

Report on the Enhanced Surveillance of Antimicrobial- Resistant Gonorrhoea (ESAG):

Results from 2018 to 2021



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Également disponible en français sous le titre :
Rapport sur le Système de Surveillance Accrue de la Résistance de la Gonorrhée aux Antimicrobiens (SARGA) :
Résultats de 2018 à 2021

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Publication date: July 2024

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Cat.: HP40-206/2024E-PDF

ISBN: 978-0-660-72002-9
Pub.: 240112

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1. Key messages

- *Neisseria gonorrhoeae* (*N. gonorrhoeae*), the bacteria that causes gonorrhoea, is considered a serious public health threat since it has been increasingly developing resistance to antimicrobial drugs recommended as treatment.
- The Public Health Agency of Canada (PHAC) launched the Enhanced Surveillance of Antimicrobial-Resistant Gonorrhoea (ESAG) system in 2013 to better understand the current trends of antimicrobial-resistant *N. gonorrhoeae*. ESAG results inform the development of treatment guidelines and public health interventions to minimize the spread of antimicrobial-resistant gonorrhoea (AMR-GC) in Canada.
- Between 2018 to 2021, there were a total of 3,377 ESAG cases with a primary culture. These data represent, on average, 19.8% of all *N. gonorrhoeae* cultures submitted to the National Microbiology Laboratory (NML) and 2.5% of all gonorrhoea cases reported to the Canadian Notifiable Diseases Surveillance System (CNDSS) across Canada for the years 2018 to 2021. Of these 3,377 ESAG cases,
 - 83.0% of cases were reported by Alberta, 14.3% by Manitoba, 1.8% by Nova Scotia, and 0.9% by the Northwest Territories
 - most cases were male (80.2%, n=2709), of which an average of 55.5% were among gay, bisexual and other men who have sex with men (GBMSM)
 - the largest proportion of cases were between 20 and 39 years of age (average proportion 72.8%, range: 70.1% to 75.4%)
 - the most common primary site of gonococcal (GC) infection varied by sex and sexual behaviour. Among GBMSM cases, rectal (average: 39.3%) and pharyngeal (average: 34.6%) infections were the most reported primary infection sites. In contrast, genital infections were most reported among heterosexual males (average: 90%) and males with unknown sexual behaviour (average: 52.5%).
 - 30.3% of cases were reported in 2018 (n=1022), 29.6% (n=999) in 2019, 21.1% (n=711) in 2020, and 19.1% (n=645) in 2021.
- Among ESAG cases with an anogenital (defined as a cervical, rectal, or urogenital GC swab isolation site) or pharyngeal primary infection site, from 2018 to 2021, the overall prescriber adherence to PHAC and provincial or territorial (PT) gonorrhoea treatment guidelines was high (average of 91.4% adherence to PHAC guidelines and 89.5% adherence to PT guidelines)

and mostly stable. Prescriber adherence to treatment guidelines was similar by sexual behaviour and site of infection; GBMSM cases were mostly prescribed the recommended regimen of azithromycin 1 g with ceftriaxone 250 mg and all other adult cases were mostly prescribed the recommended regimen of azithromycin 1 g with cefixime 800 mg.

- From 2018 to 2020, AMR-GC prevalence (as indicated by resistance to at least one tested antimicrobial) among ESAG cases was stable. However, AMR-GC prevalence increased from 69.3% in 2020 to 77.4% in 2021. This corresponded with the near doubling of cases with GC cultures demonstrating resistance or decreased susceptibility to two different antimicrobials, from 24.8% in 2020 to 44.5% in 2021.
 - In 2021, AMR-GC burden was highest among GBMSM (85.2% of cultures isolated from GBMSM were resistant to at least one tested antimicrobial), followed by heterosexual males (73.5% of cultures from heterosexual males were resistant to at least one tested antimicrobial) and females (66.7% of all GC cultures isolated from females were resistant to at least one tested antimicrobial). Resistance to ciprofloxacin and tetracycline was high among all sexual behaviour groups but highest among GBMSM.
 - From 2018 to 2020, the number and proportion of ESAG cases with decreased susceptibility to cefixime (cefiximeDS) was very low and stable (<1%). However, from 2020 to 2021, the number of ESAG cases with cefiximeDS increased nearly threefold from six (0.8%) in 2020 to 22 (3.4%) in 2021. Of the 32 cefiximeDS cases, 19 were GBMSM (59.4%).
 - ESAG cases with decreased susceptibility to ceftriaxone (ceftriaxoneDS) declined in number and proportion from eight (0.8%) cases in 2018 to one case (0.2%) in 2021.
 - The number of cases with resistance to azithromycin (azithromycinR) increased (mostly among GBMSM) from 18 (1.8%) in 2018 to 78 cases (7.8%) in 2019. However, this number decreased sharply to eight cases (1.1%) in 2020 and 12 cases (1.9%) in 2021 (below the World Health Organization's (WHO's) 5% cut-off of concern).
 - No ESAG cases demonstrated both azithromycinR and cefiximeDS or ceftriaxoneDS (the PT and PHAC recommended and most prescribed antimicrobial regimens). CefiximeDS and ceftriaxoneDS was detected in one case in each of 2018, 2020, and 2021, and three cases in 2019.
 - Between 2020 and 2021, of all the tested antimicrobials, ciprofloxacin resistance was most prevalent at 46.6% in 2020 increasing to 63.1% in 2021. The second most prevalent

antibiotic resistance detected among ESAG cases was tetracycline resistance (45.9% in 2020 and 58.6% in 2021). Prior to this, tetracycline resistance was most prevalent at 52.1% in 2018 and 51.8% in 2019. Erythromycin resistance has declined annually and sharply from 30.0% in 2018 to 8.5% in 2021. The prevalence of penicillin resistance was relatively stable from 2018 to 2020 (6.8% in 2018, 7.2% in 2019 and 8.2% in 2020) but dropped to 3.9% in 2021.

- There were 14 cases reported by public health authorities as treatment failures. However, none demonstrated resistance or decreased susceptibility to all prescribed treatment regimens suggesting these cases were either reinfected or did not take their medication correctly.
- Between 2018 and 2020, there were 396 unique *N. gonorrhoeae* multiantigen sequence typing (NG-MAST) sequence types (STs) identified from 3,377 *N. gonorrhoeae* isolates collected from ESAG cases. Overall, there were no clear trends of increasing or decreasing prevalence of azithromycinR, cefiximeDS or ceftriaxoneDS among the top 10 sequence types for each year.

2. Introduction

Gonorrhea is a sexually transmitted infection (STI) caused by an infection with the bacterium *N. gonorrhoeae*. Gonorrhea is the second most reported notifiable STI in Canada. In 2021, there were 32,192 gonorrhea cases reported, to the Canadian Notifiable Diseases Surveillance System (CNDSS), for a national rate of 84.2 cases per 100,000 population.¹ Prior to the COVID-19 pandemic, reported rates of gonorrhea tripled from 2010 (33.5 cases per 100,000 population) to 2019 (94.4 cases per 100,000 population). Between 2019 and 2021, the gonorrhea rate declined by 14%. This was likely influenced by the reduced demand for and access to gonorrhea screening, care, and public health reporting due to pandemic-related prevention measures.² Reported case counts and rates of gonorrhea underestimate the true prevalence of gonorrhea in Canada, as many gonorrhea cases are asymptomatic and go undetected and thus, are not reported.

Gonorrhea spreads easily, is associated with travel related sexual contact, is often observed alongside chlamydia, and increases the risk of acquisition of HIV. Individuals with an *N. gonorrhoeae* infection, both asymptomatic and symptomatic, may pass on the bacteria to their sexual partners. Those tested for gonorrhea are more likely to be persons who are symptomatic or persons in higher risk categories (e.g., GBMSM) who are routinely screened for STIs and gonorrhea case contacts.³

While gonorrhoea is curable with the appropriate antibiotics, it remains a serious public health threat in Canada, and globally, as the pathogen, *N. gonorrhoeae*, has developed resistance to most antibiotics over time, including currently recommended treatments in Canada and abroad. Furthermore, the prevalence of AMR-GC cultures has increased over time—the proportion of Canadian cultures resistant to at least one tested antimicrobial tripled from one-quarter of cultures in 2000 to almost three-quarters (73%) in 2021.²

Left unsuccessfully or not treated at all, gonorrhoea can cause pelvic inflammatory disease which can lead to infertility or ectopic pregnancies in females and epididymitis in men.² Gonorrhoea can also spread to the blood causing disseminated gonococcal infection (DGI), which can become life threatening. Gonorrhoea can also be passed to a baby at birth which can cause blindness, joint infection, or a life-threatening blood infection for the baby.³

Continuous monitoring of AMR-GC strains, GC treatment failures, and gonorrhoea treatment prescription data linked to epidemiologic data can inform the usefulness and accuracy of gonorrhoea treatment guidelines and help in reducing the spread of highly resistant gonorrhoea. To this end, PHAC monitors AMR-GC through two laboratory-based surveillance systems.

The first is PHAC's NML led Gonococcal Antimicrobial Surveillance Program (GASP – Canada). GASP – Canada is a passive national surveillance program initiated in the 1980's which collects and monitors AMR-GC data from antimicrobial susceptibility testing (AST) and the molecular characterization (using NG-MAST STs) of gonorrhoea cultures.² This program has rich laboratory data but limited epidemiologic data on GC cases.

The second surveillance system is ESAG, which links a subset of GASP-Canada AMR-GC data to epidemiologic and clinical data for an improved understanding of AMR-GC trends across Canada. ESAG started in 2013 and is led by PHAC's Centre for Communicable Diseases and Infection Control (CCDIC) and the NML. The goal of ESAG is to help inform public health interventions to minimize the spread of antimicrobial resistant *N. gonorrhoeae* in Canada.

This report summarizes ESAG data from 2018 to 2021. Alberta, Manitoba, Nova Scotia (Central Zone Health Authority only), and the Northwest Territories provided clinical and epidemiologic data. Additional Canadian jurisdictions are making efforts to link their AMR-GC GASP-Canada data to epidemiologic and clinical data to include in future ESAG analyses.

3. Methods

3.1. ESAG case definition

An ESAG case refers to any client 16 years or older that meets the PHAC (i.e., national) definition of a gonorrhoea case and has a GC culture analyzed either by the PHAC NML or a regional laboratory.⁴ If a client had multiple cultures obtained within a 30-day timeframe, the primary culture included in the analysis, was the culture that demonstrated the greatest antimicrobial resistance. When there was no difference in resistance patterns, the primary culture was prioritized based on the relative likelihood of treatment failure at the site of infection, in the following order (from the highest likelihood of treatment failure to lowest): pharyngeal, rectal, urethral, and cervical cultures. Only the primary culture data was used in data analyses. If a client had more than one culture greater than 30 days apart, those cultures were treated as separate ESAG cases as they were likely reinfections.

3.2. ESAG data

ESAG data includes linked (via a non-identifying unique ID) de-identified laboratory (AMR-GC resistance profile and NG-MAST sequence type), clinical (site of infection/culture, prescribed treatment, and suspected treatment failure) and epidemiologic (demographic and risk behaviour) client-level data from gonorrhoea cases.

Clinical and epidemiologic data were extracted from routine/enhanced gonorrhoea provincial and territorial case report forms and provided by health authorities from the ESAG participating PTs, Alberta, Manitoba, Nova Scotia and Northwest Territories. Laboratory data were obtained, with the consent from participating PTs, from GASP-Canada. GASP-Canada data include Antimicrobial Susceptibility Testing (AST) data and molecular characterization through *N. gonorrhoeae* Multi-antigen Sequence Typing (NG-MAST) data.

All ESAG data were entered directly or uploaded into a password-protected, web-accessible, jurisdictionally filtered database hosted on the Canadian Network for Public Health Intelligence (CNPHI) platform.

3.3. Data analysis period

Although ESAG was initiated in 2013, this report is limited to data from ESAG cases who had GC isolates collected from 2018 through 2021 data because this period reflects the latest PHAC gonorrhoea treatment guidelines (last updated in June 2017).⁵

3.4. ESAG variables created

The following variables were created from the ESAG epidemiologic data:

i) Sex:

The 'sex' variable is a mix of sex and gender data as some PTs provide sex data, some gender, and some a mix of both.

ii) Sexual behaviour:

Cases reported as male who self-reported their sexual partner as male, or both male and female, were categorized as 'GBMSM'. 'Heterosexual males' included male cases who only reported having female partners. Finally, 'males with unknown sexual behaviour' was defined as male cases that did not have sexual partner information.

iii) Primary infection site (infection site) variables:

The primary infection site is the site of infection from which the primary culture was collected. Infection sites included pharyngeal (throat), genital (urethral, urogenital, cervical, or vaginal), rectal, and other. In concordance with PHAC's Canadian Guidelines on Sexually Transmitted Infections, an 'anogenital infection' was defined as a cervical, rectal, or urogenital GC swab isolation site, as well as isolation sites in which 'other' was specified as an anogenital anatomical site (e.g., labia, perineum).⁶ GC isolation sites specified as throat were categorized as 'pharyngeal infections'.

iv) Reason for medical visit:

ESAG cases may have had one or more reasons for their medical visit. However, only one reason was included in the results output. The reason for medical visit included in all analyses was selected based on the following order: test of cure, signs and symptoms, contact with a known gonorrhoea case (case contact), screening for a STI, and other.

v) Gonorrhoea treatment prescription data variable:

'Other adults' includes heterosexual males, females, and transgender people. It does not include GBMSM or males with unknown sexual behaviour.

3.5. Laboratory Methods

3.5.1. Antimicrobial susceptibility testing of gonorrhea cultures

The Minimum Inhibitory Concentration (MIC) of an antimicrobial therapy (i.e., an antibiotic) which inhibits the growth of *N. gonorrhoeae*, was determined for azithromycin, ceftriaxone, cefixime, ciprofloxacin, erythromycin, penicillin, spectinomycin and tetracycline for all *N. gonorrhoeae* cultures using agar dilution, or an Etest® (BioMerieux, Laval, Quebec). Etest® was used for the Alberta susceptible cultures which were not sent to the NML. MIC interpretations were based on the Clinical and Laboratory Standards Institute (CLSI) breakpoints except for: cefixime decreased susceptibility (defined as a MIC \geq 0.25 mg/L); ceftriaxone decreased susceptibility (MIC \geq 0.125 mg/L); and erythromycin resistance (MIC \geq 2.0 mg/L) (refer to supplementary tables A and B for details; supplementary tables A-K are available upon request at sti-hep-its@phac-aspc.gc.ca).⁷⁻⁹

3.5.2. Sequence typing for *N. gonorrhoeae* cultures

Sequence typing was achieved for all cultures submitted to the NML using the NG-MAST method that incorporates the amplification of the porin gene (*porB*) and the transferrin-binding protein gene (*tbpB*)⁶. DNA sequences of both strands were assembled, and compared using DNASTar, Inc. software. The resulting sequences were submitted to the PubMLST NG-MAST database to determine the sequence types (ST). NG-MAST testing was not performed on the susceptible isolates whose cultures were not submitted to the NML. NG-MAST is highly distinctive and can be used to investigate gonorrhea treatment failures and outbreaks. NG-MAST STs have also shown a close association with antimicrobial resistance (AMR).²

GASP-Canada laboratory methods have been previously published and described in greater detail than what is summarized here.¹⁰

3.5.3. Data Analysis

Gonorrhea treatment prescription data was analysed for ESAG cases that i) had prescription data, ii) met the above definitions of either GBMSM or other adults and iii) had either an anogenital or pharyngeal primary site of infection (ii and iii match the gonorrhea treatment client defining categories from PHAC and PT treatment guidelines). Thus, clients with an unknown or 'other' infection site were excluded from this analysis.^{6, 11-13} The number and proportion of prescriptions that

matched i) PHAC and ii) PT gonorrhoea treatment guidelines was calculated among a) GBMSM and b) other adults stratified by an anogenital or pharyngeal gonococcal infection site.^{6,11-13}

AMR-GC trends were explored by sex and sexual behaviour categories. Results are summarized by GBMSM, heterosexual males, males with unknown sexual behaviour, and females. AMR-GC variables are not presented by female sexual behaviour due to either i) small sample size or ii) where female sexual behaviour group sample size was sufficient, similar AMR-GC trends.

Case counts and proportions were calculated for case characteristics, prescriber adherence to gonorrhoea treatment guidelines, and AMR-GC variables. Percent changes in case count proportions were calculated using non-rounded numbers.

4. Results

4.1 Number of gonorrhoea cultures provided by ESAG participating PTs, 2018 to 2021

From 2018 to 2021, there were 3,377 primary cultures (representing 3,377 ESAG cases) included in the analysis described in this report. Overall, the number of primary cultures decreased annually from 1022 cultures reported in 2018 to 645 cultures reported in 2021. These cultures represent, on average, 19.8% (range: 18.2%-22.7%) of all *N. gonorrhoeae* cultures submitted to the NML and 2.5% (range: 2.0%-2.8%) of all gonorrhoea cases reported to CNDSS across Canada for the years 2018 to 2021.^{2,14-17} From 2018 to 2021, the majority of ESAG data came from Alberta (83.0%), followed by Manitoba (14.3%), Nova Scotia (1.8%), and the Northwest Territories (0.9%) (Table 1). From 2018 to 2021, these provinces accounted for an average of 18% of the Canadian population.¹⁸ For the number and rate of gonorrhoea cases reported to CNDSS among ESAG participating PTs, please see supplementary table C.

Table 1. Number and proportions of primary gonorrhoea cultures submitted by ESAG participating provinces and territories, 2018 to 2021

Province or territory	2018		2019		2020		2021		Total	
	n	%	n	%	n	%	n	%	n	%
Alberta	812	79.5%	803	80.4%	587	82.6%	600	93.0%	2,802	83.0%
Manitoba	174	17.0%	155	15.5%	116	16.3%	39	6.0%	484	14.3%
Nova Scotia	31	3.0%	24	2.4%	1	0.1%	5	0.8%	61	1.8%
Northwest Territories	5	0.5%	17	1.7%	7	1.0%	1	0.2%	30	0.9%
Total	1022	100.0%	999	100.0%	711	100.0%	645	100.0%	3,377	100.0%

4.2. Case characteristics

Characteristics of ESAG cases are summarised in Table 2 and described below.

4.2.1. Sex and sexual behaviour of ESAG cases, 2018 to 2021

From 2018 to 2021, ESAG cases were mostly identified as male (average: 80.2%; range: 78.0% to 82.1%, n= 2709). Among males, an average of 55.5% (range: 51.6% to 59.7%) were GBMSM and 31.7% (range: 29.3% to 35.6%) were heterosexual. Annual proportions for these populations were relatively stable over the years, while the proportion of males with unknown sexual behaviour decreased from 16.8% in 2018 to 4.6% in 2021. An average of 19.1% (n=645) of cases were reported as female. Among female ESAG cases, most reported having sex with male partners (average of 62.2%, range: 55.6% to 68.1%). Females with unknown sexual behaviour ranged from 10.8% (13/120, 2021) to 32.5% (41/126, 2020). Finally, 0.2% (n=8) of ESAG cases were identified as transgender, and 0.2% (n=5) were unknown.

4.2.2. Age distribution among ESAG cases, 2018 to 2021

Between 2018 and 2021, most ESAG cases were between 20 and 39 years of age (average: 72.8%, range: 70.1% to 75.4%). The largest proportion of cases were in the 25-to-29 (average: 22.0%, range: 17.5% to 25.9%) and 30-to-34-year age categories (average: 21.6%, range: 19.0% to 24.4%).

4.2.3. Reason for medical visit among ESAG cases, 2018 to 2021

Between 2018 and 2021, most ESAG cases were tested for gonorrhoea because of experiencing GC signs/symptoms (average: 58.4%; range: 53.2% to 69.0%). This was followed by STI screening

(average: 12.6%; range: 9.0% to 15.0%) and because of case contacting (i.e., were contacted because a sexual partner had tested GC positive) (average: 10.2%; range: 8.4% to 11.8%). Eight cases (four cases in each 2020 and 2021) sought a “test of cure”. There were two cases (one in each 2018 and 2019) who were tested as potential “re-exposures” (Table 3). On average, 18.4% (range: 8.5% to 21.9%) of cases had an unknown reason for medical visit. Heterosexual males, GBMSM, and females, were primarily tested for GC due to signs and symptoms (average: 92.3%, 58.6% and 49.6%, respectively), followed by STI screening (average: 5.9%, 19.7% and 12.0%, respectively).

4.2.4. Primary site of infection among ESAG cases, 2018 to 2021

Between 2018 and 2021, the most common site of infection that corresponded with the primary culture (the primary infection site) varied by sex and sexual behaviour (Table 4). Among GBMSM cases, rectal (average 39.3%, range: 37.4% to 43.7%) and pharyngeal infections (average of 34.6%, range: 25.4% to 38.1%) were more common than genital infections (average of 26.1%, range: 24.6% to 30.8%). In contrast, genital infections were the most reported infection site among heterosexual males (average of 90%, range: 92.1% to 99.5%) and males with unknown sexual behaviour (average of 52.5%, range: 20.0% to 59.5%).

Over the reporting period, there was a decrease in the proportion of males with unknown sexual behaviour that had pharyngeal infections, from 20.9% (29/139) in 2018 to 8.3% (2/24) in 2021. Subsequently, there was an increase in males with unknown sexual behaviour reporting ‘other’ infection sites during this period, from 3.6% (5/139) in 2018 to 37.5% (9/24) in 2021 (Table 4).

Among females, from 2018 to 2021, the most reported primary infection sites were genital (average of 35.2%, range: 31.3% to 41.7%) and pharyngeal (average of 32.4%, range: 30.9% to 33.6%).

Table 2. Sex, sexual behaviour, age distribution and reason for medical visit among ESAG cases, 2018 to 2021

Case characteristics	2018		2019		2020		2021		Total
	n	%	n	%	n	%	n	%	n
Sex^a									
Male	827	80.9%	779	78.0%	584	82.1%	519	80.5%	2709
Female	191	18.7%	217	21.7%	126	17.7%	120	18.6%	654
Transgender ^b	4	0.4%	2	0.2%	0	0.0%	2	0.0%	8
Other ^b	0	0.0%	0	0.0%	1	0.1%	0	0.0%	1
Unknown	0	0.0%	1	0.1%	0	0.0%	4	0.6%	5
Total by sex/gender	1022	100.0%	999	100.0%	711	100.0%	645	100.0%	3377
Sexual Behaviour									
Male sexual behaviour									
GBMSM ^c	443	53.6%	402	51.6%	334	57.2%	310	59.7%	1489
Heterosexual males	245	29.6%	253	32.5%	171	29.3%	185	35.6%	854
Males with unknown sexual behaviour	139	16.8%	124	15.9%	79	13.5%	24	4.6%	366
Total male by sexual behaviour^c	827	100.0%	779	100.0%	584	100.0%	519	100.0%	2709
Female sexual behaviour^d									
Sex with male	130	68.1%	132	60.8%	70	55.6%	77	64.2%	409
Sex with female	2	1.0%	2	0.9%	0	0.0%	1	0.8%	5
Sex with both male and female	30	15.7%	34	15.7%	15	11.9%	29	24.2%	108
Females with unknown sexual behaviour	29	15.2%	49	22.6%	41	32.5%	13	10.8%	132
Total female by sexual behaviour	191	100.0%	217	100.0%	126	100.0%	120	100.0%	654
Sex/sexual behaviour^e									
GBMSM ^c	443	43.3%	402	40.2%	334	47.0%	310	48.1%	1489
Heterosexual male	245	24.0%	253	25.3%	171	24.1%	185	28.7%	854
Males with unknown sexual behaviour	139	13.6%	124	12.4%	79	11.1%	24	3.7%	366
Females	191	18.7%	217	21.7%	126	17.7%	120	18.6%	654
Transgender ^b	4	0.4%	2	0.2%	0	0.0%	2	0.3%	8
Other ^b	0	0.0%	0	0.0%	1	0.1%	0	0.0%	1
Unknown	0	0.0%	1	0.1%	0	0.0%	4	0.6%	5
Total sex/sexual behaviour	1022	100.0%	999	100.0%	711	100.0%	645	100.0%	3377
Age (years)^f									
16-19	29	2.8%	35	3.5%	18	2.5%	16	2.5%	98
20-24	151	14.8%	142	14.2%	104	14.6%	88	13.6%	485
25-29	265	25.9%	213	21.3%	152	21.4%	113	17.5%	743
30-34	197	19.3%	244	24.4%	135	19.0%	153	23.7%	729
35-39	157	15.4%	127	12.7%	120	16.9%	99	15.3%	503
40-44	88	8.6%	105	10.5%	58	8.2%	67	10.4%	318

45-49	54	5.3%	58	5.8%	51	7.2%	47	7.3%	210
50-54	31	3.0%	31	3.1%	28	3.9%	27	4.2%	117
55-59	36	3.5%	28	2.8%	28	3.9%	22	3.4%	114
60+	14	1.4%	15	1.5%	17	2.4%	13	2.0%	59
Total by age group	1022	100.0%	998	99.9%	711	100.0%	645	100.0%	3376
Sex work									
Yes	52	5.1%	49	4.9%	35	4.9%	21	3.3%	157
No	729	71.3%	674	67.5%	460	64.7%	474	73.5%	2337
Unknown	241	23.6%	276	27.6%	216	30.4%	150	23.3%	883
Total by sex work	1022	100.0%	999	100.0%	711	100.0%	645	100.0%	3377

^aSex variable is a mix of sex and gender as some reporting sites provide sex data and some provide gender data or both.

^bThe four transgender cases reported in 2018, all cases of unknown sex, and the other sex case were excluded from all subsequent analyses as cell counts were too low for analysis.

^cOne transgender case who identified as transgender male reported male sexual partners and was categorized as GBMSM.

^dFemale sexual behaviour was not grouped the same way as male sexual behaviour, as treatment recommendations are the same for all females (regardless of sexual behaviour). Hereafter, female data was grouped together.

^eSex/sexual behaviour variable as shown in some ESAG analysis results figures and tables below.

^fAge was not specified for one ESAG case from 2019.

Table 3. Reason for medical visit by sex and sexual behaviour among ESAG cases diagnosed by culture, 2018 to 2021

Reason for medical visit	2018		2019		2020		2021		Total
	n	%	n	%	n	%	n	%	n
GBMSM									
Signs/Symptoms	227	51.2%	201	50.0%	224	67.1%	205	66.1%	857
STI Screening	109	24.6%	105	26.1%	48	14.4%	43	13.9%	305
Case contact	81	18.3%	67	16.7%	46	13.8%	47	15.2%	241
Test of cure	N/A	N/A	N/A	N/A	3	0.9%	4	1.3%	7
Other	0	0.0%	4	1.0%	10	3.0%	7	2.3%	21
Unknown	26	5.9%	25	6.2%	3	0.9%	4	1.3%	58
Total	443	100.0%	402	100.0%	334	100.0%	310	100.0%	1489
Heterosexual males									
Signs/Symptoms	229	93.5%	228	90.1%	161	94.2%	169	91.4%	787
STI Screening	8	3.3%	12	4.7%	4	2.3%	11	5.9%	35
Case contact	3	1.2%	11	4.3%	3	1.8%	5	2.7%	22
Test of cure	N/A	N/A	N/A	N/A	1	0.6%	0	0.0%	1
Other	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0
Unknown	5	2.0%	2	0.8%	2	1.2%	0	0.0%	9
Total	245	100.0%	253	100.0%	171	100.0%	185	100.0%	854

Males with unknown sexual behaviour									
Signs/Symptoms	3	2.2%	1	0.8%	0	0.0%	0	0.0%	4
STI Screening	1	0.7%	1	0.8%	0	0.0%	0	0.0%	2
Case contact	2	1.4%	0	0.0%	0	0.0%	0	0.0%	2
Test of cure	N/A	N/A	N/A	N/A	0	0.6%	0	0.0%	0
Other	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0
Unknown	133	95.7%	122	98.4%	79	100.0%	24	100.0%	358
Total	139	100.0%	124	100.0%	79	100.0%	24	100.0%	366
Female									
Signs/Symptoms	92	48.2%	99	45.8%	58	46.0%	70	58.3%	319
STI Screening	21	11.0%	32	14.8%	12	9.5%	15	12.5%	80
Case contact	35	18.3%	19	8.8%	11	8.7%	14	11.7%	79
Test of cure	N/A	N/A	N/A	N/A	0	0.6%	0	0.0%	0
Other	0	0.0%	1	0.5%	2	1.6%	4	3.3%	7
Unknown	43	22.5%	65	30.1%	43	34.1%	17	14.2%	168
Total	191	100.0%	216	100.0%	126	100.0%	120	100.0%	653
All cases^a									
Signs/Symptoms	551	53.9%	531	53.2%	444	62.4%	445	69.0%	1971
STI Screening	141	13.8%	150	15.0%	64	9.0%	71	11.0%	426
Case contact	121	11.8%	97	9.7%	60	8.4%	69	10.7%	347
Test of Cure	0	0.0%	0	0.0%	4	0.6%	4	0.6%	8
Other	1	0.1%	7	0.7%	12	0.0%	11	0.2%	31
Unknown	208	20.4%	214	21.9%	127	19.5%	45	8.5%	594
Total	1022	100.0%	999	100.0%	711	100.0%	645	100.0%	3377

^a All cases include transgender, other, and unknown sex cases
N/A: Not available

Table 4. Primary site of gonococcal infection overall and by sex/sexual behaviour among ESAG cases diagnosed by culture, 2018 to 2021

Sex / sexual behaviour	2018		2019		2020		2021		Total
	n	%	n	%	n	%	n	%	n
GBMSM									
Rectum	172	38.8%	151	37.6%	146	43.7%	116	37.4%	585
Pharynx	161	36.3%	151	37.6%	85	25.4%	118	38.1%	515
Genital	110	24.8%	99	24.6%	103	30.8%	76	24.5%	388
Other	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0
Unknown	0	0.0%	1	0.2%	0	0.0%	0	0.0%	1
Total	443	100.0%	402	100.0%	334	100.0%	310	100.0%	1489
Heterosexual males									
Rectum	0	0.0%	1	0.4%	0	0.0%	0	0.0%	0
Pharynx	3	1.2%	20	7.9%	4	2.3%	1	0.5%	28
Genital	242	98.8%	232	91.7%	167	97.7%	184	99.5%	825
Other	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0
Unknown	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0
Total	245	100.0%	253	100.0%	171	100.0%	185	100.0%	853
Males with unknown sexual behaviour									
Rectum	32	23.0%	19	15.3%	6	7.6%	0	0.0%	57
Pharynx	29	20.9%	25	20.2	5	6.3%	2	8.3%	61
Genital	70	50.4%	62	50.0%	47	59.5%	12	50.0%	191
Other	5	3.6%	6	4.8%	2	2.5%	9	37.5%	22
Unknown	3	2.2%	12	9.7%	19	24.1%	1	4.2%	35
Total	139	100.0%	124	100.0%	79	100.0%	24	100.0%	366
Female									
Rectum	52	27.2%	57	26.3%	23	18.3%	25	20.8%	157
Pharynx	59	30.9%	73	33.6%	41	32.5%	39	32.5%	212
Genital	67	35.1%	68	31.3%	41	32.5%	50	41.7%	226
Other	8	4.2%	8	3.7%	2	1.6%	4	3.3%	22
Unknown	5	2.6%	11	5.1%	19	15.1%	2	1.7%	37
Total	191	100.0%	217	100.0%	126	100.0%	120	100.0%	654
All cases^a									
Rectum	258	25.2%	229	22.9%	175	24.6%	142	22.0%	804
Pharynx	252	24.7%	269	26.9%	136	19.1%	164	25.4%	821
Genital	490	47.9%	463	46.3%	358	50.4%	323	50.1%	1634
Other	13	1.3%	14	1.4%	4	0.6%	13	2.0%	44
Unknown	9	0.9%	24	2.4%	38	5.3%	3	0.5%	74
Total	1022	100.0%	999	100.0%	711	100.0%	645	100.0%	3377

^a All ESAG cases include transgender, other, and unknown sex cases

4.3. Antimicrobial-use appropriateness

4.3.1. Federal and provincial/territorial gonorrhea treatment guidelines, 2018 to 2021

PHAC has been taking emerging AMR-GC trends into consideration in the ongoing gonorrhea treatment guideline development. From 2018 to 2021, PHAC's gonorrhea treatment guidelines was the version dated July 2017 (Table 5).⁶ PHAC guidelines recommends prescribers follow PT-specific gonorrhea treatment guidelines over their own, as PT-specific guidelines reflect local gonorrhea and AMR-GC trend data. Among ESAG participating PTs, Alberta, Manitoba, and Northwest Territories all have PT specific guidelines, while Nova Scotia follows PHAC's GC treatment guidelines.¹¹⁻¹³

PHAC (and, thus, Nova Scotia), Alberta, and Manitoba's GC treatment recommendations depend on, i) the site of infection: anogenital or pharyngeal and ii) the client's sexual behaviour: GBMSM or other adults (other adults include youth >8 years old and non-GBMSM adults). Furthermore, therapeutic regimens are defined as 'preferred' or 'alternative'. Alternative treatments are recommended when there are contraindications to preferred treatments or if there are indications of emerging resistance or reduced drug supplies. Thus, provided alternative treatment criteria are met, it is appropriate to prescribe either the preferred or alternative therapy to a client. The Northwest Territories treatment guidelines recommend the same preferred and alternative treatment regimens for uncomplicated gonorrhea regardless of the site of infection or the client's sexual behaviour. See supplementary table D for detailed provincial and territorial treatment guidelines.

In general, PHAC and all ESAG participating PT guidelines recommend a preferred or alternative dual therapy consisting of a third-generation cephalosporin (cefixime 800mg or ceftriaxone 250mg) in combination with azithromycin (1g) to treat uncomplicated gonorrhea regardless of the infection site, sexual behaviour, or age of the client.

Table 5. Summary of PHAC’s recommended treatment of uncomplicated anogenital and pharyngeal GC infection, (July 2017 update)

	Anogenital Infections		Pharyngeal Infections	
	Preferred Therapy	Alternative Therapy	Preferred Therapy	Alternative Therapy
GBMSM	Ceftriaxone 250 mg IM ^a + Azithromycin 1 g PO ^a	Cefixime 800 mg PO ^a + Azithromycin 1 g PO ^a OR Cefixime 800 mg PO ^a + Doxycycline 100 mg PO ^b OR Ceftriaxone 250 mg IM ^a + Doxycycline 100 mg PO ^b OR Azithromycin 2 g PO ^a + Gentamicin 240 mg IM/IV ^c OR Gentamicin 240 mg IM ^d + Doxycycline 100 mg PO ^{b, e} OR Azithromycin 2 g PO ^a + Ciprofloxacin 500 mg PO ^{a, f} OR Azithromycin 2 g PO ^a + Gemifloxacin 320 mg PO ^{a, f}	Ceftriaxone 250 mg IM ^a + Azithromycin 1 g PO ^a	Cefixime 800 mg PO ^a + Azithromycin 1 g PO ^a
Other Adults	Ceftriaxone 250 mg IM ^a + Azithromycin 1 g PO ^a Cefixime 800 mg PO ^a + Azithromycin 1g PO ^a	Cefixime 800 mg PO ^a + Doxycycline 100 mg PO ^b OR Ceftriaxone 250 mg IM ^a + Doxycycline 100 mg PO ^b OR Azithromycin 2g PO ^a + Gentamicin 240 mg IM ^{c, d}	Ceftriaxone 250 mg IM ^a + Azithromycin 1 g PO ^a	Cefixime 800 mg PO ^a + Azithromycin 1g PO ^a

	OR Gentamicin 240 mg IM ^d + Doxycycline 100 mg PO ^{b, e} OR Azithromycin 2 g PO ^{a+} Ciprofloxacin 500 mg PO ^{a, f} OR Azithromycin 2 g PO ^{a+} Gemifloxacin 320 mg ^{a, f}		
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Note: PO=taken orally; IM=intramuscular; IV=intravenous

^a single dose.

^b twice daily (BID) for 7 days.

^c Gentamicin 240 mg IV infused over 30 minutes may be considered as an alternative route of administration when the IM route is not feasible.

^d Patients with cephalosporin-resistant *N. gonorrhoeae* or a history of anaphylactic reaction to penicillin or allergy to cephalosporins. Gentamicin 240 mg IM is administered in 2 separate 3-mL injections of 40 mg/mL solution.

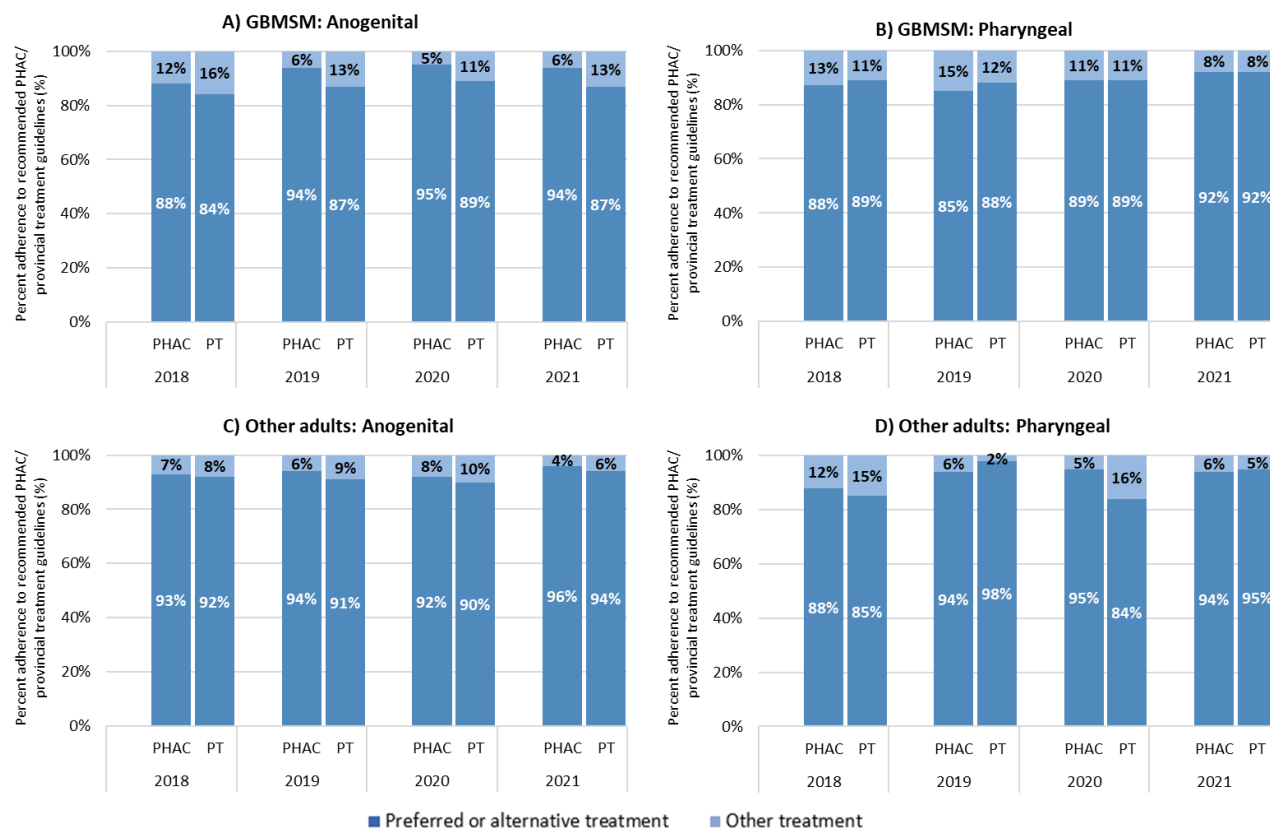
^e Patients with macrolide-resistant *N. gonorrhoeae* or a history of anaphylactic reaction to macrolides, and with contraindications to cephalosporins. Where azithromycin is not used, doxycycline 100 mg orally twice daily for 7 days should be provided unless contraindicated or there is documented tetracycline resistance. Patients should be treated with combination therapy whenever possible. This combination therapy is not recommended in pregnancy.

^f Quinolone treatment regimens. This combination therapy/ regimen should only be used if quinolone susceptibility is demonstrated or regional/ local quinolone resistance rates are under 5%. At the time of publication, gemifloxacin was not available on the Canadian or US market. In the future, gemifloxacin is expected to be marketed in the United States of America, at which time it will be made accessible through Health Canada's Special Access Program.

4.3.2. Antimicrobial-use appropriateness among ESAG cases, 2018 to 2021

ESAG measures the appropriateness of antimicrobial use by comparing the gonorrhoea treatment regimens prescribed to ESAG cases to the treatments recommended in PHAC and reporting PT gonorrhoea treatment guidelines. Adherence to treatment recommendations has been associated with reducing the development of AMR.¹⁹ To date, there is no known target for the ideal proportion of GC treatment guideline prescriber adherence to limit AMR-GC emergence.¹⁹

Figure 1. The proportion of ESAG cases (among all ESAG cases who were prescribed treatment) who were prescribed a PHAC or PT preferred or alternative gonorrhoea treatment regimen versus other prescribed treatment(s) among GBMSM and other adults, 2018 to 2021.



Note: Anogenital infections include rectal, cervical, urogenital and vaginal infections. Pharyngeal infections refer to throat infections. Other treatment includes cases prescribed a regimen that was i) known and was not a preferred or alternative treatment or ii) incomplete or unknown.

Figure 1 shows the proportion of i) GBMSM and ii) other adult ESAG cases who were prescribed a PHAC or reporting PT preferred or alternative treatment regimen (see Tables 6-9 for details) versus all other treatment regimens by infection site. Across the report period, the overall prescriber adherence to PHAC and reporting PT gonorrhoea treatment guidelines was high (average of 91.4% adherence to PHAC guidelines and 89.5% adherence to PT guidelines) and relatively stable (range adherence to guidelines: (PHAC: 88.4% to 94.6%); (PT: 87.3% to 91.6%). Overall, however, prescriber adherence to PT-specific treatment guidelines was slightly lower than to PHAC treatment guidelines.

Results were similar among GBMSM and other adults. Prescriber adherence was mostly stable over time for all groups except for other adults with pharyngeal infections. Across 2018 to 2021, prescriber adherence to PHAC and PT guidelines was high and stable for GBMSM with anogenital

(PHAC average of 92.8%; PT average of 86.7%) and pharyngeal infections (PHAC average of 88.4%; PT average of 89.4%). Prescriber adherence was similarly high among other adults with anogenital (PHAC average of 93.7%; PT average of 91.7%) and pharyngeal infections (PHAC average of 92.8%; PT average of 90.2%).

The following sections summarize the treatment regimens prescribed to ESAG cases, the frequency of these prescriptions, and whether they were recommended as per PHAC or participating PT gonorrhea treatment guidelines. The presented proportions of ESAG cases prescribed a preferred or alternative treatment are conservative.

4.3.2.a. Gonorrhea treatments prescribed among GBMSM cases, 2018 to 2021

Gonorrhea treatments prescribed among GBMSM cases with anogenital or pharyngeal infections

From 2018 to 2021, GBMSM cases were mostly prescribed the PHAC and PT recommended preferred regimen of azithromycin 1 g plus ceftriaxone 250 mg to treat anogenital infections (average: 82.9%; range: 81.4% to 84.3%) (Table 6) and pharyngeal infections (average: 86.7%; range: 85.3% to 90.7%) (Table 7). This was followed by ceftriaxone 250 mg plus doxycycline 100 mg—an alternative treatment regimen listed only in the PHAC GC treatment guidelines for anogenital infections (average: 6.3% range: 4.3% to 9.1%). While not recommended by any guideline for pharyngeal infections, it was also prescribed for pharyngeal infections (average: 4.4%; range: 2.5% to 6.0%). The proportion of GBMSM anogenital cases prescribed the PHAC and PT recommended alternative regimen of azithromycin 1 g plus cefixime 800 mg remained relatively low across all years (average: 3.5%; range: 2.4% to 6.4%). All other prescribed regimens combined accounted for less than 3.8% of GBMSM anogenital cases and 4.4% of GBMSM pharyngeal cases.

Table 6. Treatments prescribed for anogenital GC infections among GBMSM, ESAG 2018 to 2021

Gonorrhea treatment regimen	Preferred (P) or alternative treatment (A) according to PHAC or PT guidelines					Number and proportion of GBMSM cases prescribed treatment for anogenital infections								
						2018		2019		2020		2021		Total
	PHAC	Alta.	Man.	N.S. ^a	N.W.T	n	%	n	%	n	%	n	%	n
Azithromycin 1 g, Ceftriaxone 250 mg	P	P	P	P	P	227	81.4%	210	84.3%	205	82.3%	157	84.0%	799
Ceftriaxone 250 mg, Doxycycline 100 mg	A	NR	NR	A	NR	12	4.3%	15	6.0%	14	5.6%	17	9.1%	58
Other-unspecified	NR	NR	NR	NR	NR	16	5.7%	12	4.8%	7	2.9%	3	1.6%	38
Azithromycin 1 g, Cefixime 800 mg	A	A	A	A	A	7	2.5%	6	2.4%	16	6.4%	5	2.7%	34
Azithromycin 2 g ^b	NR	NR	A	NR	A	6	2.2%	1	0.4%	1	0.4%	2	1.1%	10
Azithromycin 2 g, Other-unspecified	NR	NR	NR	NR	NR	2	0.7%	2	0.8%	1	0.4%	0	0.0%	5
Doxycycline 100 mg	NR	NR	NR	NR	NR	0	0.0%	1	0.4%	1	0.4%	2	1.1%	4
Cefixime 800 mg, Doxycycline 100 mg ^c	A	NR	NR	A	NR	0	0.0%	1	0.4%	1	0.4%	0	0.0%	2
Ceftriaxone 250 mg, Other-unspecified	NR	NR	NR	NR	NR	1	0.4%	0	0.0%	1	0.4%	0	0.0%	2
Azithromycin 1 g, Ceftriaxone 250 mg, Doxycycline 100mg PO BID x 14 days	NR	NR	NR	NR	NR	2	0.7%	0	0.0%	0	0.0%	0	0.0%	2
Azithromycin 1 g, Ceftriaxone 250 mg, Doxycycline 100mg PO BID x 14 days plus Metronidazole 500mg PO BID x 14 days	NR	NR	NR	NR	NR	2	0.7%	0	0.0%	0	0.0%	0	0.0%	2
Benzathine Penicillin G 2,400,000 units	NR	NR	NR	NR	NR	0	0.0%	1	0.4%	1	0.4%	0	0.0%	2
Azithromycin 1 g	NR	NR	NR	NR	NR	1	0.4%	1	0.4%	0	0.0%	0	0.0%	2
Ceftriaxone 250 mg	NR	NR	NR	NR	NR	1	0.4%	0	0.0%	0	0.0%	1	0.5%	2
Azithromycin 2 g, Ceftriaxone 250 mg	NR	NR	NR	NR	NR	1	0.4%	0	0.0%	0	0.0%	0	0.0%	1
Cefixime 800 mg	NR	NR	NR	NR	NR	1	0.4%	0	0.0%	0	0.0%	0	0.0%	1
Total						279	100.0%	249	100.0%	249	100.0%	187	100.0%	964

Note: Preferred is indicated in the table in orange as P, alternative is indicated in blue as A and not recommended is indicated by NR.

^a NS uses PHAC treatment guidelines.

^b Case(s) who were prescribed the treatment regimen did not meet PT specific gonorrhea treatment recommendations.

^c Case(s) who were prescribed the treatment regimen met PT specific gonorrhea treatment recommendations.

Table 7. Treatments prescribed for pharyngeal GC infections among GBMSM, ESAG 2018 to 2021

Gonorrhoea treatment regimen	Preferred (P) or alternative treatment (A) according to PHAC or PT guidelines					Number and proportion of GBMSM cases prescribed treatment for anogenital infections								
						2018		2019		2020		2021		Total
	PHAC	Alta.	Man.	N.S. ^a	N.W.T	n	%	n	%	n	%	n	%	n
Azithromycin 1 g, Ceftriaxone 250 mg	P	P	P	P	P	137	85.6%	128	85.3%	72	85.7%	107	90.7%	444
Ceftriaxone 250 mg, Doxycycline 100 mg	NR	NR	NR	NR	NR	4	2.5%	9	6.0%	4	4.8%	5	4.2%	22
Other-unspecified	NR	NR	NR	NR	NR	8	5.0%	7	4.7%	4	4.8%	2	1.7%	21
Azithromycin 1 g, Cefixime 800 mg	A	A	A	A	A	3	1.9%	0	0.0%	3	3.6%	1	0.8%	7
Azithromycin 2 g ^b	NR	NR	A	NR	A	2	1.3%	2	1.3%	0	0.0%	0	0.0%	4
Azithromycin 2 g, Other-unspecified	NR	NR	NR	NR	NR	1	0.6%	0	0.0%	1	1.2%	0	0.0%	2
Azithromycin 2 g, Gentamicin 240mg IM in 2 separate 3-mL ^c	NR	A	NR	NR	NR	0	0.0%	2	1.3%	0	0.0%	0	0.0%	2
Ceftriaxone 250 mg, Other-unspecified	NR	NR	NR	NR	NR	1	0.6%	0	0.0%	0	0.0%	1	0.8%	2
Doxycycline 100 mg	NR	NR	NR	NR	NR	0	0.0%	0	0.0%	0	0.0%	2	1.7%	2
Azithromycin 1 g	NR	NR	NR	NR	NR	1	0.6%	1	0.7%	0	0.0%	0	0.0%	2
Ceftriaxone 250 mg	NR	NR	NR	NR	NR	1	0.6%	1	0.7%	0	0.0%	0	0.0%	2
Cefixime 800 mg	NR	NR	NR	NR	NR	1	0.6%	0	0.0%	0	0.0%	0	0.0%	1
Azithromycin 1 g, Ceftriaxone 250 mg, Gentamicin 240mg IM in 2 separate 3-mL injections of 40mg/mL solution	NR	NR	NR	NR	NR	1	0.6%	0	0.0%	0	0.0%	0	0.0%	1
Total						160	100.0%	150	100.0%	84	100.0%	118	100.0%	512

Note: Preferred is indicated in the table in orange as P, alternative is indicated in blue as A and not recommended is indicated by NR.

^a NS uses PHAC treatment guidelines.

^b Case(s) who were prescribed the treatment regimen met PT-specific gonorrhoea treatment recommendations.

^c Case(s) who were prescribed the treatment regimen did not meet PT-specific gonorrhoea treatment recommendations.

4.3.2.b. Gonorrhoea treatments prescribed among other adults in ESAG, 2018 to 2021

Gonorrhoea treatments prescribed among other adults include heterosexual males, females, transgender and other sex/gender. Other adults exclude males with unknown sexual behaviour and GBMSM.

Gonorrhoea treatments prescribed among other adults with anogenital infections

Between 2018 and 2021, most other adults with anogenital infections were prescribed the PHAC, Alberta, and Manitoba recommended regimen of cefixime 800 mg with azithromycin 1 g (average of 86.2%; range: 86.4% to 88.4%) (Table 8). This was followed by the PHAC, Manitoba and Nova Scotia alternative preferred regimen, the Northwest Territory's only preferred treatment and Alberta's alternative regimen, azithromycin 1g with ceftriaxone 250 mg (average of 4.1%; range: 3.2% to 5.2%) (Table 8). The combined average (from 2018 to 2021) of reporting for all other unique prescription regimens ranged from 0.1% to 1.8%.

Gonorrhoea treatments among other adults with pharyngeal infections

From 2018 to 2021, the most frequently prescribed therapy among other adults with pharyngeal infections was the alternative regimen of azithromycin 1 g with cefixime 800 mg (average 50.4%; range: 43.2% to 56.3%) which is recommended by all ESAG participating PTs (Table 9). This was followed by the preferred regimen (recommended by all ESAG participating PTs) of azithromycin 1g with ceftriaxone 250 mg (average 39.4%; range: 33.9% to 43.2% (16/37) in 2021). The combined average (from 2018 to 2021) proportion of prescriptions for all other unique treatment regimens ranged from 0.3% to 2.7%.

Table 8. Treatments prescribed for anogenital GC infections among other adults, ESAG 2018 to 2021

Gonorrhea treatment regimen	Preferred (P) or alternative treatment (A) according to PHAC or PT guidelines					Number and proportion of GBMSM cases prescribed treatment for anogenital infections								
						2018		2019		2020		2021		Total
	PHAC	Alta.	Man.	N.S. ^a	N.W.T	n	%	n	%	n	%	n	%	n
Azithromycin 1 g, Cefixime 800 mg	P	P	P	P	A	306	88.4%	299	86.4%	190	86.4%	219	88.0%	1,014
Azithromycin 1 g, Ceftriaxone 250 mg	P	A	P	P	P	11	3.2%	14	4.0%	9	4.1%	13	5.2%	47
Ceftriaxone 250mg, Doxycycline 100mg ^b	A	NR	NR	A	NR	3	0.9%	9	2.6%	4	1.8%	5	2.0%	21
Ceftriaxone 250 mg, Other-unspecified	NR	NR	NR	NR	NR	8	2.3%	0	0%	8	3.6%	1	0.4%	17
Other-unspecified	NR	NR	NR	NR	NR	5	1.4%	3	0.9%	2	0.9%	1	0.4%	11
Azithromycin 1 g	NR	NR	NR	NR	NR	1	0.3%	2	0.6%	2	0.9%	3	1.2%	8
Cefixime 800 mg, Doxycycline 100 mg ^b	A	NR	NR	A	NR	2	0.6%	4	1.2%	0	0%	3	1.2%	9
Azithromycin 2 g, Other-unspecified	NR	NR	NR	NR	NR	2	0.6%	0	0%	3	1.4%	1	0.4%	6
Ceftriaxone 250mg, Doxycycline 100mg with Metronidazole 500mg	NR	NR	NR	NR	NR	0	0%	4	1.2%	0	0%	1	0.4%	5
Azithromycin 2 g ^b	NR	NR	A	NR	A	4	1.2%	1	0.3%	0	0%	0	0%	5
Cefixime 800 mg, Azithromycin 1 g, Benzathine Penicillin G 2,400,000 units	NR	NR	NR	NR	NR	0	0%	3	0.9%	1	0.5%	1	0.4%	5
Azithromycin 2 g, Gentamicin 240mg IM in 2 separate 3-mL injections of 40mg/mL solution ^c	A	A	NR	A	NR	0	0%	2	0.6%	0	0%	1	0.4%	3
Azithromycin 1 g, Other-unspecified	NR	NR	NR	NR	NR	0	0%	2	0.6%	0	0%	0	0%	2
Azithromycin 1 g, Cefixime 800 mg, Doxycycline 100mg PO BID x 14 days	NR	NR	NR	NR	NR	2	0.6%	0	0%	0	0%	0	0%	2
Benzathine Penicillin G 2,400,000 units	NR	NR	NR	NR	NR	0	0.0%	0	0.0%	1	0.5%	0	0%	1
Levofloxacin 500mg PO OD x 14 days with metronidazole 500mg PO BID x 14 days ^a	NR	NR	NR	NR	NR	0	0%	1	0.3%	0	0%	0	0%	1
Azithromycin 2g, Gemifloxacin 320mg PO SD ^d	A	A	NR	A	NR	0	0%	1	0.3%	0	0%	0	0%	1
Ceftriaxone 250 mg	NR	NR	NR	NR	NR	0	0%	1	0.3%	0	0%	0	0%	1
Cefixime 800 mg	NR	NR	NR	NR	NR	1	0.3%	0	0%	0	0%	0	0%	1
Cefixime 400 mg	NR	NR	NR	NR	NR	1	0.3%	0	0%	0	0%	0	0%	1
Total						346	100%	346	100%	220	100%	249	100%	1,161

Note: Preferred is indicated in the table in orange as P, alternative is indicated in blue as A and not recommended is indicated by NR.

^a NS uses PHAC treatment guidelines

^b Case(s) who were prescribed the treatment regimen did not meet PT-specific gonorrhea treatment recommendations.

^c Three cases in 2018 were excluded, as treatment was left blank.

^d Case(s) who were prescribed the treatment regimen met PT-specific gonorrhea treatment recommendations.

Table 9. Treatments prescribed for pharyngeal GC infections among other adults, ESAG 2018 to 2021

Gonorrhea treatment regimen	Preferred (P) or alternative (A) according to PT Guidelines					Number and proportion of other adult cases prescribed treatment for pharyngeal infections								
						2018		2019		2020		2021		Total
	PHAC	Alta.	Man.	N.S. ^a	N.W.T	n	%	n	%	n	%	n	%	n
Azithromycin 1 g, Cefixime 800 mg	A	A	A	A	A	30	50.8%	49	56.3%	19	43.2%	19	51.4%	117
Azithromycin 1 g, Ceftriaxone 250 mg	P	P	P	P	P	20	33.9%	36	41.4%	18	40.9%	16	43.2%	89
Other-unspecified	NR	NR	NR	NR	NR	1	1.7%	1	1.1%	2	4.5%	1	2.7%	5
Ceftriaxone 250 mg, Doxycycline 100 mg	NR	NR	NR	NR	NR	0	0.0%	0	0.0%	2	4.5%	1	2.7%	5
Azithromycin 2 g, Other-unspecified	NR	NR	NR	NR	NR	2	3.4%	0	0.0%	1	2.3%	0	0.0%	3
Azithromycin 2 g ^b	NR	NR	A	NR	A	2	3.4%	0	0.0%	0	0.0%	0	0.0%	2
Ceftriaxone 250 mg, Other-unspecified	NR	NR	NR	NR	NR	2	3.4%	0	0.0%	1	2.3%	0	0.0%	1
Azithromycin 1 g, Cefixime 800 mg, Doxycycline 100mg PO BID x 14 days	NR	NR	NR	NR	NR	1	1.7%	0	0.0%	0	0.0%	0	0.0%	1
Azithromycin 1 g, Ceftriaxone 250 mg, Cefixime 800 mg, Penicillin 600 mg, BID x 10 days	NR	NR	NR	NR	NR	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1
Azithromycin 1 g	NR	NR	NR	NR	NR	0	0.0%	0	0.0%	1	2.3%	0	0.0%	1
Ceftriaxone 250 mg	NR	NR	NR	NR	NR	1	1.7%	0	0.0%	0	0.0%	0	0.0%	1
Total						59	100.0%	87	100.0%	44	100.0%	37	100.0%	226

Note: Preferred is indicated in the table in orange as P, alternative is indicated in blue as A and not recommended is indicated by NR.

^a NS uses PHAC treatment guidelines.

^b Case(s) who received the treatment regimen did not meet PT specific gonorrhea treatment recommendations.

4.3.2.c. Gonorrhea treatment among males with unknown sexual behaviour in ESAG, 2018 to 2021

Treatments prescribed for males with unknown sexual behaviour are listed in supplementary table E. These cases were primarily reported by Manitoba (88.6%, 171/193). Most males with unknown sexual behaviour who had anogenital infections were prescribed azithromycin 1 g plus cefixime 800 mg (average: 41.3%). The second most common treatment prescribed for this group, was azithromycin 1 g plus ceftriaxone 250 mg (average: 22.2%). Males with unknown sexual behaviour who had pharyngeal infections were primarily prescribed either the preferred or alternative treatment regimens (average: 90.2%).

4.3.3. Gonorrhoea treatment failure among ESAG cases, 2018 to 2021

Between 2018 and 2021, there were 14 ESAG cases reported as GC treatment failures (6/956 (0.6%) in 2018 and 8/935 (0.9%) in 2019; 92.8% (13) cases were male, 64.3% (nine) cases were GBMSM; 78.6% (11) were anogenital infections). Six cases were prescribed azithromycin 1 g and cefixime 800 mg, five cases ceftriaxone 250 mg and azithromycin 1 g, one case azithromycin 1 g, one case azithromycin 2 g and gentamicin 240 mg, and one case had unspecified treatment. Of the 13 reported treatment failures with available prescription data, none demonstrated decreased susceptibility/resistance to all treatments in their prescribed regimen; thus, none were confirmed treatment failures (supplementary table F). The case with unspecified treatment was resistant to ciprofloxacin, penicillin, and tetracycline. As none of these drugs are among the most recommended and prescribed therapies, it is unlikely that this case was a true treatment failure. The reported treatment failures may have been re-infections or individuals who did not take their treatment as prescribed.

4.3.4. Antimicrobial susceptibility among ESAG cases, 2018 to 2021

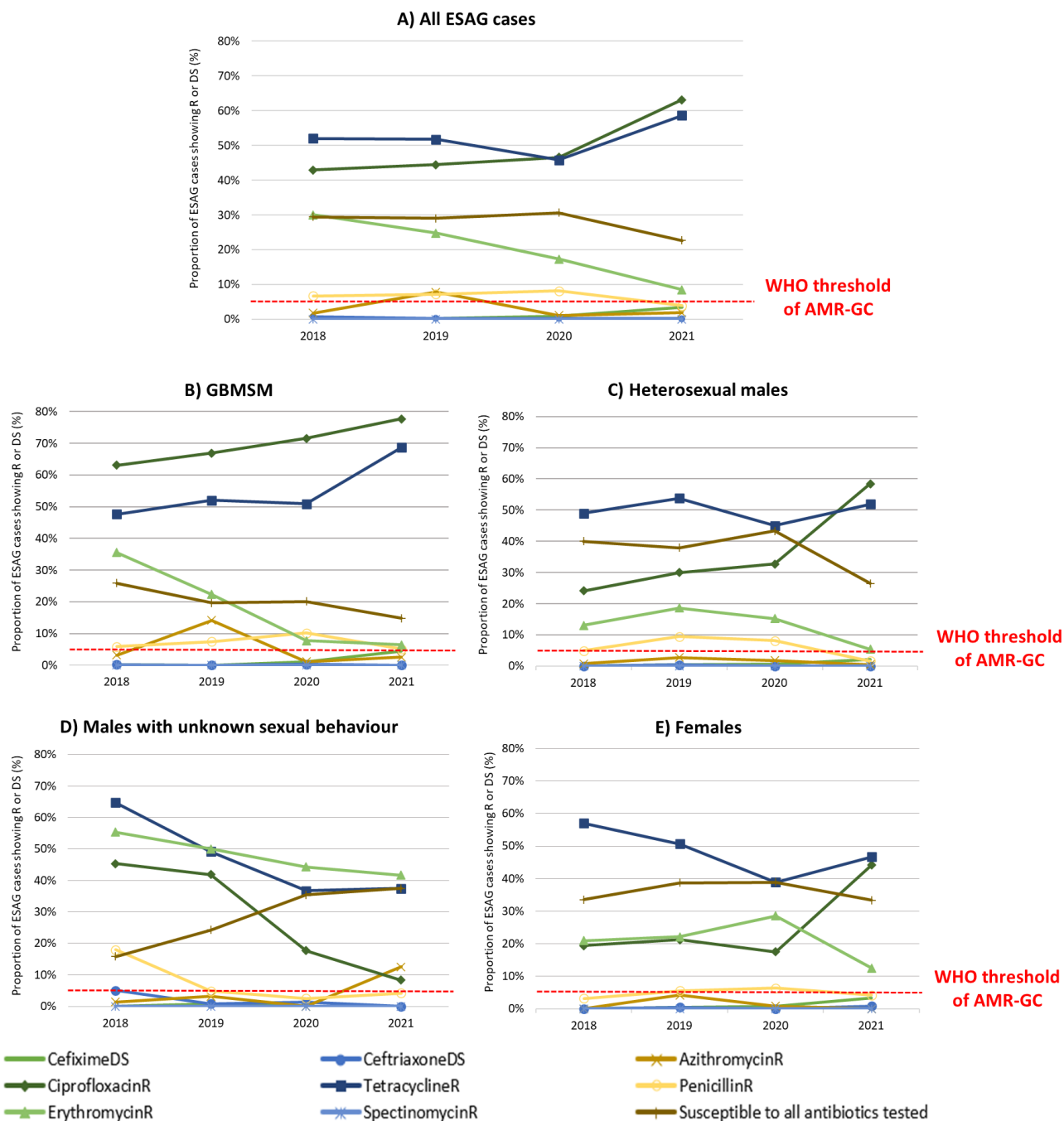
4.3.4.a. AMR-GC burden among ESAG cases and by sex/sexual behaviour

The proportion of ESAG cases with cultures that were susceptible to all tested antimicrobials (i.e., azithromycin, ceftriaxone, cefixime, ciprofloxacin, erythromycin, penicillin, spectinomycin and tetracycline) was relatively stable from 2018 to 2020 and was an average of 29.6% from 2018 to 2021 (Figure 2A, Figure 3A, Table 10). (For a breakdown by PT, please see Appendix 3). Among all ESAG cases, GBMSM had the highest burden of AMR-GC compared to heterosexual males, males with unknown sexual behaviour and females (Figures 2B-2E and 3B-3E). Among GBMSM, the proportion susceptible to all antibiotics declined from 25.9% in 2018 to 14.8% in 2021 (42.9% decline). Among heterosexual males, the proportion susceptible to all antibiotics was an average of 40.0% from 2018 to 2020 but dropped sharply to only approximately a quarter of the population (26.5%) in 2021 (Figures 2B and 3B). In contrast, among males with unknown sexual behaviour group, the proportion susceptible to all antibiotics increased from 15.8% in 2018 to 37.5% in 2021

(Figure 2D and 3D). Meanwhile, among females, the proportion susceptible to all antibiotics has fluctuated mildly from 2018 to 2021 (four-year average of 36.1%) (Figure 2E and 3E).

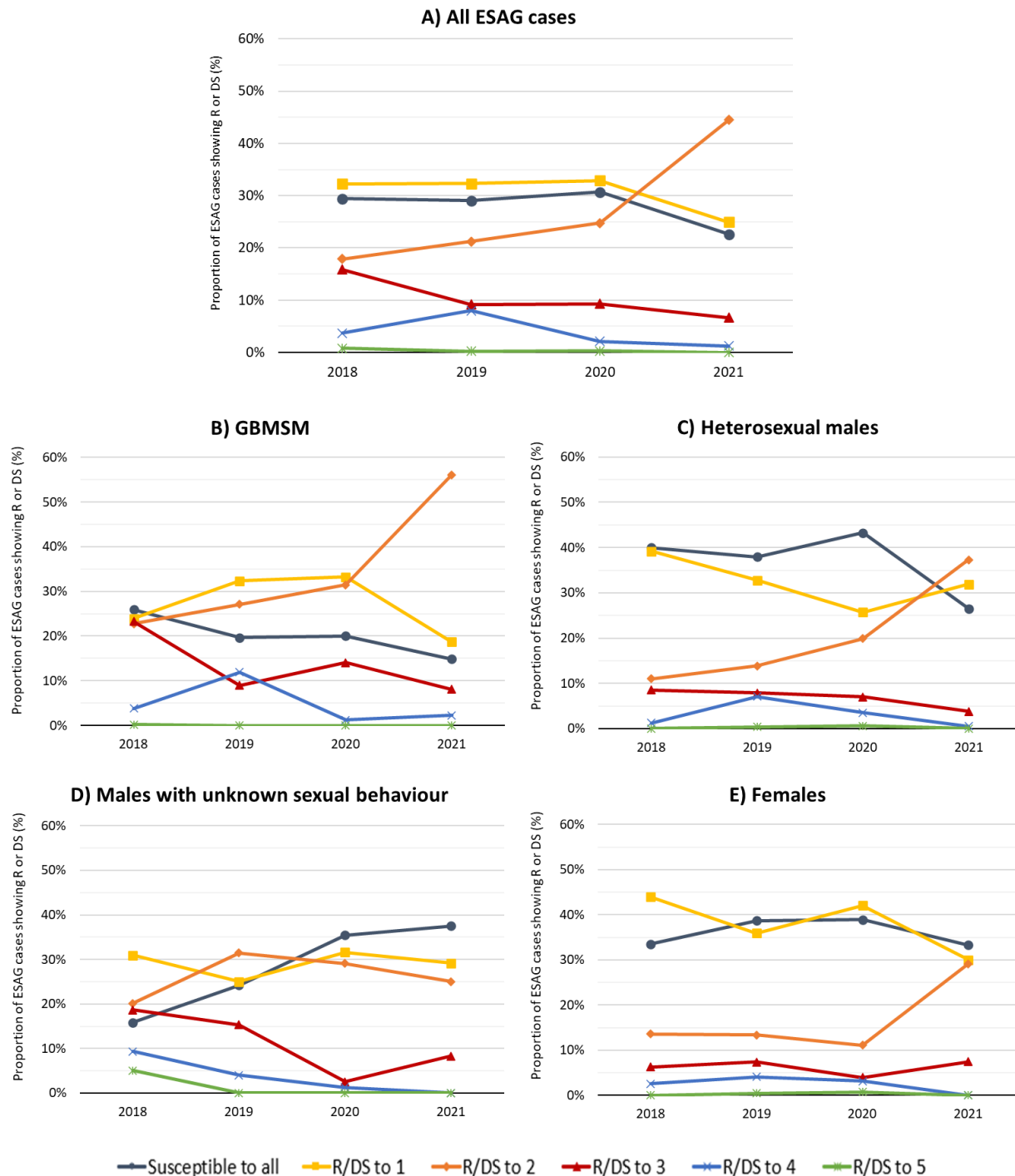
From 2020 to 2021, the proportion of cases with resistance or decreased susceptibility (R/DS) to two antimicrobials sharply increased among GBMSM (from 31.4% in 2020 to 56.1% in 2021) and heterosexual males (from 19.9% in 2020 to 37.3% in 2021), and females (from 11.1% in 2020 to 29.2% in 2021) (Figure 3B, 3C, and 3E). For a further breakdown of antimicrobial susceptibility data overall, by sex, sexual behaviour and infection site, see Supplementary tables G-I.

Figure 2. Proportion of ESAG cultures demonstrating resistance (R) to azithromycin, ciprofloxacin, erythromycin, spectinomycin, penicillin, or tetracycline or decreased susceptibility (DS) to cefixime and ceftriaxone, among all ESAG cases and by sex/sexual behaviour, 2018 to 2021



NB: The red dashed line represents the World Health Organization's (WHO) threshold of AMR-GC concern $\geq 5\%$: The resistance level at which WHO recommends that the use of an antimicrobial in empiric treatment is discontinued.²⁰

Figure 3. Proportion of ESAG cases with GC cultures demonstrating resistance (R) and/or decreased susceptibility (DS) to none or up to five antimicrobials^a, among all ESAG cases and by sex/sexual behaviour, 2018 to 2021



^aGC cultures were tested for resistance to azithromycin, ciprofloxacin, erythromycin, penicillin, spectinomycin and tetracycline and decreased susceptibility to cefixime and ceftriaxone.

4.3.4.b. AzithromycinR, cefiximeDS, and ceftriaxoneDS among all ESAG cultures and by sex/sexual behaviour

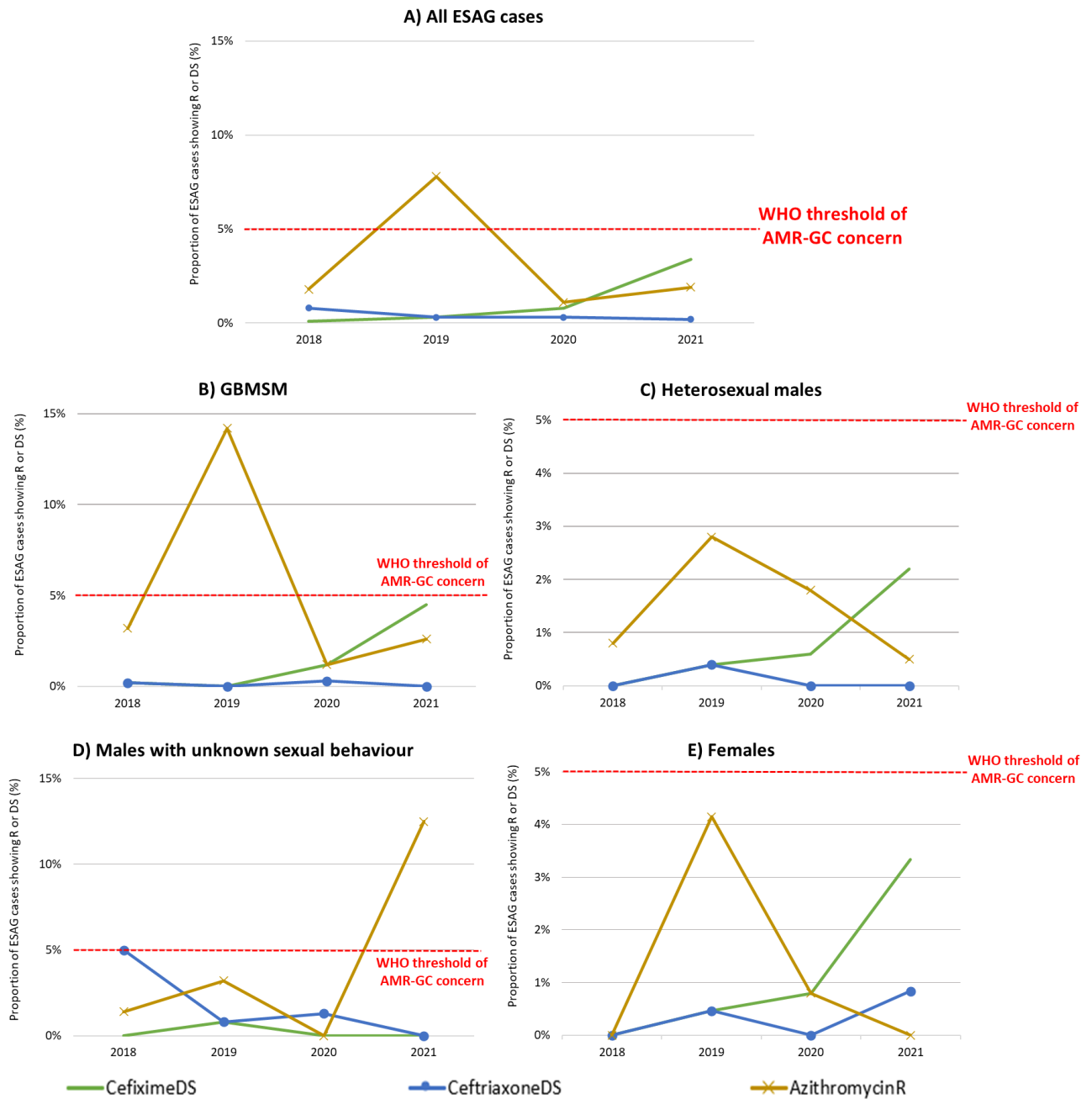
From 2018 to 2021, no cultures demonstrated azithromycinR and cefiximeDS or azithromycinR and ceftriaxoneDS (the most recommended and prescribed antimicrobial regimens) (Table 10). In general, azithromycinR, cefiximeDS, and ceftriaxoneDS prevalence was low across the reporting years (Figure 4A, Table 10). From 2018 to 2020, the prevalence of cefiximeDS was <1% and stable. However, from 2020 to 2021, the number (and proportion) of ESAG cultures demonstrating cefiximeDS increased nearly threefold from six (0.8%) in 2020 to 22 (3.4%) in 2021. In contrast, cultures demonstrating ceftriaxoneDS declined in number and proportion from 8 (0.8%) in 2018 to one (0.2%) in 2021. The frequency of cultures that demonstrated azithromycinR increased from 18 (1.8%) in 2018 to 78 (7.8%) in 2019. However, this number decreased sharply to eight (1.1%) in 2020 and 12 (1.9%) in 2021.

Figure 4B-4E shows a close-up of the within group proportions of azithromycinR, cefiximeDS and ceftriaxoneDS by sex/sexual behaviour (see supplementary table G). From 2018 to 2019, the prevalence of azithromycinR cultures increased, but this was followed by a sharp decline in azithromycinR prevalence in 2020 and 2021 among GBMSM (3.2% in 2018, 14.2% in 2019, 1.2% in 2020, 2.6% in 2021), heterosexual males (0.8% in 2018, 2.8% in 2019, 1.8% in 2020, 0.5% 2021) and females (0.0% in 2018, 4.1% in 2019, 0.8% in 2020, 0.0% in 2021). In contrast, the prevalence of azithromycinR in cultures isolated from males with unknown behaviour was very low from 2018 to 2020 but then increased from 0.0% in 2020 to 12.5% (3/24 cases) in 2021.

The within sex/sexual behaviour group prevalence of ceftriaxoneDS, was very low, <0.9%, for all years, except in 2018, when the proportion was 5.0% in cultures isolated from males with unknown sexual behaviour. The prevalence of cefiximeDS was also relatively low (<5%) for all sex/sexual behaviour groups, but there was a trend of increasing cefiximeDS across the years among GBMSM (0.2% in 2018 to 4.5% in 2021), heterosexual males (0.0% in 2018 to 2.2% in 2021) and females (0.0% in 2018 to 3.3% in 2021) but not among males with unknown sexual behaviour.

Among cases who identified as transgender or were of unknown or other gender/sex, there were no cultures identified as azithromycinR, cefiximeDS or ceftriaxoneDS (results not shown).

Figure 4. Proportion of ESAG cases with cultures demonstrating resistance (R) to azithromycin or decreased susceptibility (DS)^a to cefixime and ceftriaxone, among all ESAG cases and by sex/sexual behaviour, 2018 to 2021



^a R/DS: Resistant or decreased susceptibility.

NB: The red dashed line represents the World Health Organization's (WHO) threshold of AMR-GC concern $\geq 5\%$: The resistance level at which WHO recommends that the use of an antimicrobial in empiric treatment is discontinued.²⁰

Table 10. Number and proportion of ESAG cases with cultures demonstrating R/DS^a to the most prescribed gonorrhoea treatment combinations (azithromycin and cefixime or ceftriaxone), 2018 to 2021

Antimicrobial R/DS	2018		2019		2020		2021		Total
	n	%	n	%	n	%	n	%	n
AzithromycinR + CefiximeDS	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0
AzithromycinR + CeftriaxoneDS	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0
CefiximeDS + CeftriaxoneDS	1	0.1%	3	0.3%	1	0.1%	1	0.2%	6
Total	1		3		1		1		6

^a R/DS: Resistance or decreased susceptibility

4.3.4.c. The most prevalent resistant antimicrobials and other antimicrobial resistance trends among all ESAG cases and by sex/sexual behaviour

Among all ESAG cultures, between 2018 and 2020, of all the tested antimicrobials, ciprofloxacin resistance (ciprofloxacinR) was most prevalent at 46.6% in 2020 increasing to 63.1% in 2021, followed by tetracycline resistance (tetracyclineR) at 45.9% in 2020 and 58.6% in 2021 (Figure 3A, Table 10). Prior to this, tetracyclineR was most prevalent at 52.1% in 2018 and 51.8% in 2019, followed by ciprofloxacinR. Erythromycin resistance (erythroymicR) has declined annually and sharply from 30.0% in 2018 to 8.5% in 2021. Penicillin resistance rates were relatively stable from 2018 to 2020 (6.8% in 2018, 7.2% in 2019 and 8.2% in 2020) but dropped to 3.9% in 2021.

By sex and sexual behaviour (Fig 3B-3E), in 2021, the within group proportions of ciprofloxacinR and tetracyclineR were highest among cultures collected from GBMSM (77.7% ciprofloxacin; 68.7% tetracycline; increasing proportions over time, see supplementary tables G and I), heterosexual males (58.4% ciprofloxacin; 51.9% tetracycline) and females (44.2% ciprofloxacin; 46.7% tetracycline). ErythromycinR was most prevalent in cultures isolated from males with unknown sexual behaviour (this group has showed sharp declines in the prevalence of ciprofloxacinR and tetracyclineR over time). Antimicrobial resistance was similar by infection site among GBMSM and other adults (supplementary table I).

4.3.5. Case characteristics and sequence types of ESAG cases with cultures demonstrating azithromycinR, cefiximeDS, or ceftriaxoneDS, 2018 to 2021

4.3.5.a. Case characteristics and sequence types of ESAG cases with cultures demonstrating azithromycinR

Between 2018 and 2021, there were 116 ESAG cases with *N. gonorrhoeae* cultures demonstrating azithromycinR (Table 11). Most of these cultures were collected from males (90.5%, (105/116)); of which, 79.0% (83) were GBMSM, 34.6% (44) were 30-39 years old, and 61.9% (65) reported anogenital infections. One case (1.3%, 1/78), in 2019, was reported as a suspected treatment failure. Most cases were observed in 2019 (78/116, 67.2% of total isolates with azithromycinR).

Table 11. Characteristics of ESAG cases with GC cultures demonstrating azithromycinR, 2018 to 2021

	2018		2019		2020		2021		Total	
	n	%	n	%	n	%	n	%	n	%
Isolates with azithromycinR	18	1.8%	78	7.8%	8	1.1%	12	1.9%	116	3.4%
Total isolates	1022	100.0%	999	100.0%	711	100.0%	645	100.0%	3377	100.0%
Sequence type (ST)										
ST-12302	4	22.2%	33	42.3%	3	37.5%	0	0.0%	40	34.5%
ST-16288	3	16.7%	20	25.6%	1	12.5%	0	0.0%	24	20.7%
ST-3935	1	5.6%	5	6.4%	0	0.0%	0	0.0%	6	5.2%
ST-11508	0	0.0%	2	2.6%	0	0.0%	2	16.7%	4	3.4%
ST-11724	0	0.0%	0	0.0%	0	0.0%	4	33.3%	4	3.4%
ST-14698	3	16.7%	1	1.3%	0	0.0%	0	0.0%	4	3.4%
ST-4357	1	5.6%	2	2.6%	0	0.0%	0	0.0%	3	1.7%
STs not listed (≤ 2 or unknown) ^a	6	33.3%	15	23.1%	4	50.0%	6	50.0%	31	19.0%
Total AzithromycinR	18	100.0%	78	100.0%	8	100.0%	12	100.0%	116	100.0%
Sex/Gender										
Male	18	100.0%	68	87.2%	7	87.5%	12	100.0%	105	90.5%
Female	0	0.0%	9	11.5%	1	12.5%	0	0.0%	10	8.6%
Total AzithromycinR	18	100.0%	78	100.0%	8	100.0%	12	100.0%	116	100.0%
Male sexual behaviour										
GBMSM	14	77.8%	57	83.8%	4	57.1%	8	66.7%	83	79.0%
Heterosexual males	2	11.1%	7	10.3%	3	42.9%	1	8.3%	13	12.4%
Males with unknown sexual behaviour	2	11.1%	4	5.1%	0	0.0%	3	25.0%	9	8.6%
Total Male AzithromycinR	18	100.0%	68	100.0%	7	100.0%	12	100.0%	105	100.0%
Female sexual behaviour										
Sex with both male and female	0	0.0%	1	11.1%	0	0.0%	0	0.0%	1	10.0%
Sex with female	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Sex with male	0	0.0%	4	44.4%	1	100.0%	0	0.0%	5	50.0%
Females with unknown sexual behaviour	0	0.0%	4	44.4%	0	0.0%	0	0.0%	4	40.0%
Total Female AzithromycinR	0	0.0%	9	100.0%	1	100.0%	0	0.0%	10	100.0%

Sex/Gender and Age										
Male (years old)										
< 20	0	0.0%	1	1.5%	0	0.0%	0	0.0%	1	1.0%
20-29	6	33.3%	23	33.8%	2	28.6%	5	41.7%	36	25.0%
30-39	8	44.4%	26	38.2%	4	57.1%	6	50.0%	44	34.6%
40-49	4	22.2%	12	17.6%	0	0.0%	1	8.3%	17	12.5%
50-59	0	0.0%	6	8.8%	1	14.3%	0	0.0%	7	6.7%
60+	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total Male AzithromycinR	18	100.0%	68	100.0%	7	87.5%	12	100.0%	105	100.0%
Female (years old)										
< 20	0	0.0%	3	33.3%	0	0.0%	0	0.0%	3	33.3%
20-29	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
30-39	0	0.0%	3	33.3%	1	100.0%	0	0.0%	4	44.4%
40-49	0	0.0%	1	11.1%	0	0.0%	0	0.0%	1	11.1%
50-59	0	0.0%	2	22.2%	0	0.0%	0	0.0%	2	11.1%
60+	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total Female AzithromycinR	0	0.0%	9	100.0%	1	100.0%	0	0.0%	10	100.0%
Infection type										
Male										
Anogenital	10	55.6%	45	66.2%	5	71.5%	5	41.7%	65	61.9%
Pharyngeal	8	44.4%	23	33.8%	2	28.5%	5	41.7%	38	36.2%
Unspecified	0	0.0%	0	0.0%	0	0.0%	2	16.7%	2	1.9%
Total Male AzithromycinR	18	100.0%	68	100.0%	7	100.0%	12	100.0%	105	100.0%
Female										
Anogenital	0	0.0%	5	55.5%	0	0.0%	0	0.0%	5	50.0%
Pharyngeal	0	0.0%	3	33.3%	1	12.5%	0	0.0%	4	40.0%
Unspecified	0	0.0%	1	11.1%	0	0.0%	0	0.0%	1	10.0%
Total Female AzithromycinR	0	0%	9	100.0%	1	100.0%	0	0.0%	10	100.0%
Province or territory										
Alberta	13	72.2%	67	85.9%	8	100.0%	9	75.0%	97	83.6%
Manitoba	3	16.7%	7	9.0%	0	0.0%	3	25.0%	13	11.2%
Nova Scotia	2	11.1%	4	5.1%	0	0.0%	0	0.0%	6	5.2%
Northwest territories	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total AzithromycinR	18	100.0%	78	100.0%	8	100.0%	12	100.0%	116	100.0%
Suspected treatment failure ^b										
Yes	0	0.0%	1	1.3%	0	0.0%	0	0.0%	1	0.9%
No	18	100.0%	77	98.7%	8	100.0%	12	100.0%	115	98.3%
Total AzithromycinR	18	100.0%	78	100.0%	8	100.0%	12	100.0%	116	100.0%

^a For a list of the additional STs that showed R to Azithromycin, please see supplementary table J.

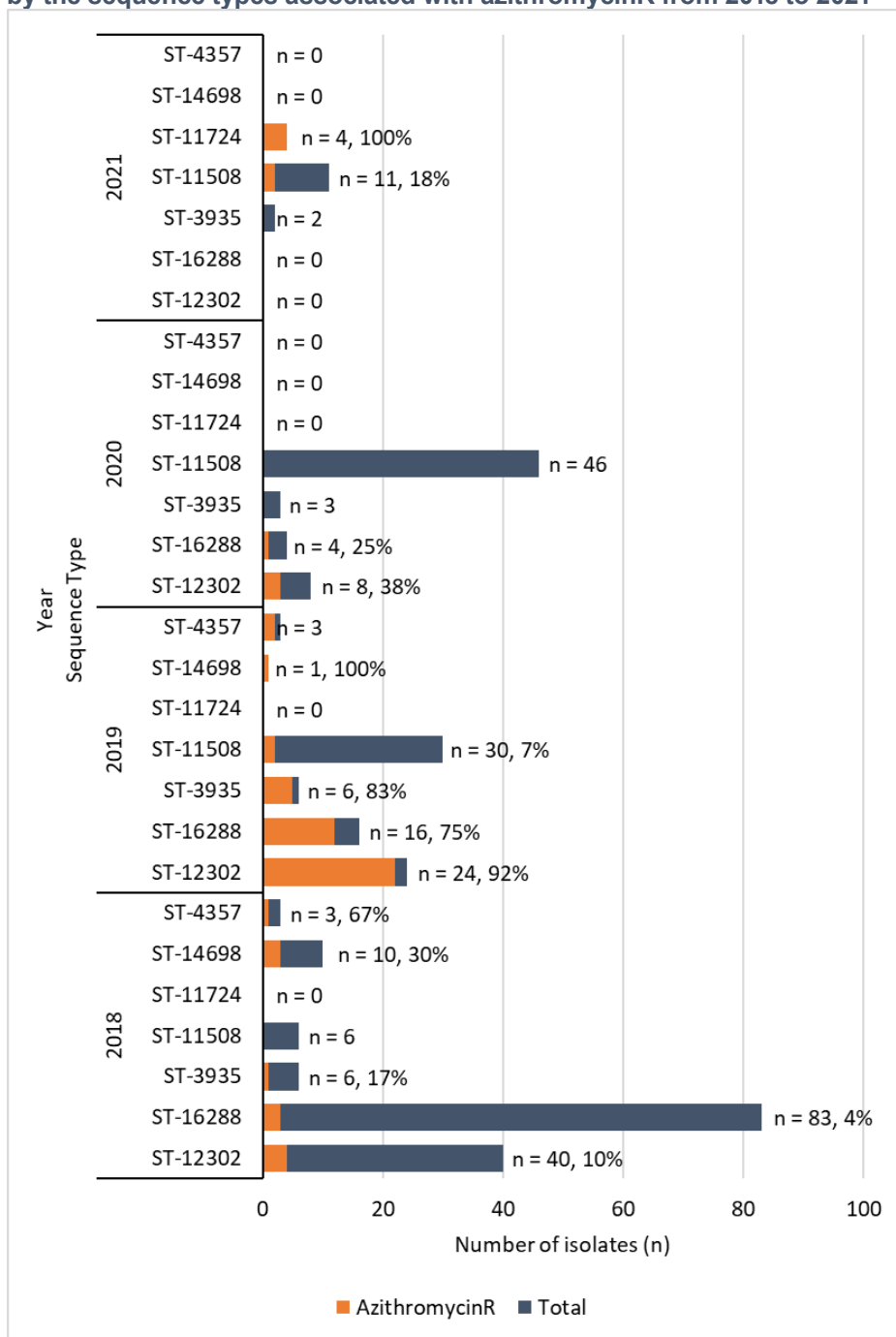
^b Suspected treatment failure is a public health report of treatment failure. It is not confirmed with laboratory testing.

There were 31 typable sequence types with azithromycinR identified between 2018 and 2021 (supplementary table J). Table 11 and Figure 5 shows the seven most common sequence types (STs) (i.e., STs associated with azithromycinR in more than two ESAG cases). The most identified NG-MAST ST was ST-12302, followed by ST-16288. These two STs accounted for 85.2% of all azithromycinR cases from 2018 to 2021 (Table 11).

In 2018, ST-16288 and ST-12302 were identified in 83 and 40 isolates, respectively (Figure 5). However, only 4% and 10% of these isolates, respectively, were identified as azithromycinR. In 2019, these STs were identified much less frequently (in 16 and 24 isolates, respectively); however, the majority of these isolates demonstrated azithromycinR (75.0% and 92.0%, respectively). The prevalence of these STs dwindled in 2020 to four and eight isolates, respectively, in 2020 and zero in 2021.

In 2021, ST-11724 was identified for the first time (since 2018) in only four isolates but 100.0% of these isolates were azithromycinR. ST-11508 (in the top ten STs identified among ESAG cases in 2019, 2020 and 2021) was present in all reporting years, but it was only in 2019 and 2021 that the ST demonstrated azithromycinR in 6.7% (2/30) and 18.2% (2/11) of isolates with this ST, respectively. All other STs associated with azithromycinR occurred infrequently and varied highly by year (Figure 5).

Figure 5. The number and proportion of ESAG cases with GC cultures demonstrating azithromycinR by the sequence types associated with azithromycinR from 2018 to 2021



Note: This figure shows the most frequently observed STs associated with AzithromycinR (among all ESAG isolates collected from 2018 to 2021), for a given calendar year. The total number of ESAG cultures with a given ST is shown in grey and the number of isolates (for a given ST) with AzithromycinR are shown in yellow. The data labels on the bars are the proportion of isolates that demonstrated AzithromycinR for each ST.

4.3.5.b. Case characteristics and sequence types of ESAG cases with cultures demonstrating cefiximeDS

Between 2018 and 2021, there were 32 ESAG cases with GC cultures demonstrating cefiximeDS (Table 12). Among these, 81.3% (26) of cultures were collected from males, of which 73.1% (19) were GBMSM and 23.1% (6) were heterosexual. Therefore, the burden of cefiximeDS was slightly higher among GBMSM compared to baseline ESAG characteristics. Of the six (18.8%) female cases with cultures demonstrating cefiximeDS, five (83.3%) were females who had sex with males. CefiximeDS was most frequently observed among males 30-39 years old (38.5%, 10 cases) and 40-49 years old (26.9%, 7 cases) and females between 20-29 years old (50.0%). The primary infection site varied between males and females; among male cases with cefiximeDS cultures, 18 (69.2%) reported an anogenital infection, while five female cases (83.3%) reported a pharyngeal infection.

Of the 11 NG-MAST STs associated with cefiximeDS, ST-17261 was identified most frequently. It was first observed in cultures from four ESAG cultures in 2020, which accounted for 66.7% of the cefiximeDS cultures typed in 2020. In 2021, it was observed in 11 cultures (50.0% of the cefiximeDS cultures typed in that year) (Table 12). However, among the 94 isolates (out of 3,377 isolates) with the ST-17261, cefiximeDS was detected in zero cultures in 2018, 9.5% (4/42) in 2020 and 22.4% (11/49) in 2021 (Figure 6). All other STs associated with cefiximeDS occurred infrequently and varied highly by year.

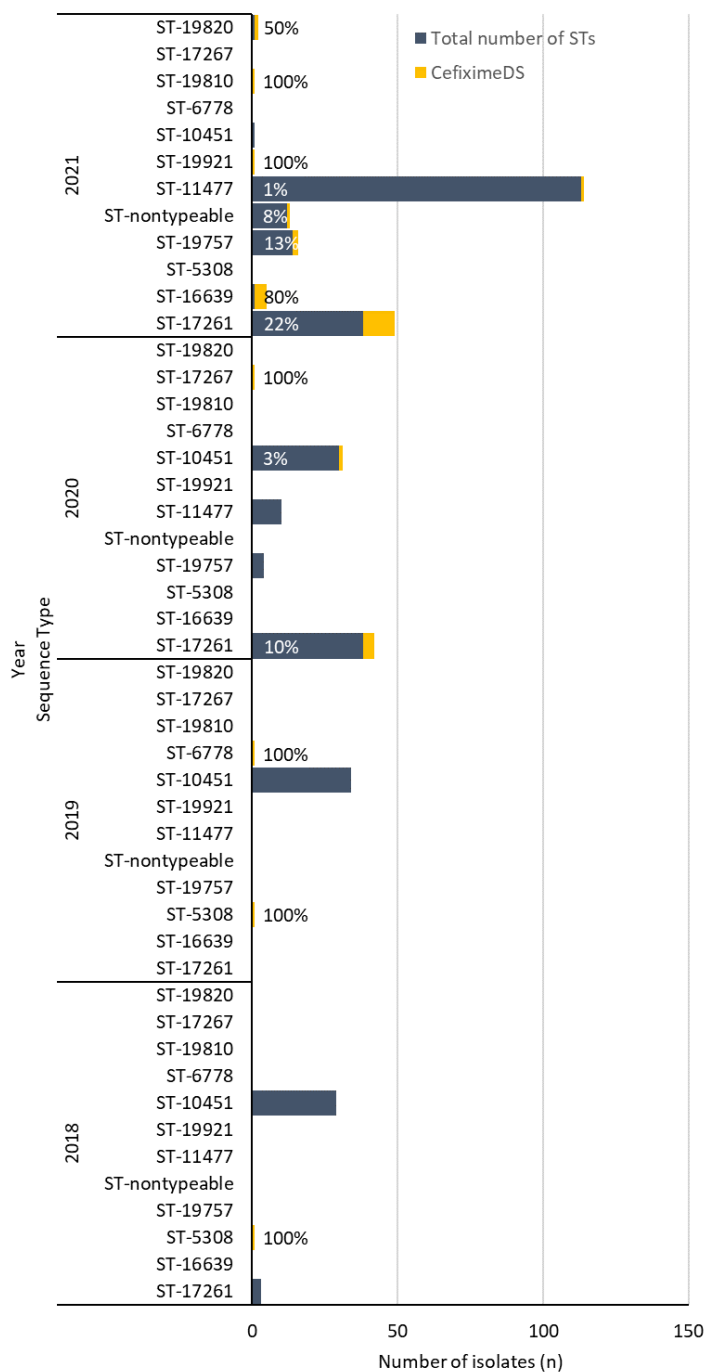
Table 12. Characteristics of ESAG cases with GC cultures demonstrating cefiximeDS, 2018 to 2021

	2018		2019		2020		2021		Total	
	n	%	n	%	n	n	%	n	%	n
Isolates with cefiximeDS	1	0.1%	3	0.3%	6	80.0%	22	410.0%	32	0.9%
Total isolates	1022	100.0%	999	100.0%	711	100.0%	645	100.0%	3377	100.0%
Sequence type										
ST-17261	0	0.0%	0	0.0%	4	66.7%	11	50.0%	15	46.9%
ST-16639	0	0.0%	0	0.0%	0	0.0%	4	18.2%	4	12.5%
ST-5308	1	100.0%	2	66.7%	0	0.0%	0	0.0%	3	9.4%
ST-19757	0	0.0%	0	0.0%	0	0.0%	2	9.1%	2	6.3%
ST-nontypeable	0	0.0%	0	0.0%	0	0.0%	1	4.5%	1	3.1%
ST-11477	0	0.0%	0	0.0%	0	0.0%	1	4.5%	1	3.1%
ST-19921	0	0.0%	0	0.0%	0	0.0%	1	4.5%	1	3.1%
ST-10451	0	0.0%	0	0.0%	1	16.7%	0	0.0%	1	3.1%
ST-6778	0	0.0%	1	33.3%	0	0.0%	0	0.0%	1	3.1%
ST-19810	0	0.0%	0	0.0%	0	0.0%	1	4.5%	1	3.1%
ST-17267	0	0.0%	0	0.0%	1	16.7%	0	0.0%	1	3.1%
ST-19820	0	0.0%	0	0.0%	0	0.0%	1	4.5%	1	3.1%
Total CefiximeDS	1	100.0%	3	100.0%	6	100.0%	22	100.0%	32	100.0%
Sex/Gender										

Males	1	100.0%	2	66.7%	5	83.3%	18	81.8%	26	81.3%
Females	0	0.0%	1	33.3%	1	16.7%	4	18.2%	6	18.8%
Total CefiximeDS	1	100.0%	3	100.0%	6	100.0%	22	100.0%	32	100.0%
Male sexual behaviour										
GBMSM	1	100.0%	0	0.0%	4	80.0%	14	77.8%	19	73.1%
Heterosexual males	0	0.0%	1	50.0%	1	20.0%	4	22.2%	6	23.1%
Male unknown	0	0.0%	1	50.0%	0	0.0%	0	0.0%	1	3.8%
Total Male CefiximeDS	1	100.0%	2	100.0%	5	100.0%	18	100.0%	26	100.0%
Female sexual behaviour										
Sex with both male and female	0	0.0%	0	0.0%	0	0.0%	1	25.0%	1	16.7%
Sex with female	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Sex with male	0	0.0%	1	33.3%	1	100.0%	3	75.0%	5	83.3%
Females with unknown sexual behaviour	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total Female CefiximeDS	0	0.0%	0	0.0%	1	100.0%	4	100.0%	6	100.0%
Sex/Gender and Age										
Male (years old)										
< 20	0	0.0%	1	33.3%	0	0.0%	0	0.0%	1	3.8%
20-29	1	100.0%	0	0.0%	1	20.0%	3	16.7%	5	19.2%
30-39	0	0.0%	0	0.0%	2	40.0%	8	44.4%	10	38.5%
40-49	0	0.0%	1	33.3%	2	40.0%	4	22.2%	7	26.9%
50-59	0	0.0%	0	0.0%	0	0.0%	2	11.1%	2	7.7%
60+	0	0.0%	0	0.0%	0	0.0%	1	5.6%	1	3.8%
Total Male CefiximeDS	1	100.0%	2	66.7%	5	100.0%	18	100.0%	26	100.0%
Female (years old)										
< 20	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
20-29	0	0.0%	1	33.3%	0	0.0%	2	50.0%	3	50.0%
30-39	0	0.0%	0	0.0%	0	0.0%	2	50.0%	2	33.3%
40-49	0	0.0%	0	0.0%	1	100.0%	0	0.0%	1	16.7%
50-59	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
60+	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total Female CefiximeDS	0	0.0%	1	33.3%	1	100.0%	4	100.0%	6	100.0%
Infection type										
Male										
Anogenital	0	0.0%	2	66.7%	3	60.0%	13	72.2%	18	69.2%
Pharyngeal	1	100.0%	0	0.0%	2	40.0%	5	27.8%	8	30.8%
Total Male CefiximeDS	1	100.0%	2	66.7%	5	100.0%	18	100.0%	26	100.0%
Female										
Anogenital	0	0.0%	0	0.0%	0	0.0%	1	25.0%	1	16.7%
Pharyngeal	0	0.0%	1	33.3%	1	100.0%	3	75.0%	5	83.3%
Total Female CefiximeDS	0	0.0%	1	33.3%	1	100.0%	4	100.0%	6	100.0%
Province or territory										
Alberta	1	100.0%	2	66.7%	6	100.0%	22	100.0%	31	96.9%
Manitoba	0	0.0%	1	33.3%	0	0.0%	0	0.0%	1	3.1%
Nova Scotia	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Northwest territories	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total CefiximeDS	1	100.0%	3	100.0%	6	100.0%	22	100.0%	32	100.0%
Suspected treatment failure^a										
Yes	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
No	1	100.0%	3	100.0%	6	100.0%	22	100.0%	32	100.0%
Total CefiximeDS	1	100.0%	3	100.0%	6	100.0%	22	100.0%	32	100.0%

^a Suspected treatment failure is a public health report of treatment failure. It is not confirmed with laboratory testing.

Figure 6. The number and proportion of ESAG cases with GC cultures demonstrating cefiximeDS by the sequence types associated with cefiximeDS, 2018 to 2021.



Note: This figure shows STs associated with cefiximeDS (among all ESAG isolates collected from 2018 to 2021), for a given calendar year. The total number of ESAG cultures with a given ST is shown in grey and the number of isolates (for a given ST) with cefiximeDS are shown in yellow. The data labels on the bars are the proportion of isolates that demonstrated cefiximeDS for each ST.

4.3.5.c. Case characteristics and sequence types of ESAG cases with cultures demonstrating ceftriaxoneDS

From 2018 to 2021, the proportion of ESAG GC cultures demonstrating ceftriaxoneDS declined annually from 0.8% (8/1022) in 2018 to 0.2% (1/645) in 2021 (period average of 0.4% (14/3377)) (Table 13). Of the 14 ceftriaxoneDS cultures, 12 (85.7%) were collected from males. Most of these male cases (9, 75.0%) had an unknown sexual behaviour and a primary anogenital infection site (7, 58.3%), and were 20-29 years old (6, 50.0%). No cases were attributed to treatment failures (Table 13).

Table 13. Characteristics of ESAG cases with GC cultures demonstrating ceftriaxoneDS, 2018 to 2021

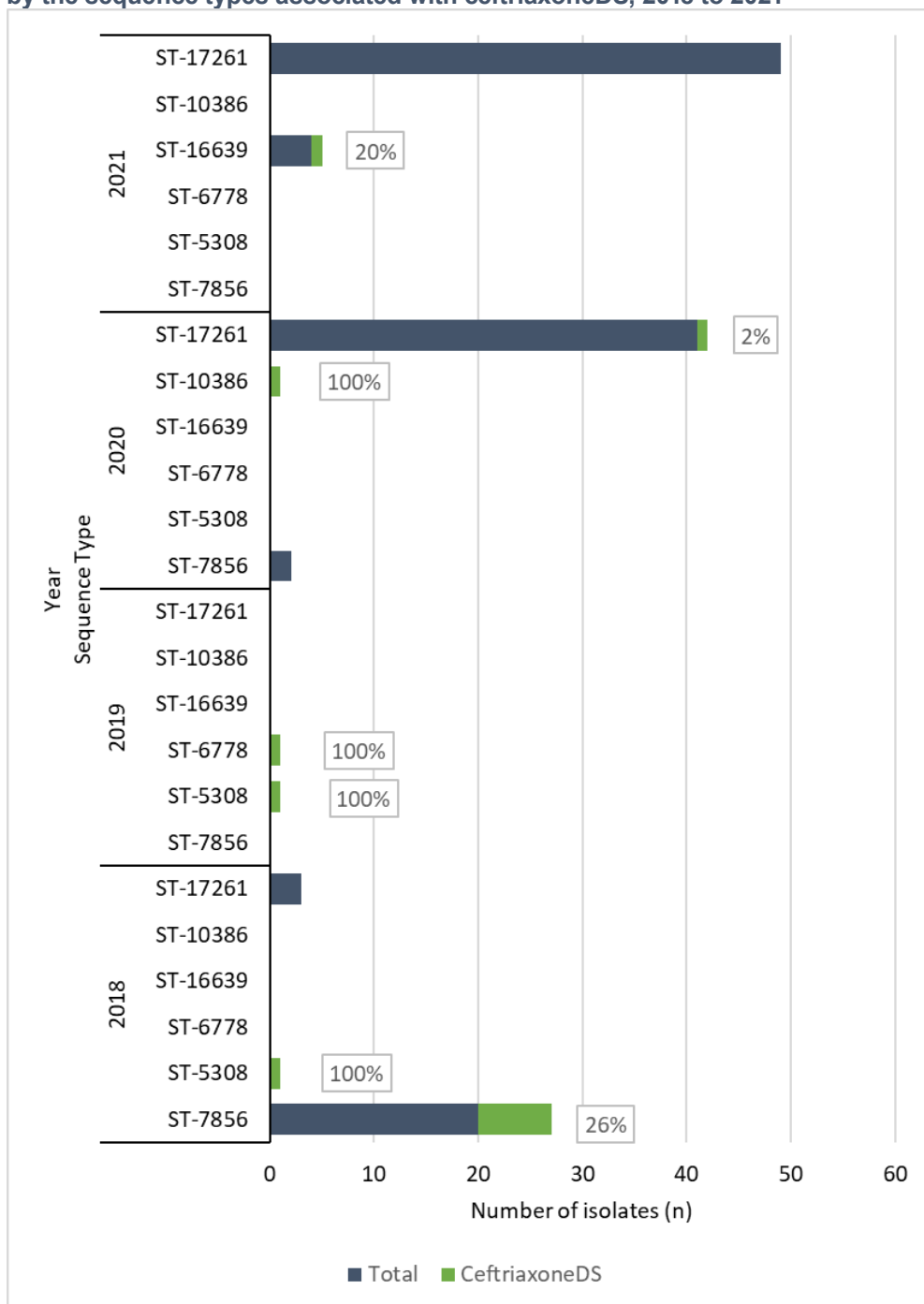
	2018		2019		2020		2021		Total	
	n	%	n	%	n	%	n	%	n	%
Isolates with ceftriaxoneDS	8	0.8%	3	0.3%	2	0.3%	1	0.2%	14	0.4%
Total isolates	1022	100%	999	100%	711	100%	645	100%	3377	100.0%
Sequence type										
ST-7856	7	87.5%	0	0.0%	0	0.0%	0	0.0%	7	50.0%
ST-5308	1	12.5%	2	66.7%	0	0.0%	0	0.0%	3	21.4%
ST-6778	0	0.0%	1	33.3%	0	0.0%	0	0.0%	1	7.1%
ST-16639	0	0.0%	0	0.0%	0	0.0%	1	100.0%	1	7.1%
ST-10386	0	0.0%	0	0.0%	1	50.0%	0	0.0%	1	7.1%
ST-17261	0	0.0%	0	0.0%	1	50.0%	0	0.0%	1	7.1%
Total CeftriaxoneDS	8	100.0%	3	100.0%	2	100.0%	1	100.0%	14	100.0%
Sex/Gender										
Male	8	100.0%	2	100.0%	2	100.0%	0	0.0%	12	85.7%
Female	0	0.0%	1	33.3%	0	0.0%	1	100.0%	2	14.3%
Total CeftriaxoneDS	8	100.0%	3	100.0%	2	100.0%	1	100.0%	14	100.0%
Male sexual behaviour										
GBMSM	1	12.5%	0	0.0%	1	50.0%	0	0.0%	2	16.7%
Heterosexual males	0	0.0%	1	50.0%	0	0.0%	0	0.0%	1	8.3%
Males with unknown sexual behaviour	7	87.5%	1	50.0%	1	50.0%	0	0.0%	9	75.0%
Total Male CeftriaxoneDS	8	100.0%	2	100.0%	2	100.0%	0	0.0%	12	100.0%
Female sexual behaviour										
Sex with both male and female	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Sex with female	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Sex with male	0	0.0%	1	0.0%	0	0.0%	1	100.0%	2	100.0%
Females with unknown sexual behaviour	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total Female CeftriaxoneDS	0	0.0%	1	0.0%	0	0.0%	1	100.0%	2	100.0%
Sex/Gender and Age										
Male										
< 20	0	0.0%	1	50.0%	0	0.0%	0	0.0%	1	8.3%
20-29	6	75.0%	0	0.0%	0	0.0%	0	0.0%	6	50.0%
30-39	0	0.0%	0	0.0%	1	50.0%	0	0.0%	1	8.3%

	40-49	2	25.0%	1	50.0%	1	50.0%	0	0.0%	4	33.3%
	50-59	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	60+	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total Male CeftriaxoneDS		8	100.0%	2	100.0%	2	100.0%	0	0.0%	12	100.0%
Female											
	< 20	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	20-29	0	0.0%	1	100.0%	0	0.0%	1	100.0%	2	100.0%
	30-39	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	40-49	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	50-59	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	60+	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total Female CeftriaxoneDS		0	0.0%	1	0.0%	0	0.0%	1	100.0%	2	100.0%
Infection type											
Male											
	Anogenital	4	50.0%	2	100.0%	1	50.0%	0	0.0%	7	58.3%
	Pharyngeal	4	50.0%	0	0.0%	1	50.0%	0	0.0%	5	41.7%
Total Male CeftriaxoneDS		8	100.0%	2	100.0%	2	100.0%	0	0.0%	12	100.0%
Female											
	Anogenital	0	0.0%	0	0.0%	0	0.0%	1	100.0%	1	50.0%
	Pharyngeal	0	0.0%	1	0.0%	0	0.0%	0	0.0%	1	50.0%
Total Female CeftriaxoneDS		0	0.0%	1	0.0%	0	0.0%	1	100.0%	2	100.0%
Province or territory											
	Alberta	1	12.5%	2	66.7%	1	50.0%	1	100.0%	5	35.7%
	Manitoba	7	87.5%	1	33.3%	1	50.0%	0	0.0%	9	64.3%
	Nova Scotia	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Northwest territories	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total CeftriaxoneDS		8	100.0%	3	100.0%	2	100.0%	1	100.0%	14	100.0%
Suspected treatment failure^a											
	Yes	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	No	8	100.0%	2	66.7%	2	100.0%	1	100.0%	13	92.9%
Total CeftriaxoneDS		8	100.0%	3	100.0%	2	100.0%	1	100.0%	14	100.0%

^aSuspected treatment failure is a public health report of treatment failure. It is not confirmed with laboratory testing.

There were six NG-MAST STs identified among ESAG cultures demonstrating ceftriaxoneDS between 2018 and 2021. ST-7856 was identified most frequently and accounted for half (average of 50.0%; 7/14) of ceftriaxoneDS cases (all were from 2018) (Table 13). Among all 27 (out of 3,377 cases) ESAG isolates identified as ST-7856 (only identified in the years 2018 and 2020), 26.0% (7/27) demonstrated ceftriaxoneDS in 2018 and zero in 2020 (Figure 7). All other STs associated with ceftriaxoneDS occurred infrequently and varied highly by year (Figure 7).

Figure 7. The number and proportion of ESAG cases with GC cultures demonstrating ceftriaxoneDS by the sequence types associated with ceftriaxoneDS, 2018 to 2021



Note: This figure shows STs associated with ceftriaxoneDS (among all ESAG isolates collected from 2018 to 2021), for a given calendar year. The total number of ESAG cultures with a given ST is shown in grey and the number of isolates (for a given ST) with ceftriaxoneDS are shown in yellow. The data labels on the bars are the proportion of isolates that demonstrated ceftriaxoneDS for each ST.

4.4. Sequence Typing

There were 396 unique NG-MAST STs identified from 3377 *N. gonorrhoeae* isolates, collected from ESAG cases between 2018 and 2021. The top 10 most frequently observed STs represented slightly more than half of all identified STs within each reporting year (Table 14).

Table 14. The number and proportion of GC cultures collected from ESAG cases with a top 10 ST among all typable isolates, 2018 to 2021

Number of isolates	2018		2019		2020		2021	
	n	%	n	%	n	%	n	%
With a top 10 ST for a given year	491	57.4%	476	55.8%	301	54.0%	332	52.9%
Total isolates	855	100.0%	853	100.0%	557	100.0%	628	100.0%

Table 15. The proportion of ESAG cases with azithromycinR, cefiximeDS and ceftriaxoneDS among isolates of the top 10 sequence types (ST) annually, 2018 to 2021

	2018	2019	2020	2021
AzithromycinR				
AzithromycinR in top 10 STs	7	25	0	3
Total AzithromycinR (N)	18	55	8	11
Proportion (%)	38.9%	45.5%	0.0%	27.3%
CefiximeDS				
CefiximeDS in top 10 STs	0	0	5	15
Total CefiximeDS (N)	1	2	6	22
Proportion (%)	0.0%	0.0%	83.3%	68.2%
CeftriaxoneDS				
CeftriaxoneDS in top 10 STs	7	0	1	0
Total CeftriaxoneDS (N)	8	2	2	1
Proportion (%)	87.5%	0.0%	50.0%	0.0%

There was no clear trend in the proportion of ESAG cases with cultures that had a top 10 ST and demonstrated either azithromycinR, cefiximeDS or ceftriaxoneDS (Table 15). The proportion of cultures, with one of the top 10 STs, with AzithromycinR varied across the years but declined overall (38.9%, 7/18 cases in 2018; 45.5%, 25/55 in 2019; 0.0%, 0/8 in 2020; and 27.3%, 3/11 in 2021).

While cultures demonstrating cefiximeDS and ceftriaxoneDS occurred infrequently across all reporting years, cefiximeDS was mostly detected in cultures from cases with a top 10 ST for the years 2020 (83.3%, 5/6 cases) and 2021 (68.2%, 15/22 cases) only. CeftriaxoneDS was mostly

detected in cultures that were among the top 10 STs for the year 2018 (87.5%, 7/8 cases) and half of cultures in 2020 (50.0%, 1/2 cases) only.

Figures 8-11 show the top 10 STs by the number of isolates with that ST, the number of isolates with that ST meeting the cut-offs for azithromycinR, cefiximeDS or ceftriaxoneDS, and the proportion of ESAG cases with those STs by i) sexual behaviour and ii) the primary infection type for the years 2018 to 2021. (ST changes across this time period among the 10 most frequent STs are shown in supplementary table K). The most prevalent STs varied across the reporting years by type, frequency and in their resistance profiles. Below, the discussion is focused on those 10 STs associated with cefiximeDS, ceftriaxoneDS, and azithromycinR.

Figure 8: The 10 most frequent NG-MAST sequence types in *N. gonorrhoeae* isolates and the proportion by sex/gender and sexual behaviour and by infection type, 2021.

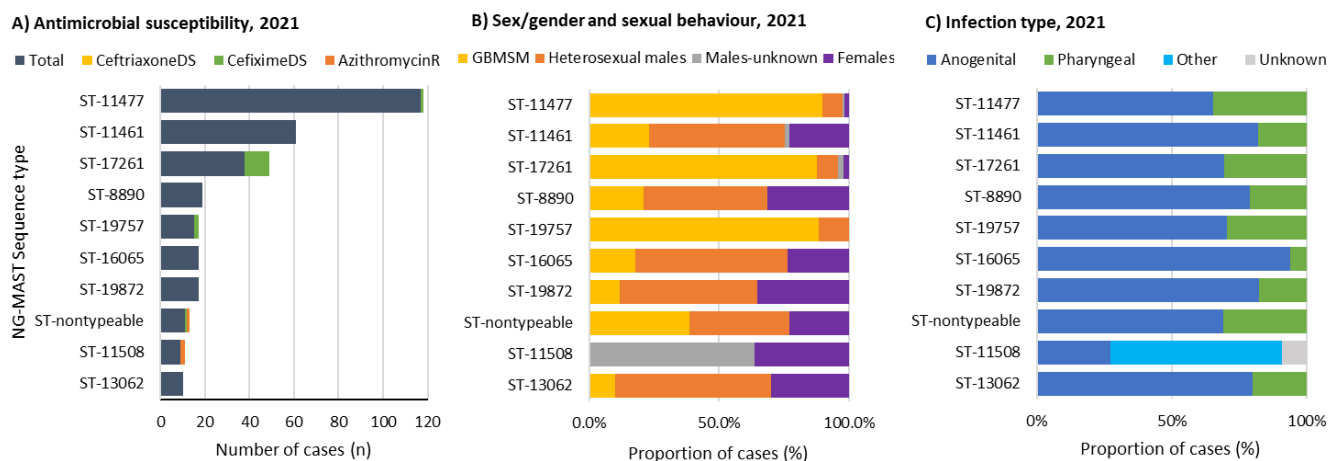


Figure 9: The 10 most frequent NG-MAST sequence types in *N. gonorrhoeae* isolates and the proportion by sex/gender and sexual behaviour and by infection type, 2020.

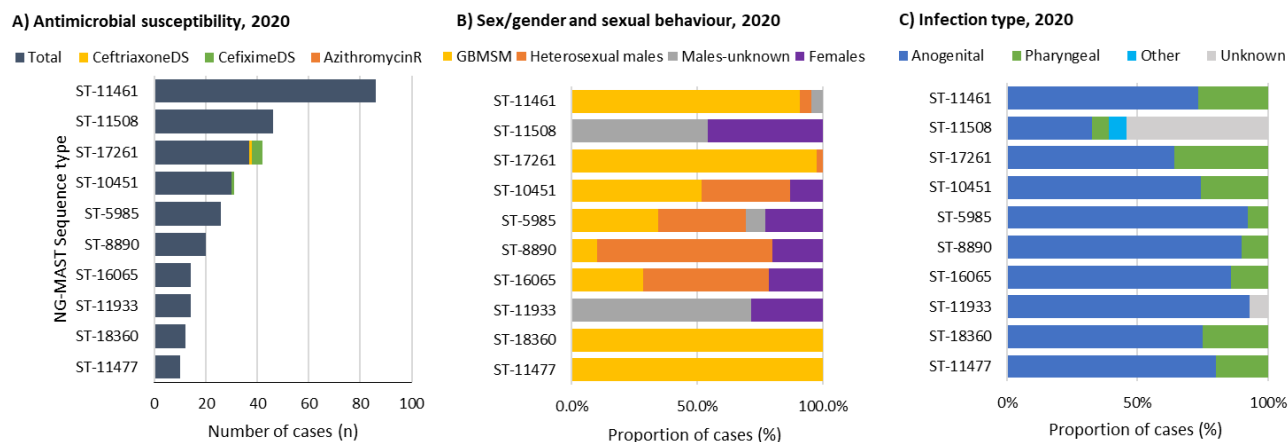


Figure 10: The 10 most frequent NG-MAST sequence types in *N. gonorrhoeae* isolates and the proportion by sex/gender and sexual behaviour and by infection type, 2019.

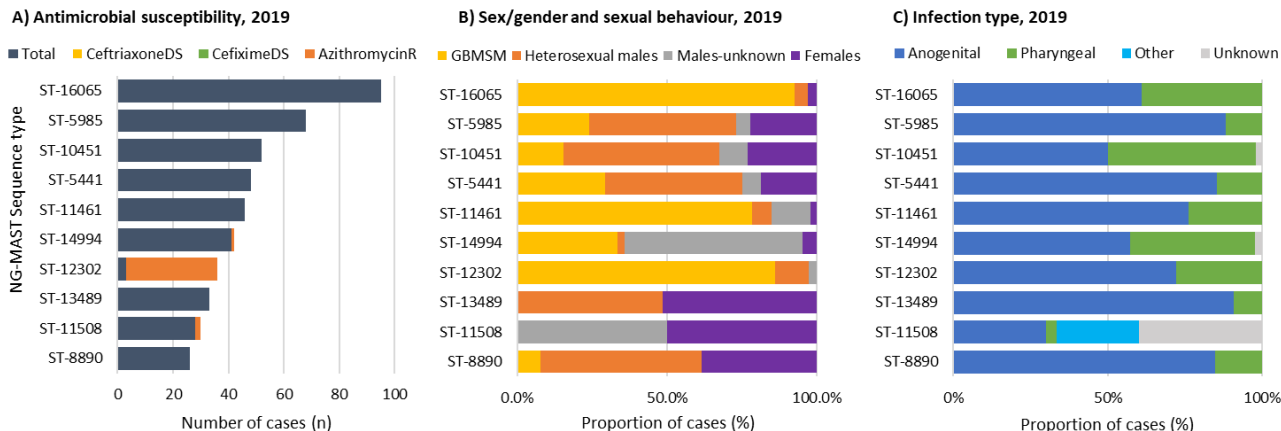
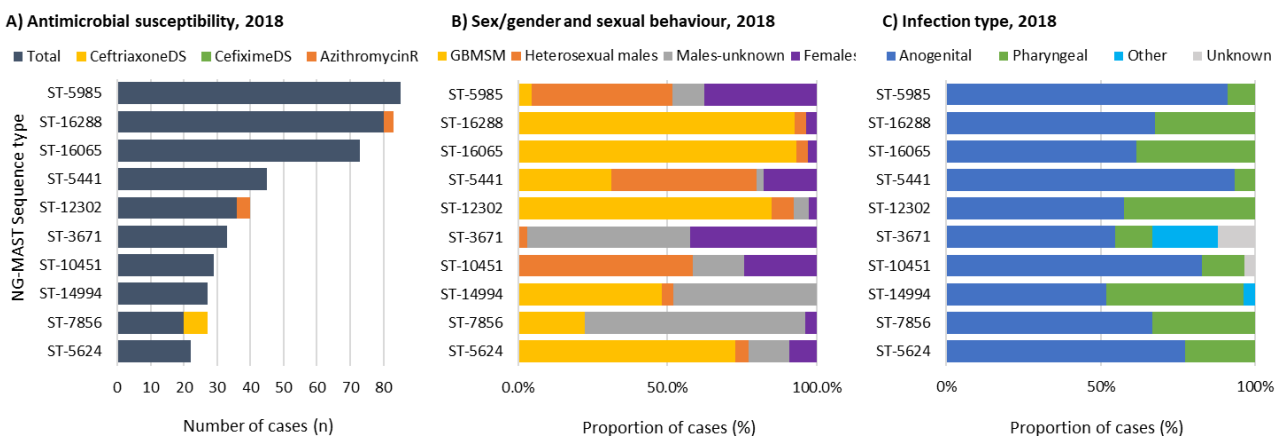


Figure 11: The 10 most frequent NG-MAST sequence types in *N. gonorrhoeae* isolates and the proportion by sex/gender and sexual behaviour and by infection type, 2018.



In 2021, three of the top ten STs were associated with cefiximeDS (ST-11477, ST-17261, ST-19757) and one demonstrated azithromycinR (ST-11508). There was no ceftriaxoneDS detected from the top ten STs in 2021. While ST-11477 was the most frequently observed ST in 2021 (18.3%, 118/645), only one isolate with ST-11477 demonstrated cefiximeDS (0.8%, 1/118) and none demonstrated azithromycinR or ceftriaxoneDS (Figure 8A). This ST was primarily observed in isolates collected from males (98.3%, 116/118), specifically GBMSM (89.8%, 106/118) and among ESAG cases with anogenital infections (65.3%, 77/118) (Figure 8B and 8C).

Also in 2021, ST-19757 newly emerged as one of the top 10 STs (n=17; 5th most common ST). ST-19757 was associated with cefiximeDS in two cases (11.8%, 2/17) and was predominantly detected among GBMSM (88.2%, 15/17) followed by heterosexual males (11.8%, 2/17). In addition, there were

two cases (2/11, 18.2%) of ST -11508 (the 9th most common ST in 2021) demonstrating azithromycinR in 2021, all cases were among males with unknown sexual behaviour (63.6%, 7/11) and females (36.4%, 4/11). Interestingly, this ST has been in the top 10 ST since 2019 (9th top ST in 2019; 2nd top ST in 2020) and was associated with azithromycinR in 2019 (6.7%, 2/30), but not in 2020 (0.0% 0/46).

In 2021 and 2020, ST-17261 emerged as the third most observed ST (16.3% (49/301) in 2021 and 13.9%, (42/301) in 2020) and was associated with the most resistance of the top 10 STs for these years. Specifically, this ST was associated with cefiximeDS in 2021 (22.4%, 11/49) and 2020 (9.5%, 4/42) and ceftriaxoneDS (2.4%, 1/42) in 2020 (Figure 8A and Figure 9A). In both years, ST-17261 was mostly detected among GBMSM (87.8% (43/49) in 2021; 97.6% (41/42) in 2020) followed by heterosexual males (8.2% (4/49) in 2021; 2.4% (1/42) in 2020). In 2021, ST-17261 was also detected among females (2.0%, 1/43) and males with unknown sexual behaviour (2.0%, 1/43). ST-17261 was not a top ten ST prior to 2020.

In 2020, ST-10451 (N=31; 4th top ST) and ST-17261 were the only two STs among the top 10 STs to demonstrate reduced drug susceptibility (Figure 9A). ST-10451 was associated with cefiximeDS (2.4%, 1/31) and was primarily observed among GBMSM (51.6%, 16/31), followed by heterosexual males (35.5%, 11/31) and females (12.9%, 4/31) (Figure 9B). While also, a top 10 ST in 2018 and 2019, there were zero instances of reduced drug susceptibility for those years.

In 2019, in addition to ST-11508, ST-14994 and ST-12302 were also associated with azithromycinR (Figure 10A).²¹ None of the top ten STs in 2019 were associated with ceftriaxoneDS or cefiximeDS. Both ST-14994 and ST-12302 were also in the top 10 STs in 2018. The proportion of ST-14994 isolates with azithromycinR increased from 2.6% (1/39) in 2019 from 0.0% in 2018, while the proportion of azithromycinR cases of ST-12302 increased from 10.0% (4/40) to 91.7% (33/36). In 2019, ST-14994 was primarily identified among males with unknown sexual behaviour (59.5%, 25/42) followed by GBMSM (33.3%, 14/42); meanwhile, ST-12302 was primarily detected among GBMSM (86.1%, 31/36). However, both STs disappeared from the top 10 ST in 2020 and 2021.

In 2018, ST-16288 (2nd top ST in 2018) and ST-12302 (5th top ST in 2018) were associated with azithromycinR (10.0%, 4/40 for ST-16288 and 3.6%, 3/83 for ST-12302) (Figure 11A). Additionally, ST-7856 (9th top ST in 2018) was associated with ceftriaxoneDS (25.9%, 7/27). ST-16288 was predominantly detected among GBMSM (92.8%, 77/83) while ST-7856 was predominantly detected among males with unknown sexual behaviour (74.1%, 20/27). The prevalence of both STs declined

after 2018 as neither were in the top STs for 2019, 2020, or 2021. No decreased susceptibility to cefixime was observed from isolates with any of the top 10 NG-MAST STs in 2018.

5. Limitations

5.1. Data quality

During this reporting period, the variables ‘sex work status’ and ‘travel-related GC infection’ which have been shown in previous ESAG reports could not be presented due to insufficient data collection.

5.2. Limitations and considerations

- Results from ESAG are not representative of all gonorrhea cases or culture-confirmed gonorrhea cases in Canada, since most gonorrhea cases are diagnosed by Nucleic Acid Amplification Tests (NAATs). Of the four provinces and territories that provided 2018 to 2021 ESAG data, most ESAG data came from Alberta. Sentinel sites within Nova Scotia may not be representative of this province as a whole. Aggregated results should be interpreted with caution.
- Approximately 80.5% of cases captured in ESAG were male, of which 55.5% were GBMSM. However, in 2021, 62.9% of all gonorrhea cases reported nationally to PHAC were male (sexual orientation data is unavailable for nationally reported gonorrhea cases).¹
- Gonorrhea client-level public health data collection may be more likely to be completed within certain medical clinics with client populations which may not be generalizable across the PT or Canada.
- The reported proportions of cases prescribed a recommended preferred or alternative gonorrhea treatment are conservative. The availability of recommended antimicrobials, reporter error (for example, erroneously reporting prescriptions used to treat co-infections/co-morbidities or providing incomplete gonorrhea prescription treatment information), and co-morbidity or risk behaviour considerations, are all possible reasons for not meeting recommended gonorrhea treatment guidelines. For example, PHAC gonorrhea treatment guidelines recommend considering chlamydia treatment (i.e., azithromycin 1 g (in a single dose) and doxycycline 100 mg (for 7 days)) alongside gonorrhea treatment if a sexual partner is found to have gonorrhea or if follow-up is not assured.

- Tests of cure and treatment failures can be difficult to measure using surveillance data because they rely on the ability to detect negative results. Additionally, it is unknown how well gonorrhea treatment failures are detected or reported by jurisdictions. Thus, treatment failures may be underreported.
- PTs had a reduced ability to deliver regular and routine gonorrhea screening, care, and public health reporting activities during 2020 and parts of 2021 due to numerous factors related to the COVID-19 pandemic.

6. Discussion

This is the fourth ESAG results report describing AMR-GC trends overall and among key groups and GC treatment prescribing practices among ESAG participating PTs. In the previous ESAG 2015 to 2017 report, ESAG participating PTs increased the number of gonorrhea cultures collected over time.⁵ However, from 2018 and onward, the number of cultures among ESAG PTs decreased each year. The COVID-19 pandemic may also have contributed to this decrease, with many PTs having to adapt and change their strategies for STBBI care (see limitations section).²² Changes in PT data collection methods over this period may have also played a role in the decrease in ESAG cases and can not be ruled out.

After three years of stability (2018 to 2020), AMR-GC prevalence (as indicated by resistance to at least one tested antimicrobial) among ESAG cases increased from 69.3% in 2020 to 77.4% in 2021. In 2021, AMR-GC burden was highest among ESAG cases who were GBMSM (85.2%), followed by heterosexual males (73.5%) and females (66.7%). Resistance to ciprofloxacin and tetracycline was high among all sexual behaviour groups but highest among GBMSM. This is important information to continuously monitor as early studies have documented the short-term effectiveness of doxycycline as post-exposure prophylaxis for bacterial STI among cisgender GBMSM and transgender women.^{23,24} As a result, some doxycycline are recommending or considering its use as post exposure prophylaxis in the GBMSM population.²³

Between 2018 and 2021, while there were 14 reports of suspected treatment failure, laboratory resistance profiles showed that none demonstrated resistance to all prescribed treatment regimens suggesting these clients were either reinfected or did not take their medication correctly, or at all (as most of the prescribed therapies for these clients were one-time doses). Thus, there were no

confirmed treatment failures among ESAG cases with gonorrhoea treatment prescriptions over the period. This is in the context of stable and high adherence to gonorrhoea treatment guidelines and despite 3.4% of cases (116/3377) demonstrating azithromycinR, 0.4% (14) demonstrating ceftriaxoneDS, and 0.9% (32) demonstrating cefiximeDS. The discrepancy between the suspected and confirmed treatment failures among ESAG cases reinforces PHAC's recommendation of culturing isolates when antibiotic resistance is suspected and performing a test of cure for all positive sites in all GC cases.²⁵

Encouragingly, the vast majority of GBMSM and other adult ESAG cases were prescribed either the PHAC or PT-described preferred or alternative gonorrhoea therapy across all reporting years (average of 91.4% adherence to PHAC guidelines and 89.5% adherence to PT guidelines). High adherence to PHAC guidelines has been observed in previous ESAG reports. This is the first report that summarizes PT-specific GC treatment guideline adherence (adherence was slightly higher to PHAC versus PT guidelines). Among all GBMSM cases, the majority received the anogenital and pharyngeal preferred therapy of azithromycin with ceftriaxone. This was followed, though infrequently, by ceftriaxone and doxycycline (a tetracycline) which is not a PT-recommended regimen, although it is a PHAC-recommended alternative therapy for anogenital infections. Among other adults (i.e., non-GBMSM ESAG cases), most were prescribed azithromycin and cefixime (one of the two preferred treatment regimens for anogenital infections but an alternative regimen for pharyngeal infections). This finding has been noted in previous ESAG reports and may be because the client was first diagnosed by NAAT and treated as an anogenital infection, and later found to also have a pharyngeal infection. For all people, pharyngeal infections are often asymptomatic and possibly screened less frequently.

Despite its high prescriber rate, isolates with ceftriaxoneDS have remained few, with no increasing trend, for all sexual behaviour groups, which is encouraging and supports its widespread recommendation in national and PT treatment guidelines.^{6, 11-13} Of the 14 ceftriaxoneDS cases, the majority (eight) occurred in 2018 (three in 2019, two in 2020 and one in 2021) and nine cases were among males with unknown sexual behaviour, which makes data difficult to interpret. Very few (two) cases were GBMSM or female.

While the prevalence was low, cefiximeDS has been rising since 2019 for GBMSM (0.0% in 2019 to 4.5% in 2021) and since 2018 for those who are most often prescribed this drug, heterosexual males (0.0% in 2018 to 2.2% in 2021) and females (0.0% in 2018 to 3.3% in 2021). Although, a greater than

baseline proportion of all cefiximeDS ESAG cases were among GBMSM. The WHO recommends carefully watching any antimicrobial whose prevalence is above 5.0% of isolates or is rapidly rising.²⁰ Future reports will be informative of cefiximeDS trends within these populations.

AzithromycinR prevalence was similar in 2018 to what was observed in the previous ESAG report, but increased to 7.8% in 2019 followed by a sharp drop to 1.9% in 2021 overall (these trends were also observed by sexual behaviour group).⁵ Between 2018 and 2021, the majority of the azithromycinR ESAG cases were disproportionately among males (90.5%), of which, 79.0% were GBMSM. Similar azithromycinR trends were observed in the latest GASP report, where it was noted that azithromycinR decreased significantly between 2017 (11.7%) and 2021 (7.6%) ($p < 0.001$). However, the GASP report noted a significant increase ($p < 0.001$) in the proportion of cultures with an azithromycin minimum inhibitory concentration of $\geq 1\text{mg/L}$ (2017=22.2% to 2021=28.1%).¹⁴ (For further comparisons between ESAG and GASP-Canada 2021 results, see Appendix 2, in this document). AzithromycinR was driven by the STs, ST-16288 and ST-12302. Fortunately, the prevalence of these STs dwindled to four and eight ESAG isolates, respectively, in 2020 and zero in 2021.

7. Conclusion

The ESAG system continued to monitor *N. gonorrhoeae* antimicrobial susceptibility, clinician prescribing practices, reason for medical care visit, and treatment failure data by demographic and sexual behaviour variables from 2018 to 2021. This data supplements PHAC's laboratory-based passive surveillance of AMR-GC through GASP-Canada. The ESAG data for 2018 to 2021 demonstrated a low prevalence, overall, to the most prescribed and recommended GC treatments of ceftriaxoneDS and cefiximeDS, although a slight increase in cefiximeDS among ESAG cases (particularly among GBMSM) was observed in 2021. It also showed a lowered prevalence of azithromycinR in 2020 and 2021 compared to in 2018 and 2019.

Gonorrhoea treatment resistant to azithromycin and ceftriaxone are a global concern and have been reported in several countries world-wide. Aside from Canada, ceftriaxoneR has been documented in Australia, Austria, China, Denmark, France, Japan, Slovenia, Sweden, and the United Kingdom.^{2, 26-36}

ESAG demonstrates the possibility of improved AMR-GC surveillance by integrating existing local/ provincial/ territorial GC and national laboratory surveillance. ESAG has allowed for the monitoring of GC antimicrobial susceptibility despite the decreasing use of culture in clinical practice for gonorrhea diagnosis and antimicrobial susceptibility testing. As Canada faces increasing numbers of gonorrhea cases and the continued evolution, emergence and spread of AMR-GC, efforts are ongoing to recruit additional ESAG sites to allow the collection of more representative data.

The continuous monitoring of AMR-GC patterns via surveillance is of paramount importance to ensure the effectiveness of the recommended antimicrobials to treat GC infection. ESAG can play an important role in assessing and monitoring the effectiveness of GC treatment options and for the success of Canadian initiatives to combat AMR-GC.

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Appendix 1. List of supplementary figures and tables

Supplementary tables A-K are available upon request at sti-hep-its@phac-aspc.gc.ca.

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Appendix 2. Comparison of GASP-Canada and ESAG 2021 results

GASP-Canada 2021 report results	ESAG 2021 report results	ESAG vs GASP-Canada results comparison summary
Culture data		
<p>There were 3,439 of cultures reported to GASP-Canada in 2021- 9.9% <u>increase</u> since 2020 (n= 3130).</p> <p>While the number of GC cultures across Canada increased slightly between 2020 (n=3,130) and 2021 (n=3,439), there were 30% less than what was seen in 2019 (n=4,859).</p>	<p>There were 645 cultures (cases) reported to ESAG in 2021- 9.3% <u>decrease</u> from 2020 (n=711).</p> <p>There was a steady decline in the number of ESAG cases from 2018 to 2021 (1022 cases in 2018, 999 cases in 2019, 711 cases in 2020 and 645 cases in 2021).</p>	<p>Difference in trends: GASP-Canada saw an increase in the number of submitted GC cultures from 2020 to 2021. ESAG saw a decline in the number of GC cultures (cases) from 2020 to 2021.</p>
<p>In 2021, most AMR-GC data comes from Quebec (n=1561), followed by Ontario (n=886) and Alberta (n=783).</p>	<p>83.0% of ESAG cases were reported by Alberta, 14.3% by Manitoba, 1.8% by Nova Scotia, and 0.9% by the Northwest Territories.</p>	<p>Different main PT data sources.</p>
Case characteristics		
<p>In 2021, 71.2% of <i>N. gonorrhoeae</i> GASP-Canada cultures were from individuals between the ages of 21 and 40.</p>	<p>Between 2018 and 2021, 72.8% of ESAG cases were between 20 and 39 years of age.</p>	<p>Similar ages of ESAG and GASP-Canada cases.</p>
<p>In 2021, 84.4% of cultures were primarily collected from males and 15.1% (438/2,909) from females.</p>	<p>Between 2018 and 2021, 80.4% of ESAG cases were male and 19.1% of cases were female.</p>	<p>Very similar proportions of male and female ESAG and GASP-Canada cases.</p>

		ESAG also presents data by sexual behavior. GASP-Canada does not collect sexual behaviour data.
In 2021, the most prevalent primary gonococcal isolation site in males was the penis/urethra (56.8%) and for females it was the throat (33.8%, 148/438).	<p>Between 2018 and 2021, the most prevalent primary gonococcal isolation site for males and females was genital (34.6% for females and 51.8% for males). It was followed by the rectum for males (23.7%) and the pharynx for females (32.4%).</p> <p>Among males, the primary GC infection site was, among GBMSM, rectal (39.3%) and pharyngeal (34.6%) and among heterosexual males, the penis/urethra (i.e., genital) (26.1%).</p>	<p>Similar primary isolation site by sex.</p> <p>ESAG also presents data by sexual behavior. GASP-Canada does not collect sexual behaviour data.</p>
AMR-GC Trends		
In 2021, over 70% (72.7%, n=2,501/3,349) of GC cultures submitted to GASP-Canada were resistant to at least one antibiotic.	In 2021, over 70% (77.4%, n=499/645) of GC cultures submitted to ESAG were resistant to at least one antibiotic.	Similar results – GASP-Canada and ESAG reported that over 70% of cultures were resistant to at least 1 antibiotic in 2021.
No significant change in the proportion of GASP-Canada GC cultures that demonstrated ceftriaxoneDS was detected between 2017 (0.55%) and 2021 (0.6%) (p>0.001). However, one ceftriaxone resistant isolate was identified.	CeftriaxoneDS declined in number and proportion from 8 (0.8%) cases in 2018 to one case (0.2%) in 2021. All ESAG cultures were susceptible to ceftriaxone in 2020 and 2021.	<p>Slightly different results: In 2021, a marginally larger proportion of ceftriaxoneDS GC cultures were detected among GASP-Canada cultures (0.6%) than among ESAG cultures (0.2%).</p> <p>Over the reporting periods, ceftriaxoneDS prevalence trends</p>

		remained stable among GASP-Canada GC cultures, while they decreased marginally among ESAG GC cultures.
<p>CefiximeDS increased significantly from 0.6% in 2017 to 1.5% in 2021 ($p < 0.001$), but also decreased significantly from the 2.8% reported in 2020 ($p < 0.001$).</p> <p>The 2020 higher proportion of isolates with cefiximeDS was primarily caused by isolates identified as ST-16639 in Ontario and Québec. The proportion of this ST decreased from 3.3% ($n=53/1,590$) in 2020 to 1.3% ($n=26/2,006$) in 2021.</p>	<p>From 2018 to 2020, the number and proportion of ESAG GC cultures demonstrating cefiximeDS increased from 0.1% in 2018 to 3.4% in 2021.</p>	<p>In 2021, a larger proportion of cefiximeDS cultures were detected among ESAG cultures (3.4%) than among GASP-Canada cultures (1.5%).</p> <p>Over the reporting periods, there was an increase in the proportion of ESAG and GASP-Canada cultures demonstrating cefiximeDS. The trends have fluctuated between 2020 and 2021 for GASP-Canada; while ESAG maintained a steady increase.</p>
<p>AzithromycinR prevalence increased from 7.6% in 2018 to 11.7% of cases in 2019 and declined to 6.10% and 7.6% of cases in 2020 and 2021, respectively.</p>	<p>AzithromycinR increased from 18 cases (1.8%) in 2018 to 78 cases (7.8%) in 2019. However, this number decreased sharply to eight cases (1.1%) in 2020 and 12 cases (1.9%) in 2021.</p>	<p>In 2021, a larger proportion of azithromycinR cultures were detected among GASP-Canada cultures (7.6%) than among ESAG cultures (1.9%).</p> <p>Overall, there was a decrease in the proportion of ESAG and GASP-Canada cultures demonstrating azithromycinR from 2019 to 2021 after a rise in cases in 2019.</p>
<p>CiprofloxacinR prevalence remained high and stable (between 49% and 57%) from 2017 to 2021</p>	<p>CiprofloxacinR was the most prevalent AMR-GC in 2021 (63.1%) and in 2020 (46.6%). It was the second most prevalent AMR-GC in 2019 (44.0%) and 2018 (43.0%).</p>	<p>Very similar findings: Ciprofloxacin resistance and Tetracycline resistance prevalence was high among ESAG and GASP-Canada cultures.</p>

<p>TetracyclineR prevalence fluctuated but remained high and stable in 2017 to 2020 (between 40% and 50%). In 2021, it was at an all-time high of 65.9%.</p>	<p>TetracyclineR was the most prevalent AMR-GC at 52.1% in 2018 and 51.8% in 2019 and the second most prevalent AMR-GC in 2020 (45.9%) and 2021 (58.6%).</p>	
<p>ErythromycinR fluctuated from 2017 to 2021. The prevalence was around 60% in 2017 but declined annually to around 30% in 2020. It then increased to 51.5% in 2021.</p>	<p>ErythromycinR has declined annually and sharply from 30% in 2018 to 8.5% in 2021.</p>	<p>Different results: In 2021, erythromycinR prevalence was much higher among GASP-Canada cultures (51.5%) than among ESAG cultures (8.5%).</p> <p>ErythromycinR prevalence has fluctuated over time for GASP-Canada but declined for ESAG.</p>
<p>From 2017 to 2021, penicillin was below 7%.</p>	<p>PenicillinR rates were relatively stable from 2018 to 2020 (6.8% in 2018, 7.2% in 2019 and 8.2% in 2020) but dropped to 3.9% in 2021, which is below the WHO's cut-off of concern (5%).</p>	<p>PenicillinR trends were similar in both groups; although, in 2021, prevalence is slightly lower in ESAG cultures (3.9%) than in GASP-Canada cultures (7.0%).</p>
<p>Sequence Types</p>		
<p>In 2021, the most frequently detected NG-MAST sequence type in Canada was ST-19875 (15.3%, n=306), followed by ST-11477 (n=137) and ST-17972 (n=127).</p> <p>Approximately 20.3% of ST-19875 isolates were identified with AziR, While ST-11477 was primarily resistant to ciprofloxacin and tetracycline,</p> <p>And ST-17972 isolates were primarily resistant ciprofloxacin and erythromycin.</p>	<p>ST-11477 was the most frequently observed ST in 2021 (18.3%, 118/645), only one isolate with ST-11477 demonstrated cefiximeDS (0.8%, 1/118) and none demonstrated azithromycinR or ceftriaxoneDS.</p> <p>ST-11461 and ST-17261 are the second and third most common STs observed in 2021.</p>	<p>Different findings: Different trends of STs between the GASP-Canada and ESAG samples.</p>

<p>* The ST-19875 was first identified in 2020 in low numbers (n=22) and only in Québec. In 2021, this ST type has spread to five more provinces.</p> <p>* From 2017 to 2020, ST-12302 and ST-14994 were the most prevalent, while in 2021, they were the eighth and ninth most prevalent STs, respectively. While the number of isolates with ST-12302 (n=47) has been decreasing, in 2021, 15 other STs were identified with two or fewer base pair differences compared to ST-12302 (this cluster made n= 144 of isolates). 61.8% (n=89/144) were AziR accounting for 34.1% (n=89/261) of AziR isolated in 2021.</p>	<p>ST-12302 was the 5th most frequently observed ST in 2018 and the 8th most frequently observed ST in 2019. More than 50% of the isolates with ST-12302 in 2019 were AziR.</p> <p>Note that ST-19875 and ST-17972 did not rank in the top 10 most frequent STs for ESAG in any year between 2018 and 2021.</p>	
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Appendix 3. Drug resistance (R) and decreased susceptibility (DS) to selected antimicrobials by province or territory, 2018 to 2021

Susceptibility	Alberta				Manitoba				Northwest Territories				Nova Scotia			
	2018	2019	2020	2021	2018	2019	2020	2021	2018	2019	2020	2021	2018	2019	2020	2021
Susceptible to all	267 (32.9%)	236 (29.4%)	177 (30.2%)	130 (21.7%)	28 (16.1%)	48 (31.0%)	41 (35.3%)	16 (41.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	6 (19.4%)	5 (20.8%)	0 (0.0%)	0 (0.0%)
R/DS* to 1	267 (32.9%)	272 (33.9%)	188 (32.0%)	146 (24.3%)	56 (32.2%)	39 (25.2%)	40 (34.5%)	14 (35.9%)	3 (60.0%)	10 (58.8%)	6 (85.7%)	0 (0.0%)	4 (12.9%)	2 (8.3%)	0 (0.0%)	1 (20.0%)
R/DS to 2	141 (17.4%)	155 (19.3%)	144 (24.5%)	275 (45.8%)	37 (21.3%)	42 (27.1%)	31 (26.7%)	7 (17.9%)	1 (20.0%)	5 (29.4%)	1 (14.3%)	1 (100.0%)	4 (12.9%)	10 (41.7%)	0 (0.0%)	4 (80.0%)
R/DS to 3	120 (14.8%)	66 (8.2%)	62 (10.6%)	41 (6.8%)	26 (14.9%)	21 (13.5%)	3 (2.6%)	2 (5.1%)	1 (20.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	15 (48.4%)	4 (16.7%)	1 (100.0%)	0 (0.0%)
R/DS to 4	16 (2.0%)	72 (9.0%)	14 (2.4%)	8 (1.3%)	20 (11.5%)	5 (3.2%)	3 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)	3 (12.5%)	0 (0.0%)	0 (0.0%)
R/DS to 5	1 (0.1%)	2 (0.2%)	2 (0.3%)	2 (0.0%)	7 (4.0%)	5 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	812 (100.0%)	803 (100.0%)	587 (100.0%)	600 (100.0%)	174 (100.0%)	155 (100.0%)	116 (100.0%)	39 (100.0%)	5 (100.0%)	17 (100.0%)	7 (100.0%)	1 (100.0%)	31 (100.0%)	24 (100.0%)	1 (100.0%)	5 (100.0%)

*R/DS: resistance/ decreased susceptibility

GC cultures were tested for resistance to azithromycin, ciprofloxacin, erythromycin, penicillin, spectinomycin and tetracycline and decreased susceptibility to cefixime and ceftriaxone.