PhD defence Kara Osbak

Contemporary syphilis epidemics: efforts to improve syphilis diagnostics

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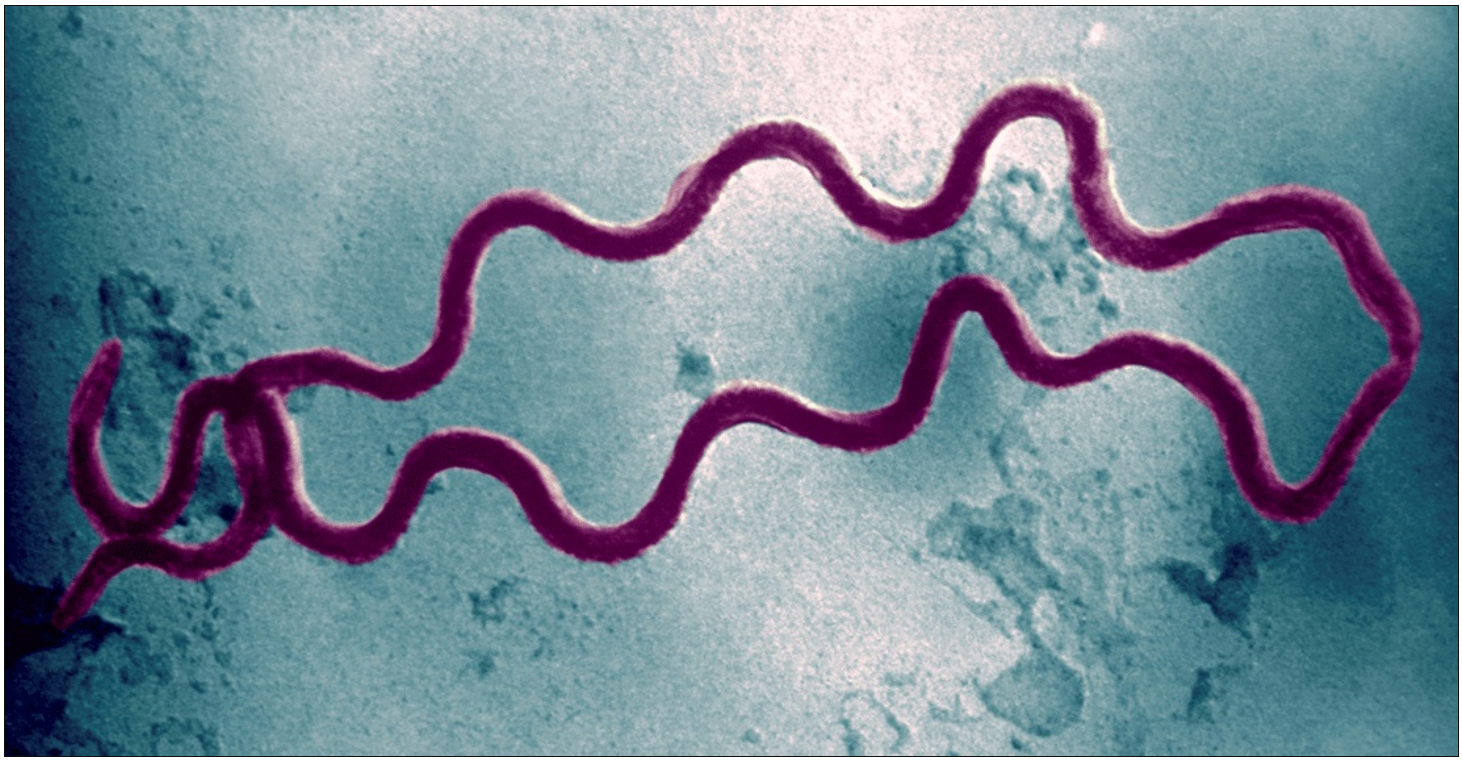

Dit is de omschrijving

Supervisors

- Prof. Dr. Chris Kenyon (ITM)
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Summary

Syphilis, a multistage curable chronic disease caused by the spirochete *Treponema pallidum ssp. pallidum (T. pallidum)*, has re-emerged during the last 15 years as a major global public health problem, with an estimated 6 million new infections each year worldwide. Men who have sex with men (MSM) populations have been particularly affected, accounting for more than 90% of incident syphilis infections in Belgium, whereby half of these are reinfections. If not treated promptly, syphilis can cause serious morbidity and adverse pregnancy events. Work presented in Section I of this thesis aimed to answer two important questions related to the relationship between syphilis and HIV. First, we assessed if there was a country-level association between antenatal syphilis prevalence from early in the HIV epidemics (1990-1999) and peak HIV prevalence to help better elucidate the underlying determinants of variations in HIV spread. Linear regression analyses of data from 76 countries revealed that syphilis prevalence in the 1990s predicted approximately 53% of the variation in peak HIV prevalence. Second, we assessed if we could use the HIV phylogenetic tree constructed from HIV-1 sequences of 1169 clients in follow-up at a cohort in Antwerp, Belgium to see if there was evidence for clustering of syphilis infections. No evidence of clustering was found, however, analyses revealed potential cases of sexual identity misclassification of MSM as heterosexuals. We discuss the role these individuals may play as a high-risk bridge population. Diagnosis of *T. pallidum* (re)-infection and post-treatment follow-up to determine pathogen eradication remains onerous for clinicians due to inadequate assays based on century-old techniques. Therefore, the development of a diagnostic test that could directly detect *T. pallidum* antigens in human biofluids would improve individual care and prevention efforts. Section II of this thesis details studies related to improving syphilis diagnostics. First, in vivo rabbit cultured *T. pallidum* were purified to study the *T. pallidum* proteome during infection via complementary mass spectrometric (MS) approaches, resulting in the most extensive proteome investigation of *T. pallidum* to date. In total, 54% of the whole *T. pallidum* proteome (577 proteins) were characterized and semi-quantified, yielding novel insights into *T. pallidum* biology and potential biomarkers for diagnostic applications. Eleven candidate biomarker proteins were shortlisted from this analysis and incorporated into a targeted multiple reaction monitoring assay. No endogenous *T. pallidum* peptide signals were detected in undepleted protein extracts from urine and plasma from individuals with syphilis, likely due to the very low (femtomoles/liter) predicted concentrations of biomarker proteins. Nevertheless, findings from this pioneering study could be useful to other researchers considering employing similarly challenging techniques. Lastly, an automated immunoturbidimetric nontreponemal assay was evaluated for clinical appropriateness using serum samples collected during a two-year observational cohort study of syphilis patients (N=120) and controls (N=30) conducted at the Institute of Tropical Medicine in Antwerp, Belgium. Test performance deficiencies were highlighted. Independent and comprehensive assay evaluations using well-characterized clinical samples are essential to improving diagnostic methods. In conclusion, (molecular) epidemiological studies of STIs can yield insights that could help inform prevention efforts. The application of proteomics approaches to study syphilis has broadened our understanding of the enigmatic spirochete *T. pallidum*. These findings could be useful for the development of a syphilis antigen test.