Chlamydia trachomatis viability testing

Citation for published version (APA):

Document status and date:
Published: 01/01/2019

DOI:
10.26481/dis.20191106kj

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:
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Download date: 14 Jun. 2020
Valorisation
The World Health Organisation (WHO) recently estimated that about 130 million new cases of Chlamydia trachomatis (CT) are acquired annually worldwide. In addition to the immediate clinical impact, infection with CT can cause serious reproductive tract complications over time such as pelvic inflammatory disease (PID), infertility, and ectopic pregnancy. Therefore, preventing the spread of sexually transmitted CT has been recognized as a major public health priority worldwide.

The advent of highly sensitive and specific nucleic acid amplification tests (NAATs) in the field of STI testing has greatly enhanced our ability to identify patients at risk and optimize disease control strategies. Therefore, the value of NAAT for the detection of CT cannot be disputed, however NAATs also have inherent limitations to keep in mind when interpreting test results. Tests used in routine do not distinguish between viable bacteria (infectious and pathogenic) and non-viable molecular remnants. The latter can give a positive test result, which is not clinically relevant. Therefore, the clinical and epidemiological relevance of CT detection by NAAT can be discussed and additional information on the viability of CT might be essential. Traditionally, CT culture is the gold standard method for the assessment of viability, however CT culture is labour-intensive, technically demanding, and lacks sensitivity.

Development and application of novel approaches to determine whether the detected CT are viable can directly impact patient care. In this light, the research presented in this thesis has a clear societal and economic relevance in addition to the scientific relevance.

Current CT testing guidelines only consider rectal testing in women after report of anal sex or rectal symptoms, i.e. rectal testing on indication. However, clinicians, researchers and policymakers are currently discussing the need for routine rectal testing in women, as rectal CT has been demonstrated to be as common in women without indication for rectal testing as it is in women with an indication for rectal testing. Clinicians and policymakers need to have a better understanding of the clinical and epidemiological relevance of rectal CT in women so that they can optimize STI testing guidelines and inform patients appropriately. In case rectal CT detection in women is shown to be associated with true infections, rectal testing would likely become part of the recommended testing routine. In the studies in this thesis, viability testing has already showed that viable CT could be detected in at least half of rectal CT NAAT diagnosed women. This means that rectal CT in these women might be a potential source of ongoing transmission and subsequent development of disease-related complications.

In case viability testing can establish that rectal CT in women is clinically relevant, this could also have a direct impact on clinical patient management. According to current treatment guidelines both azithromycin and doxycycline can be used for the treatment of CT infections.
However, recent studies have shown that the effectiveness of doxycycline exceeds that of azithromycin for the treatment of rectal CT in women (99% vs. 83% respectively). Therefore, several countries including The Netherlands adjusted treatment guidelines to use doxycycline as first-line treatment for rectal CT. On the other hand, however, concerns have been raised regarding treatment adherence when using doxycycline for CT treatment, as a twice-daily administration for multiple days is required to complete the treatment. Previous studies have shown that the majority of women diagnosed with genital CT also have a concurrent rectal CT. Maybe, in the near future when viability testing is more widely implemented, only patients with relevant (viable) rectal CT will be treated with doxycycline, while azithromycin can still be used for the treatment of genital CT in patients with non-relevant (non-viable) rectal CT.

The research to date demonstrated frequent (up to 40%) intermittent detection of CT after treatment, raising concerns about potential reproductive tract complications due to treatment failure, persistent infections, and re-infection with CT. The value of performing a NAAT-based test of cure (TOC) after treatment can be discussed and is currently not recommended (<3 weeks post-treatment) due to the prolonged detection of non-viable molecular remnants. Also here, the introduction of viability methods for TOC would have a significant impact in clinical management of patients, as detection of viable CT would be a strong indication of inadequate treatment.

Currently, all NAAT-positive patients are receiving antibiotic treatment regardless of whether the detected CT are viable or not. However, it is known that CT infections can be subject to natural clearance. The studies presented in this thesis showed that some women cleared their CT infection in the time interval between diagnosis and treatment, with a reported clearance rate of 6% at the vaginal site and 16% at the rectal site. Yet, NAAT-based assessment of clearance might underestimate the ‘true’ clearance rate due to detection of non-viable molecular remnants. Indeed, based on viability testing it was shown that the clearance rates increased to 12% at the vaginal site and 40% at the rectal site. Maybe, in the near future when viability testing methods are more widely implemented, patients with no evidence of viable CT will no longer require antibiotic therapy. This may result in less overtreatment, thereby avoiding potential development of antimicrobial resistance in other bacterial species (e.g. *N. gonorrhoeae* and *M. genitalium*).

Viability testing methods presented in this thesis have the potential to be automated, which is a valuable aspect for the implementation in a high throughput workflow or a point-of-care setting. When viability testing will become routinely used in the diagnostic workflow for detection of CT infections, current NAAT assays can be adapted or adjusted to incorporate the presented strategies (v-PCR) or use the presented PCR targets (mRNA).
To conclude, this thesis provides some new pieces of the puzzle regarding the knowledge gaps in our current evidence-base for CT control. The assessment of CT viability may be implemented in high-throughput routine diagnostics in the near future, further expanding our toolbox to inform and optimize disease control strategies.