

A decade of multi-drug resistant
N. gonorrhoea in Coventry, UK
2007 to 2016.

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- The world's first documented case of treatment failure to dual ceftriaxone (MIC 0.25mg/L) and azithromycin (MIC 1.0mg/L) was reported in England in 2015
- This was an imported isolate from Japan.
- No Treatment failures of gonorrhoea acquired within the UK have been identified.
- Our concern is the emergence of high level resistance to azithromycin (>256mg/L MIC)

WHO

- Antibiotic Resistant gonorrhoea on the rise, new drugs are needed.
- An estimated 78 million people are infected with N.g.
- Widespread resistance to older and cheaper antibiotics

Surveillance

- Local
- National
- Global

Microbiology:

Neisseria gonorrhoea

Neisseria Meningitidis

Gram – Negative diplococci

N. gonorrhoea

- Columnar epithelial,
- Transitional Epithelium - Mucosal surface
- Endocervix
- Urethral
- Rectum
- Pharynx
- Conjunctive – adult as well as
- Ophthalmia Neonatorum

N. gonorrhoea

- No polysaccharide capsule but has multiple serotype
- Marked antigenic variation in the gonococcal pili
- More than 100 serotypes
- 3 outer membrane proteins (I, II, III)
- Protein II plays a role in attachment

Pathogenesis

- Only in humans
- Sexually transmitted
- Neonatal infection
- N. g is very sensitive to dehydration and cool conditions

Pili

- Virulence
- Mediate attachment
- Antiphagocytic

Virulence

Factors in the cell wall

- Endotoxin (Lipo oligo saccharide , Los)
- Outer membrane proteins

IgA Protease – Hydrolyze secretory IgA

Main host defence

- IgA and IgG
- Complement
- Neutrophils

Laboratory Diagnosis

- Gram Staining
- NAAT
- Culture

Specimen collection

Clinical features

Men – Urethral infections

- urethral discharge >80%
- Dysuria >50%
- Can be asymptomatic $\approx$ 10%

Rectal Infection:

- usually asymptomatic
- Discharge $\approx 12\%$
- Pain/discomfort 7%

Pharyngeal Infection:

- Usually asymptomatic $>90\%$

Women:

- Endocervix, Asymptomatic $\approx 50\%$
- Increased vaginal discharge $\approx 50\%$
- Lower abdominal pain up to 25%
- Urethral infection, dysuria $\approx 12\%$

Complications:

Transluminal spread

- epididymis, prostate $\approx 1\%$
- endometrium, pelvic organs $<10\%$

Disseminated infection: $<1\%$

- arthritis, tenosynovitis
- skin infections
- Ophthalmia Neonatorum

Treatment:

Prior to 1950:

Penicillin

Low level resistance to Penicillin,
Tetracycline mediated through
chromosome.

1976 – Penicillinase – Producing N.g.

- High level resistance
- through Plasmid encoded

1980/90 - Fluoroquinolones resistance

- Ciprofloxacin

2000 - Cephalosporines

2008 - Ceftriaxone 500g IM and
Azithromycin 1g stat

Alternative therapy:

- Cefixime 400mg oral – single dose
- Spectinomycin 2g IM
- Azithromycin 2g Stat
- Ciprofloxacin 500mg oral

Pregnancy & breast feeding

- Ceftriaxone 500mg IM & Azithromycin 1g

Gonococcal PID:

Ceftriaxone 500mg IM stat &
Doxycycline 100mg BD +
Metronidazole 400mg BD for 14 days

Gonococcal Conjunctivitis:

Ceftriaxone 500mg IM daily for 3 days,
irrigate the eye with saline/water.

Disseminated gonococcal infection:

Ceftriaxone 1g IM or IV for 7 days,
may be switched to oral treatment after
48 hours if symptoms improve, ie Cefixime
400mg BD.

Test of Cure:

Two weeks after completion of treatment.

- Asymptomatic patients – NAAT
- Symptomatic patients – culture
≈ 72 hours after treatment

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Overall a TOC with NAAT was performed between 6 and 77 days post-treatment with a mean, median and mode of 18, 14 and 14 days respectively.

Year	Number of days after initial treatment of GC	Time Range	Mean	Median	Mode
2013		4 – 49	18.5	16	14
2014		7 – 50	18	15	14
2015		7 - 50	17	14	14
2016		6 - 77	18	14	14

Abstract:

Antibiotic resistance to *Neisseria gonorrhoea* (N.g) is rapidly developing and changing worldwide.

Methods:

All N.g cases in our clinic between 1st January to 30th June 2007 to 2016 were identified and analysed for antibiotic sensitivity.

Antibiotic Resistance profiles	2007	2009	2011	2012	2013	2014	2015	2016
Total number of cases	41	78	75	66	136	126	151	131
Percentage of GC fully sensitive to antibiotic testing panel	46%	67%	59%	49%	79%	59%	43%	55%
Reduced susceptibility to 1 antibiotic group	27%	15%	20%	38%	10%	20%	23%	23%
Multi-drug resistant	27%	12%	21%	11%	8%	21%	26%	23%
Reduced susceptibility to Cefuroxime	0%	0%	0%	0%	0%	0%	0%	1%

	Fully Sensitive N.G	MDR	
Number	43	18	
Age (yrs) mean	24	30	P=0.02
PH Chlamydia	5%	27%	P=0.05
PH GC	18%	22%	P=0.51 (NS)

Conclusion:

The emergence of cephalosporin resistance is a worrying trend. Continued close monitoring with research to identify new treatment is urgently needed.

Research to predict MDR *N. gonorrhoea* infection is an urgent priority for the international scientific community.

Prevention:-

- Condoms
- Prompt treatment
- Contact tracing

Symptomatic Male patient:

- All partners within the last 2 weeks
or the last partner if more than 2 weeks

Asymptomatic Male patient – 3 months

Women – 3 months

New Diagnosis of gonorrhoea in England
>40,000 in 2015/2016

High risk groups – MSM
- Black Caribbean

Prescribing practice in England 91% of patients received the recommended therapy.

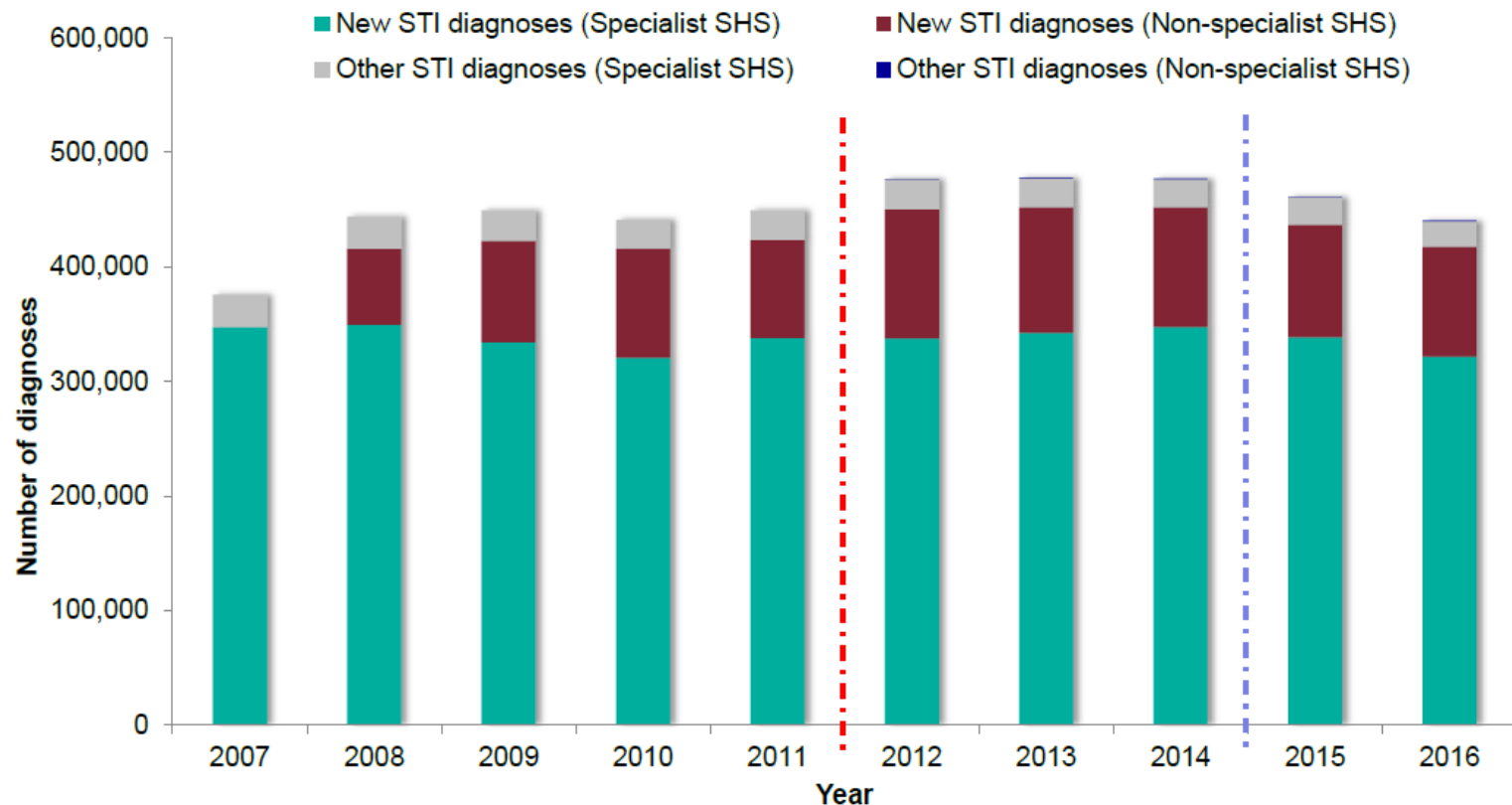
97% in Coventry, UK

Results

Criterion	2007	2008	2009	2011	2012	2013	2014	2015	2016
1.All patients treated for GC should be recommended to have a test of cure (TOC)				(36% had a TOC)	91% (66% had a TOC)	84.6% (52.9% had a TOC)	82% (60% had a TOC)	91% (61% had a TOC)	87% (61% had a TOC)
2.All patients with gonorrhoea should be screened for genital infection with Chlamydia trachomatis or receive presumptive treatment for this infection	100%	100%	100%	98.6%	100%	100%	100%	99.3%	100%
3.All patients identified with gonorrhoea should have partner notification carried out according to the published standards of the BASHH Clinical Standards unit	82%	95%	92%	92%	88%	90.4%	92%	96.7%	88%
4.All patients identified with gonorrhoea should be offered written advice about STIs and their prevention	32%	64%	81%	61%	50%	66%	27%	74%	56%
5.All patients with gonorrhoea should receive 1 st line treatment*, or the reasons for not doing so should be documented	77%	96%	100%	97%	88%	100%	96%	93.4%	97%

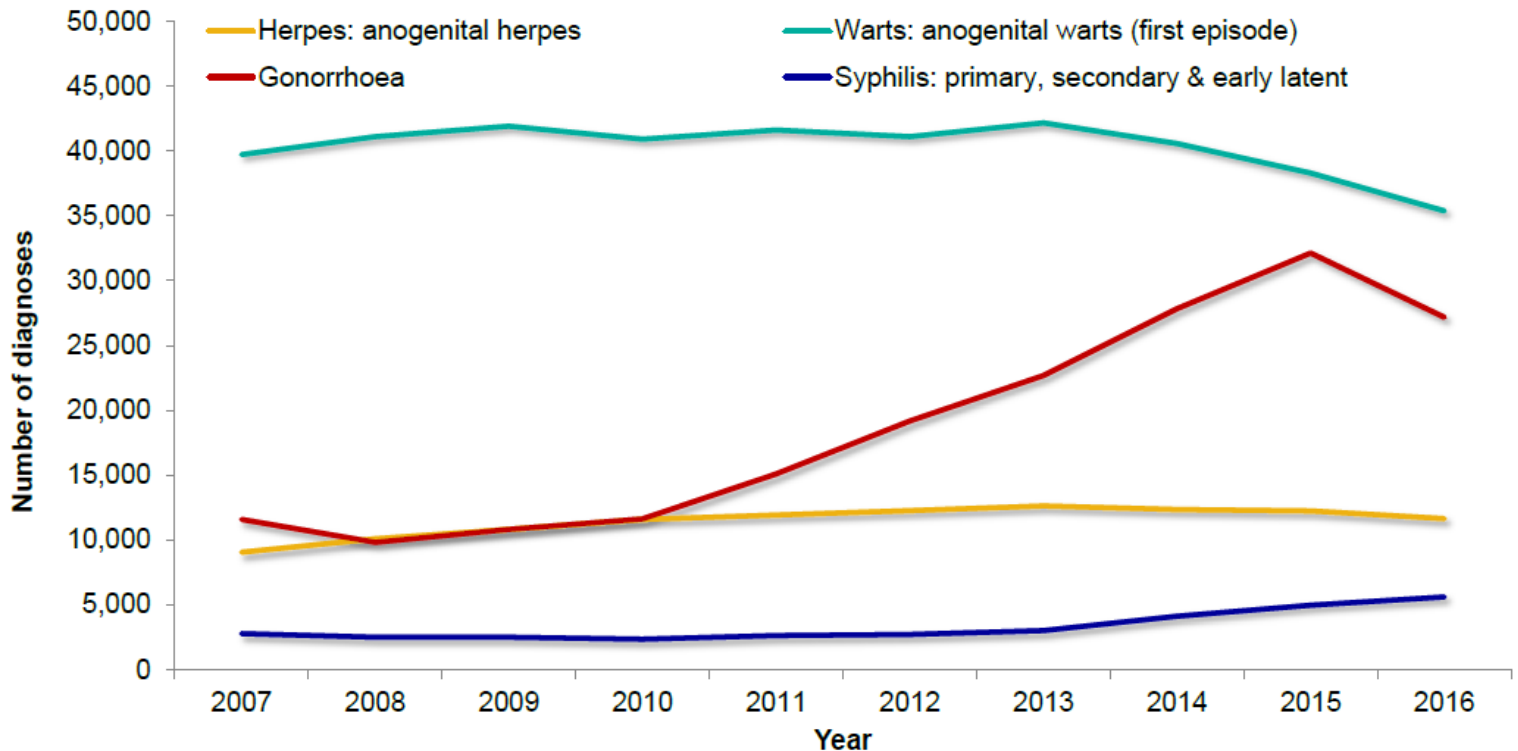
*.At least 95% of the cases of genital gonorrhoea should be cured by first-line therapy (BASHH Guidelines 2011)

Total number of STI diagnoses: England, 2007–2016



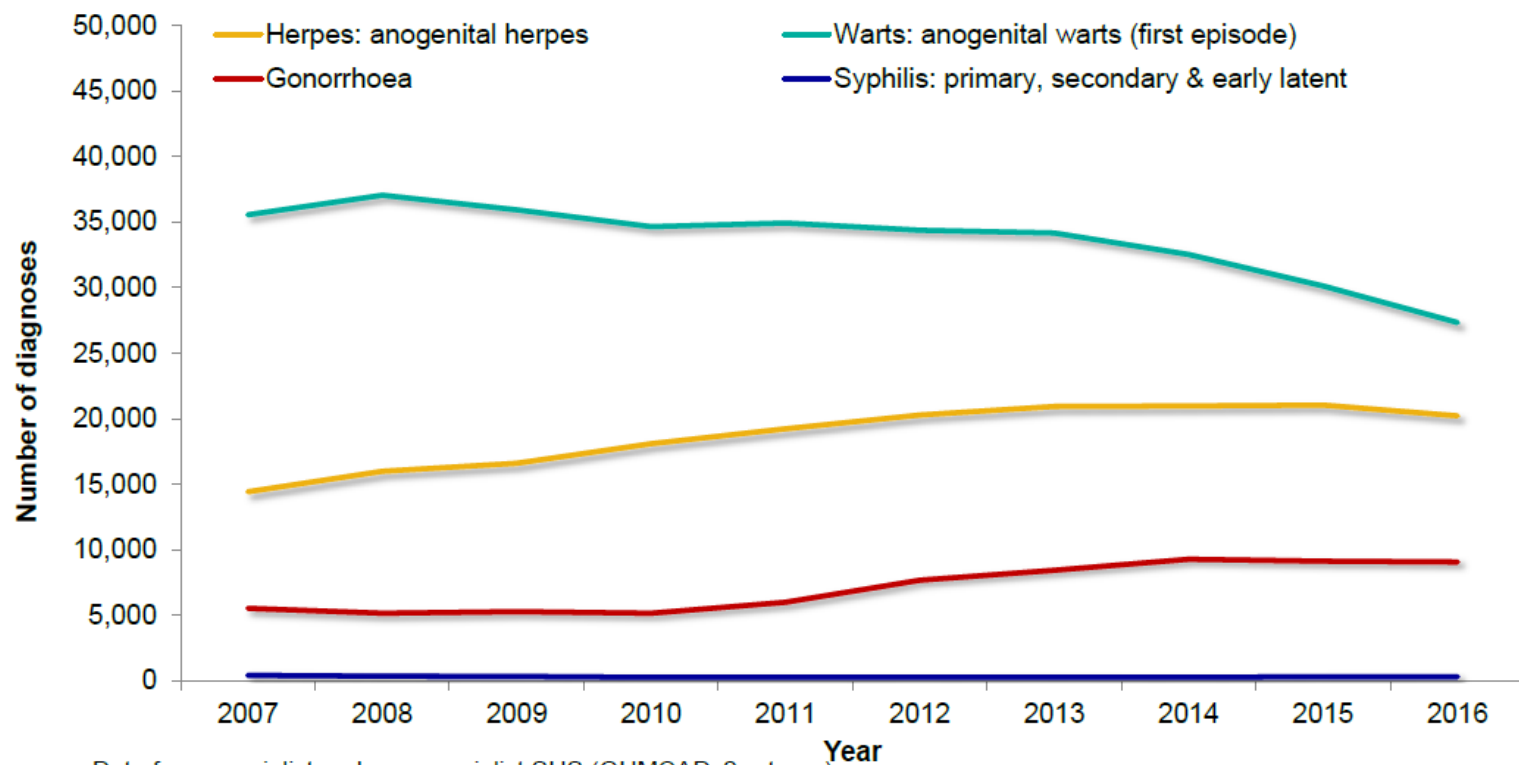
- Data from specialist and non-specialist SHS (GUMCADv2 and CTAD returns)
- Data for new STI diagnoses from 2012 onwards, & from 2015-16, are not comparable to data from previous years (please see Notes 3 to 5 in the 'Notes' slide for more details)
- Data type: service data

Number of STI diagnoses among men: England, 2007–2016



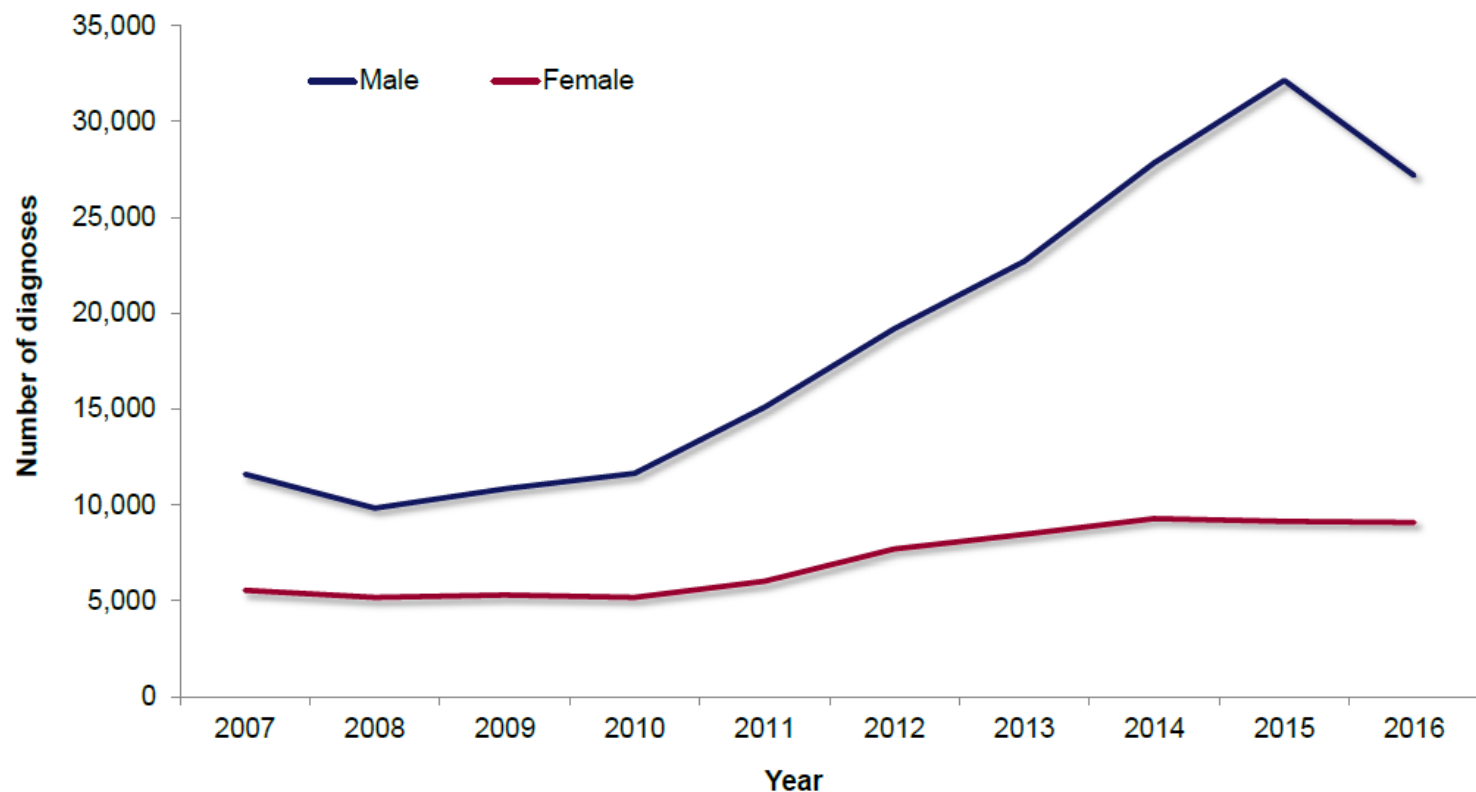
- Data from specialist and non-specialist SHS (GUMCADv2 returns)
- Chlamydia data excluded due to high numbers (see slide 13)
- Data type: service data

Number of STI diagnoses among women: England, 2007–2016



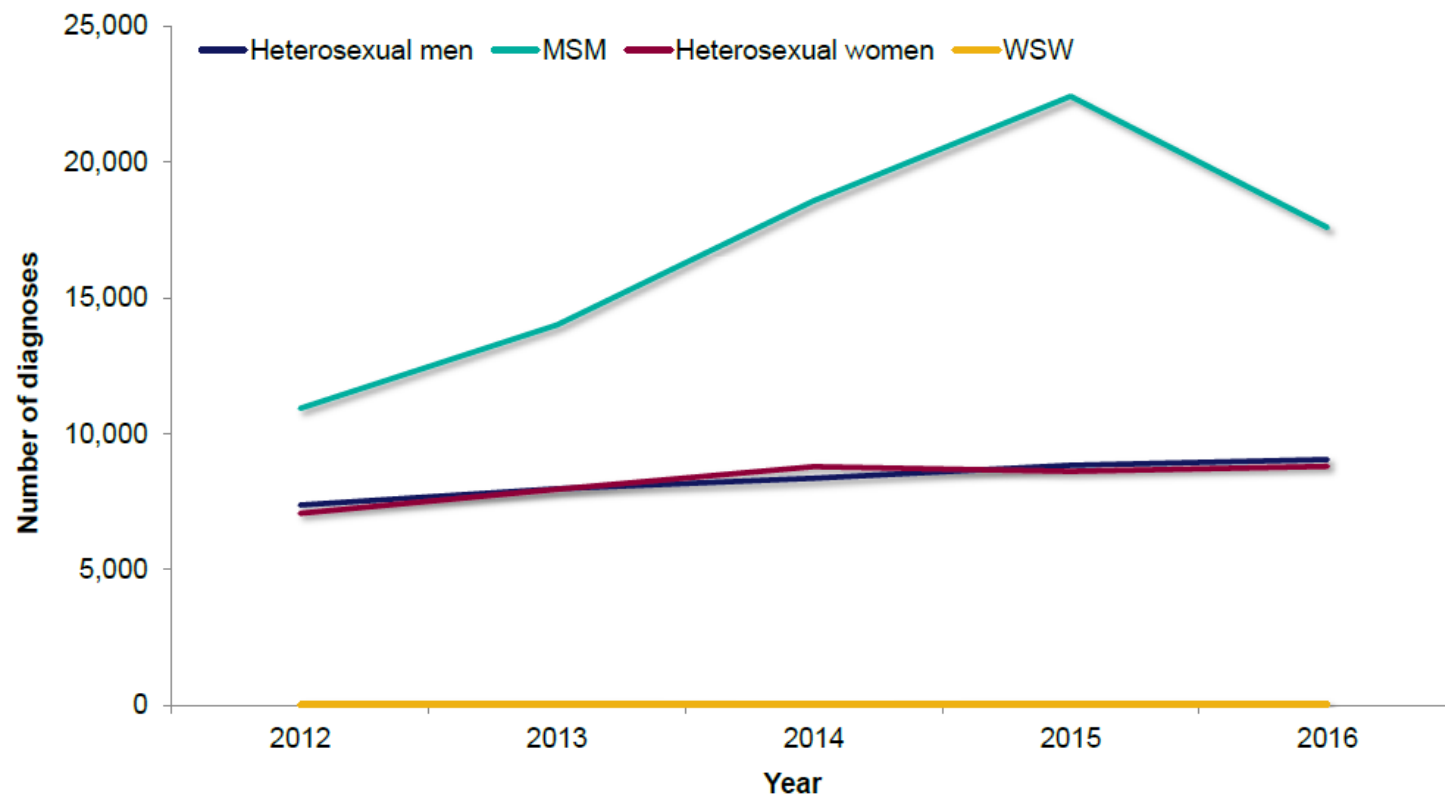
- Data from specialist and non-specialist SHS (GUMCADv2 returns)
- Chlamydia data excluded due to high numbers (see slide 14)
- Data type: service data

Number of gonorrhoea diagnoses by gender: England, 2007–2016



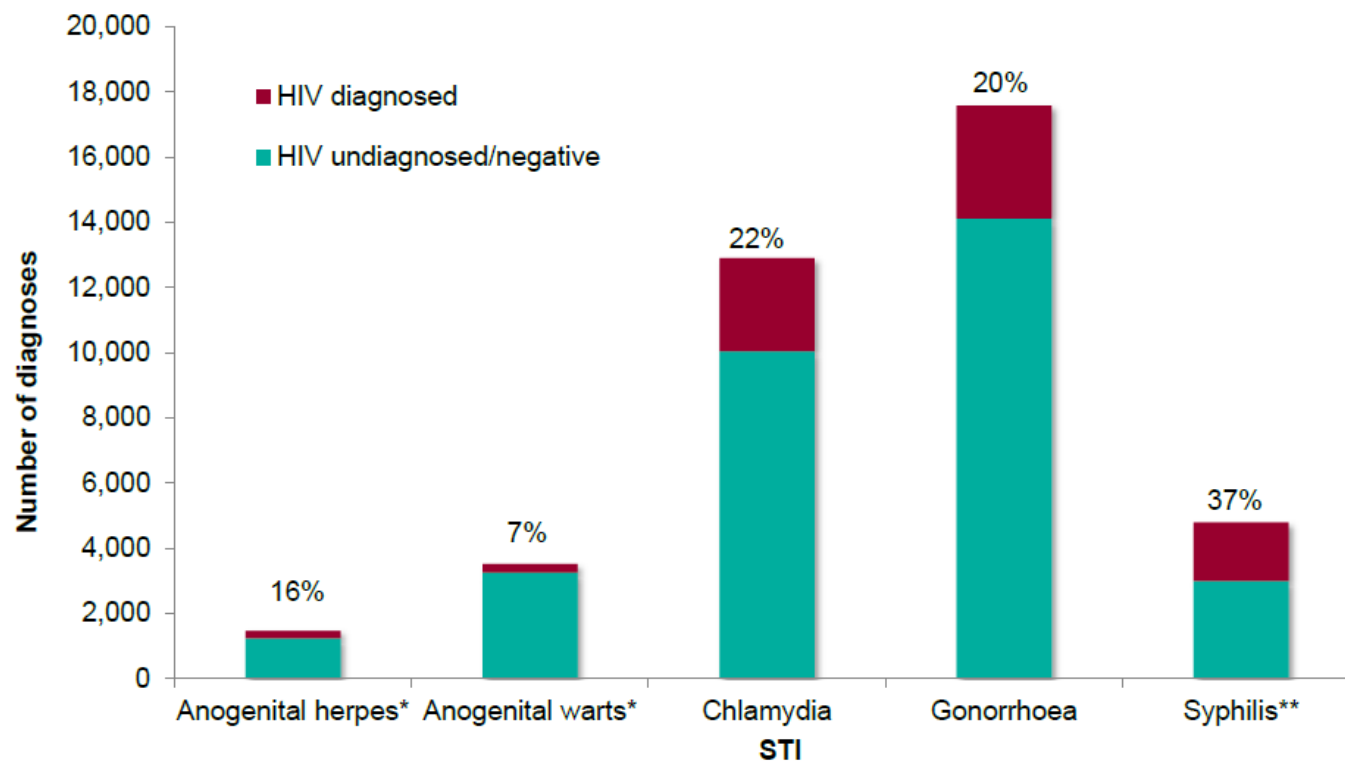
- Data from specialist and non-specialist SHS (GUMCADv2 returns)
- Data type: service data

Number of gonorrhoea diagnoses by sexual risk: England, 2012–2016



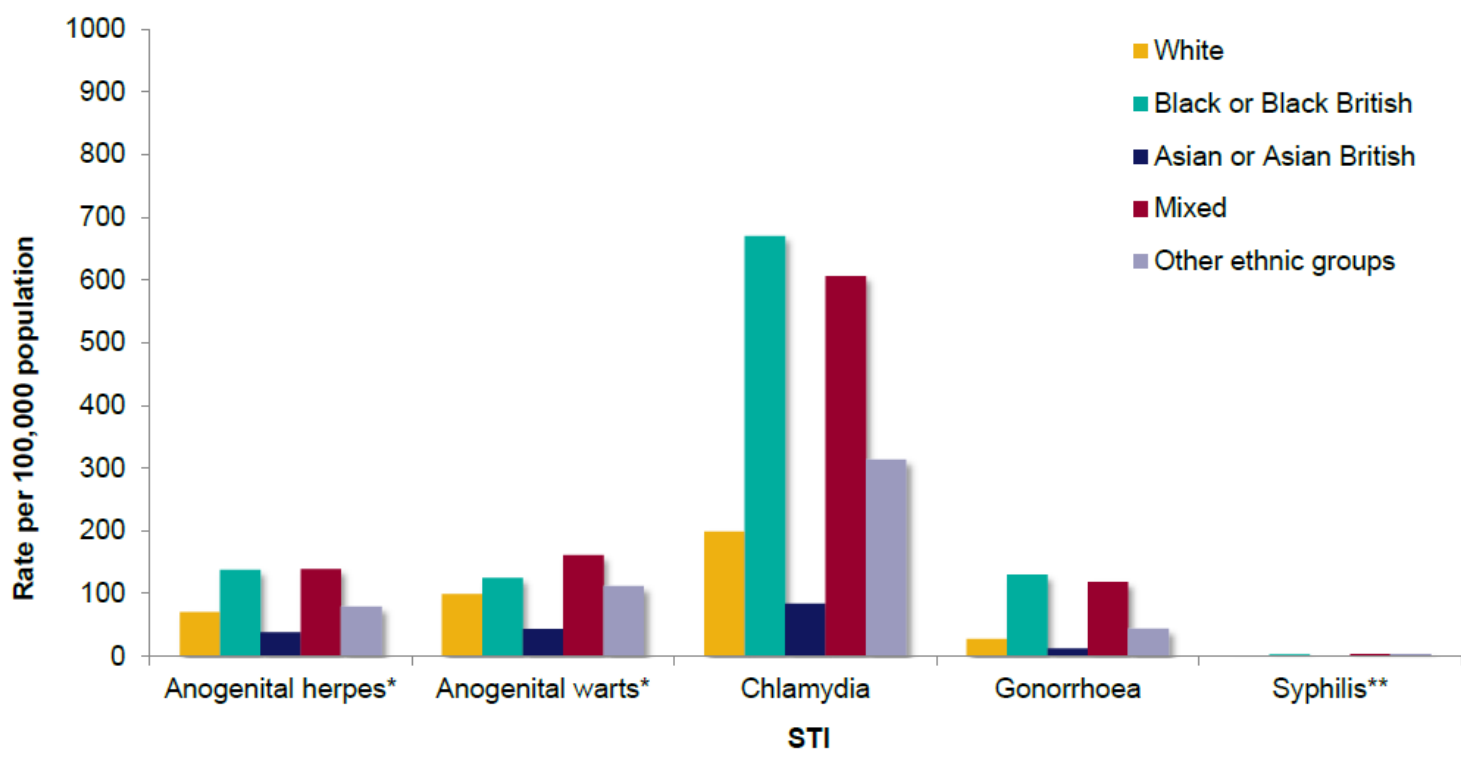
- Data from specialist and non-specialist SHS (GUMCADv2 returns)
- Data type: service data

Number of STI diagnoses among MSM by HIV status: England, 2016



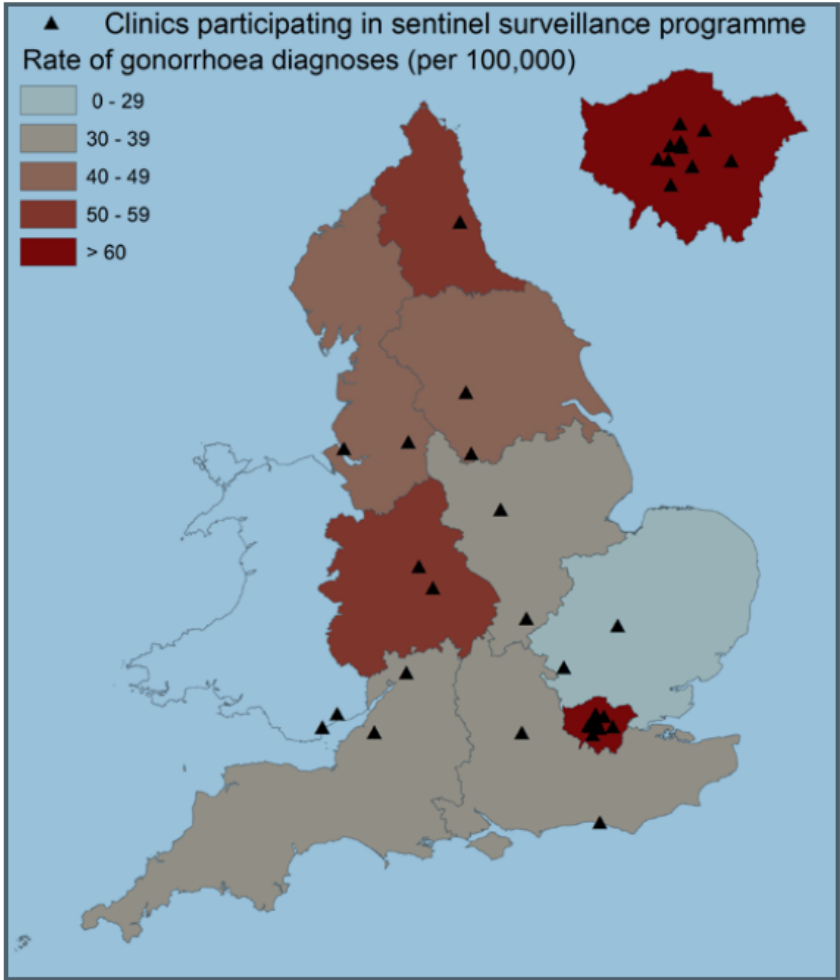
- Data from specialist and non-specialist SHS (GUMCADv2 returns)
- Percentages represent the proportion of STI diagnoses that were made in MSM known to be HIV positive
- * First episode; ** Includes diagnoses of primary, secondary & early latent syphilis
- Data type: service data

Rates of STI diagnoses among women by ethnic group: England, 2016



- Data from specialist and non-specialist SHS (GUMCADv2 returns)
- * First episode; ** Includes diagnoses of primary, secondary & early latent syphilis
- Data type: service data

* PHE Centre areas: East Midlands, East of England, London, North East, North West, South East, South West, West Midlands, Yorkshire and the Humber



Box 1: Definitions of antimicrobial resistance in the sentinel surveillance system

Resistance Classification

Resistance to ceftriaxone*

Resistance to azithromycin

High-level resistance to azithromycin

Resistance to cefixime*

Resistance to ciprofloxacin*

Resistance to penicillin*

Penicillinase-producing *N. gonorrhoeae* (PPNG)

Resistance to tetracycline

Resistance to spectinomycin

Definition

Ceftriaxone MIC ≥ 0.125 mg/L

Azithromycin MIC > 0.5 mg/L

Azithromycin MIC ≥ 256 mg/L

Cefixime ≥ 0.125 mg/L

Ciprofloxacin MIC ≥ 1.0 mg/L

Penicillin MIC ≥ 1.0 mg/L

or β -lactamase positive

β -lactamase positive

Tetracycline MIC ≥ 2.0 mg/L

Spectinomycin MIC ≥ 128

mg/L

*Please note these are different to EUCAST breakpoints

EUCAST breakpoints:

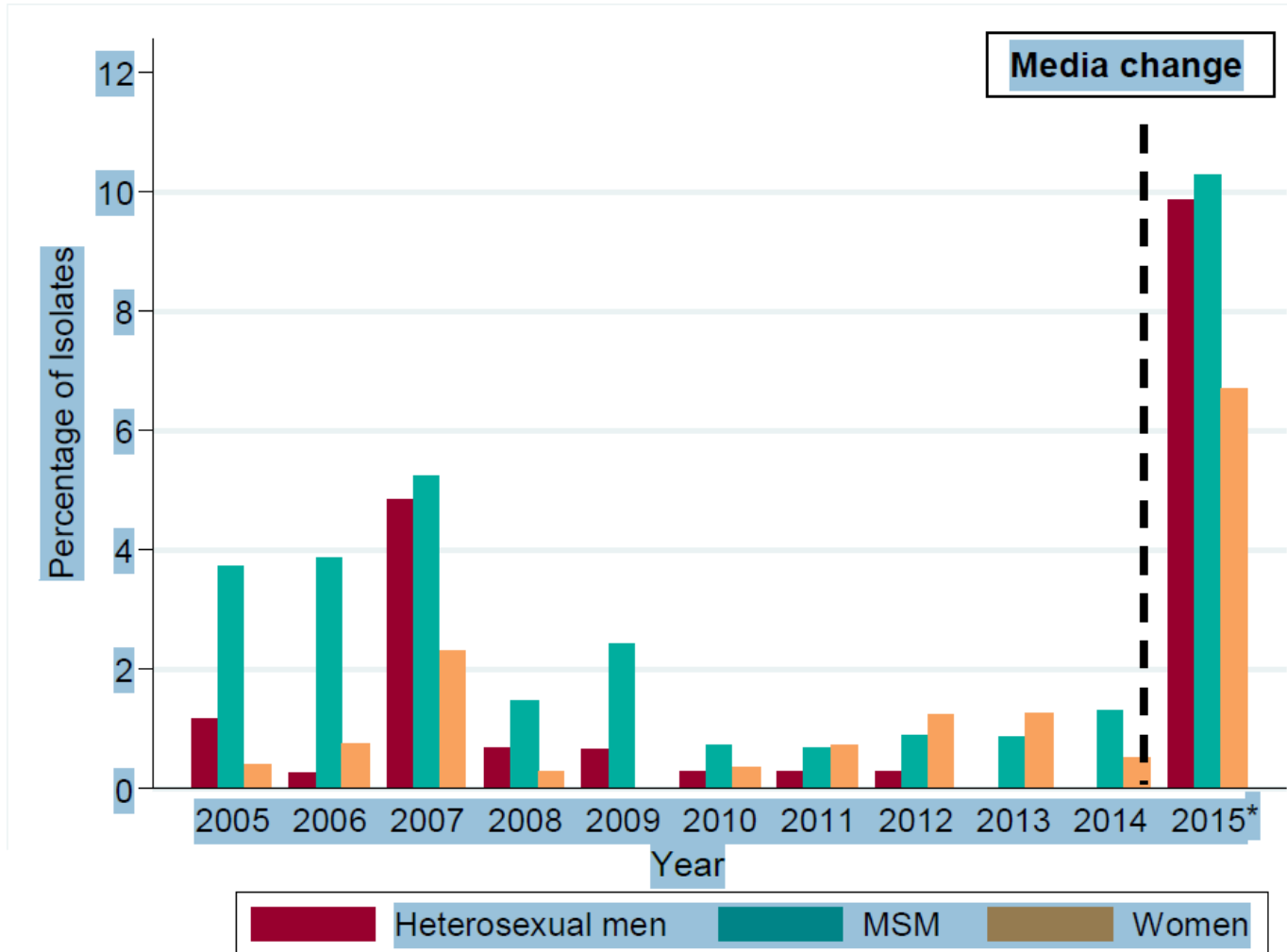
- Resistance to ceftriaxone (MIC > 0.125 mg/L)
- Resistance to cefixime (MIC > 0.125 mg/L)
- Resistance to ciprofloxacin (MIC > 0.06 mg/L)
- Resistance to penicillin (MIC > 1.0 mg/L)

	2014 (N=18,536)	2015 (N=19,372)
Ceftriaxone	87.2 (68.2-98.6)	91.1 (79.1-98.6)
Azithromycin	80.1 (20.5-97.3)	88.1 (35.7-98.9)
Cefixime	66.4 (27.1-92.5)	62.7 (41.6-88.5)
Ciprofloxacin	88.8 (70.3-99.5)	91.0 (80.4-99.7)
Penicillin	59.2 (32.0-99.6)	59.7 (29.9-95.6)
Tetracycline	49.8 (33.5-84.8)	53.2 (37.3-85.9)
Spectinomycin	68.4 (3.4-91.2)	67.6 (2.4-92.2)

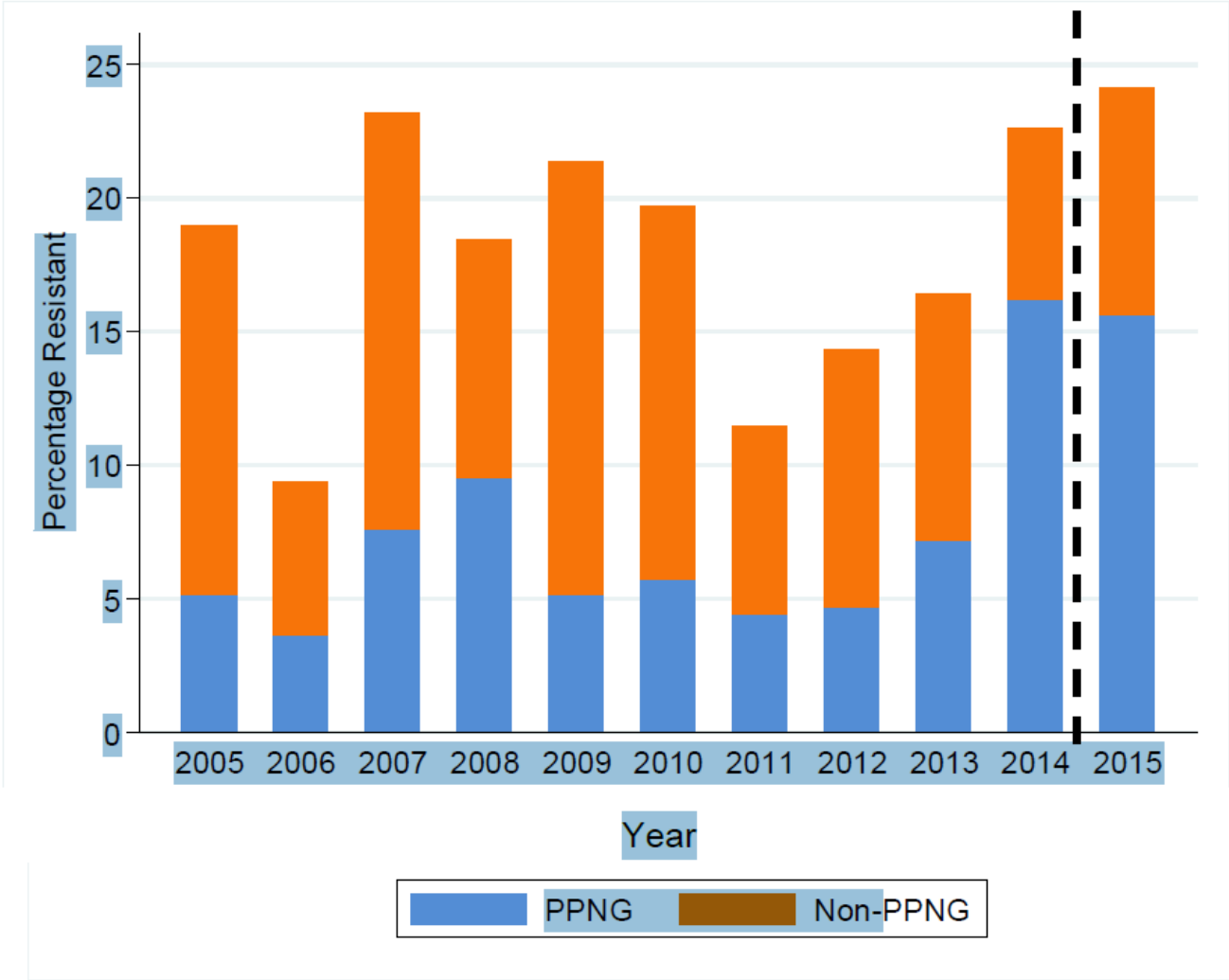
Table 3: Number of isolates susceptibility tested and percentage of gonococcal isolates in primary diagnostic laboratories reported resistant to selected antimicrobials, SGSS: 2014 and 2015

Antimicrobial	Percentage of episodes resistant (range across PHE centre)		Number of isolates susceptibility tested (n)	
	2014	2015	2014	2015
Ceftriaxone	0.3 (0.0-0.8)	0.5 (0.0-2.4)	16,155	17,650
Azithromycin	1.3 (0.6-3.8)	1.6 (0.7-5.2)	14,845	17,057
Cefixime	0.3 (0.0-1.3)	0.6 (0.3-2.7)	14,286	15,589
Ciprofloxacin	30.0 (14.7-37.3)	29.0 (15.7-35.5)	16,465	17,619
Penicillin	25.1 (11.0-40.8)	29.3 (17.0-42.3)	10,960	11,583
Tetracycline	19.9 (8.3-24.9)	20.9 (15.9-26.7)	9,234	10,329
Spectinomycin	0.4 (0.0-3.7)	0.2 (0.0-0.9)	12,685	13,088

cannot be compared with resistance prevalence in previous years



Media change



7.7 Table 7: Percentage of gonococcal isolates that were resistant to selected antimicrobials from Europe, Canada, Australia and the USA surveillance programmes

	Cefixime (MIC >0.12mg/L)	Ceftriaxone (>0.064mg/L)	Azithromycin (MIC >0.5 mg/L)	Ciprofloxacin (MIC >0.5 mg/L)
GRASP (2015)	0.4%	0%	9.8%	39.1%
GRASP (2014) ¹²	0.1%	0.0%	1.0%	37.2%
Euro-GASP (2014) ¹³	2%	2.8%	7.8%	50.7%
USA GISP (2014) ¹⁴	0.8%	0.1%	7.1%	19.2%
Canada (2014) ¹⁵	1.1%	2.7%	3.3%*	No data
Australia AGSP (2014) ¹⁶	No data	0.6%	2.5%	36%

*Resistance MIC >0.1 mg/L

Neisseria gonorrhoea

Continued surveillance in all parts of the world.

Prompt and appropriate treatment.

Partner notification and management.

Prevention.

Research into new antibiotics.