley, S.F., Piot, P. *Global prevalence and incidence estimates of selected curable STDs.* Sex Trans Infect 1998, 74(Suppl. 1): S12-6.
5. Miller, W.C., Ford, C.A, Morris, M. et al. *Prevalence of chlamydial and gonococcal infections among young adults in the United States*. JAMA 2004, 291: 2229-36.
6. van Valkengoed, I.G.M., Morré, S.A., van den Brule, A.J.C., Meijer, C.J.L.M., Bouter, L.M., Boeke, A.J.P. *Overestimation of complication-rates of Chlamydia trachomatis screening programmes: Implications for cost-effectiveness analyses*. Int J Epidemiol 2004, 33: 416-25.
7. Hillis, S.D., Owens, L.M., Marchbanks, P.A., Amsterdam, L.F., MacKenzie, W.R. *Recurrent chlamydial infections increase the risks of hospitalization for ectopic pregnancy and pelvic inflammatory di*sease. Am J Obstet Gynecol 1997, 176: 103-7.
8. van Valkengoed, I.G., Morré, S.A., van den Brule, A.J., Meijer, C.J., Bouter, L.M., van Eijk, J.T., Boeke, A.J. *Partner notification among asymptomatic Chlamydia trachomatis cases, by means of mailed specimens.* Br J Gen Pract 2002, 52(481): 652-4.
9. Lin, J-S.L., Donegan, S.P., Heeren, T.C. et al. *Transmission of Chlamydia trachomatis and Neisseria gonorrhoeae among men with urethritis and their female sex partners*. J Infect Dis 1998, 178: 1707-12.
10. van Valkengoed, I.G., Morré, S.A., van den Brule, A.J., Meijer, C.J., Bouter, L.M., van Eijk, J.T., Boeke, A.J. *Follow-up, treatment, and reinfection rates among asymptomatic chlamydia trachomatis cases in general practice*. Br J Gen Pract 2002, 52(481): 623-7.
11. Zimmermann, H.L., Potterat, J.J., Dukes, R.L., Muth, J.B., Zimmermann, H.O., Fogle, J.S., Pratts, C.I. *Epidemiologic differences between chlamydia and gonorrhea*. Am J Public Health 1990, 80: 1338-42.
12. Stamm, W.E. *Diagnosis of Chlamydia trachomatis genitourinary infections*. Ann Intern Med 1988, 108: 710-7.
13. Morré, S.A., Rozendaal, L., van Valkengoed, I.G.M. et al. *Urogenital Chlamydia trachomatis serovars in men and women having either a symptomatic or an asymptomatic infection: An association with clinical manifestations?* J Clin Microbiol 2000, 38(6): 2292-6.
14. Morré, S.A. Chlamydia trachomatis Infections in the Human Urogenital Tract. Detection, Typing and Clinical Aspects. Thesis, VUmc, Amsterdam: 1999.
15. Golden, M.R., Schillinger, J.A., Markowitz, L., St. Louis, M.E. *Duration of untreated genital infections with Chlamydia trachomatis. A review of the literature.* Sex Transm Dis 2000, 27: 329-37.
16. Morré, S.A., van den Brule, A.J., Rozendaal, L., Boeke, A.J., Voorhorst, F.J., de Blok, S., Meijer, C.J. *The natural course of asymptomatic Chlamydia trachomatis infections: 45% clear-*

*ance and no development of clinical PID after one-year follow-up*. Int J STD AIDS 2002, 13(Suppl. 2): 12-8.

17. Golden, M.R., Whittington, W.L., Handsfield, H.H. et al. *Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection.* N Engl J Med 2005, 352(7): 676-85.
18. Weström, L., Joesoef, R., Reynolds, G., Hadgu, A., Tompson, S.E. *Pelvic inflammatory disease and fertility. A cohort study of 1844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results.* Sex Trans Dis 1992, 19: 185-92.
19. Morré, S.A., Ouburg, S., Brand, A. *The EU FP6 EpiGenChamydia Consortium: Contribution of molecular epidemiology and host-pathogen genomics to understanding Chlamydia trachomatis-related disease*. Drugs Today (Barc) 2009, 45(Suppl. B): 7-13.
20. Morré, S.A., Karimi, O., Ouburg, S. *Chlamydia trachomatis: Identification of susceptibility markers for ocular and sexually transmitted infection by Immunogenetics*. FEMS Immunol Med Microbiol 2009, 55(2): 140-53.
21. Catsburg, A., van Dommelen, L., Smelov, V. et al. *TaqMan Assay for Swedish Chlamydia trachomatis variant*. Emerg Infect Dis 2007, 13(9): 1432-4.
22 Lyons, J.M., Ito, J.I., Jr, Pena, A.S., Morré, S.A. *Differences in growth characteristics and elementary body associated cytotoxicity between Chlamydia trachomatis oculogenital serovars D and H and Chlamydia muridarum*. J Clin Pathol 2005, 58(4): 397-401.
23. Lyons, J., Igietseme, J.U., Black, C.M., Morré, S.A. *Identification of candidate genes using the murine model of female genital tract infection with Chlamydia trachomatis.* Drugs Today (Barc) 2009, 45(Suppl. B): 51-59.
24 Ito, J.I., Jr, Lyons, J.M., Airo-Brown, L.P. *Variation in virulence among oculogenital serovars of Chlamydia trachomatis in experimental genital tract infection*. Infect Immun 1990, 58(6): 2021-3.
25. Bax, C.J., Dorr, P.J., Trimbos, J.B., Spaargaren, J., Oostvogel, P.M., Pena, A.S., Morré, S.A. *Chlamydia trachomatis heat shock protein 60 (cHSP60) antibodies in women without and with tubal pathology using a new commercially available assay*. Sex Transm Infect 2004, 80(5): 415-6.
26. Bax, C.J., Mutsaers, J.A., Jansen, C.L., Trimbos, J.B., Dorr, P.J., Oostvogel, P.M. *Comparison of serological assays for detection of Chlamydia trachomatis antibodies in different groups of obstetrical and gynecological patients*. Clin Diagn Lab Immunol 2003, 10(1): 174-6.
27. Bax, C.J., Oostvogel, P.M., Mutsaers, J.A., Brand, R., Craandijk, M., Trimbos, J.B., Dorr, P.J. *Clinical characteristics of Chlamydia trachomatis infections in a general outpatient department of obstetrics and gynaecology in the Netherlands.* Sex Transm Infect 2002, 78(6): E6.
28. Vanrompay, D., Hoang, T.Q.T, De Vos, L., Verminnen, K., Chiers, K., Morré, S.A., Cox, E. *Specific pathogen free pigs as an additional animal model for studying Chlamydia trachomatis genital infection*. Infect Immun 2005, 73(12): 8317-21.
29. Vanrompay, D., Cox, E., Volckaert, G., Goddeeris, B. *Turkeys are protected from infection with Chlamydia psittaci by plasmid DNA vaccination against the major outer membrane protein*. Clin Exp Immunol 1999, 118(1): 49-55.
30. Vanrompay. D., Charlier, G., Ducatelle, R., Haesebrouck, F. *Ultrastructural changes in avian Chlamydia psittaci serovar A-, B-, and D-infected Buffalo Green Monkey cells*. Infect Immun 1996, 64(4): 1265-71.
31. Morré, S.A., Ossewaarde, J.M., Savelkoul, P.H., Stoof, J., Meijer, C.J., van den Brule, A.J. *Analysis of genetic heterogeneity in Chlamydia trachomatis clinical isolates of serovars D, E, and F by amplified fragment length polymorphism*. J Clin Microbiol 2000, 38(9): 3463-6.
32. Meijer, A., Morré, S.A., van den Brule, A.J., Savelkoul, P.H., Ossewaarde, J.M. *Genomic relatedness of Chlamydia isolates determined by amplified fragment length polymorphism analysis*. J Bacteriol 1999, 181(15): 4469-75.
33. Peters, R.P., van Agtmael, M.A., Danner, S.A., Savelkoul, P.H., Vandenbroucke-Grauls, C.M. *New developments in the diagnosis of bloodstream infections.* Lancet Infect Dis 2004, 4(12): 751-60.
34. Nieuwenhuis, R.F., Ossewaarde, J.M., Götz, H.M. et al. *Resurgence of lymphogranuloma venereum in Western Europe: An outbreak of Chlamydia trachomatis serovar l2 proctitis in the Netherlands among men who have sex with men*. Clin Infect Dis 2004, 39(7): 996-1003.
35. Ossewaarde, J.M., Meijer, A. *Molecular evidence for the existence of additional members of the order Chlamydiales.* Microbiology 1999, 145 (Pt 2): 411-7.
36. van der Snoek, E.M., Ossewaarde, J.M., van der Meijden, W.I., Mulder, P.G., Thio, H.B. T*he use of serological titres of IgA and IgG in (early) discrimination between rectal infection with non-lymphogranuloma venereum and lymphogranuloma venereum serovars of Chlamydia trachomatis.* Sex Transm Infect 2007, 83(4): 330-4.
37. Pannekoek, Y., Heurgue-Hamard, V., Langerak, A.A., Speijer, D., Buckingham, R.H., van der Ende, A. *The N5-glutamine S-adenosyl-L-methionine-dependent methyltransferase PrmC/HemK. In Chlamydia trachomatis methylates class 1 release factors*. J Bacteriol 2005, 187(2): 507-11.
38. Pannekoek, Y., Morelli, G., Kusecek, B., Morre, S.A., Ossewaarde, J.M., Langerak, A.A., van der Ende, A. *Multi locus sequence typing of Chlamydiales: Clonal groupings within the obligate intracellular bacteria Chlamydia trachomatis*. BMC Microbiol 2008, 28 8(1): e42.
39. Pannekoek, Y., Spaargaren, J., Langerak, A., Merks, J., Morré, S.A., van der Ende, A. *Interrelationship between poly-*

*morphism of incA, fusogenic properties of Chlamydia trachomatis strains.* J Clin Microbiol 2005, 43(5): 2441-3.

40. Spaargaren, J., Fennema, H.S.A., Morré, S.A., de Vries, H.J.C., Coutinho, R.A. *New lymphogranuloma venereum Chlamydia trachomatis variant, Amsterdam.* Emerg Infect Dis 2005, 11(7): 1090-2.
41. de Vries, H.J.C., Smelov, V., Middelburg, J.G., Pleijster, J., Speksnijder, A.G.C.L., Morré, S.A. *Microbial cure of lymphogranuloma venereum proctitis with doxycycline*. CID 2009, 48(5): e53-6.
42. de Vries, H.J.C., van der Bij, A.K., Fennema, J.S.A. et al. *Lymphogranuloma venereum proctitis in men who have sex with men is associated with anal enema use and high-risk behavior.* Sex Transm Dis 2008, 35(2): 203-8.
43. van Bergen, J., Götz, H.M., Richardus, J.H., Hoebe, C.J., Broer, J., Coenen, A.J.; PILOT CT study group. *Prevalence of urogenital Chlamydia trachomatis increases significantly with level of urbanisation and suggests targeted screening approaches: Results from the first national population based study in the Netherlands.* Sex Transm Infect 2005, 81(1): 17-23.
44. van Bergen, J.E., Postma, M.J., Peerbooms, P.G., Spangenberg, A.C., Tjen-A-Tak, J., Bindels, P.J. *Effectiveness and cost-effectiveness of a pharmacy-based screening programme for Chlamydia trachomatis in a high-risk health centre population in Amsterdam using mailed home-collected urine samples*. Int J STD AIDS 2004, 15(12): 797-802.
45. Götz, H.M., van Bergen, J.E., Veldhuijzen, I.K. et al. *Lessons learned from a population-based chlamydia screening pilot.* Int J STD AIDS 2006, 17(12): 826-30.
46. Fiddelers, A.A., Land, J.A., Voss, G., Kessels, A.G., Severens, J.L. *Cost-effectiveness of Chlamydia antibody tests in subfertile women.* Hum Reprod 2005, 20(2): 425-32.
47. Land, J.A., van Bergen, J.E.A.M., Morré, S.A., Postma, M.J. *Epidemiology of Chlamydia trachomatis infection in women and the cost-effectiveness of screenin*g. Hum Reprod Update 2009 (in press).
48. Fiddelers, A.A., Dirksen, C.D., Dumoulin, J.C. et al. *Cost-effectiveness of seven IVF strategies: Results of a Markov decision-analytic model.* Hum Reprod 2009, 24(7): 1648-55.
49. Vincelette, J., Schirm, J., Bogard, M. et al. *Multicenter evaluation of the fully automated COBAS AMPLICOR PCR test for detection of Chlamydia trachomatis in urogenital specimens*. J Clin Microbiol 1999, 37(1): 74-80.
50. Morré, S.A., Catsburg, A., de Boer, M. et al. *Monitoring the potential introduction of the Swedish Chlamydia trachomatis variant (swCT) in the Netherlands.* Euro Surveill 2007, 12(10): E9-10.
51. Verkooyen, R.P., Noordhoek, G.T., Klapper, P.E. et al. *Reliability of nucleic acid amplification methods for detection of Chlamydia trachomatis in urine: Results of the first international collaborative quality control study among 96 laboratories.* J Clin Microbiol 2003, 41(7): 3013-6.
52. van der Helm, J.J., Hoebe, C.J, van Rooijen, M.S., Brouwers, E.E., Fennema, H.S., Thiesbrummel, H.F., Dukers-Muijrers, N.H. *High performance and acceptability of self-collected rectal swabs for diagnosis of Chlamydia trachomatis and Neisseria gonorrhoeae in men who have sex with men and women.* Sex Transm Dis 2009, 36(8): 493-7.
53. Götz, H.M., van Bergen, J.E., Veldhuijzen, I.K. et al. *Lessons learned from a population-based chlamydia screening pilot.* Int J STD AIDS 2006, 17(12): 826-30.
54. van Bergen, J., Götz, H., Richardus, J.H., Hoebe, C., Broer, J., Coenen T, PILOT CT Study Group. *Prevalence of urogenital Chlamydia trachomatis infections in the Netherlands suggests selective screening approaches. Results from the PILOT CT Population Study.* Drugs Today (Barc) 2006, 42(Suppl. A): 25-33.
55. Richardus, J.H., Götz, H.M. *Risk selection and targeted interventions in community-based control of chlamydia.* Curr Opin Infect Dis 2007, 20(1): 60-5.
56. Götz, H.M., Veldhuijzen, I.K., Ossewaarde, J.M., de Zwart, O., Richardus, J.H. *Chlamydia trachomatis infections in multi-ethnic urban youth: A pilot combining STI health education and outreach testing in Rotterdam, Netherlands.* Sex Transm Infect 2006, 82(2): 148-52.