Molecular epidemiology of Chlamydia trachomatis
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**Summary**

*Chlamydia trachomatis* infections are the most prevalent bacterial sexually transmitted infections (STI) worldwide. In the Netherlands, most infections are found among heterosexual adults under 25 years in age, certain migrant groups and men who have sex with men (MSM). Among the latter, an outbreak of a more aggressive strain of *C. trachomatis*, which causes lymphogranuloma venereum (LGV), is seen since 2003. Although *C. trachomatis* infections are often asymptomatic, late complications, such as pelvic inflammatory disease, may occur. These can ultimately lead to infertility. In addition, *C. trachomatis* infections may facilitate the transmission of HIV. Due to the high prevalence, *C. trachomatis* infections are a large burden on society, from a public health perspective and from an economic perspective. A better understanding of the transmission of *C. trachomatis* may contribute to improved screening and prevention programs in the future and ultimately alleviate this burden. Through the use of various typing methods, better understanding can be achieved by discriminating between clinically, biologically or epidemiologically different *C. trachomatis* strains. By applying these typing methods in large epidemiological studies, the transmission patterns of these different *C. trachomatis* strains can be discerned.

In Chapter 2, we evaluated the diagnostic performance of a newly developed *pmpH* real time PCR as a discrimination assay between LGV-inducing and non LGV-inducing *C. trachomatis* strains. The new typing assay had the same sensitivity for LGV-inducing strains as reverse hybridisation or *ompA* sequencing techniques, for no LGV-inducing strains were missed in the studies using this real time PCR. The sensitivity of the assay did not decrease in the presence of a concomitant non LGV-inducing strain. In addition, we investigated the non LGV genovar distribution in rectal samples from MSM and investigated the frequency of concomitant infections in men infected with LGV and non LGV-inducing strains. The genovars G, D, and J were the most frequent non-LGV genovars found, and in 6% of the LGV positive samples, a concomitant non-LGV genotype was detected.

In Chapter 3, we investigated which high resolution typing method was most suitable for molecular epidemiological analysis of *C. trachomatis* transmission patterns in sexual networks. We compared conventional *ompA* typing of *C. trachomatis* with the previously published multilocus sequence typing (MLST) and multilocus variable-number tandem-repeat (VNTR) analysis (MLVA). These high resolution typing methods were adapted to be more suitable for clinical samples by using shorter target regions and nested PCR. MLST, MLVA, and a combination of MLST and MLVA had discriminatory indexes (D) ranging from 0.95 to 0.99, meeting the guidelines set for molecular epidemiological studies.
The discriminatory capacity of all MLST and MLVA methods is much higher than that of \textit{ompA} genotyping (D = 0.78). Although the methods were comparable in resolution, the data of the MLVA method became ambiguous when the repeat lengths increased, which made it difficult to interpret the results in a consistent manner. Therefore the adjusted MLST procedure was selected as our method of choice for molecular epidemiological studies.

In Chapter 4, differences in circulating \textit{C. trachomatis} strains between MSM and heterosexuals were investigated using a modified MLST. Using \textit{ompA} genovar typing, heterosexuals were mainly infected with genovars E, F, and D, while MSM had predominantly genovars D, G, and J infections. When MLST was applied, differences in \textit{C. trachomatis} strain distribution proved to be much more apparent. Eight clusters, containing 10–128 samples were identified of which 4 consisted of samples from MSM (90%–100%), with genovars D, G, J, and L2b. The other 4 clusters consisted mainly of samples from heterosexuals (87%–100%) with genovars D, E, F, I, and J. Genetic diversity was much lower in the MSM clusters than in heterosexual clusters.

To study geographical variation, we investigated samples from MSM from the Netherlands, Sweden, and the United States, and samples from women from the Netherlands and Sweden. The distribution of urogenital strains found among MSM in the Netherlands was very similar to the distribution found among MSM in Sweden and the United States, while much more differences were seen between the distribution of strains found among women in the Netherlands and Sweden. Both tissue tropism as well as epidemiological network structures could explain the linkage between specific genetic variants and sexual orientation.

Finally, we assessed whether circulating \textit{C. trachomatis} strains were linked to certain subpopulations of MSM, as characterised by demographics, sexual risk behaviour, sexual partnerships, and lifestyle. No associations were found between the urogenital strains and age, ethnicity, lifestyle, partner characteristics, or sexual behaviour among the MSM population in Amsterdam, the Netherlands. In addition, various men were infected with different \textit{C. trachomatis} strains at different visits, or with different strains at different anatomical locations at the same visit. The distribution over the clusters did not seem to change over time. We therefore concluded that there was a co-occurrence of different \textit{C. trachomatis} strains, endemic within the MSM population at large. However, when distinguishing MSM- from heterosexual-associated strains, we did find some associations. MSM who were younger and MSM who reported sex with women were more often infected with heterosexual-associated strains.

In Chapter 5, we assessed whether Surinamese migrants in the Netherlands form a bridge population facilitating transmission of \textit{C. trachomatis} between Suriname and the Netherlands. We investigated the sexual mixing with
native Surinamese and native Dutch partners and compared the distribution of \textit{C. trachomatis} genotypes found among Surinamese migrants with those found among the native Surinamese or native Dutch population. Within the Netherlands, high levels of mixing were seen between the native Dutch and the Surinamese migrant populations. These Surinamese migrants also mixed with the native Surinamese population. However, no clear evidence was found that strains associated with the native Dutch population were transmitted via the Surinamese migrants to the native Surinamese population, or vice versa. The distribution of \textit{C. trachomatis} strains found among the Surinamese migrant population differed from both the native Surinamese and Dutch distributions, but did not form an intermediate reflection of the native groups. In addition, when we examined the distribution of \textit{C. trachomatis} strains among the participants that reported sexual mixing and those who did not, no significant differences could be found between the two in the distribution of \textit{C. trachomatis} clusters.

In addition, we elucidated determinants for \textit{C. trachomatis} infections in Suriname, such as ethnicity and ethnic sexual mixing, and identified transmission patterns and sexual networks using molecular epidemiological network analyses. Age, ethnicity, and recruitment site were significantly associated with \textit{C. trachomatis} infections. Participants of Creole and Javanese ethnicity were more frequently infected with \textit{C. trachomatis}. Although sexual mixing with other ethnic groups did differ significantly per ethnicity, this mixing was not an independent determinant of \textit{C. trachomatis} infections. Although the proportion from various ethnic groups differed significantly between the three \textit{C. trachomatis} clusters found among the participants, all major ethnic groups were represented in all clusters. Therefore, differences in prevalence between ethnic groups could not be explained by sexual mixing.

Finally, we investigated the effect of geographical distance on the distribution of \textit{C. trachomatis} genotypes by comparing strains found among heterosexuals from Nanjing, China with those found in Amsterdam, the Netherlands. Most strains were specific to Nanjing, but some clustered with strains from Amsterdam. This demonstrates geographical variation in \textit{C. trachomatis} previously left undetected. Interestingly, while many MLST genotypes were unique to Nanjing, a few were identical to strains circulating in Amsterdam.

In the general discussion of this thesis, we addressed the main findings of this thesis and made recommendations for future research, based on recent literature. We found that the MSM and heterosexual populations harbour distinct \textit{C. trachomatis} strains. In addition, within the MSM-associated \textit{C. trachomatis} strains less variation was observed compared to the heterosexual-associated strains. Among heterosexuals, the distribution of strains varied between countries and between subgroups within one country. This variation was absent among MSM. These
differences could arise from biological differences between the risk group-associated strains or can be accounted to differences in the transmission networks between the two risk populations. Future research should elucidate these differences and how these findings can be exploited to improve screening and prevention programs.