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RESEARCH ARTICLE

Antimicrobial resistance in *Neisseria gonorrhoeae* isolates and gonorrhoea treatment in the Republic of Belarus, Eastern Europe, 2009-2019

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Abstract

Background: Increasing antimicrobial resistance (AMR) in *Neisseria gonorrhoeae*, including to first-line treatment options, is a great concern worldwide. However, very limited gonococcal AMR data are available in Eastern Europe. We investigated the AMR in *N. gonorrhoeae* isolates (n=522) cultured in three regions of the Republic of Belarus, 2009–2019, antimicrobial treatment recommended nationally, and treatment given to 1652 gonorrhoea patients in two of the regions (Minsk, 2013–2018; Mogilev, 2010–2019).

Methods: Determination of minimum inhibitory concentrations (MICs) of eight antimicrobials was performed using Etest and, where available, resistance breakpoints from the European Committee on Antimicrobial Susceptibility Testing were applied. β -lactamase production was examined using a Nitrocefin test. Gonorrhoea treatment was analysed from medical records.

Results: In total, 27.8% of isolates were resistant to tetracycline, 24.7% to ciprofloxacin, 7.0% to benzylpenicillin, 2.7% to cefixime, and 0.8% to azithromycin. No isolates were resistant to ceftriaxone, spectinomycin, or gentamicin. However, four (0.8%) isolates had a ceftriaxone MIC of 0.125 mg/L, which is exactly at the resistance breakpoint (MIC>0.125 mg/L). Only one (0.2%) isolate, from 2013, produced β -lactamase. From 2009-2019, the levels of resistance to ciprofloxacin and tetracycline were relatively stably high. Resistance to cefixime was not identified before 2013, but peaked at 22.2% in 2017. Only sporadic isolates with resistance to azithromycin were found in 2009 (n=1), 2012 (n=1) and 2018–2019 (n=2). Overall, 862 (52.2%) patients received first-line treatment in accordance with national guidelines (ceftriaxone 1 g). However, 154 (9.3%) patients received a nationally recommended alternative treatment (cefixime 400 mg or ofloxacin 400 mg), and 636 (38.5%) patients were given treatment non-compliant to the Belarusian national gonorrhoea guideline.

Conclusions: Ceftriaxone 1 g, in combination with azithromycin 2 g particularly when chlamydial infection has not been excluded, should be recommended as empiric first-line treatment. Spectinomycin 2 g, where available, together with azithromycin 2 g could be an alternative treatment. When susceptibility has not been confirmed by testing, fluoroquinolones should not be used for treatment. Timely updating of and high compliance to national evidence-based gonorrhoea treatment guidelines that are based on quality-assured AMR data is imperative. Continued and expanded gonococcal AMR surveillance in Belarus is crucial.

Keywords: *Neisseria gonorrhoeae*; antimicrobial resistance; surveillance; treatment; ceftriaxone; azithromycin; Belarus; Eastern Europe.

Background

Gonorrhoea is one of the most common sexually transmitted infections (STIs) worldwide [1-3]. According to the World Health Organization (WHO), in 2016, 86.9 million new cases of gonorrhoea among adults were estimated [2]. In the Republic of Belarus, the incidence of reported gonorrhoea (cases per 100,000 inhabitants) has substantially decreased, i.e., from 63 in 2005 to 44.4 in 2009, and finally to 10.5 in 2018 [4]. However, the reported incidence in Belarus, as well as in many other East-European countries, is most likely underestimated due to limited testing, particularly of extragenital specimens, insufficient use of nucleic acid amplification tests (NAATs), incomplete reporting and epidemiological surveillance [5-7].

Alarming, the level of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* to a wide range of drugs has increased worldwide, including to first-line treatment [3,5,8-11]. The extended-spectrum cephalosporin (ESC) ceftriaxone is the only remaining option for empiric first-line monotherapy in most countries. However, decreased susceptibility or resistance, *in vitro* and clinical, to ceftriaxone has emerged in many settings globally [3,5,8-28]. Consequently, WHO global gonorrhoea treatment guidelines and guidelines in Europe, Australia, Canada, and USA recommend dual antimicrobial first-line therapies, mainly ceftriaxone 500-1000 mg×1 intramuscularly (IM) plus azithromycin 1-2 g×1 orally [8,11,29-31]. However, some countries such as Japan, Ukraine and, since 2019, the United Kingdom recommend high-dose (mainly 1 g) ceftriaxone monotherapy, i.e. when chlamydial infection has been excluded [32-34]. Nevertheless, the first global failure to cure gonorrhoea with dual therapy was reported in 2016 [27] and in 2018 the first gonococcal strain with ceftriaxone

resistance combined with high-level azithromycin resistance was identified in both England [24] and Australia [35].

WHO has developed a global action plan to control the spread and minimise the impact of AMR in *N. gonorrhoeae* [10]. One of its key strategies is to enhance the quality-assured gonococcal AMR surveillance globally; to identify emerging AMR, monitor AMR trends, and to ensure effective patient management by timely and evidence-based refinements of treatment guidelines. In the European Union/European Economic Area (EU/EEA), the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) is monitoring the AMR since 2004 [12,36-38]. However, in the non-EU/EEA countries of the WHO European Region, gonococcal AMR surveillance is extremely limited [5,6], and only sporadically available in Belarus, Russia and Ukraine [33,39-44].

The empirical treatment of gonococcal infections in Belarus is guided by the Clinical protocol for the diagnosis and treatment of patients with sexually transmitted infections approved by order of the Ministry of Health of the Republic of Belarus 10/29/2009, No. 1020 (below referred to as ‘2009 Belarusian national gonorrhoea guideline’) [45]. For treatment of uncomplicated gonorrhoea, first-line treatment is ceftriaxone 1 g×1 IM; and alternative treatment is cefixime 400 mg×1 orally or spectinomycin 2 g×1 IM for men and 4 g×1 IM for women or ofloxacin 400 mg×1 orally, or lomefloxacin 800 mg×1 orally [45]. For treatment of complicated gonorrhoea, ceftriaxone 1 g IM or IV every 24 hours for 7 days is the recommended first-line therapy; and spectinomycin 2 g IM every 12 hours for 7 days or ofloxacin 200 mg orally every 12 hours for 7–14 days or lomefloxacin 400 mg orally every 24 hours for 7–14 days are recommended alternative regimens [45]. Notable, spectinomycin is currently not available in all settings of Belarus [46].

The objectives of the present study were to analyse the trends in *N. gonorrhoeae* AMR levels in Belarus (2009–2019), review the antimicrobial treatments recommended nationally

as well as compliance to these recommendations in Belarus, and provide quality-assured gonococcal AMR data for informing the 2009 Belarusian national gonorrhoea guideline [45].

Methods

Study population

Gonorrhoea patients (n=522) diagnosed at the following STI Healthcare Institutions: Mogilev Regional Dermatovenerologic Dispensary, Mogilev (n=409), Minsk City Clinical Dermatovenerologic Dispensary, Minsk (n=83) and Vitebsk Regional Dermatovenerologic Dispensary, Vitebsk (n=30) in Belarus, September 2009– June 2015 and July 2017–December 2019 were included in the study. For description of longitudinal AMR data, this cohort includes previously published data (273 patients) from 2009 (n=80) [39] and 2010–2013 (n=193) [40]. Cervical specimens from females and urethral specimens from males were collected and delivered to the bacteriological laboratory in Amies Transport Medium with Charcoal (Research and production center Chemmedsynthesis, Minsk, Belarus). Demographic data (gender and age) were collected. Informed consent was obtained from all patients. Exclusion criteria were: i) not confirmed gonococcal infection or ii) not providing informed consent. All patients and their sexual partners were aimed to be managed in accordance with the 2009 Belarusian national gonorrhoea guideline [45].

Culture of *Neisseria gonorrhoeae*

All urogenital swabs were inoculated on the selective Chocolate agarTM + PolyViteX VCAT3 media (bioMerieux, Marcy-l'Etoile, France), followed by incubation in 5±1% CO₂-enriched humid atmosphere at 36±1°C for 24 h, and – if negative – for additional 24 h. Isolates were confirmed as *N. gonorrhoeae* based on identification of Gram-negative diplococci in microscopy, rapid oxidase reaction, a Vitek® 2 automatic bacteriological analyser

(bioMérieux, Durham, NC, USA) with Vitek® 2 NH ID cards (bioMérieux, Marcy-l’Etoile, France), a polymerase chain reaction assay (AmpliSens *Neisseria gonorrhoeae*-screen-F1; InterLabServices, Moscow, Russia), and matrix-assisted laser desorption-ionisation time-of-flight mass spectrometry (MALDI-TOF MS; Microflex LT, Bruker Daltonik, Bremen, Germany), according to manufacturer’s instructions.

The isolates were stored in a liquid preservation medium containing trypticase-soy broth, yeast extract, agar and horse serum, in liquid nitrogen (-196°C) or in a low-temperature freezer (-80 °C).

Antimicrobial susceptibility testing

At the WHO Collaborating Centre for Gonorrhoea and other STIs, Sweden, the minimum inhibitory concentrations (MICs; mg/L) of eight antimicrobials (ceftriaxone, cefixime, azithromycin, spectinomycin, ciprofloxacin, tetracycline, benzylpenicillin, and gentamicin) were determined by Etest (bioMérieux, Marcy-l’Etoile, France), following manufacturer’s instructions and as described previously [39,40]. Results were interpreted using whole MIC dilutions and, where available, clinical breakpoints for susceptibility (S) and resistance (R) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [47]. For azithromycin, no clinical breakpoints exist, and the EUCAST azithromycin epidemiological cut-off value (ECOFF) of MIC>1 mg/L [47] was used to indicate isolates with azithromycin resistance determinants (considered as azithromycin resistant below). For gentamicin, previously published interpretative criteria were used [48]. β -lactamase production was identified using a Nitrocefin test (Oxoid, Basingstoke, England). The 2016 WHO *N. gonorrhoeae* reference strains [49] were used for quality controls.

Treatment of gonorrhoea

The medical records of gonorrhoea patients (n=1652) diagnosed and treated at the Minsk City Clinical Dermatovenerologic Dispensary in 2013–2018 (n=749) and Mogilev Regional Dermatovenerologic Dispensary in 2010–2019 (n=903) were analysed. Uncomplicated and complicated gonorrhoea cases were defined according to the international statistical classification of diseases and related health problems [50]. Gonorrhoea treatment compliance to the 2009 Belarusian national gonorrhoea guideline [45] was evaluated.

Statistical analysis

Statistical analysis was performed using the MedCalc Statistical Software v18.11.3 (MedCalc Software bvba, Ostend, Belgium). The 95% confidence interval (95% CI) was calculated using the exact binominal distribution method. Z-test, Fisher exact and Mann-Whitney U tests were used for comparison between groups, as appropriate. The level of significance was set at $P < 0.05$.

Results

Patients and *Neisseria gonorrhoeae* isolates characteristics

N. gonorrhoeae isolates (one per patients) from urogenital sites of 522 patients were examined; 430 (82.4%) males, 84 (16.1%) females and eight (1.5%) with gender not reported. The isolates were cultured in Mogilev (78.4%, 409/522), the capital city Minsk (15.9%, 83/522), and Vitebsk (5.7%, 30/522), in 2009 (n=81), 2010 (n=72), 2011 (n=6), 2012 (n=75), 2013 (n=101), 2014 (n=56), 2015 (n=17), 2017 (n=36), in 2018 (n=19), and 2019 (n=59).

Demographic data (gender and age) were available from 514 (98.5%) patients. Briefly, the median age for the males was 25 years (range: 16–61 years) and for the females 25 years (range: 16–74 years). The gender and age distributions were relatively similar during 2009-

2019. The median of male/female ratio was 5.9 (range: 1.8-7.6), with decreasing trends over the years.

Antimicrobial susceptibility of *Neisseria gonorrhoeae* isolates (n=522) from Belarus, 2009–2019

The overall antimicrobial susceptibility of all *N. gonorrhoeae* isolates (n=522) is summarised in Table 1.

Table 1 Antimicrobial susceptibility in *Neisseria gonorrhoeae* isolates (n=522) from Minsk, Mogilev and Vitebsk, Belarus, 2009-2019

Antimicrobials	Susceptible (S)/Susceptible, increased exposure (I)/Resistant (R), % ^a							
	2009 ^b	2010–2011 ^b	2012 ^b	2013 ^b	2014–2015	2017	2018–2019	Total ^b
	n=81	n=78	n=75	n=101	n=73	n=36	n=78	n=522
CRO	100/NA/0	100/NA/0	100/NA/0	100/NA/0	100/NA/0	100/NA/0	100/NA/0	100/NA/0
CFM	100/NA/0	100/NA/0	100/NA/0	98.0/NA/2.0	100/NA/0	77.8/NA/22.2	94.9/NA/5.1	97.3/NA/2.7
AZM	98.8/NA/1.2	100/NA/0	98.7/NA/1.3	100/NA/0	100/NA/0	100/NA/0	97.4/NA/2.6	99.2/NA/0.8
SPC	100/NA/0	100/NA/0	100/NA/0	100/NA/0	100/NA/0	100/NA/0	100/NA/0	100/NA/0
CIP	65.4/0/34.6	64.1/2.6/33.3	78.7/0/21.3	72.3/0/27.7	90.4/0/9.6	69.4/0/30.6	83.3/0/16.7	74.9/0.4/24.7
PEN	29.6/60.5/9.9	–/–/–	62.6/30.7/6.7	59.4/31.7/8.9	80.8/16.4/2.8	55.6/33.3/11.1	51.3/44.9/3.8	56.3/36.7/7.0
TET	55.5/21/23.5	56.4/10.3/33.3	56/9.3/34.7	62.4/8.9/28.7	76.7/5.5/17.8	69.4/0/30.6	61.5/11.5/26.9	61.9/10.3/27.8
GEN	72.8/27.2/0	97.4/2.6/0	58.7/41.3/0	40.6/59.4/0	67.1/32.9/0	55.6/44.4/0	87.2/12.8/0	68.4/31.6/0

CRO, ceftriaxone; CFM, cefixime; AZM, azithromycin; SPC, spectinomycin; CIP, ciprofloxacin; PEN, benzylpenicillin; TET, tetracycline; GEN, gentamicin;

NA, not applicable; –, not tested.

^aThe clinical breakpoints (susceptible, resistant) were as follows: ceftriaxone and cefixime (MIC≤0.125 mg/L, MIC>0.125 mg/L), ciprofloxacin (MIC≤0.032 mg/L, MIC>0.064 mg/L), azithromycin (MIC≤1 mg/L, MIC>1 mg/L), spectinomycin (MIC≤64 mg/L, MIC>64 mg/L), benzylpenicillin (MIC≤0.064 mg/L, MIC>1.0 mg/L), tetracycline (MIC≤0.5 mg/L, MIC>1.0 mg/L), and gentamicin (MIC≤4 mg/L, MIC>16 mg/L) [47,48].

^bOf the 335 isolates from 2009-2013, 273 have been previously published [39,40]

Briefly, in 2018-2019 the resistance to tetracycline, ciprofloxacin, cefixime, benzylpenicillin, and azithromycin was 26.9%, 16.7%, 5.1%, 3.8%, and 2.6%, respectively. During 2009-2019, the resistance levels were as follows: tetracycline 27.8% (range: 17.8-34.7%), ciprofloxacin 24.7% (9.6-34.6%), benzylpenicillin 7.0% (2.8-11.1%), cefixime 2.7% (0-22.2%), and azithromycin 0.8% (0-2.6%) (Table 1). Only one (0.2%) β -lactamase producing isolate was found (in 2013). No isolates resistant to ceftriaxone, spectinomycin or gentamicin were detected (Table 1). However, four (0.8%) isolates had a ceftriaxone MIC of 0.125 mg/L, which is exactly at the resistance breakpoint (MIC>0.125 mg/L), and 31.6% of isolates had a decreased susceptibility to gentamicin.

During 2009-2019, the levels of resistance to tetracycline were relatively stably high. The level of resistance to ciprofloxacin significantly decreased to 9.6% in 2014–2015, but subsequently significantly increased to 30.6% in 2017 ($P<0.05$). The levels of resistance to benzylpenicillin non-significantly fluctuated, i.e. from 2.8% to 11.1% over the years. Notable, no resistance to cefixime was found prior to 2013 (when 2.0% resistance was detected), however, the cefixime resistance then significantly increased to a peak of 22.2% in 2017 ($P<0.05$). Only sporadic isolates with resistance to azithromycin were found in 2009 ($n=1$, 1.2%), 2012 ($n=1$, 1.3%) and 2018–2019 ($n=2$, 2.6%) (Table 1).

The MIC distributions for ceftriaxone and azithromycin, included in the internationally recommended first-line dual antimicrobial therapy [8,11,29-31], and cefixime are presented in figure 1.

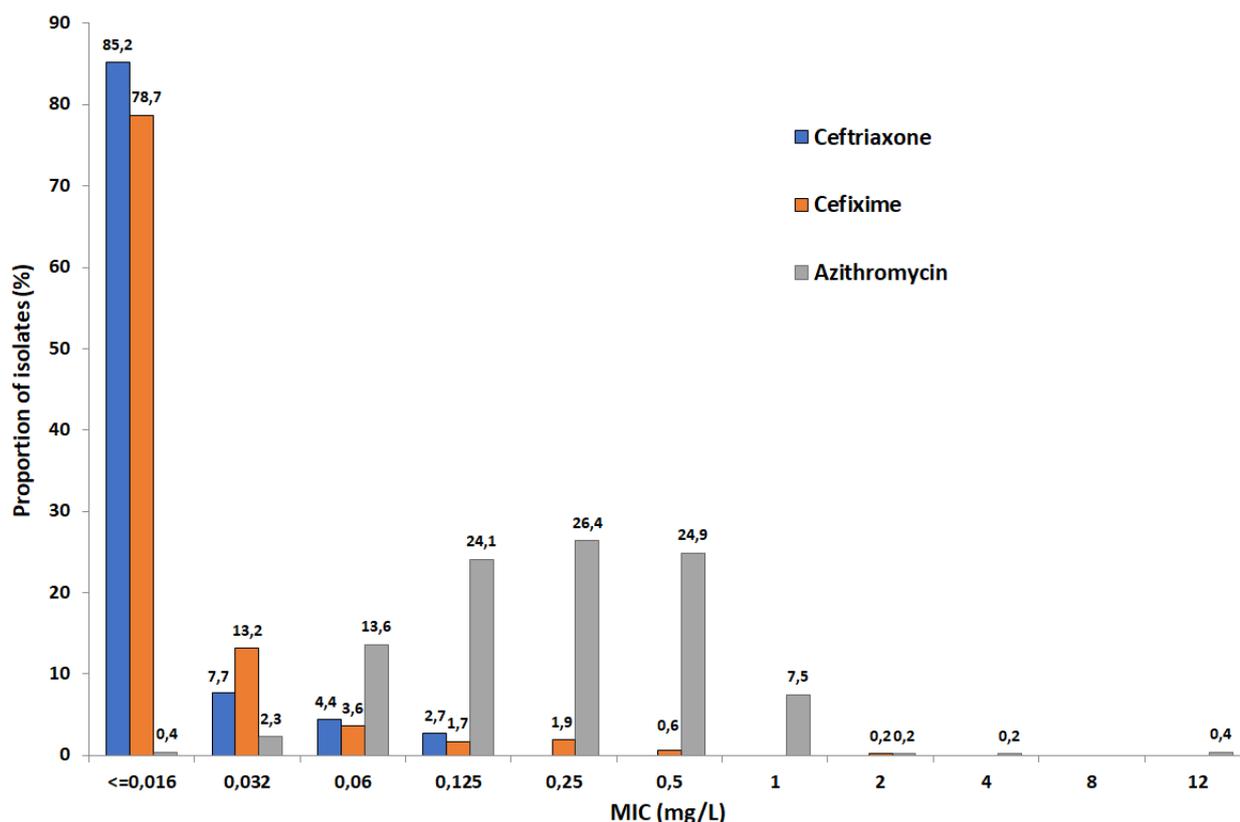


Figure 1. MIC distributions for ceftriaxone, cefixime and azithromycin for *Neisseria gonorrhoeae* isolates (n=522) from Belarus, 2009–2019

In total, 0.8% (4/522) of isolates had a ceftriaxone MIC of 0.125 mg/L, which is at the ceftriaxone resistance breakpoint [47]: 1.2% (1/81) in 2009, 1% (1/101) in 2013 and 5.6% (2/36) in 2017. The proportion of isolates with ceftriaxone MIC \leq 0.016 mg/L was 85.2%, and in general, the annual MIC distribution for ceftriaxone appeared to shift to lower MICs during 2009–2019 (data not shown). For cefixime, 78.7% (411/522) of isolates had a MIC \leq 0.016 mg/L; however, 2.7% (14/522) of isolates were resistant to cefixime, highest MIC=2 mg/L (one isolate in 2013), and additionally 1.7% (9/522) of isolates had a cefixime MIC of 0.125 mg/L, i.e. at the cefixime resistance breakpoint [47]. With the exception of four (0.8%) azithromycin-resistant isolates (MICs 2-12 mg/L), the azithromycin MIC distribution appeared to represent a wild-type distribution.

Antimicrobial treatment of gonorrhoea patients in Belarus, 2010–2019

Compliance to the treatment of gonococcal infections to the 2009 Belarusian national gonorrhoea guideline [45] at the Minsk City Clinical Dermatovenerologic Dispensary (2013–2018) and Mogilev Regional Clinical Dermatovenerologic Dispensary (2010–2019) for 1652 patients is described in table 2.

Table 2 Compliance to the 2009 Belarusian national gonorrhoea guideline [45] in Minsk (749 patients, 2013–2018) and Mogilev (903 patients, 2010–2019), Belarus

Prescribed antimicrobials	Minsk, No. (% , 95% CI)	Mogilev, No. (% , 95% CI)
Recommended first-line treatment [45]		
CRO 1 g×1 IM (uncomplicated gonorrhoea) or CRO 1 g×1 IM or IV every 24 hours, 7 days (complicated gonorrhoea) ^a	354 (47.3, 43.7- 51.0)	508 (56.3, 53.0-59.6)
Alternative treatment [45]		
CFM 400 mg×1 orally	5 (0.7, 0.2-1.6)	0
OFX 400 mg×1 orally	26 (3.5, 2.3-5.1)	123 (13.6, 11.4-16.0)
Non-compliant treatment		
Non-compliant antimicrobials or doses, usually higher than recommended, given	364 (48.6, 45.0- 52.3) ^b	272 (30.1, 27.1-33.2) ^c

No., number; CI, confidence interval; CRO, ceftriaxone; IM, intramuscularly; IV, intravenously; CFM, cefixime; OFX, ofloxacin.

^aFrequently, additional antimicrobials were given to treat other non-viral STIs, which had been confirmed or not excluded by appropriate laboratory diagnostics. These included doxycycline, other tetracyclines, different macrolides, fluoroquinolones, oral cephalosporins, penicillins, and nitroimidazoles.

^bMore than >1 g of ceftriaxone was rather frequently given, approximately 10% of patients received benzylpenicillin, about 5% a tetracycline/macrolide regimen, and one (0.1%) patient was given rifampicin.

*More than >1 g of ceftriaxone was rather frequently given, very rarely a benzylpenicillin regimen was given, and for some few percentages of patients >400 mg ofloxacin or a tetracycline/macrolide regimen was given.

Many different antimicrobial treatment regimens were administered (Table 2). Overall, only 862 (52.2%) patients received the recommended first-line treatment (ceftriaxone 1 g (uncomplicated gonorrhoea) or >1 g (complicated gonorrhoea) as monotherapy or in combination with other antimicrobials) in accordance with the 2009 Belarusian national gonorrhoea guideline [45], and 154 (9.3%) patients were given a recommended alternative treatment (cefixime 400 mg or ofloxacin 400 mg as a single oral dose) [45]. Consequently, 38.5% of the patients received treatment not compliant with the 2009 Belarusian national gonorrhoea guideline [45]. Worryingly, despite the high level of ciprofloxacin resistance, ofloxacin 400 mg×1 was given to 149 (9.0%) patients.

Discussion

This study describes the first internationally reported gonococcal AMR surveillance data, quality-assured according to WHO standards [5,49,51,52], for isolates cultured in Belarus during an extended time period, i.e., from 2009 to 2019 in Minsk, Vitebsk and Mogilev. The AMR levels were significant and relatively comparable to the neighbouring EU/EEA countries [12,36,37], Russia [41-44], and many other countries globally [5,52]. The AMR levels were also clearly higher than in neighbouring Ukraine [33]. It would be valuable to compare the Belarusian gonococcal population with the *N. gonorrhoeae* strains spreading internationally, i.e. using whole-genome sequencing which is utilised in the Euro-GASP surveillance [37,53] and has also been recently used in the gonococcal AMR surveillance in Ukraine [54] and many other countries globally [55-60].

The prevalence of resistance to the previously recommended gonorrhoea antimicrobials tetracycline, ciprofloxacin, and benzylpenicillin was 27.8%, 24.7% and 7% respectively, in

Belarus. None of these antimicrobials should be recommended for empirical first-line gonorrhoea monotherapy in Belarus, which is in concordance with most settings globally [3,5,8-12,28-34,36,37,39-44]. Worryingly, despite the high resistance to ciprofloxacin, the other fluoroquinolones ofloxacin and lomefloxacin remain to be recommended in the 2009 Belarusian national gonorrhoea guideline [45], and particularly ofloxacin was rather frequently used in monotherapy or in combination with other antimicrobials. When susceptibility has not been confirmed by laboratory testing, fluoroquinolones should not be used for treatment [8], and accordingly ofloxacin and lomefloxacin should be excluded from the empiric treatment recommended in the Belarusian national gonorrhoea guideline [45]. Interestingly, β -lactamase producing gonococcal strains were exceedingly rare (0.2%, 1/522 isolates) in Belarus, which is also a fact in the neighbouring East-European countries Russia and Ukraine [33,39-44]. This indicates that no imported β -lactamase producing strains have managed to establish any domestic transmission and no such strains have emerged in Belarus. However, overall 7% of isolates had a chromosomally-mediated resistance to benzylpenicillin and additionally 36.7% of isolates displayed a decreased susceptibility. Azithromycin resistance (0.8%) was rare compared to in most EU/EEA countries [12,36,37], and only sporadic isolates (n=4) resistant to azithromycin were found. The overall resistance to cefixime was 2.7% and the resistance fluctuated from 0% to 22.2% in 2017. However, only 36 gonococcal isolates were examined in 2017 and the high cefixime resistance appeared to be phenotypically represented by a single clone. No gonococcal resistant to ceftriaxone, spectinomycin and gentamicin was identified. However, spectinomycin is currently not available in all settings of Belarus [46]. The lack of ceftriaxone resistance and in general relatively low ceftriaxone MICs may be explained by the long-term use of ceftriaxone 1 g (in monotherapy or dual therapy) as the recommended empirical first-line treatment of gonorrhoea [45], and the fact that the less potent ESC cefixime has been rarely used for

treatment of gonorrhoea in Belarus. Worryingly, the compliance to the 2009 Belarusian national gonorrhoea guideline [45] was relatively low and many non-compliant suboptimal antimicrobials were prescribed to a large proportion of patients. This may select for AMR in *N. gonorrhoeae*, etiological agents of other STIs, and bystander organisms [3,62]. Furthermore, in Belarus antimicrobials such as several penicillins and tetracyclines are readily available “over-the-counter” in the pharmacies without any prescriptions, which is crucial to abandon to mitigate self-medication and a further selection of AMR.

The present study has several limitations. Firstly, gonococcal isolates were collected in only three neighbouring regions of the six regions of Belarus. But taking into account that these three regions represent 60% of the Belarusian population including the capital city Minsk (https://en.wikipedia.org/wiki/Regions_of_Belarus), this geographical bias should be limited and results possible to extrapolate to the whole country. Secondly, the number of isolates per year was low. Thirdly, no pharyngeal or rectal specimens were collected. Finally, no data regarding epidemiological or clinical characteristics such as sexual behaviour and treatment outcomes were collected. Accordingly, the gonococcal AMR surveillance in Belarus should be further strengthened and expanded in Belarus, by increasing the number of representative isolates collected annually, ideally including additional regions, collection of also pharyngeal and rectal specimens and additional epidemiological and clinical data of patients. For this expansion of the gonococcal AMR surveillance, training of clinicians and laboratory workers (e.g., in sample collection, sample transportation, and gonococcal culture), implementation of quality-assured gonococcal culture in additional Belarusian laboratories, and political and financial commitment are imperative.

Conclusions

We describe the first internationally reported gonococcal AMR surveillance data for isolates cultured in Belarus during an extended time period, i.e., from 2009 to 2019 in Minsk, Mogilev and Vitebsk regions, quality-assured according to WHO standards [5,49,51,52]. Based on the gonococcal AMR data presented in this paper, Belarus has also been included in the WHO Global GASP [5]. Briefly, in 2009–2019, the gonococcal population in Belarus showed relatively stably high resistance to tetracycline, ciprofloxacin, and benzylpenicillin. More sporadic resistance to azithromycin and fluctuating resistance to cefixime was found. However, no resistance to ceftriaxone, spectinomycin or gentamicin was identified. Accordingly, ceftriaxone 1 g, in combination with azithromycin 2 g particularly when chlamydial infection has not been excluded, should be recommended as empiric first-line treatment. Spectinomycin 2 g, where available, together with azithromycin 2 g could be an alternative treatment. When susceptibility has not been confirmed by testing, fluoroquinolones should not be used for treatment. Continued and expanded quality-assured surveillance of gonococcal AMR and ideally also gonorrhoea treatment failures in Belarus is essential to monitor AMR emergence and trends of the susceptibility to particularly ESCs (ceftriaxone and cefixime), azithromycin and doxycycline, and to provide evidence-based AMR data for timely and regular refinements of the national gonorrhoea guideline in Belarus [45], which is essential to ensure effective management and control of gonorrhoea in Belarus.

Abbreviations

AMR: antimicrobial resistance; ECOFF: epidemiological cut-off value; ESC: extended-spectrum cephalosporin; EU/EEA: European Union/European Economic Area; EUCAST: European Committee on Antimicrobial Susceptibility Testing; Euro-GASP: European

Gonococcal Antimicrobial Surveillance Programme; IM: intramuscularly; IV: intravenously; MIC: minimum inhibitory concentration; WHO: World Health Organization; 2009 Belarusian national gonorrhoea guideline: Clinical protocol for the diagnosis and treatment of patients with sexually transmitted infections approved by order of the Ministry of Health of the Republic of Belarus 10/29/2009, No. 1020.

Declarations

Ethics approval and consent to participate

The present study and publication of its results were approved by the Expert Commission at the Belarusian Medical Academy of Postgraduate Education (BelMAPO), Minsk, Belarus.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AAAn, ISh and MU designed the study. AAAn with support of ISh, IB and MU analysed all the data and wrote the first draft of the manuscript. TG, DG, ISt, SJ, and AAd were involved in collection of samples and/or laboratory examinations. All authors were involved in finalising the manuscript and approved the final version of the manuscript.

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Figures

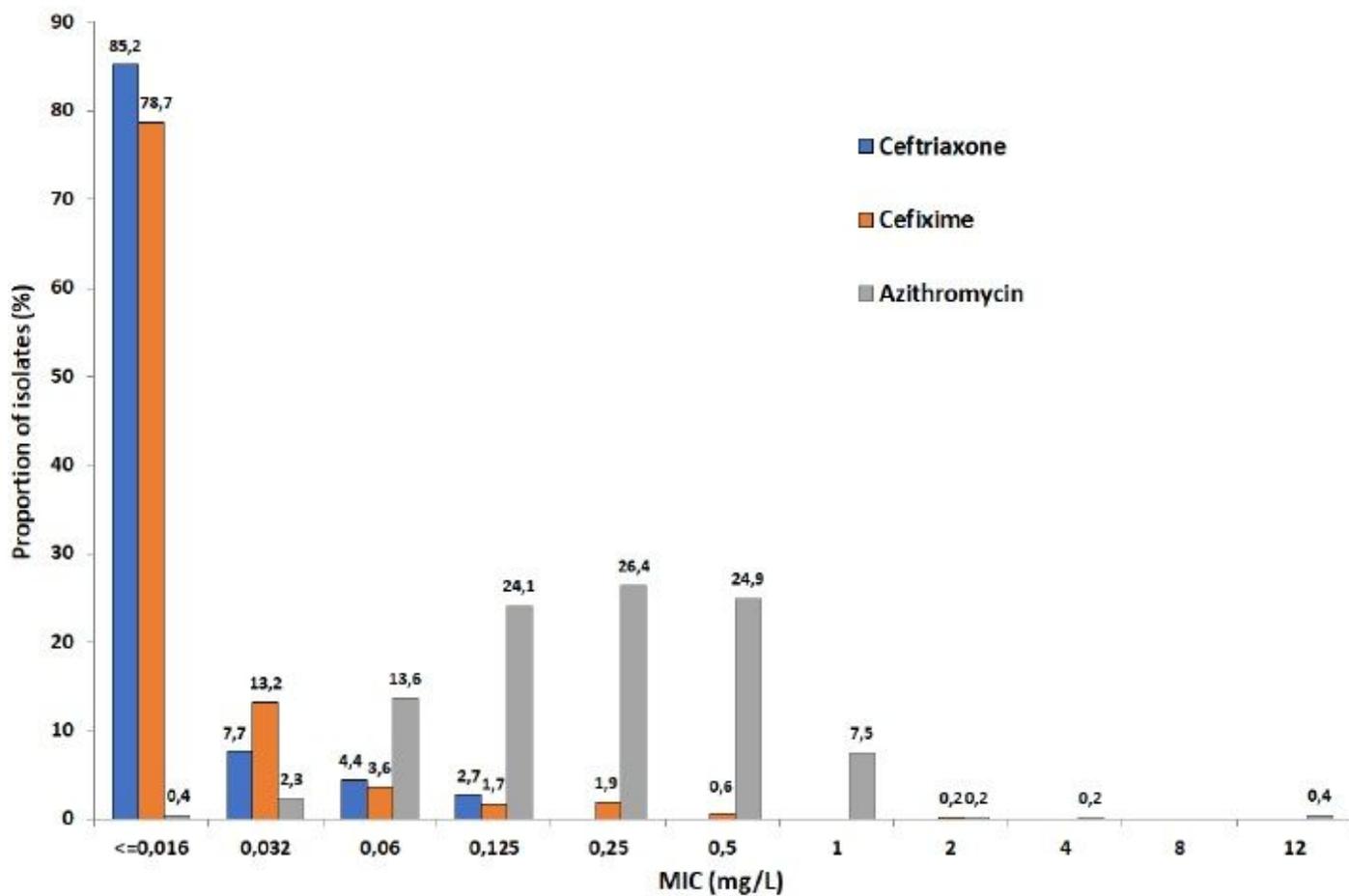


Figure 1

MIC distributions for ceftriaxone, cefixime and azithromycin for *Neisseria gonorrhoeae* isolates (n=522) from Belarus, 2009-2019