

***Neisseria gonorrhoeae* antimicrobial resistance  
surveillance report of Belgium – 2021**



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## 1. Rationale – Background

The Institute of Tropical Medicine (ITM) is the National Reference Centre of Sexually Transmitted Infections (NRC-STI) of Belgium since 2010. Besides chlamydia, gonorrhoea is the second most detected bacterial STI in Belgium.<sup>1,2</sup> However, more worrying is the fact that *Neisseria gonorrhoeae*, the causative agent of gonorrhoea, is evolving into a superbug. It acquired resistance to all classes of antimicrobials used for treating infections.<sup>3</sup> Given the extraordinary capacity of *N. gonorrhoeae* to acquire resistance mechanisms, it is likely that *N. gonorrhoeae* may become untreatable in the not-too-distant future. As such, an important surveillance activity of the NRC-STI is the follow-up of antimicrobial resistance of *N. gonorrhoeae* to anticipate resistance of *N. gonorrhoeae* to certain antimicrobials and to adapt treatment guidelines when necessary.

## 2. Methods

The NRC-STI receives presumable *N. gonorrhoeae* isolates from every district of Belgium. At the NRC-STI, confirmation of the identification of *N. gonorrhoeae* is performed by Gram stain, oxidase test, and molecular detection (isolates obtained from outside the ITM polyclinic) or via the enzymatic/sugar assay API-NH (isolates obtained from patients attending the ITM polyclinic). When *N. gonorrhoeae* is confirmed, additional antimicrobial susceptibility testing is performed to determine the minimal inhibition concentration or MIC to a certain antibiotic. The MIC allows interpretation of resistance to a specific antibiotic based on breakpoints available in the EUCAST guidelines version 12.0. **Table 1** lists the antibiotic tested, the method, the breakpoint for resistance, and the frequency at which antimicrobial susceptibility testing (AST) is performed. Multidrug resistance is defined to be resistant to azithromycin, ciprofloxacin and ceftriaxone. A *N. gonorrhoeae* isolate acquired high-level resistance to azithromycin if the MIC is above 256 mg/L.

**Table 1: Antibiotic susceptibility testing of *N. gonorrhoeae* at the NRC-STI**

Antibiotic	Test method	Resistance breakpoint (EUCAST)	AST frequency
Azithromycin	Etest (Biomerieux, France)	>1 mg/L	Yearly
Ciprofloxacin	Etest (Biomerieux, France)	> 0.06 mg/L	Yearly
Ceftriaxone	Etest (Biomerieux, France)	>0.125 mg/L	Yearly
Cefixime	Agar dilution method	>0.125 mg/L	Yearly*
Penicillin	Agar dilution method	>1 mg/L	Every three years -2022
Tetracycline	Agar dilution method	>1 mg/L	Every three years -2022
Spectinomycin	Agar dilution method	> 64 mg/L	Every three years -2022
Gentamicin	Agar dilution method	No breakpoint defined	Every three years -2022

\*MIC of cefixime is only tested on a maximum of 200 isolates collected between September till December as required by the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP). AST: Antimicrobial susceptibility testing

### 3. Results

#### 3.1 Characteristics of *N. gonorrhoeae* isolates

In 2021, the NRC-STI received 615 samples originating from all Belgian regions (Flanders, Brussels and Wallonia). However, 8.5% (52/615) of the isolates did not survive the transport, one isolate was contaminated (0.2%), and two isolates were not confirmed to be *N. gonorrhoeae* (no *Neisseria spp.*) which brings the number of *N. gonorrhoeae* isolates to 560. Annex one lists the number of *N. gonorrhoeae* isolates by the 63 different laboratories (58.7% Flanders , 17.5% Brussels, and 23.8% Wallonia). After review, two isolates were found to be duplicates and were not included in the analysis (n=558).

In 2021, four-fifth of the isolates were found among men (441/558; 79.0%), 21% (116/558) among women and one *N. gonorrhoeae* strain was isolated from a transwoman. **Figure 1** shows the percentage of isolates from 2013 to 2021 stratified by gender over the years.

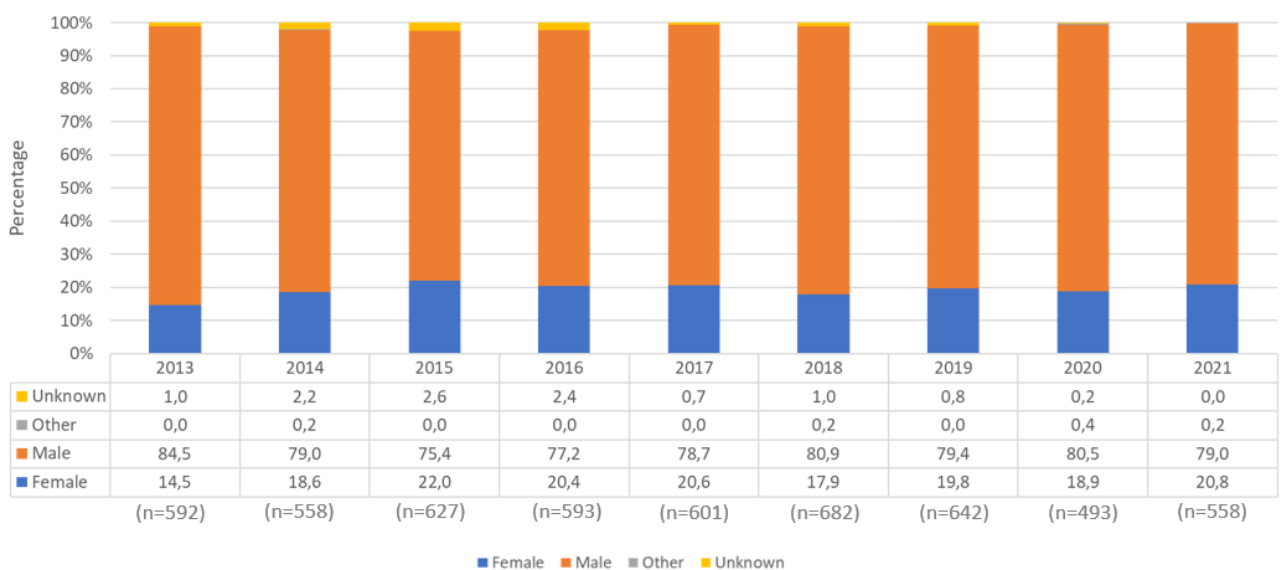


Figure 1: Percentage of *N. gonorrhoeae* isolates from 2013 to 2021 stratified by gender. Other includes *N. gonorrhoeae* isolates of transgender individuals. The total number of confirmed *N. gonorrhoeae* isolates is between brackets.

The infection site of the *N. gonorrhoeae* isolates for 2021 is shown in **Table 1**. Most isolates originated from the urogenital anatomical sites followed by the anorectum.

**Table 1: Infection site of the *N. gonorrhoeae* isolates of 2021**

Biological origin	Female (n=116)		Male (n=441)		Other (n=1)		Total (n=.....)	
	N	%	N	%	N	%	N	%
Genital	111	95.7	265	60.1	1	100	377	67.6
Urine	2	1.7	109	24.7	0	0	111	19.9
Anorectal	0	0	54	12.2	0	0	54	9.7
Throat	1	0.9	1	0.2	0	0	2	0.4
Other*	2	1.7	8	1.8	0	0	10	1.8
Unknown	0	0	4	0.9	0	0	4	0.7

\*Other includes the following infections sites: blood (1), biopsy of the breast (1), cerebrospinal fluid (1) pus (3), ulcer (1), eye (2), and joint fluid (1)

### 3.2 Antimicrobial resistance of *N. gonorrhoeae*

**Table 2** lists the MICs of the *N. gonorrhoeae* isolates of 2021 for the following antibiotics: ciprofloxacin, ceftriaxone, azithromycin and cefixime.

**Table 2: Minimal Inhibitory Concentration (MIC) and final interpretation of the *N. gonorrhoeae* isolates 2021**

	S			I		R			
	N	%	MIC limit value mg/L	N	%	MIC limit value mg/L	N	%	MIC limit value mg/L
<b>Azithromycin</b>	454	81.4	≤ 1	-	-	-	104	18.6	>1
<b>Ciprofloxacin</b>	245	43.9	≤ 0.032	1	0.2	0.06	312	55.9	>0.06
<b>Ceftriaxone</b>	556	99.6	≤ 0.125	-	-	-	2	0.4	>0.125
<b>Cefixime*</b>	197	35.2	≤ 0.125	-	-	-	2	0.4	>0.125

MIC Breakpoints according to EUCAST guidelines . S: Susceptible; I: Susceptible, Increased Exposure; R: Resistant \*MIC of cefixime is limited to 200 isolates collected between September to December as required by Euro-GASP.

In 2021, two ceftriaxone resistant cases were detected in male urethral samples. **Table 3** describes the MIC to the different antibiotics of both cases. Both isolates were also resistant to ciprofloxacin, however the MIC of azithromycin remains just below the breakpoint of resistance (>1mg/L). High-level resistance to azithromycin (MIC >256 mg/L) was present in two cases in 2021 in male urethral samples. Both isolates were sensitive to ciprofloxacin and ceftriaxone.

**Table 3: Minimal Inhibitory Concentration (MIC) for ciprofloxacin, ceftriaxone and azithromycin for the *N. gonorrhoeae* isolates that were resistant to ceftriaxone in 2021.**

Antibiotic	Case 1 (M – urethra)		Case 2 (M-urethra)	
	MIC (mg/L)	Final Interpretation	MIC (mg/L)	Final Interpretation
<b>Azithromycin</b>	0.75	S	1	S
<b>Ciprofloxacin</b>	>32	R	>32	R
<b>Ceftriaxone</b>	0.25	R	0.19	R

**Figures 2 to 4** show the antimicrobial resistance of *N. gonorrhoeae* to the different antibiotics over the years. Resistance to spectinomycin is not yet detected in Belgium. Resistance to ceftriaxone has been detected in 13 cases since 2013.

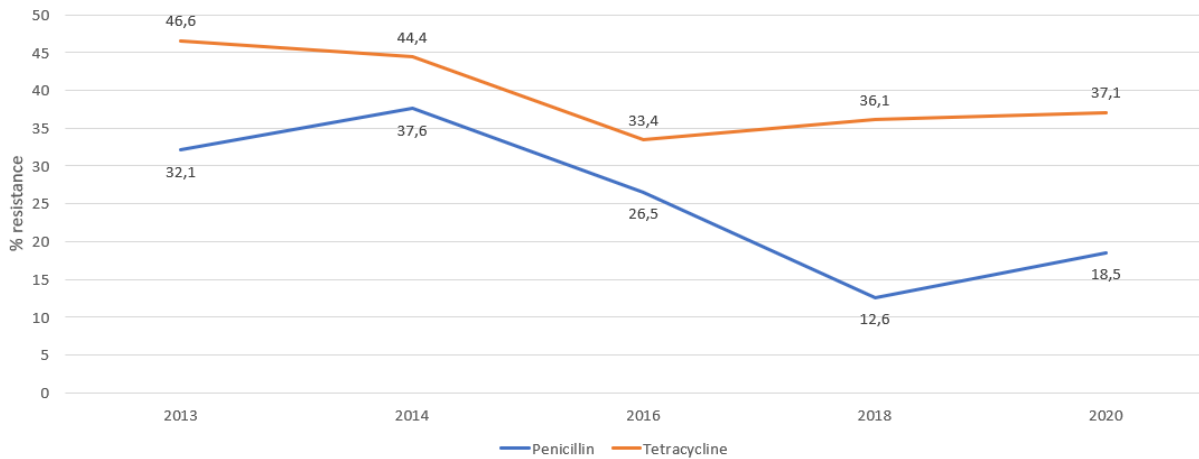


Figure 2: Antimicrobial resistance (%) of *Neisseria gonorrhoeae* to penicillin and tetracycline from 2013 to 2020 in Belgium. These antibiotics were not tested in 2021.

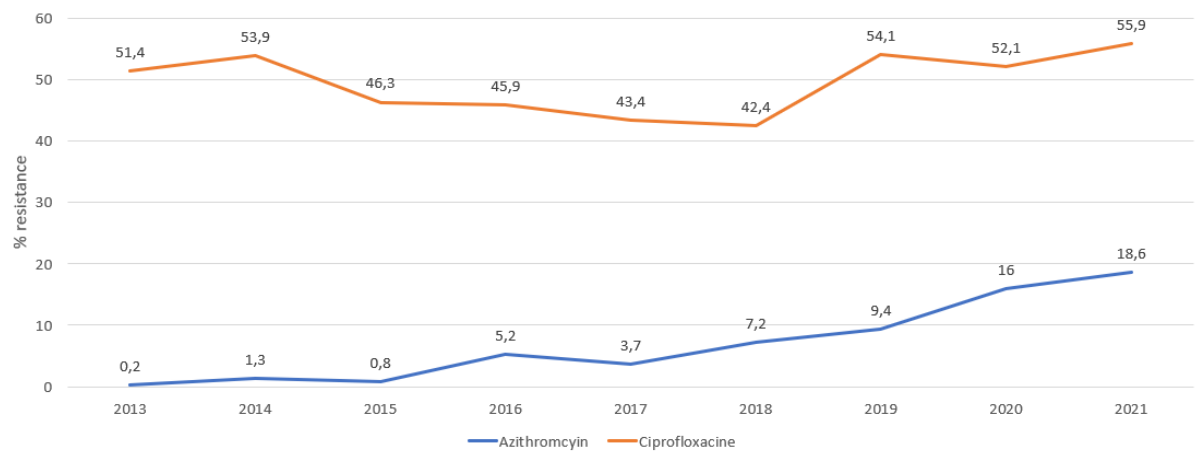


Figure 3: Antimicrobial resistance (%) of *Neisseria gonorrhoeae* to azithromycin and ciprofloxacin from 2013 to 2021 in Belgium.

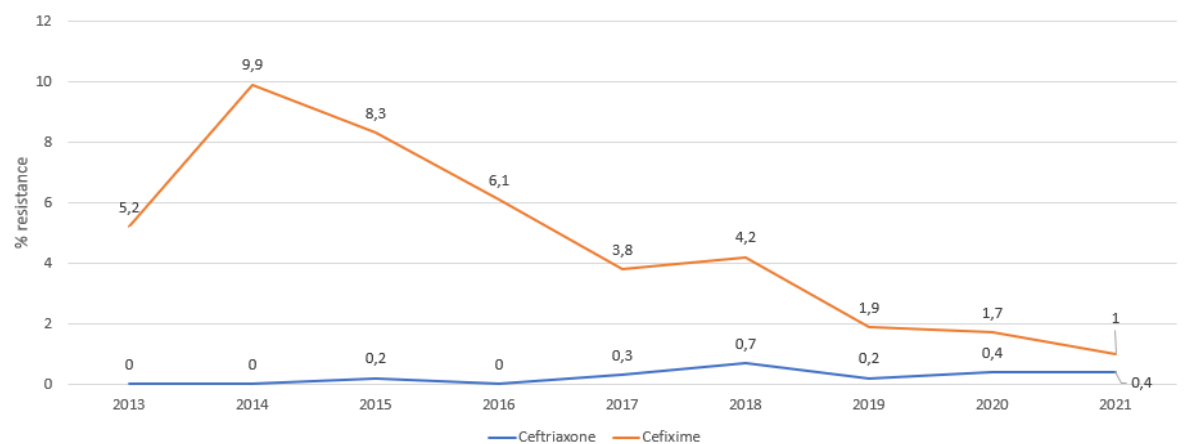


Figure 4: Antimicrobial resistance (%) of *Neisseria gonorrhoeae* to extended spectrum cephalosporines cefixime and ceftriaxone from 2013 to 2021 in Belgium.

Resistance of *N. gonorrhoeae* to ciprofloxacin is above 50% and remains stable over time. A steady increase of resistance to azithromycin over time is seen. The proportion of isolates resistant to azithromycin is 18.6%. The increase in resistance to azithromycin is found to be

higher among men who have sex with men (MSM) (27.6%) compared to heterosexual individuals (14.4%) (see Figure 5).

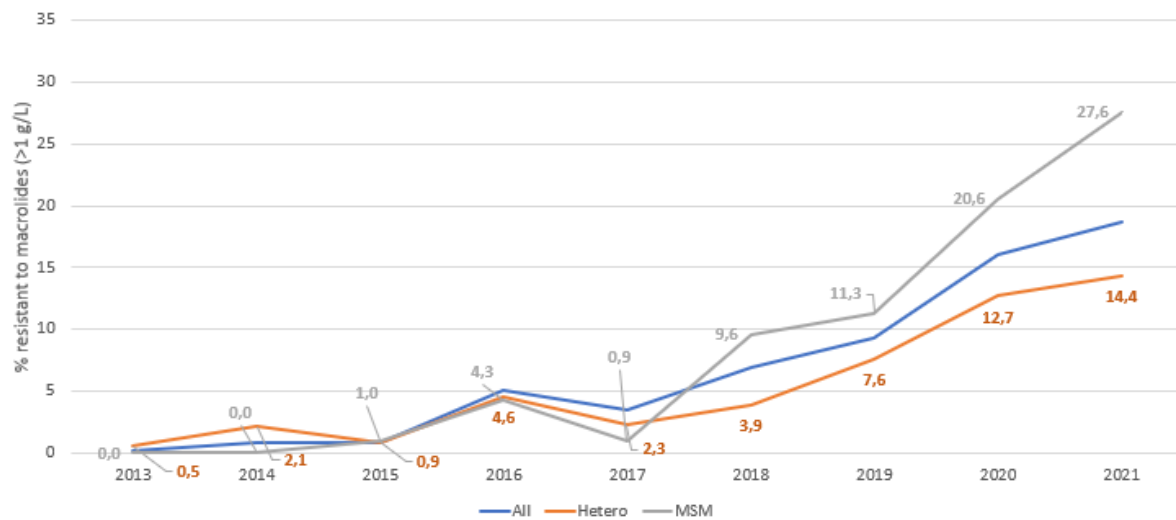


Figure 5: Resistance to macrolides of *N. gonorrhoeae* stratified by sexual orientation. Heterosexuals comprises all females and heterosexual males. MSM: Men who have sex with men.

#### 4. Discussion

Whilst the antimicrobial resistance of *N. gonorrhoeae* to ciprofloxacin remains stable over time, we note an increase of antimicrobial resistance of *N. gonorrhoeae* to azithromycin. In fact, almost one if five *N. gonorrhoeae* isolates exhibited resistance to azithromycin. Although the increase in azithromycin resistance is higher in MSM, we also see a steady increase of resistance to azithromycin among heterosexual individuals. This may suggest spill over of macrolide resistance to the general population via sexual bridging.<sup>4</sup> As a response, the NRC-STI will perform additional whole genome sequencing on all isolates resistant to macrolides and all isolates with a decreased susceptibility to ceftriaxone (MIC >0.125 mg/L) collected in 2020 and 2021. Hereto, we will be able to provide insights on the local emergence and transmission of *N. gonorrhoeae*, including antimicrobial resistance lineages.

Currently, the Belgian guidelines for diagnosis and treatment of gonorrhoea still recommend the use of ceftriaxone 500 mg intramuscular and 2g azithromycin in a single dose.<sup>5</sup> However, the increasing resistance of *N. gonorrhoeae* to macrolides in Belgium adds to the growing body of literature that the treatment guidelines of *N. gonorrhoeae* in Belgium should be revisited.<sup>6,7</sup> In the recent European IUSTI guideline of 2020 for the diagnosis and treatment of gonorrhoea in adults, dual treatment (azithromycin and ceftriaxone) is still recommended to avoid the emergence of resistance to ceftriaxone, an extended spectrum cephalosporine.<sup>8</sup> Ceftriaxone is in many settings worldwide, the last remaining option for empirical first-line antimicrobial therapy.<sup>9</sup> However, the European guidelines also offer the choice to use ceftriaxone 1g intramuscular as a single dose for uncomplicated gonorrhoea infection.<sup>10</sup>

As a response and due to the rapid emergence of resistance to azithromycin in *N. gonorrhoeae* as well as in other bacteria such as *Mycoplasma genitalium*, many treatment guidelines over the world are changing their guidelines to switch to monotherapy ceftriaxone.<sup>7,11</sup>

Luckily, resistance to ceftriaxone remains rare in European countries, as in Belgium, even in countries that implemented monotherapy with ceftriaxone instead of dual therapy such as

The Netherlands and the United Kingdom.<sup>12,13</sup> Multi-drug resistant *N. gonorrhoeae* (or resistance to ceftriaxone, azithromycin and ciprofloxacin) are not yet identified in Belgium.

Our findings confirm that the national treatment guidelines of *N. gonorrhoeae* should be revisited to monotherapy of ceftriaxone 1g intramuscular. Moreover, the usage of macrolides to treat other STIs such as *Chlamydia trachomatis* and *Mycoplasma genitalium* should be limited. Continued national surveillance of antimicrobial resistance of *N. gonorrhoeae* and other STIs is imperative.

## 5. Acknowledgements

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## 6. References

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## 7. Annex 1

Laboratory	Number of isolates sent
11603 UZ Antwerpen Edegem	1
11642 AZ Monica Middelaes Deurne	2
11653 AML Antwerpen	18
11677 St Augustinus / St Vincentius / St Jozef Wilrijk	11
11704 ITG Antwerpen	129
12612 AZ St. Maarten Campus Zwartustersvest	2
12616 Somedi Heist-Op-Den-Berg	10
12647 AKL Lier	2
13618 AZ St Jozef Turnhout	4
13656 CMA Herentals	100
23666 Labo Med. Ontledingen BVBA Groot-Bijngaarden	1
24650 MCH Leuven	3
26678 LHUB-ULB Porte de Hal Brussel	12
26692 LHUB-ULB Brussel	2
26726 Cebiodi Brussel	15
26750 Clin Universitaires St Luc Brussel	1
27729 Inst de Biologie Clin Brussel	1
28604 Europaziekenhuizen Brussel	2
28612 Chirec Delta Brussel	6
28615 ULB Hop Erasme Brussel	1
29636 UZ Brussel	3
31628 AZ St Jan Brugge	1
31656 AZ St Lucas Brugge	1
31669 Centraal Labo AZ Zeno Knokke Heist	1
34605 Labo van Poucke Kortrijk	1
34612 AZ Groeninge Kortrijk	3
34615 OLV van Lourdes ZH Waregem	1
35607 AZ Damiaan Oostende	1
36606 St Jozefkliniek Izegem	2
36609 AZ Delta Roeselare-Menen	3
36654 Klinisch Labo Declerck Ardooie	9
41658 OLV ZH Aalst	5
42609 Medina Dendermonde	47
42615 AZ St Blasius Dendermonde	1
43620 AZ ALMA Eeklo	1
44624 Medilab Gent	1
44644 AZ Jan Palfijn Gent	3
44696 AZ St Lucas Gent	9
44700 UZ Gent	4
44711 Bvba Cri Zwijnaarde	5
46615 AZ Nikolaas St Niklaas	3
52610 SYNLAB Heppignies	9

Laboratory	Number of isolates sent
52626 Hop Civil Marie Curie Lodelinsart	2
53624 LIMS - MB next SPRL Louvain-la-Neuve	4
53639 EpiCURA Hornu	7
55604 CHU Tivoli La Louviere	1
55614 CHR de la Haute Senne Soignies	6
56603 CSF Chimay	4
57606 CHWapi Notre Dame Tournai	2
61602 CHR Huy	2
62668 CHC MontLégia Liège	37
62730 CHR Citadelle Liege	3
62960 CHU Sart Tilman Liege	4
71604 LKO-LMC St Truiden	10
71615 ZH Virga Jesse Hasselt	3
71620 AZ St Trudo St Truiden	2
71622 ZH Oost-Limburg St Jan Genk	7
71725 Labo Rigo Genk	12
81602 Clin d'Arlon Aarlen	2
84609 CHA Libramont	1
91605 CHU UCL Namur Yvoir	1
92611 CHR Namur	2
92629 Clin St Luc Bouge	11