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Experience of the Moscow Scientific and Practical Center for Dermatovenerology and Cosmetology in using a novel multiplex PCR test for STIs

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ABSTRACT

Background. Due to the high prevalence of sexually transmitted infections (STIs) in the Russian Federation and their challenging diagnosis, developing novel, personalized approaches to managing patients is necessary.

Objective. To analyze the experience of MSPCDC using a modern test based on real-time multiplex polymerase chain reaction (PCR) for STIs diagnosis.

Material and methods. The results of the identification of the four most common STI pathogens (*N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, *T. vaginalis*) and their DNA concentrations using a novel multiplex PCR test of samples from 1.082 patients aged 16 to 68 years treated at MSPCDC in 2021, as well as statistics on STI registration among MSPCDC patients from 2014 to 2021 were analyzed.

Results. The following pathogens were identified: *C. trachomatis* (45.9%), *M. genitalium* (20.1%), *N. gonorrhoeae* (29.5%), and *T. vaginalis* (4.5%). The majority (54.2-84.7%) of patients had predominantly low pathogen concentrations (up to 104 GE/mL). Only males with gonococcal infection had a predominance of individuals with a high bacterial load of *N. gonorrhoeae* (72.6%) DNA. Since the introduction of the novel multiplex PCR test in 2018, the STIs detection rate has increased significantly (gonorrhea in females by 280.6% and in males by 177.9%; chlamydia in females by 71.2% and in males by 31.1%; trichomoniasis in males by 123.1%; *M. genitalium* in males by 41.1%).

Conclusion. The novel multiplex PCR test contributes to the etiological diagnosis, detection of co-infections, and determination of the pathogen load in the biological samples, which can be used to personalize therapy and reduce the economic burden of STIs.

Keywords: *sexually transmitted infections, C.trachomatis, N.gonorrhoeae, T.vaginalis, M.genitalium, PCR.*

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Introduction

Sexually transmitted infections (STIs) are known to have significant medical and social relevance due to the risk of severe complications that have a negative impact on reproductive health [1, 2].

The most common STIs reported in the Russian Federation include infections caused by bacterial and protozoal pathogens: *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis*. In 2019, these infections accounted for 59.5% of all STIs subject to official registration; in 2020 — 59.4% **(Fig. 1)**.

The figure may be even more impressive if we add the yet unregistered infection caused by *M. genitalium*.

Since all the above infections are localized in one biotope and have no pathognomonic symptoms, it is urgent to develop new approaches to optimize their diagnosis and treatment.

Until recently, the approaches to diagnosing STIs caused by *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, and *T. vaginalis* have been rather diverse and often not entirely evidence-based. Recent dermatovenerology guidelines recommend highly sensitive and specific molecular-biological (especially) and cultural methods as priority

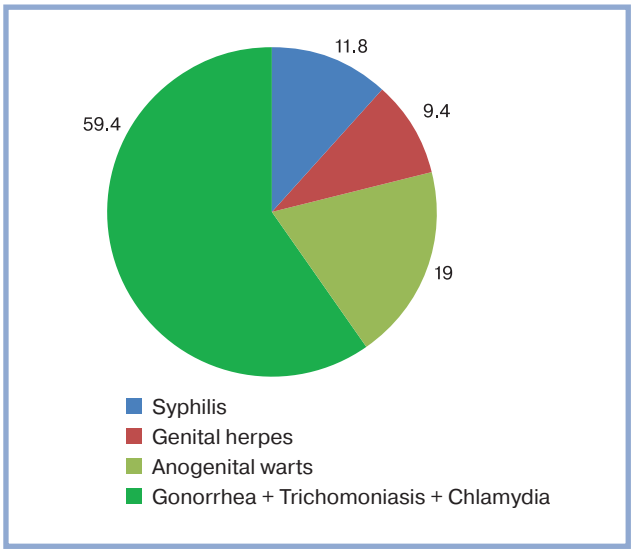

Fig. 1. **Structure of STIs subject to official registration in the Russian Federation. 2020.**

diagnostic methods [3-10]. At the same time, in the previous edition of the Medical Care Procedure in Obstetrics and Gynecology [11], microscopy was indicated as a method of choice, which is known to have neither proper sensitivity nor specificity. This method has been recommended, in particular, as part of the primary screening for pregnant women for the diagnosis of gonococcal infection and as part of the B-complex examination for the detection of aerobic and facultative anaerobic microorganisms. The use of PCR was recommended only for the identification of *C. trachomatis*. The new edition of the Medical Care Procedure in Obstetrics and Gynecology [12] pays much attention to examining pregnant women (including laboratory examination) to prevent fetal malformations, genetic syndromes, and chromosomal anomalies. However, these guidelines do not mention methods and timing for laboratory diagnosis of STIs in pregnant women and persons with gynecological conditions; modern, highly specific, and sensitive molecular biology diagnostic methods are not appropriately addressed. The molecular biology laboratory is identified only as part of the perinatal center. However, it is not included in any other units related to medical care (antenatal clinic, day hospital for the diagnosis and treatment of obstetric and gynecological conditions, maternity hospital, etc.). Thus, physicians of related specialties, who sometimes manage patients with STIs (obstetrician-gynecologists, urologists, and dermatovenerologists), still use outdated approaches for STI diagnosis based on microscopic examination or long, laborious and lo w sensitivity (compared to molecular methods) cultural/bacteriological method, and ignore advanced molecular technologies.

Currently, all patients with diagnosed STIs are given etiological treatment regardless of the severity of their clinical presentation. The only thing that matters is detecting a particular pathogen [3-10]. However, there are many challenges associated with currently accepted approaches to STI treatment: the variety of existing therapies with different antimicrobial doses and regimens approved by current clinical guidelines, along with regulated prescribing approaches, prevent the use of a personalized treatment approach and too high or too low doses of antimicrobials may result in adverse events (intolerance, side effects, incomplete eradication of pathogens, relapses). The current approach does not correspond to the setting of the Strategy for Scientific and Technological Development of the Russian Federation, approved by Presidential Decree No. 642 of 01.12.2016 "On the Strategy for Scientific and Technological Development of the Russian Federation" on the "transition to personalized medicine, high-tech healthcare and health-saving technologies, *including rational use of medicines (primarily antibacterial*)."

According to current scientific evidence, one of the problems with STI treatment is that the concentration of pathogens in the urogenital tract is not considered when prescribing therapy. At the same time, many foreign and domestic studies suggest that pathogen concentration, or bacterial/protozoal load, may play an essential role in STI therapy effectiveness.

Thus, Horner [13] noted that women with high concentrations of chlamydia are at increased risk of treatment failure.

Jennifer Walker et al. [14] studied the efficacy of *M. genitalium* infection therapy with azithromycin in women and showed that a higher load of *M. genitalium* was associated with treatment failure. The authors concluded that bacterial load might be essential in azithromycin treatment failure.

The paper by A.E. Gushchin et al., published abroad [15], addressed the eradication of *M. genitalium* in males with urethritis treated with macrolides. It was found that the eradication of *M. genitalium* occurred significantly faster in patients with a lower *M. genitalium* load before treatment. Half of the patients with a high load of *M. genitalium* before treatment remained positive even after treatment. The authors concluded that the bacterial load of *M. genitalium* before treatment might predict the eradication efficacy with macrolides.

Kong et al. [16] indicated that high bacterial load is associated with failure of azithromycin treatment of rectal infection.

The results of a study of the *N. gonorrhoeae* bacterial load are presented in B.M.J.W. van der Veer et al. [17]. The authors showed a difference in the *N. gonorrhoeae* bacterial load in the examination of different anatomical loci (urethra, rectum, oropharynx) in men who have sex with men and showed that the severity of their genital symptoms was associated with a higher bacterial load of *N. gonorrhoeae* in patient urine samples.

Thus, based on the above data, it can be assumed that the concentration of STI pathogens may affect both the clinical course and the effectiveness of STI therapy and should be considered when prescribing treatment.

The **objective of the study** is to analyze the experience of the Moscow Research and Practical Center for Dermatovenerology and Cosmetology (MRPCDC) using a modern real-time multiplex PCR-based AmpliPrime NCMT test to screen patients for STI (*N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, *T. vaginalis*).

The pathogen identification and concentration measurement results in biological material of patients in 2021 were analyzed. Also, the test effectiveness analysis was performed based on assessing the trends in detecting STIs caused by these pathogens from 2014 to 2021.

Materials and methods

The study included patients with established STIs caused by *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*, *M. genitalium*, who were managed at the MRPCDC in 2021 (n=1082, including 843 (77.9%) males and 239 (22.1%) females aged 16 to 68 years). The study also analyzed statistical data regarding the frequency of STI detection and registration among MNPDC patients from 2014 to 2021.

The material for the study was scrapings/discharge from the mucosa of the urogenital tract organs of patients with STIs. Biological material from the following anatomical loci was obtained from each study participant for subsequent PCR testing: in men from the urethra and in women, combined material from the urethra, vagina, and cervical canal.

Sampling was done using disposable sterile probes to obtain the required cellular material from the studied loci.

Biological samples were placed in disposable polypropylene test tubes with a transport medium containing mucolytic agent (Registration Certificate No. FSR 2009/05514, Federal Budget Institution of Science «Central Research Institute for Epidemiology» of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing) and stored at room temperature for not more than 2 h; in case of need for more extended storage, the samples were placed in a refrigerator at 2–8 °C for not more than 24 h.

All samples of biological material were tested for the presence of gonococcal, chlamydial, trichomonad, and *M. genitalium* infections by real-time PCR with fluorescent signal detection using a PCR-based AmpliPrime NCMT reagent kit (Registration Certificate No. RZN 2015/3168 dated 13.10.2015, NextBio Ltd., Russia, Moscow) designed for qualitative and quantitative determination (with DNA concentration measurement, GE/ml) of *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, and *T. vaginalis* in biological material sampled from mucous membranes of the urogenital tract. The amplification and analysis of its results were performed using a Rotor-Gene Q instrument with a real-time hybridization-fluorescence detection system. MagnoPrime FAST kit (NextBio Ltd., Russia) was used for DNA extraction. Tests were performed according to the reagent kit manuals.

Tests were performed according to the reagent kit manuals. Bacterial/protozoal load was considered low when the concentration of pathogens in the biomaterial sample was 104 GE/mL and below and high when the pathogens' DNA concentration in the biomaterial sample was above 104 GE/mL.

Statistical processing of the obtained data was performed using Excel software (MS Office package).

Results

Based on the results of clinical and laboratory examination, *C. trachomatis* was detected in 497 (45.9%) patients, *M. genitalium* in 218 (20.1%), *N. gonorrhoeae* in 319 (29.5%), *T. vaginalis* in 48 (4.5%). Thus, urogenital chlamydial infection was the most common (45.9%).

Mixed infections were detected in 100 (9.2%) of 1082 patients. Males predominated among those with mixed infections (82/82.0%); in females, mixed infection was detected in 18.0% of cases (n=18). Co-infection with *C. trachomatis* + *N. gonorrhoeae* was the most common (77/77.0%). Co-infection with other pathogens was less common: *C. trachomatis* + *M. genitalium* in 11 (11/0%) patients, *M. genitalium* + *N. gonorrhoeae* in 7 (7.0%), *N. gonorrhoeae* + *T. vaginalis* in 1 (1.0%), *C. trachomatis* + *T. vaginalis* in 1 (1.0%), *C. trachomatis* + *M. genitalium* + *N. gonorrhoeae* in 3 (3.0%) **(Fig. 2)**.

C. trachomatis was detected in 398 (80.1%) males and 99 (19.9%) females. A low concentration of *C. trachomatis* DNA was detected in 60.3% of males and 72.8% of females, and a high concentration in 39.7% of males and 27.2% of females. Thus, most male and female patients with urogenital chlamydial infections had low concentrations of *C. trachomatis* DNA **(Fig. 3)**.

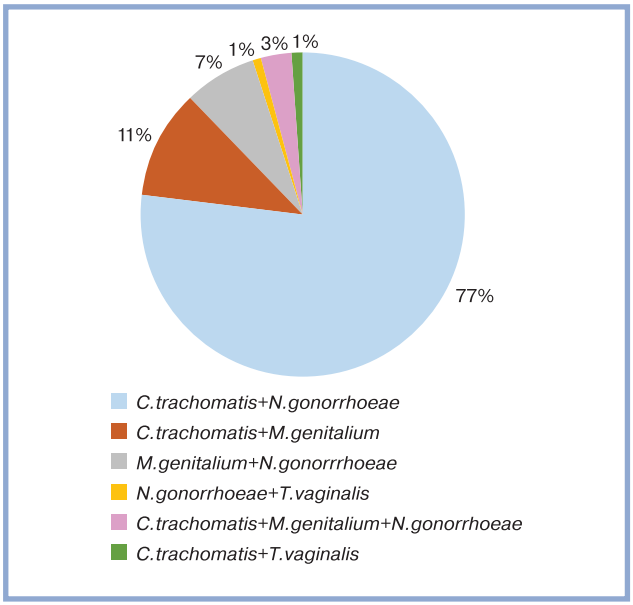

Fig. 2. **Results of co-infection detection in biological samples from males and females.**

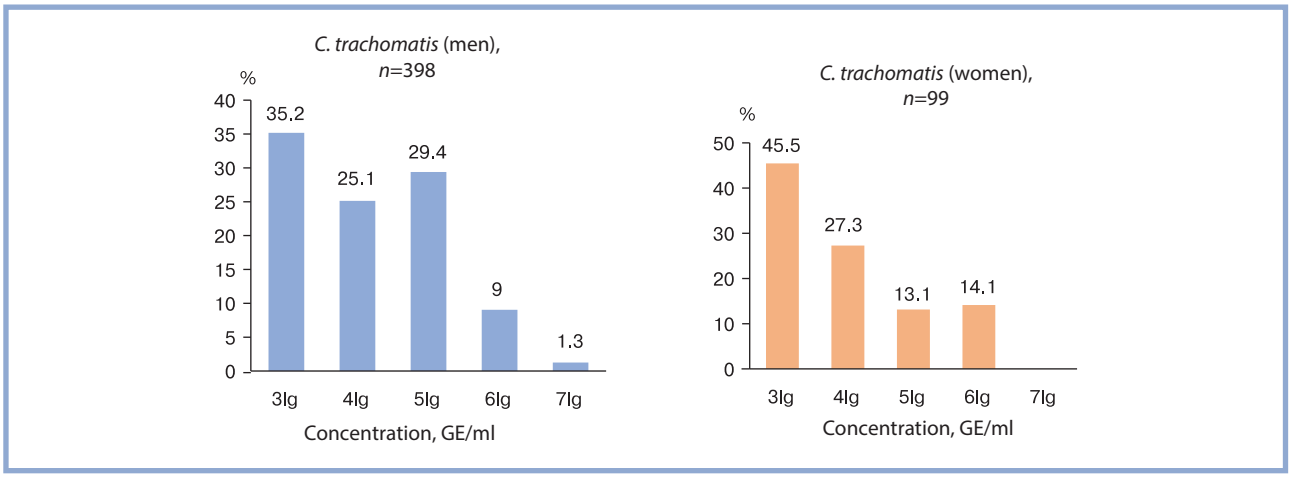

Fig. 3. **Results of measuring the concentration (bacterial load) of *C. trachomatis* in biological samples from males and females with chlamydial infections.**

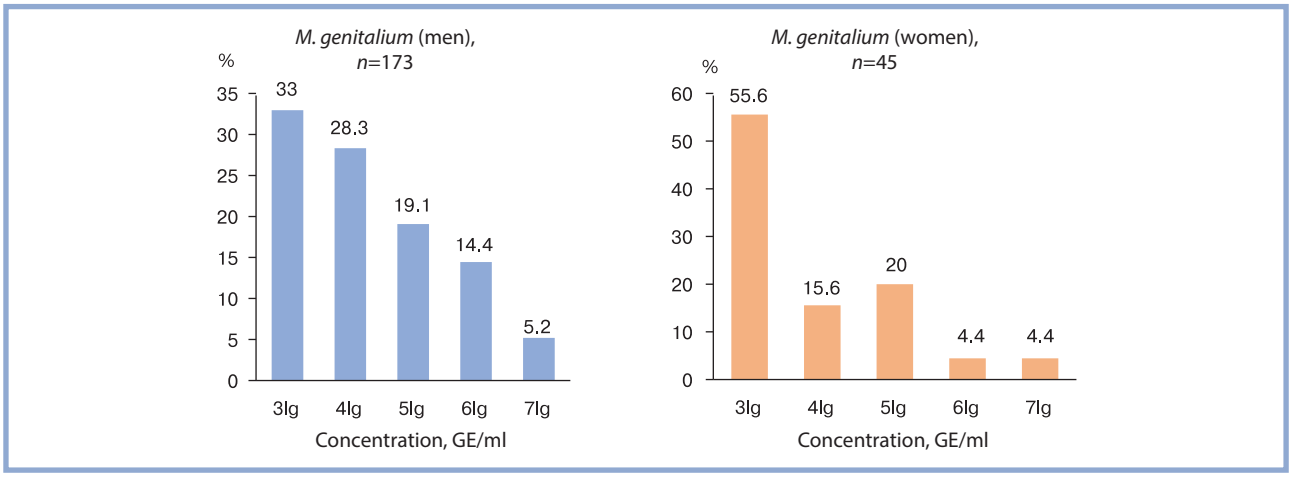

Fig. 4. **Results of measuring the concentration (bacterial load) of *M. genitalium* in biological samples from males and females with *M. genitalium* infection.**

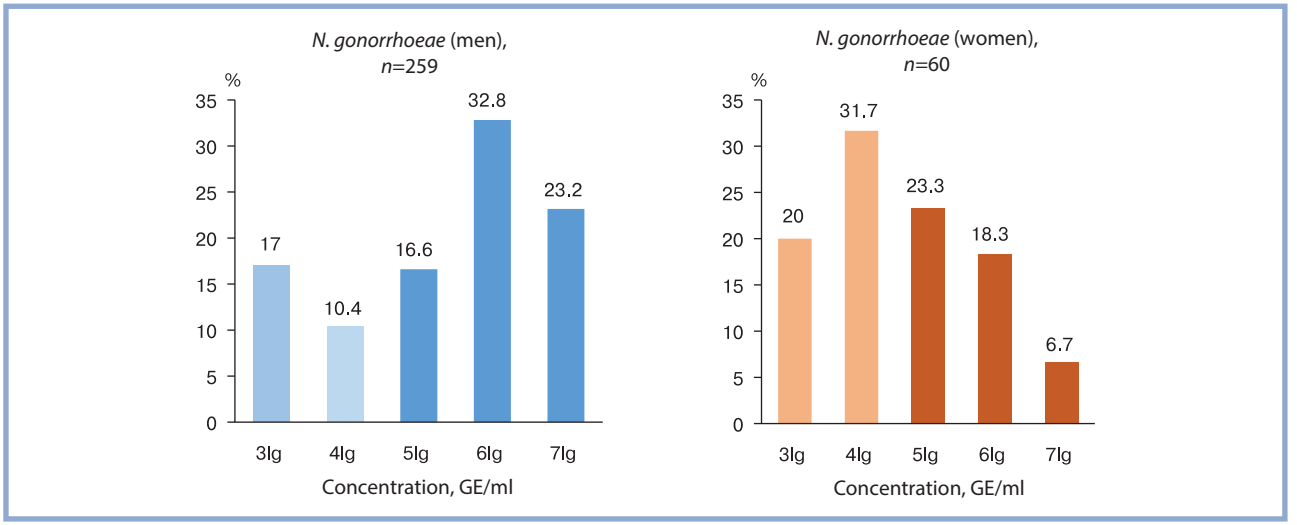

Fig. 5. **Results of measuring the concentration (bacterial load) of *N. gonorrhoeae* in biological samples from males and females with gonococcal infection.**

M. genitalium was detected in 178 (81.6%) males and 45 (18.4%) females. A low concentration of *M. genitalium* DNA was detected in 61.3% of males and 72.8% of females, high concentration in 38.7% of males and 28.8% of females. Thus, among patients with *M. genitalium*, a trend similar to that of *C. trachomatis* infections was observed: most patients had low concentrations of *M. genitalium* **(Fig. 4)**.

N. gonorrhoeae was detected in 259 (81.2%) males and 60 (18.8%) females. A low concentration of *N. gonorrhoeae* DNA was detected in 27.4% of males and 51.7% of females, high concentration in 72.6% of males and 48.3% of females. Thus, women with gonococcal infection were slightly more likely to have a low bacterial load. At the same time, the opposite tendency was observed in the group of male patients with gonococcal infection — the subjects with a high bacterial load were 1.8 times more than those with a low pathogen concentration **(Fig. 5)**.

T. vaginalis was detected in 13 (27.1%) males and 35 (72.9%) females. A low concentration of *T. vaginalis* DNA was detected in 84.7% of males and 54.2% of females, high concentration in 15.3% of males and 45.8% of females. Thus, in trichomoniasis patients, individuals with low pathogen concentration were much more common, especially among males **(Fig. 6)**.

To assess the AmpliPrime NCMT test effectiveness in practical healthcare and its impact on the detection of STI pathogens, the trends of the STI absolute number according to patient referrals to the MRPCDC from 2014 to 2021 were analyzed. It should be noted that the AmpliPrime NCMT test has been implemented at the MRPCDC since 2018 **(Fig. 7)**.

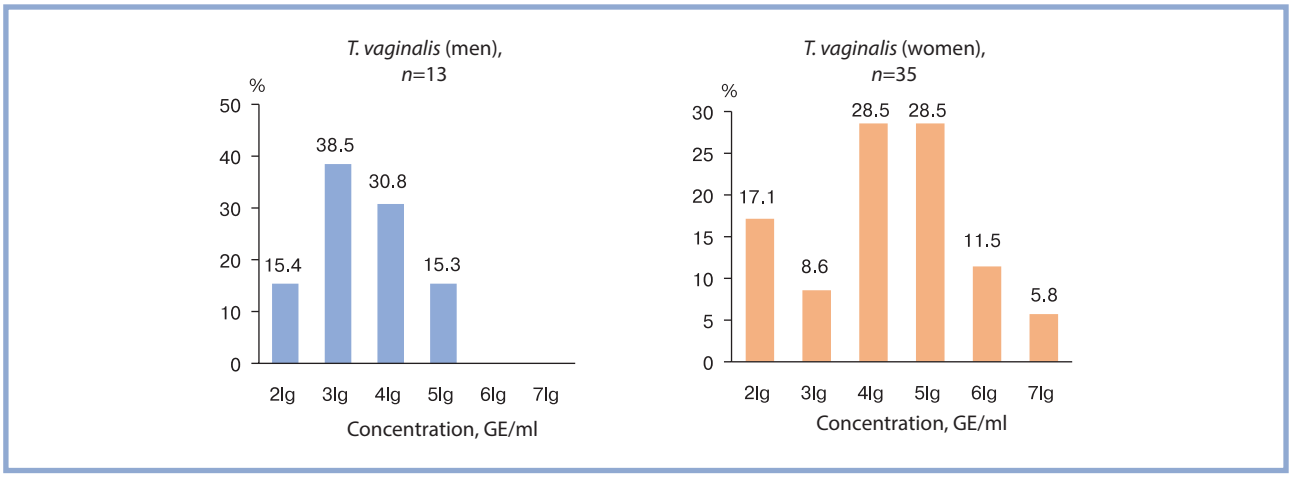

Fig. 6. **Results of measuring the concentration (parasite load) of *T. vaginalis* in biological samples from males and females with trichomoniasis.**

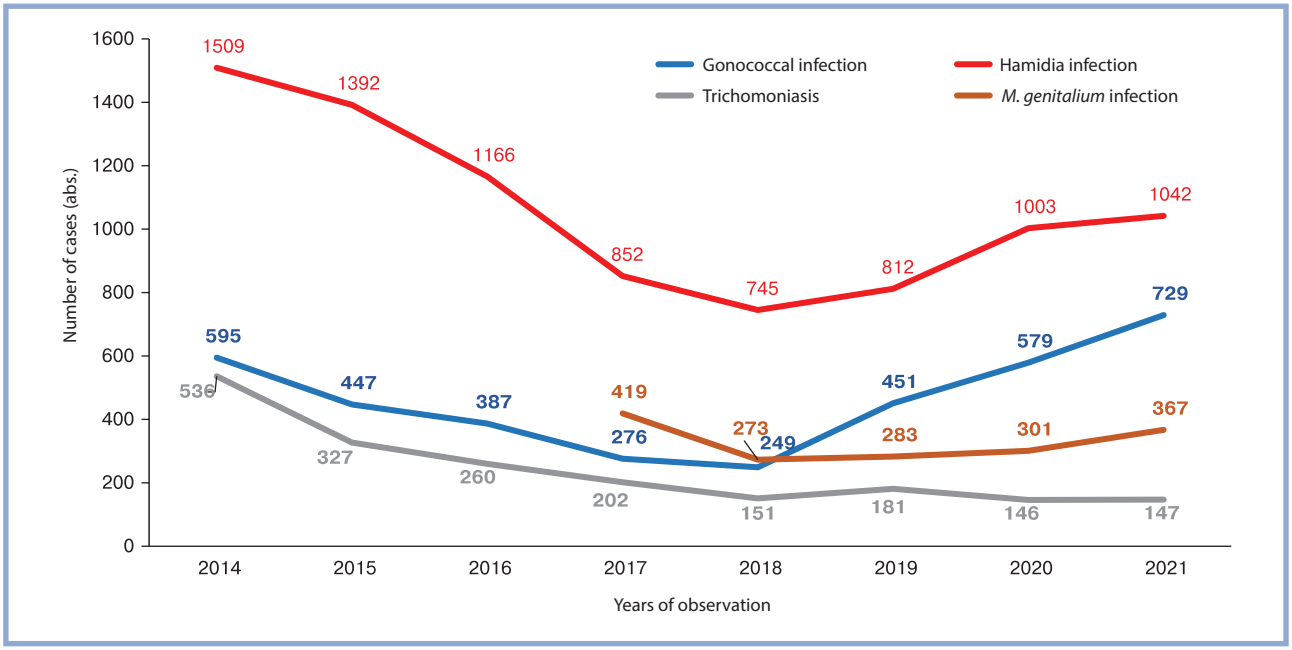

Fig 7. Incidence of STIs according to patient referrals to MRPCDC (2014-2021).

According to **Fig. 7**, between 2014 and 2018, the incidence decreased for all infections (gonococcal, urogenital chlamydia, trichomoniasis) and *M. genitalium* infection, which started to be registered in the MRPCDC in 2017. Since the introduction of the AmpliPrime NCMT test, detecting the causative agents of these infections in both males and females by a molecular-biological method, an upward trend in detecting all infections has been observed. The detection rate of gonococcal infection increased by 2.9 times (192.8%). The detection rate of chlamydial infection increased 1.4-fold (39.9%), and *M. genitalium* infection 1.3-fold (34.4%). The detection rate of trichomoniasis (based on the overall data, without dividing patients by gender) did not change significantly.

Analysis of detection rate trends separately in males and females showed that from 2018 to 2021, gonorrhea detection increased most significantly in females (3.8-fold, an increase of 280.6%) and 2.8-fold in males (177.9%), while the ratio of males to females decreased from 5.9 in 2018 to 4.3 in 2021. The detection of urogenital chlamydial infections also increased more in females (1.7-fold, 71.2%) than in males (1.3-fold, 31.1%).

As for trichomoniasis and *M. genitalium* infection, which started to be registered in the MRPCDC in 2017, slightly different trends were observed. The detection rate of trichomoniasis increased 2.2-fold (by 123.1%) in males, while it decreased slightly (by 14.5%) in females. A similar trend was observed in the *M. genitalium* infections: in men, the detection rate has increased 1.4-fold (by 41.1%) since 2018, while in females, it has increased 1.2-fold (by 17.1%) **(Fig. 8)**.

According to the analysis results, after the introduction of the AmpliPrime NCMT test into practice, there was a significant increase in the detection of the studied STIs, especially gonococcal infection (most significant in females), chlamydial infection (twice as significant in females as in males), as well as trichomoniasis and *M. genitalium* infections (mainly in males).

Conclusion

The present study is the first to be conducted in Moscow and aims to summarize the interim results of the AmpliPrime NCMT test use, introduced into practice in MRPCDC in 2018 to screen patients for STIs.

We analyzed the results of a large cohort of STI patients (n=1082), aged 16 to 68, identified in Moscow and examined at MRPCDC in 2021. Males (77.9%) were predominant among those examined. Females accounted for 22.1%. The exception was trichomoniasis, where females dominated the cases (72.9%).

The most common infection detected using the AmpliPrime NCMT test was urogenital chlamydiosis, detected in 45.9% of patients. This observation is consistent with the current evidence that currently urogenital chlamydia is the most frequently reported bacterial STI in many countries worldwide (18).

On the other hand, gonococcal infection (29.5%), *M. genitalium* infection (20.1%), and especially trichomoniasis (4.5%) were detected significantly less frequently in patients. The low detection rate of trichomoniasis, especially in males, may be related to the asymptomatic or low-symptomatic disease [19] or to the low sensitivity of the test methods used to diagnose trichomoniasis since

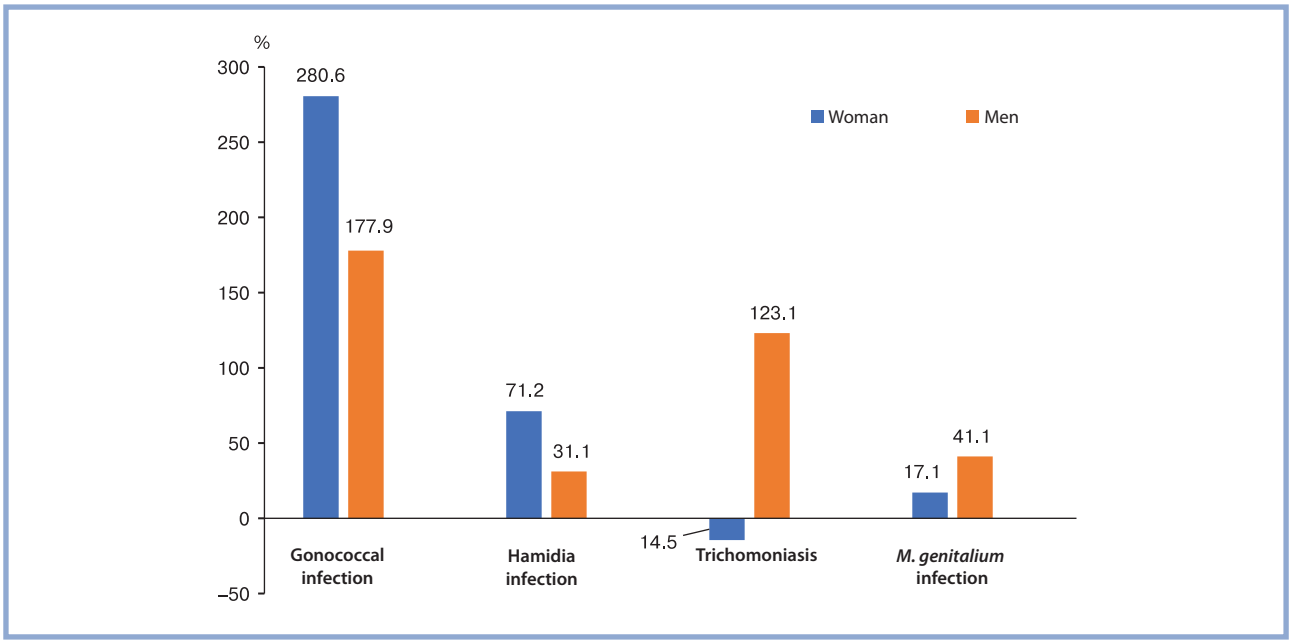

Fig. 8. **Trends of STI detection rate (gonorrhea, chlamydia, trichomoniasis, and *M. genitalium* infection) in MSPCDC after the introduction of the NCMT test (2021 versus 2018).**

the optimal diagnostic method in males has not yet been defined [20], despite the intensive advancement of nucleic acid amplification methods [21].

As a result of the study of STI pathogen concentration in the biological material of the patients, it was found that a low pathogen concentration (up to 104 GE/ml) prevailed. It was true for urogenital chlamydial infection, where most patients had low *C. trachomatis* DNA concentration (60.3% of males and 72.8% in females), *M. genitalium* infection, where low bacterial load predominated among the patients (61.3% of males and 72.8% of females), and trichomoniasis with low protozoal load in 84.7% of males and 54.2% of females. The predominance of low pathogen DNA concentrations in these infections could be related to the low-symptomatic or asymptomatic diseases [22] or the widespread use of macrolide and fluoroquinolone antibacterial agents, frequently used to treat other infections (in particular, diseases of the bronchopulmonary system and ENT organs, bronchitis, laryngitis, pharyngitis, maxillary sinusitis, pneumonia, etc.) and probably reducing the bacterial load in Chlamydia and Mycoplasma infections.

Gonococcal infection was an exception in the distribution of bacterial load in STI patients. In this group of patients (consisting of 4.3 times more males than females), in females, as in the previous patient groups, most patients (51.7% of all females examined) had low pathogen concentration in the biological material. At the same time, 72.6% of the males examined had a high bacterial load of *N. gonorrhoeae*. These findings can be due to the gender distribution of patients with gonococcal infection in the RF. It is well known from the literature and current clinical observations that in the RF, patients with gonococcal infection are primarily males, actively presenting corresponding signs and symptoms (urinary tract discharge, dysuria, dyspareunia, etc.); the number of females with gonococcal infection detected is significantly lower than that of males. This observation is primarily due to the shortcomings of the current approaches to detecting gonococcal infection in the RF in males and females and to the continued use of a microscopic method for diagnosis that underdiagnoses infection in females. In other countries (USA, Europe), the approach is entirely different: molecular diagnostic methods are used to diagnose gonococcal infection, so the number of males and females detected is about the same [23]. So it is no surprise that: 1) males dominated the cohort of examined patients with gonococcal infection, and 2) these male patients were symptomatic and likely had high pathogen concentrations in their biological material.

Analysis of STI incidence trends based on MRPCDC patient referrals (absolute number) showed that while from 2014 to 2017-2018, the number of patient referrals to MRPCDC has been increasing, there was a downward trend in the incidence of all the infections studied. Since 2019, after introducing the multiplex molecular biological test AmpliPrime NCMT, there has been an increase in detecting these infections. Thus, the gonococcal infection detection rate in females increased by 280.6% from 2018 to 2021 and in males by 177.9%; the urogenital chlamydial infection detection rate also increased, more in females (by 71.2%) than in males (by 31.1%). In males, the detection rate of trichomoniasis increased by 123.1% and *M. genitalium* infection by 41.1%. The observed patterns could also be due to other reasons, such as increased tourism, migration of the population within the country and from neighboring foreign countries, and natural fluctuations in microorganisms' pathogenicity. However, we consider these trends a result of increased pathogen detection due to the widespread introduction of the molecular-biological AmpliPrime NCMT test into practical healthcare in Moscow. These findings are evidenced, in particular, by a significant increase in the incidence of gonococcal (especially) and chlamydial infections in females and trichomoniasis in males; the detection of pathogens in these categories of patients in the setting of the established priorities of Russian laboratory diagnosis (with the predominance of microscopy method) is often challenging. In addition, the years 2020-2021 were not the most favorable for tourism and migration in Russia in general and Moscow in particular due to the COVID-19 pandemic and significant restrictions, so the impact of this factor on the infection detection and incidence increase is unlikely.

Thus, the MRPCDC experience using the AmpliPrime NCMT test to detect STI pathogens showed that this test simultaneously detects four STI pathogens (gonorrhea, chlamydia, trichomoniasis, and *M. genitalium*) in a single sample. The test provides the etiological diagnosis, the co-infection detection, and the determination of pathogen concentrations (*N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, *T. vaginalis*) in the urogenital tract of patients, which can be further used to personalize therapy.

It is important to note that determining the concentration of pathogens in the samples of patients by using molecular biological techniques can be an essential adjunct to examining individuals with suspected STIs; it will allow switching to a personalized approach to treating patients with a high and low concentration of STI pathogens, which is more reasonable for preventing excessive toxic effects of high doses of antimicrobials and more cost-effective.

Authors' contributions:

The concept and design of the study: A.E. Guschin, N.N. Potekaev

Collecting and interpreting the data, statistical analysis: E.S. Negasheva, S.A. Polevshchikova

Drafting the manuscript, data analysis: N.V. Frigo, E.S. Negasheva, A.E. Guschin,

Revising the manuscript: G.A. Dmitriev

The authors declare no conflict of interest.

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