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Analysis of *Neisseria Gonorrhoeae* Resistance Dynamics to Antimicrobial Drugs in The Russian Federation (2005–2021)

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Background. Using its innate mechanisms for resistance gene acquisition, *Neisseria gonorrhoeae* can rapidly develop resistance to antimicrobial agents increasing the risk the incurable forms of the disease will appear during gonococcal therapy. The purpose of the present study was to summarize the results of the Russian Gonococcal Antimicrobial Surveillance Programme (RU-GASP) over a 16-year period and assess *N. gonorrhoeae* resistance to the antimicrobials used in gonococcal treatment regimens in Russia.
Materials and methods. The study included 5356 isolates of *N. gonorrhoeae* obtained under RU-GASP (January 2005 to December 2021) by State Research Center of Dermatovenereology and Cosmetology (SRCDC) from specialized dermatology and venerology hospitals in 37 regions of the Russian Federation. Primary identification of *N. gonorrhoeae* was performed using bacterioscopic and bacteriological methods. The cultures identified as *N. gonorrhoeae* were frozen in a cryogenic medium and transported to SRCDC. Received cultures were verified by biochemical criteria on a VITEK 2 Compact analyzer. For the cultures identified as *N. gonorrhoeae* with less than 99% probability, mass spectrometric analysis was performed on a time-of-flight ionization mass spectrometer MALDI Microflex (Bruker Daltonics GmbH, Germany).
Antimicrobial susceptibility testing. Sensitivity tests of *N. gonorrhoeae* to six antimicrobials (penicillin, spectinomycin, ceftriaxone, tetracycline, azithromycin and ciprofloxacin) included serial dilution in agar to detect the minimum antibiotic concentration (MAC) that inhibits microbial growth. *N. gonorrhoeae* sensitivity to antibacterial agents was evaluated as per EUCAST criteria (European Committee on Antimicrobial Susceptibility Testing, 2022, http://www.eucast.org).
Results. The study has shown the absence of significant changes in the ratio of sensitive and resistant *N. gonorrhoeae* strains and proved the effectiveness of RU-GASP which allowed excluding drugs with a high proportion of identified resistant strains from therapeutic use.
Conclusion. Analysis of RU-GASP results over a 16-year period has confirmed III-generation of cephalosporin (Ceftriaxone, Cefixime) as the drug of choice for gonococcal therapy, and spectinomycin as its effective alternative. The ongoing evolution of *N. gonorrhoeae* molecular mechanisms of antibiotic resistance dictates the need for extending RU-GASP.

Keywords: ***Neisseria gonorrhoeae*, antibiotic resistance, antimicrobial agents, monitoring**

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Анализ динамики устойчивости *Neisseria gonorrhoeae* к антимикробным препаратам в РФ за период 2005–2021 гг.

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Обоснование. *Neisseria gonorrhoeae* может быстро развить резистентность к противомикробным агентам благодаря врожденным механизмам приобретения генов устойчивости к антибиотикам. Вследствие быстрого формирования механизмов резистентности *N. gonorrhoeae* к используемым в схемах терапии гонококковой инфекции антимикробным препаратам высок риск возникновения неизлечимых форм заболевания.

Цель исследования. Обобщить результаты RU-GASP за 16-летний период и оценить тенденции устойчивости *N. gonorrhoeae* к антимикробным препаратам, используемым в схемах антибиотикотерапии гонококковой инфекции в России.

Методы. Объект исследования. В исследование включены 5356 изолятов *N. gonorrhoeae*, поступивших с января 2005 г. по декабрь 2021 г. в ФГБУ «ГНЦДК» Минздрава России (далее — ГНЦДК) в рамках программы RU-GASP из специализированных медицинских организаций дерматовенерологического профиля 37 субъектов Российской Федерации. Первичную идентификацию *N. gonorrhoeae* проводили бактериоскопическим и бактериологическим методами. Идентифицированные как *N. gonorrhoeae* культуры замораживали в криосреде и транспортировали в ГНЦДК. Поступившие культуры верифицировали по биохимическим критериям на анализаторе VITEK 2 Compact. Для культур, определенных как *N. gonorrhoeae* с менее чем 99% вероятностью, проводили масс-спектрометрическое исследование на времяпролетном масс-спектрометре с ионизацией MALDI Microflex (Bruker Daltonics GmbH, Германия).

Тестирование чувствительности к исследуемым антимикробным препаратам. Тестирование чувствительности *N. gonorrhoeae* к шести антимикробным препаратам — пенициллину, спектиномицину, цефтриаксону, тетрациклину, азитромицину и ципрофлоксацину осуществляли методом серийных разведений в агаре с определением минимальных подавляющих концентраций (МПК, мг/л). Оценку чувствительности *N. gonorrhoeae* к антибактериальным препаратам проводили в соответствии с критериями EUCAST (The European Committee on Antimicrobial Susceptibility Testing, 2022, http://www.eucast.org).

Результаты. Проведенное исследование показало отсутствие значимых изменений в соотношении чувствительных и устойчивых к действию антимикробных препаратов штаммов *N. gonorrhoeae*, что является следствием эффективности реализации программы RU-GASP, позволившей своевременно исключить из терапевтического применения препараты, в отношении которых наблюдалась высокая доля выявленных устойчивых штаммов.

Заключение. Анализ результатов RU-GASP за 16-летний период подтверждает использование в качестве препаратов выбора для терапии гонококковой инфекции цефалоспоринов III поколения (цефтриаксон, цефиксим), а в качестве альтернативного препарата — аминоциклитольный антибиотик спектиномицин. Продолжающаяся эволюция молекулярных механизмов антибиотикорезистентности *N. gonorrhoeae* диктует необходимость продолжения программы RU-GASP.

Ключевые слова: ***Neisseria gonorrhoeae*; антимикробная резистентность; антимикробные препараты; мониторинг**

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Introduction

Internationally, gonorrhea caused by *Neisseria gonorrhoeae*, Gram-negative bacteria remains one of the most common sexually transmitted infections [1] and a significant public health threat due to its rapidly increasing incidence and antibiotic resistance [2]. The growing risk the incurable forms of gonorrhea would appear was the reason the WHO included the disease into the draft of its Global Health Strategy for 2016-2021 as one of the strategic priorities [3]. In the Russian Federation, the disease is combated through the Russian Gonococcal Antimicrobial Surveillance Programme (RU-GASP) that was established in 2004 after the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) had been initiated [4]. RU-GASP is also a part of a worldwide network of laboratories coordinated by the WHO European Collaborating Center for Gonorrhea and Other Sexually Transmitted Infections [5]. The program's main objectives are annual monitoring of the emergence and spread of antimicrobial resistance (AMR) in *N. gonorrhoeae* and identification of genetic AMR determinants in order to improve gonorrhea surveillance in the Russian Federation and timely revise national guidelines on gonorrhea treatment [6].

In this respect, the present study intended to summarize RU-GASP results of over a 16-year period and evaluate the trends in N. gonorrhoeae resistance to the antimicrobials used for gonococcal therapy in Russia.

Materials and methods

The study included 5356 isolates of N. gonorrhoeae obtained under RU-GASP (January 2005 to December 2021) by Federal State Research Center of Dermatovenereology and Cosmetology (SRCDC) from specialized dermatology and venerology hospitals in 37 regions of the Russian Federation. Primary identification of *N. gonorrhoeae* was performed using the bacterioscopic and bacteriologic methods described in Standard Operating Procedures (SOPs) for Conducting Gonorrhea Species Identification (SOP # 003/04 GON, SOP # 004/04 GON, SOP # 005/04 GON https://cnikvi.ru/upload/files/369_SOP_ident_gonorei.pdf). The isolated cultures were frozen in the medium containing 20% glycerol and transported to SRCDC as per SOP for Transportation and Delivery of Biological Material and Isolated Gonorrhea Cultures (SOP No. 001/03 GON, https://cnikvi.ru/upload/files/369_SOP_transp_dostavka.pdf). Upon arrival, they were spread on chocolate agar plates supplemented with 1% ISOVitalex growth additive and 1% VCAT selective additive (Becton Dickinson, USA) to be tested for biochemical parameters using NH cards on a VITEK 2 Compact analyzer (bioMérieux, France). For the cultures identified as *N. gonorrhoeae* with less than 99% probability, mass spectrometric analysis was performed on a time-of-flight ionization mass spectrometer MALDI Microflex (Bruker Daltonics GmbH, Germany).

Antimicrobial susceptibility testing

For the microorganisms identified as *N. gonorrhoeae*, their sensitivity to six antimicrobial agents (penicillin, spectinomycin, ceftriaxone, tetracycline, azithromycin and ciprofloxacin) was investigated. For that purpose, serial dilutions in agar were performed as required by SOP for Methods for Determining Gonococcus Sensitivity to Antibacterial Drugs (SOP No. 006/03 GON, 2008, https://cnikvi.ru/files/369_SOP_chustv_gonokok_antibakt.pdf) to detect the minimum antibiotic concentration (MAC) that inhibits microbial growth. The sensitivity was assessed using the ATCC 49226 strain from a collection of typical *N. gonorrhoeae* cultures as a control as per EUCAST criteria (European Committee on Antimicrobial Susceptibility Testing, 2022, http://www.eucast.org) (Table 1).

Statistical analysis

Statistical analysis of the obtained data was performed using R and the RStudio (v. 4.2.2) software. The data were distributed using the Shapiro-Wilk test and presented as graphs of relative occurrence frequencies (%) of sensitive, sensitive to increased exposure to antibiotics, and resistant strains by years to draw a local polynomial regression trend line at CI 95%. Polynomial trend analysis performed for the strains with different sensitivity to antibiotics, enabled us to estimate the dynamics of *N. gonorrhoeae* antibiotic

Table 1. EUCAST 2022 AMR criteria of *N. gonorrhoeae*
Таблица 1. Критерии чувствительности *N. gonorrhoeae* к АМР (EUCAST 2022 г.)

Antimicrobial (mg/l)	S	I	R	ATCC 4922 reference strain
Penicillin	≤0.06	0.12–1	>1	0.25–1
Ceftriaxone	≤0.125	–	>0.125	0.004–0.015
Tetracycline	≤0.5	1	>1	0.25–1
Spectinomycin	≤64	–	>64	8–32
Azithromycin*		–		
Ciprofloxacin	≤0.03	0.06	>0.06	0.001–0.008

Note. S — susceptible, standard dosing regimen; I — susceptible, increased exposure; R — resistant.
*Azithromycin is always used in combination with another effective agent. For testing purposes, to identify acquired resistance mechanisms, ECOFF has been 1 mg/L since 2019.

Примечание: S — чувствительный при стандартном режиме дозирования; I — чувствительный при увеличенной экспозиции; R — резистентный.
*Азитромицин всегда используется в сочетании с другим эффективным средством. В целях тестирования с целью выявления механизмов приобретенной резистентности с 2019 г. ECOFF составляет 1 мг/л.

resistance over the period under study. Due to the non-Gaussian distribution of the data, MAC indices by years were compared using the Kruskal-Wallis Criterion with Dunn's posterior test and the Bonferroni correction for multiple comparisons. The differences were considered statistically significant at $p < 0.05$.

Results

N. gonorrhoeae resistance dynamics to penicillin

Figure 1 shows the relative frequencies of penicillin sensitivity/resistance for gonococcal strains categorized as S, I and R by years. The data show that although the frequency rose to 61% in 2016, there was a decline to 41% by 2021 (levels of 2009, 2014 and 2015). Comparative analysis of the MAC values obtained for different years found significant differences: in 2008, MAC was the lowest and significantly different from those in 2005 ($p < 0.0001$), 2006 ($p = 0.0012$), 2007 ($p < 0.0001$), 2016 ($p = 0.0045$), and 2017 ($p = 0.0011$). Despite some changes between absolute MAC values within the studied period, no significant differences were found between 2005 and 2021.

When analyzing the MAC values of penicillin-resistant strains, it was found that the highest MAC values recorded in 2016 were significantly different from those in 2005, 2006, 2007, 2009, 2010, 2011, 2013, and 2019 ($p < 0.001$). However, just as in the case of sensitive strains, no significant differences were found between 2005 and 2021. The frequencies obtained for the resistant strains showed a downward trend from 2012 to 2021 (albeit with a small jump to 14% in 2019). The maximum of penicillin-resistant strains (44 %) was observed in 2008.

N. gonorrhoeae resistance dynamics to spectinomycin

Analysis of the absolute MAC values showed that the highest of them were observed in 2006, 2008, 2013-2015. Figure 2 displays the occurrence frequencies for sensitive and resistant *N. gonorrhoeae* strains to spectinomycin. Analysis of the relative frequencies trend for sensitive strains over the studied period found no significant fluctuations, except for 2008. As for the resistant strains, their frequency in 2008 was 45% and only 10% in 2011. It should be noted that no resistant strains (0%) were recorded between 2013 and 2020, and no significant differences were found when analyzing absolute MAC indices between 2005 and 2021.

N. gonorrhoeae resistance dynamics to ceftriaxone

Fig. 3 shows the relative frequencies of the strains sensitive and resistant to ceftriaxone over the entire study period. Polynomial trend analysis of sensitive strain frequencies showed no significant fluctuations in their dynamics. As for the resistant strains, their trend showed no pronounced fluctuations, the highest (9%) being 2009.

N. gonorrhoeae resistance dynamics to tetracycline

The relative frequencies of tetracycline-sensitive strains (Fig. 4) show the peak of occurrence was between 2014 and 2019 (over 70%, with a drop in 2021 (34%), and even below the baseline (47%) in 2005). Meanwhile, the relative frequencies of resistant strains were the lowest in 2018 and 2019 (7 and 16%, respectively), and the highest in 2008 and 2021 (66 and 46%, respectively). The strains classified as category I had no significant trend, so their relative frequency was 15% in 2005 and 20% in 2021, with a slight drop to 8% in 2014–2015.

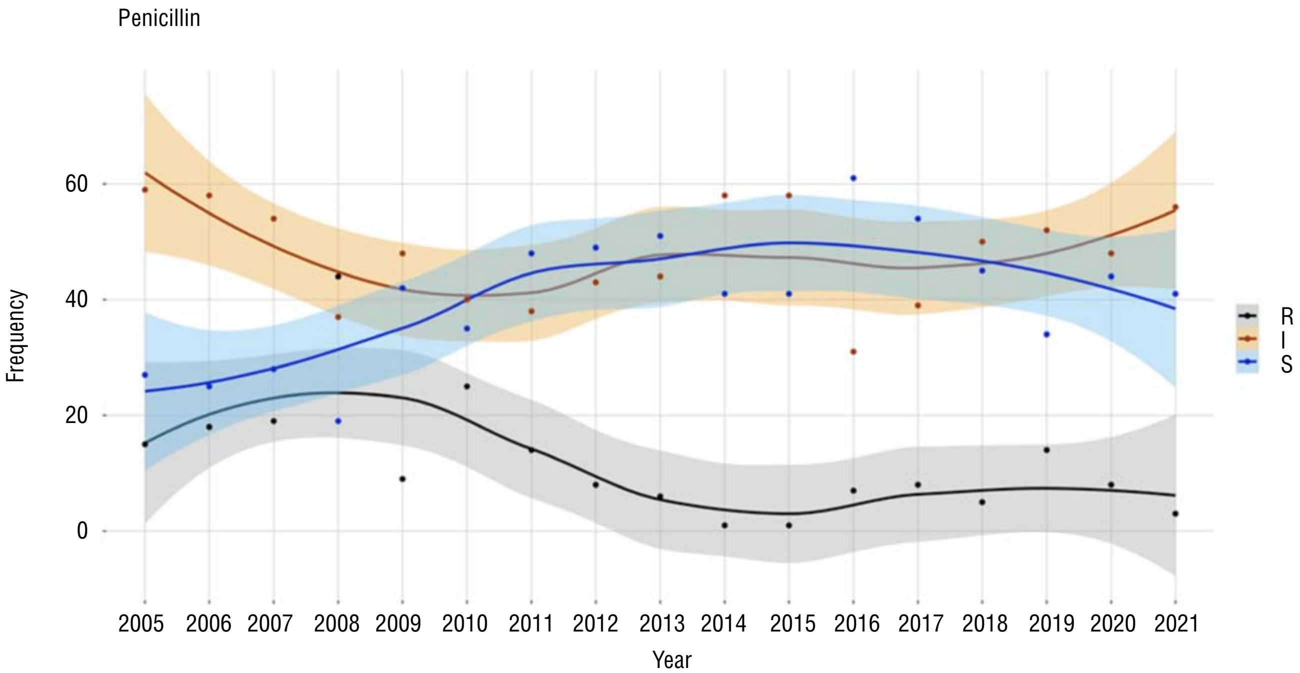

Fig. 1. Relative frequency of penicillin sensitivity/resistance (%) for different *N. gonorrhoeae* strains between 2005 and 2021: R — resistant, I — susceptible, increased exposure, S — susceptible, standard dosing regimen

Рис. 1. Относительная частота (в %) различных штаммов в период 2005–2021 гг. R — резистентные штаммы, I — чувствительные при увеличенной экспозиции, S — чувствительные при стандартном режиме дозирования

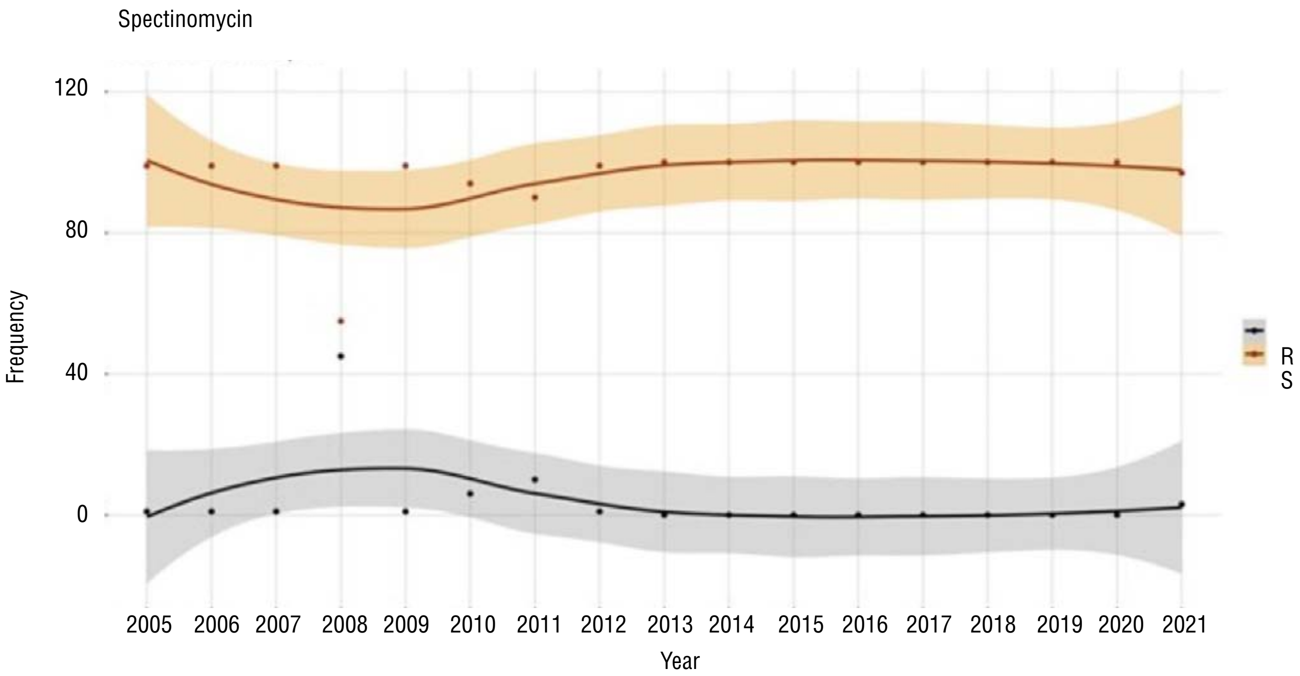

Fig. 2. Relative frequency of spectinomycin sensitivity/resistance (%) for different *N. gonorrhoeae* strains between 2005 and 2021: R — resistant, I — susceptible, increased exposure, S — susceptible, standard dosing regimen.

Рис. 2. Относительная частота (в %) различных штаммов в период 2005–2021 гг. R — резистентные штаммы, I — чувствительные при увеличенной экспозиции, S — чувствительные при стандартном режиме дозирования

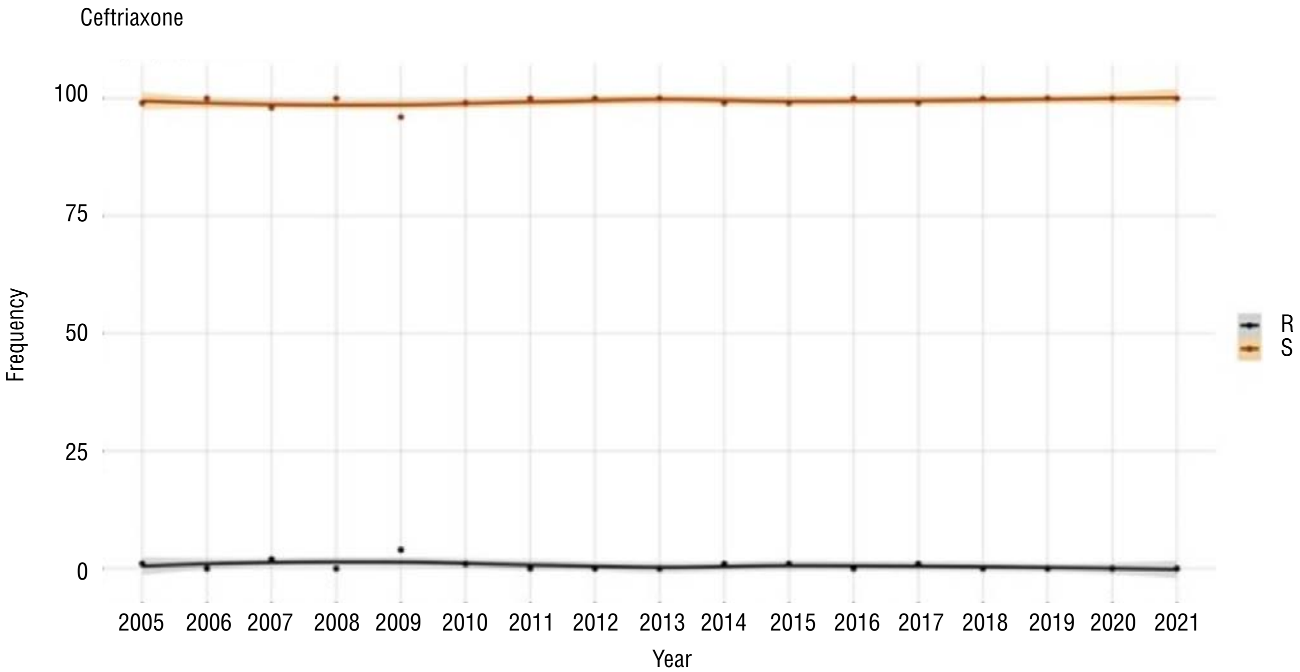

Fig. 3. Relative frequency of ceftriaxone sensitivity/resistance (%) for different *N. gonorrhoeae* strains between 2005 and 2021: R — resistant, I — susceptible, increased exposure, S — susceptible, standard dosing regimen.

Рис. 3. Относительная частота (в %) различных штаммов в период 2005–2021 гг. R — резистентные штаммы, I — чувствительные при увеличенной экспозиции, S — чувствительные при стандартном режиме дозирования

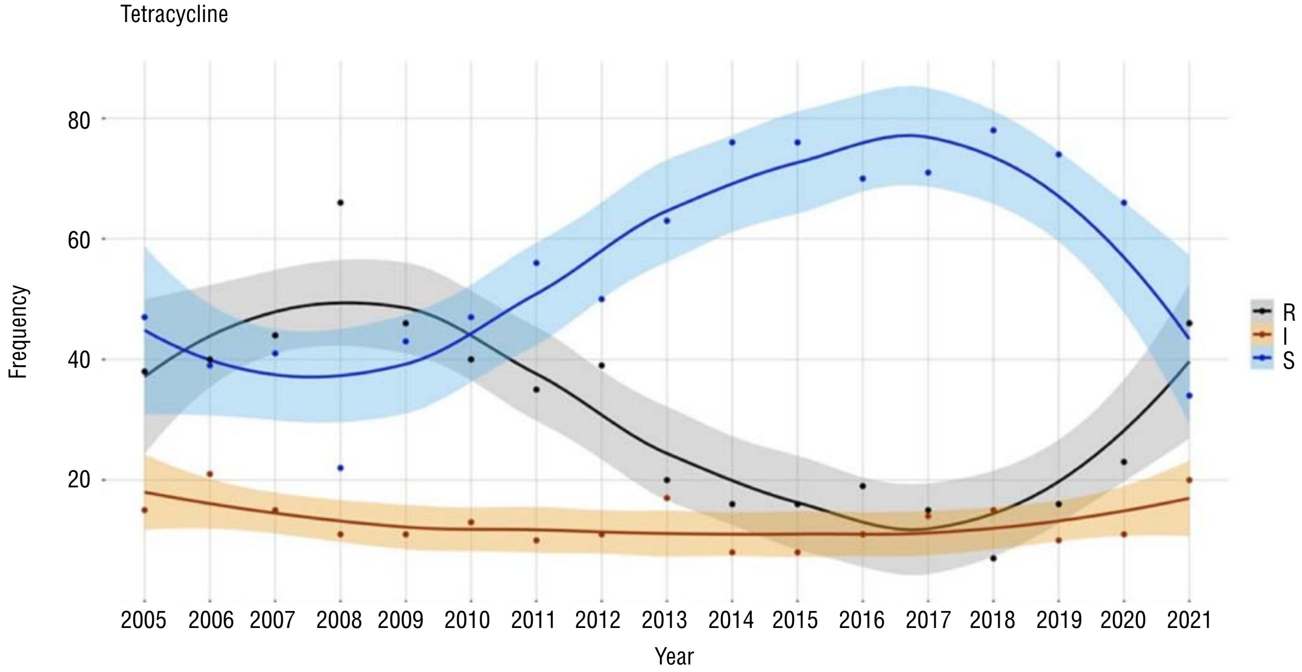

Fig. 4. Relative frequency of tetracycline sensitivity/resistance (%) for different *N. gonorrhoeae* strains between 2005 and 2021: R — resistant, I — susceptible, increased exposure, S — susceptible, standard dosing regimen.

Рис. 4. Относительная частота (в %) различных штаммов в период 2005–2021 гг. R — резистентные штаммы, I — чувствительные при увеличенной экспозиции, S — чувствительные при стандартном режиме дозирования

N. gonorrhoeae resistance dynamics to azithromycin

Analysis of the MAC values for azithromycin showed the highest absolute values were observed in 2008, 2009, 2016, 2018, 2020 and 2021, and the lowest in 2014 and 2015. Trend analysis for the relative frequencies of azithromycin-sensitive strains (Fig. 5) revealed that, despite fluctuations over the study period, they did not differ significantly between 2007 and 2021, being 89 and 83%, respectively. The highest frequency (more than 90%) for azithromycin-sensitive strains was observed between 2013 and 2019. As for azithromycin-resistant strains, their highest frequency was observed in 2008 and 2009 (57 and 51%, respectively) and the lowest in 2017 and 2018 (8%). However, despite the above fluctuations, in general, the frequency values observed in 2021 were similar to those in 2007.

N. gonorrhoeae resistance dynamics to ciprofloxacin

Analysis of the polynomial trend for the relative frequencies of ciprofloxacin-sensitive strains (Fig. 6) revealed that the highest ones (>60%) were observed between 2011 and 2020, with peaks in 2013 (75%) and 2019 (72%) and a pronounced decline (29%) in 2021. At the same time, no pronounced fluctuations were detected for the strains included in category I, their frequency peak being 7% in 2021. As for the relative frequencies, they were the lowest between 2011 and 2020 (40% or less) with an uptick in 2021 (up to 64%).

Discussion

The obtained results have demonstrated that, despite the observed fluctuations in occurrence frequencies of the strains sensitive to the studied antibiotics, the ratio of antimicrobial-resistant and antimicrobial-sensitive strains did not change significantly from 2005 over the 16-year observation period. An interesting finding of this study is the persisting high levels of resistance to penicillins, tetracyclines, and fluoroquinolones despite they have long been excluded from recommended treatment regimens for gonorrhea. Another interesting finding is the steady trend towards *N. gonorrhoeae* had been gradually restoring its sensitivity to penicillins, tetracyclines and fluoroquinolones since 2010. As shown previously [6], this is due to the gradual elimination of genetic resistance determinants (D345a in *penA* gene; L421P in *pon*A gene; V57M in *rpsJ* gene; S91Y and D95G in *gyrA* gene) to these antimicrobials. However, starting from 2017, the sensitivity began a decreasing trend to the values it had had at the start of the monitoring program in 2005. This fact may be explained by *N. gonorrhoeae* accumulating plasmid determinants *bla(TEM-1)* and *tet(M)* during this time that spread rather quickly by "horizontal" transfer and significantly change the resistance level to the three groups of antibacterial drugs [7].

The obtained data on *N. gonorrhoeae* resistance dynamics have shown that only ceftriaxone (III-generation cephalosporin) and spectinomycin (aminocyclitol) meet the WHO criterion stating that the total proportion of gonococcal strains sensitive to an antibiotic drug should not be lower than 95% (WHO, 2012). For that reason, ceftriaxone is currently the drug of choice for treating of gonococcal infection in Russia. Our study substantiates this position as no strains resistant to this drug were identified in 2021. Moreover, our earlier studies had shown that the level of sensitivity of *N. gonorrhoeae* to ceftriaxone in the Russian Federation and its constituent entities amounted to 100% [8]. At the same time, we cannot ignore the fact that foreign scientific publications often mention the *N. gonorrhoeae*

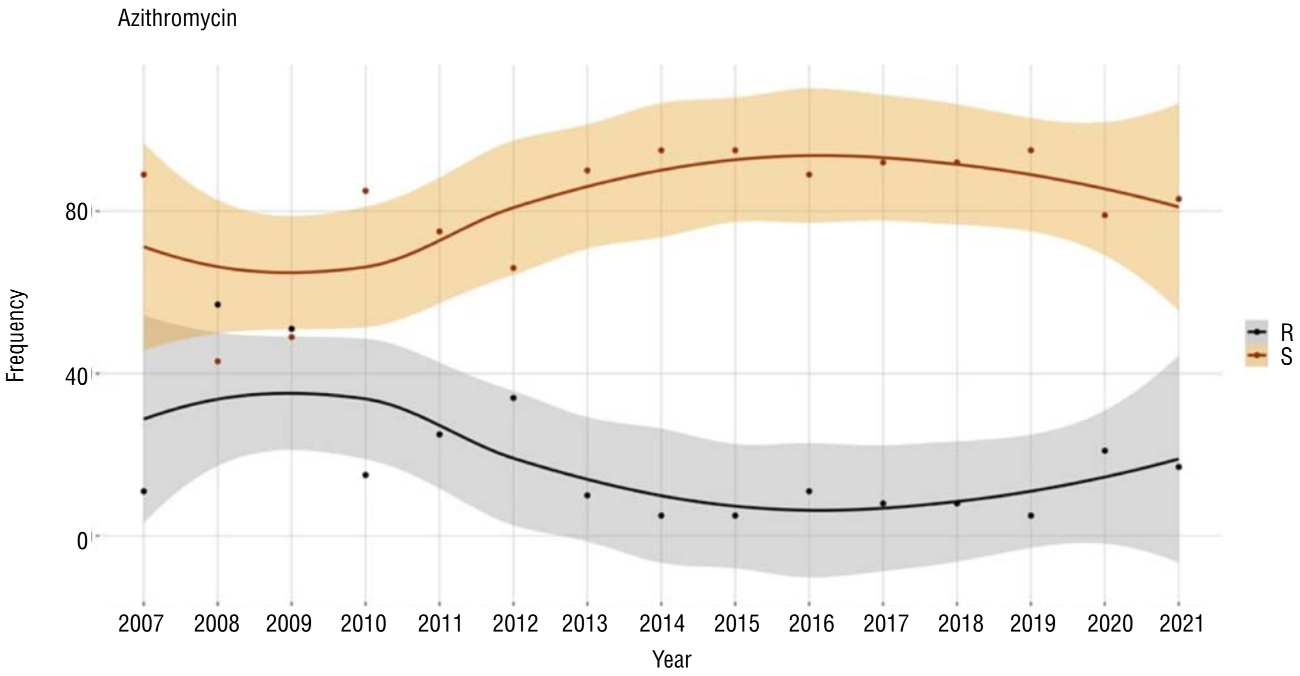

Fig. 5. Relative frequency of azithromycin sensitivity/resistance (%) for different *N. gonorrhoeae* strains between 2005 and 2021: R — resistant, I — susceptible, increased exposure, S — susceptible, standard dosing regimen.

Рис. 5. Относительная частота (в %) различных штаммов в период 2007–2021 гг. R — резистентные штаммы, I — чувствительные при увеличенной экспозиции, S — чувствительные при стандартном режиме дозирования

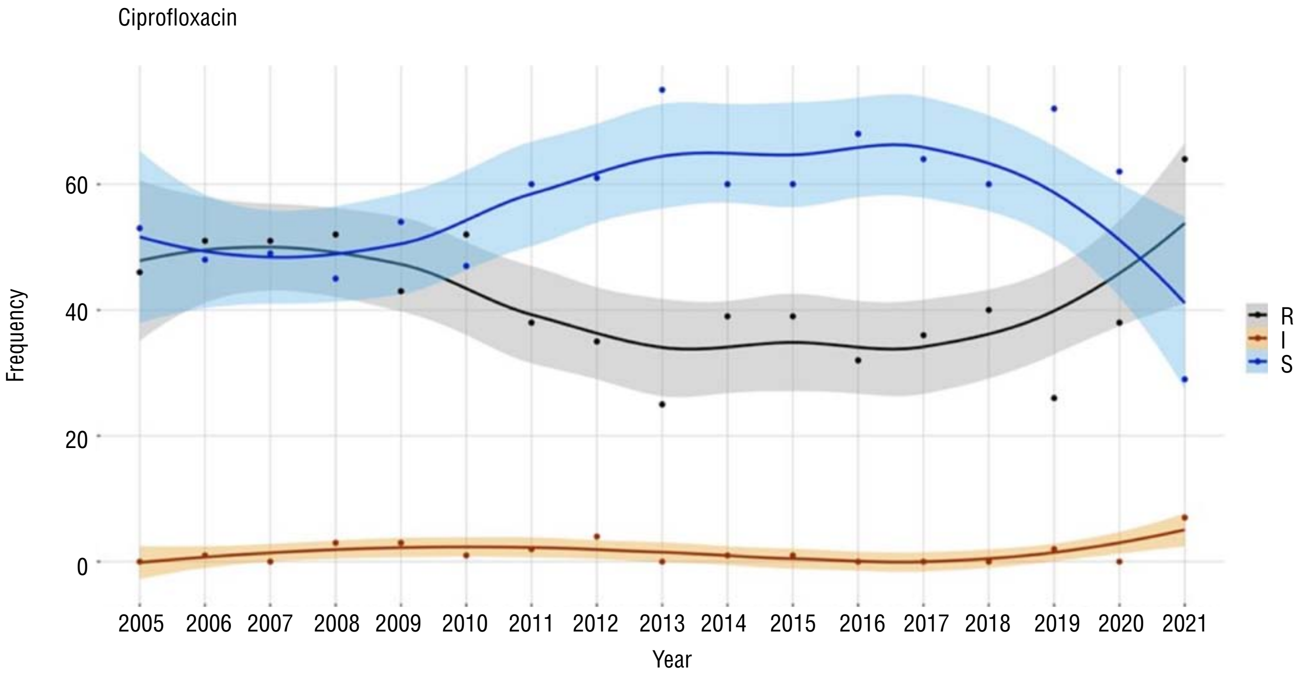

Fig. 6. Relative frequency of ciprofloxacin sensitivity/resistance (%) for different *N. gonorrhoeae* strains between 2005 and 2021: R — resistant, I — susceptible, increased exposure, S — susceptible, standard dosing regimen.

Рис. 6. Относительная частота (в %) различных штаммов в период 2005–2021 гг. R — резистентные штаммы, I — чувствительные при увеличенной экспозиции, S — чувствительные при стандартном режиме дозирования

strains resistant to ceftriaxone that come from such countries as China (Wang et al., 2020), Brazil [9], etc. For instance, during 2012-2017 in South Korea, a surge (from 1.1 to 23.9%) in the cephalosporin-resistant isolates containing the *penA* mosaic allele was observed (Lee et al., 2019). Another reason for such resistance might have been the SNPs of the *penA* and *porB1b* genes and the *mtrR* gene mutations [10]. Spreading of the strains resistant to ceftriaxone, as well as the patients who can possibly develop hypersensitivity to cephalosporins to the degree of anaphylactic shock [11], make searching for candidate drugs for alternative gonorrhea therapy a relevant task.

Analysis of *N. gonorrhoeae* spectinomycin-sensitivity trend has confirmed the drug's previously proven high efficacy in the treatment of this infection [8]. Moreover, in 2021, only 3% of strains resistant to spectinomycin were detected, which is within the 5-percent limit set by the WHO for an effective antibacterial therapy (WHO, 2012). At the same time, this threshold is currently being debated, both toward increasing the upper limit for resistant strains [12] and lowering it to 1–3% for "the key population groups with the potential for more frequent transmission to many sexual partners, such as sex workers and men who have sex with men" [13]. Although spectinomycin as an alternative treatment is administered only after testing the sensitivity of a particular clinical isolate, it remains the most promising alternative drug for the treatment of gonococcal infection.

Azithromycin, as a potential reserve drug to treat gonococcal infection, was included in RU-GASP in 2007. It was known to be used for gonorrhea therapy outside Russia, but it was not included in in the regimens for our country, because there was no data either on its effect on the domestic strains or its optimal dosage [14]. The results of this study have demonstrated that in 2021 16% of the total number of analyzed *N. gonorrhoeae* strains were resistant to azithromycin, which removes the question of its possible use for gonorrhea treatment. At the same time, the drug is widespread abroad and prescribed in combination with ceftriaxone for combined therapy of gonococcal infection to improve treatment efficacy and reduce the likelihood gonococcus becoming resistant to each of these drugs individually. However, the first strain resistant to this combination that emerged in 2018 calls for revising this regimen [15].

Due to its cross-resistance, ciprofloxacin is used as an indicator drug to study *N. gonorrhoeae* resistance to all the drugs of fluoroquinolone group, so the strains resistant to ciprofloxacin are also resistant to other fluoroquinolones. In the Russian Federation, the drug is not recommended for gonococcal therapy. Our study has shown the drug had its lowest resistance frequencies between 2011-2020 (40% or less) with an uptick in 2021 (up to 64%) that is generally consistent with literature data, e.g., Unemo et al. who in 2017-2018 found more than 90% of strains to be resistant to ciprofloxacin in 100% of the Southeast Asian countries and 50% of the African countries participating in the study, a level to be called nothing but extreme [16].

Thus, our study has found no significant phenotypic changes in the antimicrobial resistance of *N. gonorrhoeae* strains in the Russian Federation. Undoubtedly, this is a consequence of the effective implementation of RU-GASP, which over the given time, allowed for significant reduction of gonorrhea incidences in Russia from 71.7 cases per 100,000 population in 2005 to 6.7 cases in 2020 [17], despite the incidence of gonorrhea in Europe has been noticeably and gradually increasing [18]. This fact, of course, significantly increases the likelihood of resistant strains entering the territory of Russia with migration and tourist flows, which calls for continuation of RU-GASP and expansion of the list of tested antimicrobials.

Conclusion

Our analysis of RU-GASP results over a 16-year period has confirmed the use of III-generation cephalosporins (ceftriaxone, cefixime) as the drugs of choice for gonococcal therapy, and that of spectinomycin (aminocyclitol) as an alternative antimicrobial drug. The ongoing evolution of molecular mechanisms of *N. gonorrhoeae* antibiotic resistance dictates the need to continue RU-GASP.

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