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Corresponding author:
Erlangga Yusuf,
Email: angga.yusuf@gmail.com

Abstract

The aim of this paper is to describe the prevalence of Mycoplasma genitalium and Trichomonas vaginalis in patients who visited general practitioners in the Netherlands. Additionally, we describe the prevalence of M. genitalium resistance to azithromycin and moxifloxacin. We used data from 7,411 consecutive female patients who were screened for Chlamydia trachomatis, Neisseria gonorrhoeae, M. genitalium, and T. vaginalis and data from 5,732 consecutive male patients screened for C. trachomatis, N. gonorrhoeae, and M. genitalium.

The prevalence of M. genitalium and T. vaginalis in female patients was 6.7% (95% CI: 6.2 to 7.4) and 1.9% (95% CI: 1.6 to 2.2%), respectively. M. genitalium prevalence in male patients was 3.7% (3.3 to 4.3). M. genitalium co-occurred with C. trachomatis in 1.4% (0.3 to 0.6%) of female and in 0.7% (0.5 to 0.9%) of male patients. Macrolide resistance gene mutations and fluoroquinolone resistance gene mutations were detected in 73.8% and 9.9%, respectively. We concluded that M. genitalium is relatively infrequently found in a large general practitioner population in the Netherlands. It can co-occur with C. trachomatis, and is often resistant to azithromycin. Therefore, when treating sexually transmitted infections, these prevalence and resistance data should be taken into account.

Introduction

Sexually transmitted infections (STIs) have a significant impact on quality of life and reproductive health. The rates of STIs have increased substantially worldwide, including in high-income countries during the 21st century [1]. There are more than 30 different bacteria, viruses, and parasites that can be transmitted through sexual contact [2]. While surveillance data are widely available for Chlamydia trachomatis and Neisseria gonorrhoeae, the epidemiology of Mycoplasma genitalium and Trichomonas vaginalis is less known [3, 4]. A meta-analysis published in 2018 included only two studies from Europe on the prevalence of M. genitalium in the general population, and three studies on men who have sex with men (MSM) who visited a community-based clinic in Europe [5]. Arguably, the prevalence of STI pathogens can be affected by a variety of reasons such as the study setting, the structure of the health care system, and whether the individuals with STI complaints are advised to go to primary care or to an STI clinic. In the general population of British individuals who did not exhibit symptoms of STI, the prevalence of M. genitalium was 1.2% in men and 1.3% in women [6]. In patients who underwent STI screening in France, the prevalence was comparable, that is 1.7% [7]. In the same French study, the prevalence of T. vaginalis was 3.4%. In the USA, the T. vaginalis positivity rate in a population-based study was reported at 2.3% among adolescents [8] and 3.1% among reproductive-age women [9]. There is also paucity of data on the co-occurrence of M. genitalium and T. vaginalis with C. trachomatis and N. gonorrhoeae.

In the Netherlands, there is limited data on the prevalence of M. genitalium and T. vaginalis, and the available data come from a mixed population. In a study of samples taken from primary care and hospital care settings, the prevalence of M. genitalium was 1.9% and T. vaginalis was 0.6% [10]. Another study conducted in the Netherlands that collected samples from STI clinics, general practitioners (GPs), and hospitals found M. genitalium and T. vaginalis prevalence of 1.4% and 4.5%, respectively [11]. Additional data are required on the epidemiology of M. genitalium and T. vaginalis in the primary care population of the Netherlands.

Therefore, the aim of this study is to describe the epidemiology of M. genitalium and T. vaginalis, especially in light of their co-occurrence with STI pathogens C. trachomatis and N. gonorrhoeae in patients who visited GPs in the Netherlands. As a second objective, we sought to describe the prevalence of M. genitalium genotypically resistant to azithromycin and fluoroquinolones.
Materials and methods

Study setting and population

The data used in this study were derived from specimens (pharyngeal-, urethral- (only in men), and vaginal swabs (only in women) and urine) submitted to the Star-shl Medical Laboratory during a four-year period (between January 2018 and December 2021). The specimens were obtained from patients who visited GPs due to urethral symptoms (that is dysuria or discharge) or vaginal symptoms (that is dysuria, discharge, or vaginal blood loss), or from their sexual contacts. The Star-shl Medical Laboratory provides services for 1,500 GPs, mostly from the southwestern region of the Netherlands. This region has an estimated population of 3.5 million inhabitants. In the whole country, there are around 12,000 GPs [12], and people can go to either their GP or the Municipal Public Health Service (GGD in Dutch) for an STI test. STI testing offered by the GGD is anonymous and frequently sought by high-risk patients, such as men who have sex with men (MSM) and sex workers. The present study was not required.

Sampling and molecular testing

Swabs and first-void urine were collected and transferred to appropriate sample collection media, and transported to the laboratory within the same day. For the detection of appropriate sample collection media, and transported to the laboratory. Sampling and molecular testing was not required. The Star-shl Medical Laboratory provides services for 1,500 GPs, mostly from the southwestern region of the Netherlands. This region has an estimated population of 3.5 million inhabitants. In the whole country, there are around 12,000 GPs [12], and people can go to either their GP or the Municipal Public Health Service (GGD in Dutch) for an STI test. STI testing offered by the GGD is anonymous and frequently sought by high-risk patients, such as men who have sex with men (MSM) and sex workers. The present study was not required.

Macrolide and fluoroquinolone resistance in M. genitalium

Macrolide resistance—associated gene mutations were detected in 149 out of 202 (73.8%) randomly selected M. genitalium positive samples. The frequency of fluoroquinolone resistance—associated gene was much lower than macrolide resistance, that is 20 out of 202 (9.9%) randomly selected M. genitalium positive samples. Both macrolide and fluoroquinolone gene mutations were detected in five patients. The mutations associated with macrolide and fluoroquinolone resistance found in this study are presented in Table 1.

Results

Prevalence

During the study period, GPs ordered tests for all four pathogens in 7,411 female patients (median age 29.4 years (IQR 23.4 to 38.5)), and for C. trachomatis, N. gonorrhoeae, and M. genitalium in 5,732 male patients (30.4 years (24.5 to 40.2)).

In male patients, 7.0% (95% CI: 6.4 to 7.6) were positive for C. trachomatis and 0.8% (0.6 to 1.0) were positive for N. gonorrhoeae. M. genitalium was positive in 6.7% (6.2 to 7.4) and T. vaginalis was positive in 1.9% (1.6 to 2.2).

In male patients, 5.5% (95% CI: 4.9 to 6.1) were positive for C. trachomatis and 1.7% (1.4 to 2.1) were positive for N. gonorrhoea. M. genitalium was positive in 3.7% (3.3 to 4.3). M. genitalium co-occurred with C. trachomatis in 1.4% (0.3 to 0.6) of female patients and in 0.7% (0.5 to 0.9) of male patients. T. vaginalis co-occurred with C. trachomatis only in 0.2% (0.1 to 0.3) of female patients. The co-occurrence of M. genitalium and N. gonorrhoea was rarely observed, that is in 0.1% (0.04 to 0.2) of female patients, and in 0.2% (0.1 to 0.4) of male patients.

<table>
<thead>
<tr>
<th>Resistance Type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolide resistance</td>
<td>149 (73.8)</td>
</tr>
<tr>
<td>A2058G</td>
<td>61</td>
</tr>
<tr>
<td>A2059G</td>
<td>50</td>
</tr>
<tr>
<td>A2058T</td>
<td>25</td>
</tr>
<tr>
<td>A2509C</td>
<td>4</td>
</tr>
<tr>
<td>A2509T</td>
<td>6</td>
</tr>
<tr>
<td>Invalid</td>
<td>4</td>
</tr>
<tr>
<td>Fluoroquinolone resistance</td>
<td>20 (9.9)</td>
</tr>
<tr>
<td>G248T</td>
<td>10</td>
</tr>
<tr>
<td>G259A</td>
<td>8</td>
</tr>
<tr>
<td>G248A</td>
<td>2</td>
</tr>
<tr>
<td>G259C, G259T, A247C</td>
<td>0</td>
</tr>
</tbody>
</table>

Statistical analysis

Statistical analyses were conducted in Rstudio (version 2022.07.1), using R version 4.2.1. We calculated and presented the proportion of patients who tested positive for the STI pathogens investigated in this study (including the percentage and their 95% confidence interval, 95% CI). We also calculated the proportion of patients with a co-occurrence of M. genitalium or T. vaginalis with C. trachomatis and N. gonorrhoeae. No formal statistical testing was performed since this study did not pose any particular hypothesis.
Discussion

Dutch guidelines do not recommend routine screening for asymptomatic patients for *M. genitalium* and *T. vaginalis* [17, 18], and perhaps this is the reason why knowledge on the co-occurrence of these pathogens with other STIs in the Netherlands is scarce. The difference in the prevalence of STI pathogens is determined largely by the population and the test that is used. The comparison should therefore be made, for example between GP populations and mixed-study populations (e.g. hospitals, patients visiting STI clinics). Plausibly, our GP patient population will have a lower prevalence of STIs including *M. genitalium* than the population of patients who visited the GGD. Due to anonymous testing, the GGD is frequently sought by high-risk patients, such as MSM and sex workers. The prevalence of *M. genitalium* in our study population (5.5% combined male and female) is three times higher than the prevalence of *M. genitalium* in a mixed GP and hospital population in a bordering region in the Netherlands (2.1%) [10]. The prevalence of *T. vaginalis* in our study was also slightly higher than in that study (1% combined male and female versus 0.7%). An explanation for this could be the high sensitivity of the TMA-based Aptima assay [19] used in our study. Another study from the Netherlands using a mixed-study population (STI clinics, GPs, and hospitals), where no separate data could be derived for the GP population, showed a prevalence of *M. genitalium* and *T. vaginalis* of 4.5% and 1.4%, respectively [11]. In that study, an in-house PCR was used.

Our study confirmed a very high percentage of a genotypic macrolide resistance as also found in the study from Hetem and colleagues from the Netherlands. It was shown in that study that 66% of positive *M. genitalium* samples showed macrolide resistance–associated mutations [18]. This study was published after a systematic review and meta-analysis that showed macrolide resistance proportions of 27.5% in non-Nordic European countries. The range is however wide, from 6.5% in Belgium to 74.3% in the UK [16]. In this systematic review, the proportion of *M. genitalium* that was resistant to fluoroquinolone in non-Nordic countries was 3.2%, lower than the 9.9% found in our study.

Our findings present several new recommendations for practice. Since *M. genitalium* is occasionally found, it is recommended that it should be tested when test results for *C. trachomatis* or N. gonorrhoeae turn out to be negative but the patient still experiences STI symptoms. Another recommendation is that macrolide resistance should be performed for patients who retain symptoms after macrolide treatment. The number of macrolide resistance gene mutations may be high, but a discrepancy between genotypic and phenotypic resistance may occur.

Our study has several limitations. It does not collect specific clinical data, but our study was not designed to link the clinical data to STI pathogens. Another limitation is that we only performed macrolide or fluoroquinolone resistance testing in 30% of the samples due to limited funding.

In conclusion, we revealed the relatively low prevalence of *M. genitalium* in a large GP population in the Netherlands, but, co-occurrence with *C. trachomatis* and resistance to azithromycin may be observed. Therefore, when treating STIs, these prevalence and resistance data should be taken into account.

Data availability statement. The data that support the findings of this study are available on request from the corresponding author.


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Competing interest. The authors declare no competing interests.

References


