



IST : émergence de la résistance aux antibiotiques

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SCIENCE & IMPACT

Déclaration d'intérêts de 2014 à 2018

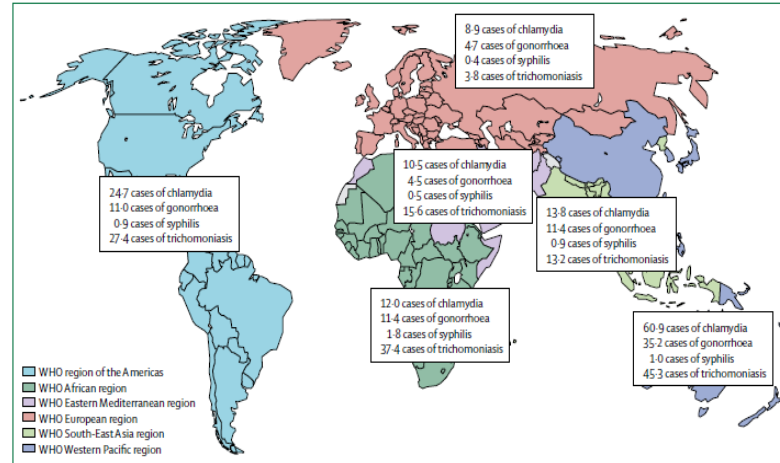
Investigateur principal d'une évaluation de trousse diagnostiques :

- Hologic,
- SpeeDx

INTRODUCTION

WHO 2012: 357 million new cases for curable non viral STIs in adults

- **Chlamydia** 131 million
- **Gonorrhoea** 78 million
- **Syphilis** 5.6 million



Newman et al PLoS One 2015; Unemo, Bradshaw et al, *Lancet Infect Dis*, 2017;17:e235-79

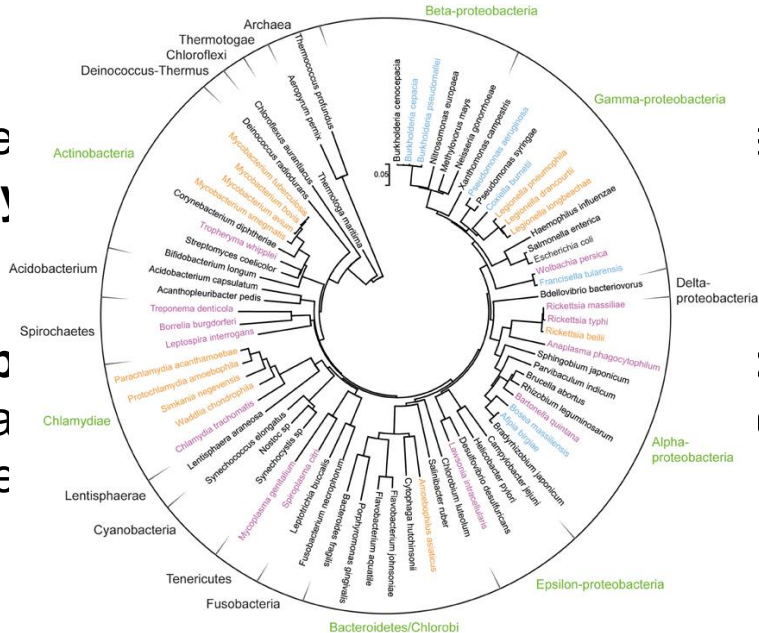
- Emerging STI pathogen: ***Mycoplasma genitalium***, exceedingly prevalent
- Emergence of **antimicrobial resistance (AMR)** in these bacterial STIs
→ reduced treatment options and STIs control

Chlamydia trachomatis

- **Chlamydiae**: intracellular bacteria, a distinct phylogenetic lineage among Gram-negative bacteria and very limited evidence of horizontally acquired foreign DNA

- 1st line tre
- **Azithromy**

- **Heterotyp**
- subpopula
- less susce



⋮

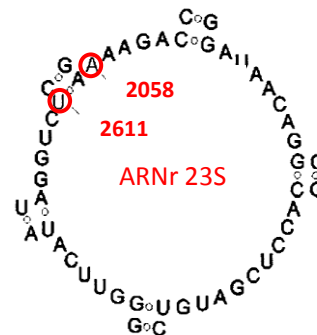
ctious loads:
d growth rate,

C. trachomatis: acquired resistance

Exceptional !

- **Macrolides**
 - **Resistance** described for 4 clinical strains
 - > **ribosomal mutations**

Misyurina et al, Antimicrob Agents Chemother, 2004;
Binet et al, Antimicrob Agents Chemother, 2007; Zhu et al, Andrologia, 2010



- **Tetracyclines**
 - **No clinical resistance**
 - ***In vitro* horizontal transfer** of a tetracycline resistance gene between *C. trachomatis* and *C. suis*, a porcine species

Dugan et al., Antimicrob Agents Chemother, 2004; Suchland et al., Antimicrob Agents Chemother 2009; Jeffrey et al., BMC Microbiol 2013

C. trachomatis: acquired resistance

- Fluoroquinolones
- No clinical resistance
- In vitro-selected mutants

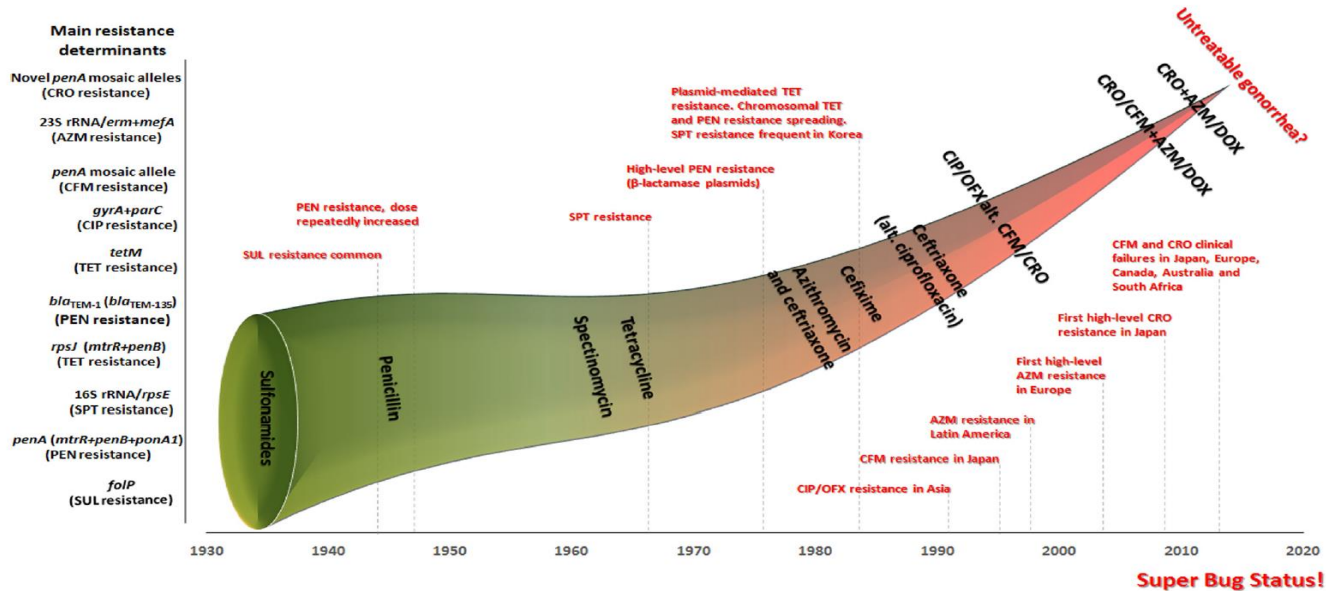
TABLE 2. Antibiotic susceptibilities of the reference strain and fluoroquinolone-resistant mutants of *C. trachomatis* L2

Strain	Selecting agents	MIC ($\mu\text{g/ml}$) ^a						
		OFX	SPX	PFX	CFX	NFX	ERY	DOX
Reference	None	1	0.03	2	1	12	0.4	0.05
L2-OFXR	Ofloxacin	64	32	32	32	96	0.4	0.05
L2-SPXR	Sparfloxacin	32	32	32	16	48	0.4	0.05

^a OFX, ofloxacin; SPX, sparfloxacin; PFX, pefloxacin; CFX, ciprofloxacin; NFX, norfloxacin; ERY, erythromycin; DOX, doxycycline.

N. gonorrhoeae: antibiotic resistance

- NG has an extraordinary capacity to alter its genetic material
- It is naturally competent for transformation and can also change its genome through all types of mutations



N. gonorrhoeae: antibiotic resistance

- Super bug status

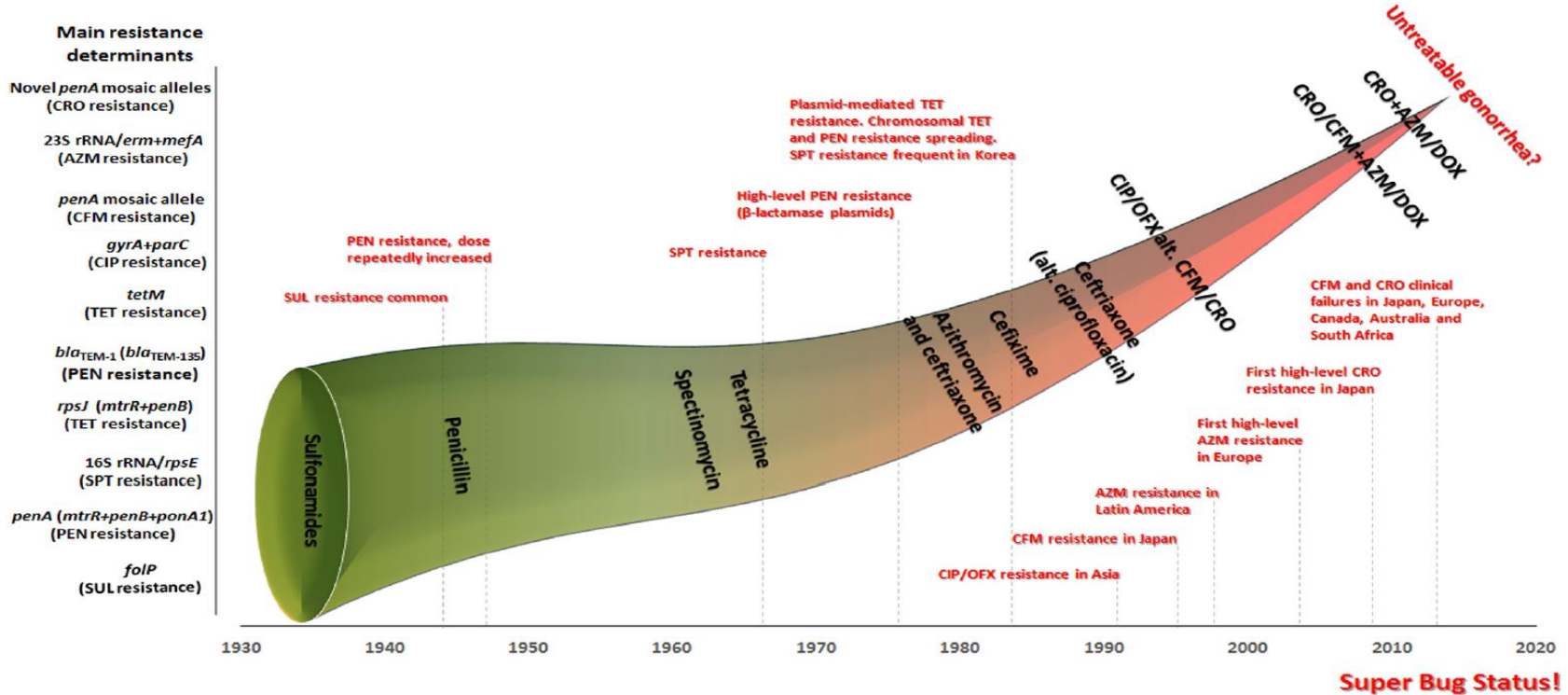


ECDC, 2012

- Empirical 1st-line treatment
for uncomplicated gonorrhoea (WHO, Europe, USA)
Dual antimicrobial therapy: **ceftriaxone + azithromycin**

WHO 2016; Bignell and Unemo Int. J. STD AIDS 2013; Workowski, et al. MMWR Recommend Rep 2015; Public Health Agency of Canada. 2013; Australasian Sexual Health Alliance. www.sti.guidelines.org.au/sexually-transmissibleinfections/gonorrhoea#management 2016.

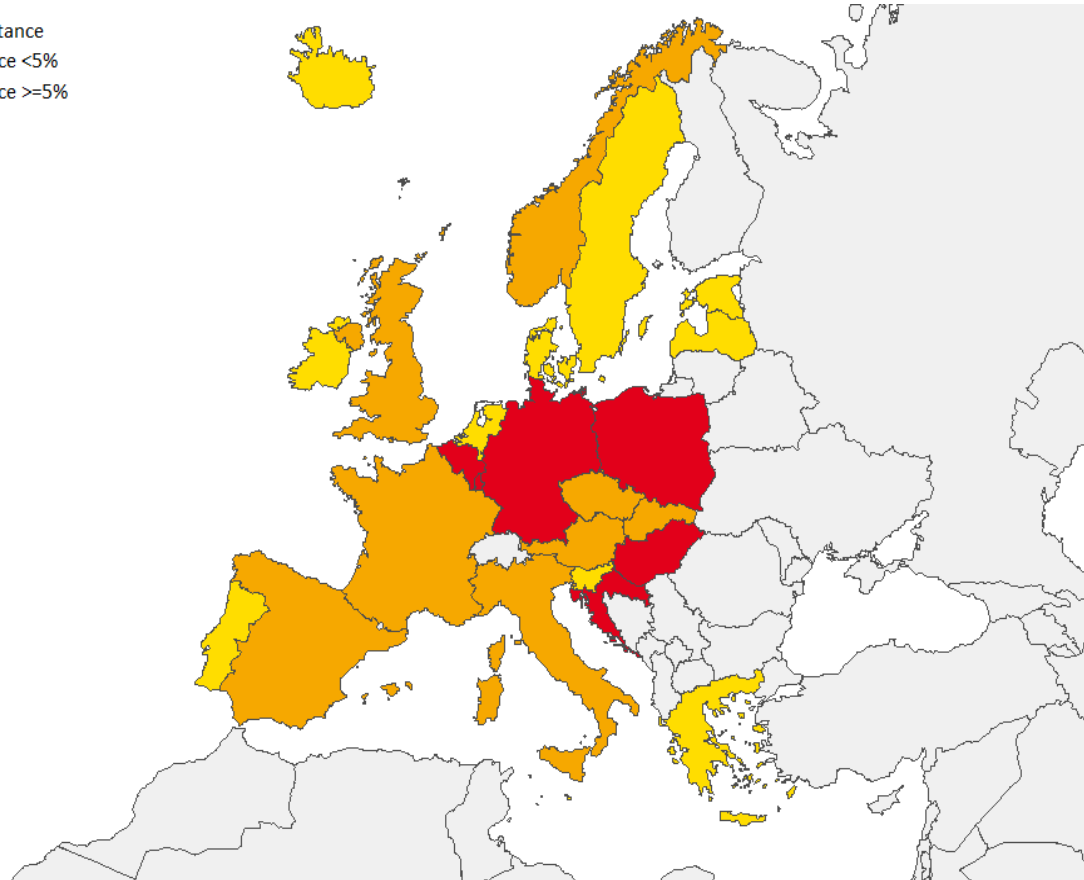
N. gonorrhoeae: antibiotic resistance



% of isolates with decreased susceptibility or resistance to cefixime in 2016 (Euro-GASP-ECDC)

- No cefixime resistance
- Cefixime resistance <5%
- Cefixime resistance >=5%

- Liechtenstein
- Luxembourg
- Malta



N. gonorrhoeae: antibiotic resistance

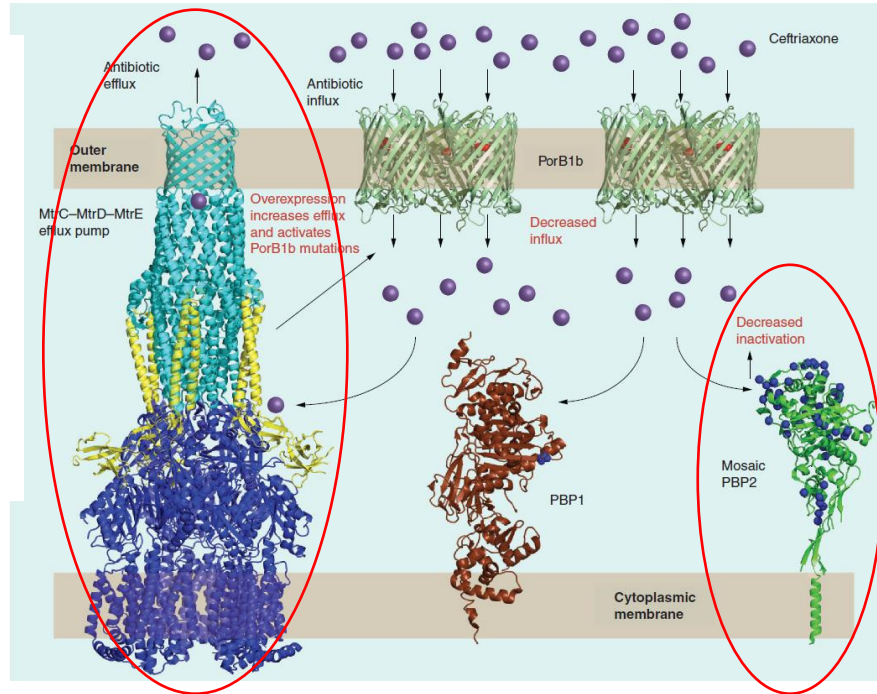
- Resistance to 3rd generation cephalosporins : 0.3% cefixime-R strains, no ceftriaxone-R strain in France in 2018

Mosaic *penA* gene

Alteration of PBP2, the lethal target for ESCs

Hyperexpression of the MtrCDE efflux pump

Enhanced efflux & decreased influx of ESCs



N. gonorrhoeae: antibiotic resistance

- **Azithomycin resistance: 2% - 8%**

Europ EURO-GASP 2016 (n=22659) 25 countries	Australia 2015 n=5411	United States GISP 2014 (n=5093), 27 sites
7.5%	2.6%	2.5%

- **6.5% - 17.3% according to networks in France in 2018**

- Low and more rarely high-level resistance, ribosomal mutations (23S rRNA)

- **Fluoroquinolone resistance: 30 % – 50 %**

- 47% - 55% according to networks in France in 2018**

- High-level resistance, mutations in the enzyme targets (gyrase)



Saint Louis

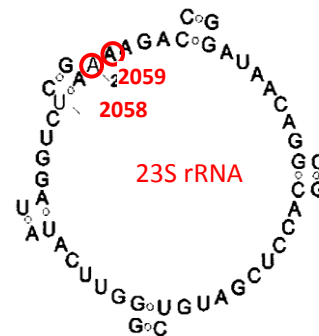
- **Tetracycline resistance: > 50%**

- **47.3 % - 63.8% according to networks in France in 2018**

- High-level resistance (*tet(M)* gene on a transposon)

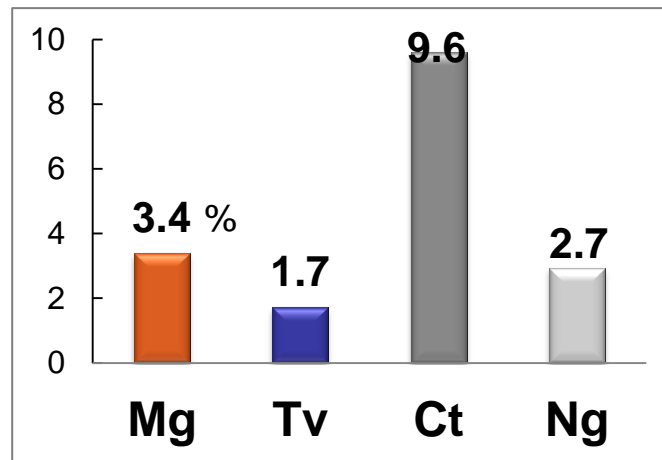
Treponema pallidum: antibiotic resistance

- Since > 50 decades, 1st-line treatment for syphilis is **benzathine penicillin G** (WHO 2016, IUSTI Europe 2014, MMWR 2015):
 - For all stages of syphilis
 - no clinical AMR described
- **Alternatives**: doxycycline or azithromycine
 - No clinical resistance to tetracyclines
 - **Macrolide resistance (AZM) highly prevalent**
 - Ribosomal mutations (23S rRNA)
 - **France (86.4% in 2018)**, UK (66%), Australia (84%), USA (80%) China (100%)



Mycoplasma genitalium

- **STI pathogen:**
 - 15-20% NGU
 - 10-30% cervicitis
 - 2-20% salpingitis
- **Prevalence**
 - 1-3% general population
 - 4-38% high risk population
- **Prevalence in France 2014-2015**
- **Diagnostic by NAAT**
- **1st line treatment with macrolides (azithromycin)**



Urogenital specimens submitted for *C. trachomatis* (Ct) and *N. gonorrhoeae* (Ng) detection (2594 patients)

Pereyre Clin. Microbiol. Infect. 2016

REVIEW ARTICLE

2016 European guideline on *Mycoplasma genitalium* infections

J.S. Jensen,^{1*} M. Cusini,² M. Gomberg,³ H. Moi^{4,†}

¹Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark

²Fondazione IROCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

³Moscow Scientific and Practical Centre of Dermatovenereology and Cosmetology, Moscow, Russia

⁴Olafia Clinic, Oslo University Hospital, Institute of Medicine, University of Oslo, Oslo, Norway



- **All *M. genitalium*-positive test should be followed up with an assay capable of detecting macrolide resistance-associated mutations**

Detection of macrolide resistance-associated mutations

- **Amplification and sequencing of 23S rRNA**
 - Time-consuming, not adapted to routine
- **Published in-house methods**
 - **Ex : FRET real-time PCR** (Touati *et al.* J. Clin. Microbiol. 2014)
- **Commercial kits**
 - **ResistancePlus™ MG kit (SpeeDx, Australia) : multiplex real-time PCR**
Detection of Mg and 5 mutations (Le Roy, J. Clin. Microbiol. 2017)
 - **S-DiaMGRes kit (Diagenode, Belgium)**
 - **Real accurate TVMG^{RES} (Pathofinder)**
 - **Others expected (Seegene, Elitech, Cepheid ...)**



M. genitalium: antibiotic resistance

- **Tetracyclines: low eradication rate for *M. genitalium* clinically (30-40%)**
 - No acquired resistance described
- **Recommended treatment for uncomplicated *M. genitalium* infections**
 - **Azithromycin 500 mg (day 1), then 250 mg (days 2-5)**

DOI: 10.1111/jdv.13849

JEADV

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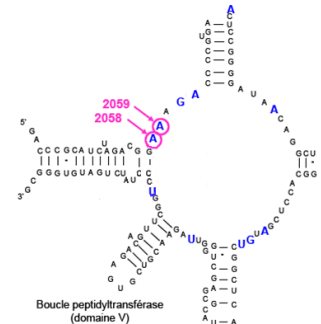
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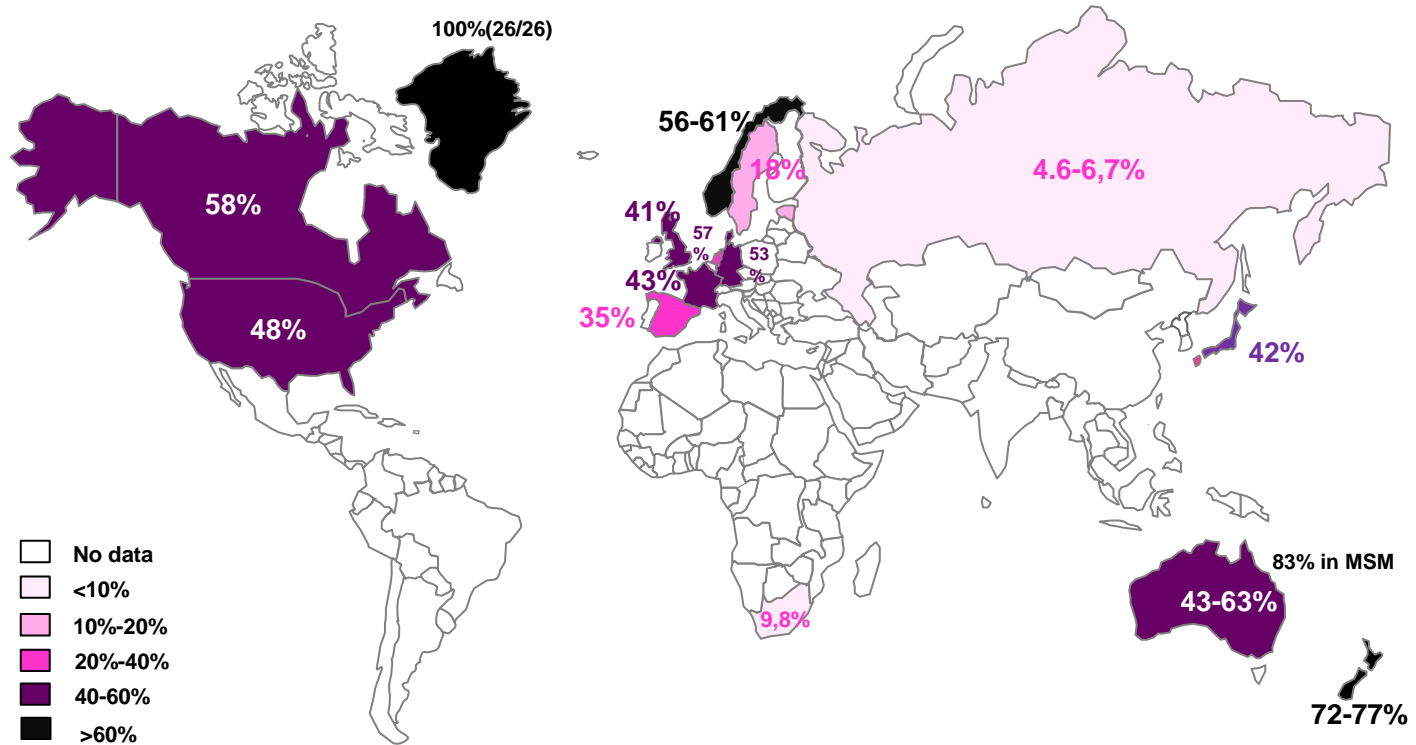
⁴Olafta Clinic, Oslo University Hospital, Institute of Medicine, University of Oslo, Oslo, Norway



- **Clinical acquired resistance to macrolides**
 - **By mutations in the macrolide target (23S rRNA)**
 - **Most likely caused by azithromycin 1g single dose**

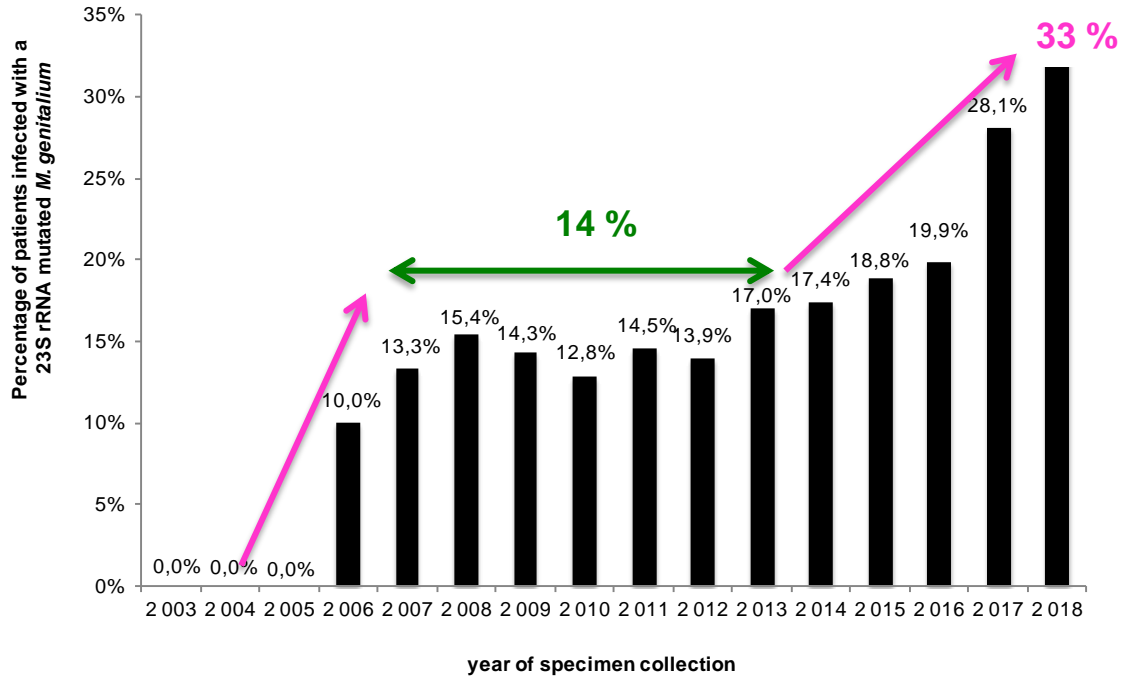


Prevalence of macrolide resistance in *M. genitalium*



Anagnrus, *PloS one* 2013; Tagg, *J. Clin. Microbiol.* 2013; Pond, *Clin. Inf. Dis.* 2014; Salado-Rasmussen, *Clin. Inf. Dis.* 2014; Kikuchi, *J. Antimicrob. Chemother.* 2014; Hay, *Sex. Transm. Dis.* 2015; Gushin, *BMC Infect. Dis.* 2015; Nijhuis, *J. Antimicrob. Chemother.* 2015; Gesink, *Can. Fam. Physician*, 2016; Getman, *J. Clin. Microbiol.* 2016; Gossé, *J. Clin. Microbiol.* 2016; Shiptitsina, *Plos One*, 2017; Basu, *J. Clin. Microbiol.* 2017; Tabrizi, *J. Clin. Microbiol.* 2017; Barbera, *Sex. Transm. Dis.* 2017; Dumke, *Diagn Microbiol infect Dis*, 2016; Coorevits, *J. Glob. Antimicrob. Resist.* 2017; Anderson, *J. Clin. Microbiol.* 2017; Unemo, *Clin. Microbiol. Infect.* 2017. Bébéar C, French National Center for STI report, 2018.

Macrolide resistance in *M. genitalium* Bordeaux, France



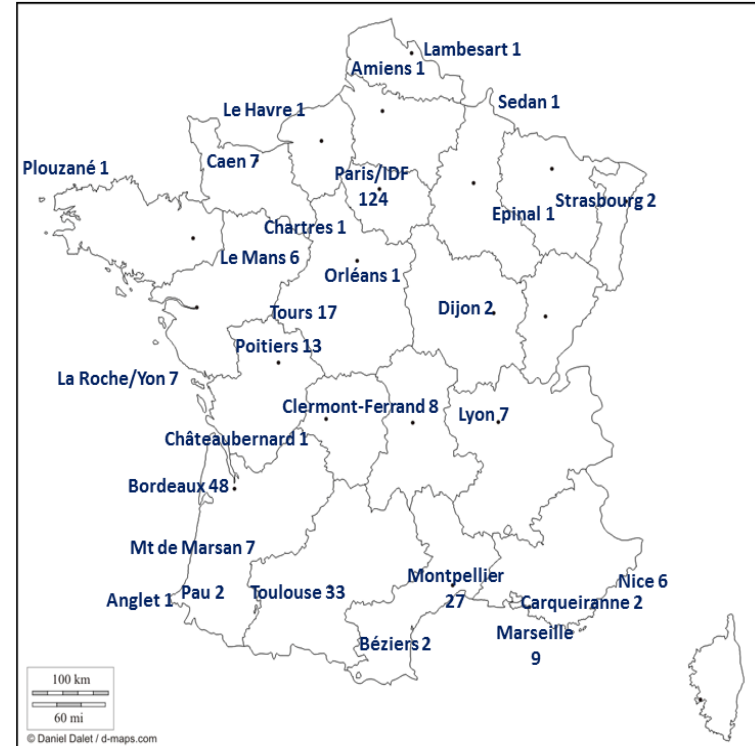
Chrisment et al. *J. Antimicrob. Chemother.* 2012; Touati et. al, *J. Clin. Microbiol.* 2014; Le Roy et al., *Emerg. Inf. Dis.*, 2016; Bébéar C, *French National Center for STI report*, 2018.

Macrolide resistance in France

September 15 - October 15, 2018



- **42.6% resistance in 2017 in France**
- **43% resistance in 2018 in France**
 - 270 patients (60% M, 40% F)
 - MR for 58.8% M vs 18.5% for F ($p < 0.001$)
 - MR for 49.3% patients HIV(+) vs 18.7% for patients HIV(-) ($p < 0.001$)
 - A2059G > A2058G >> A2058T/C



M. genitalium: antibiotic resistance

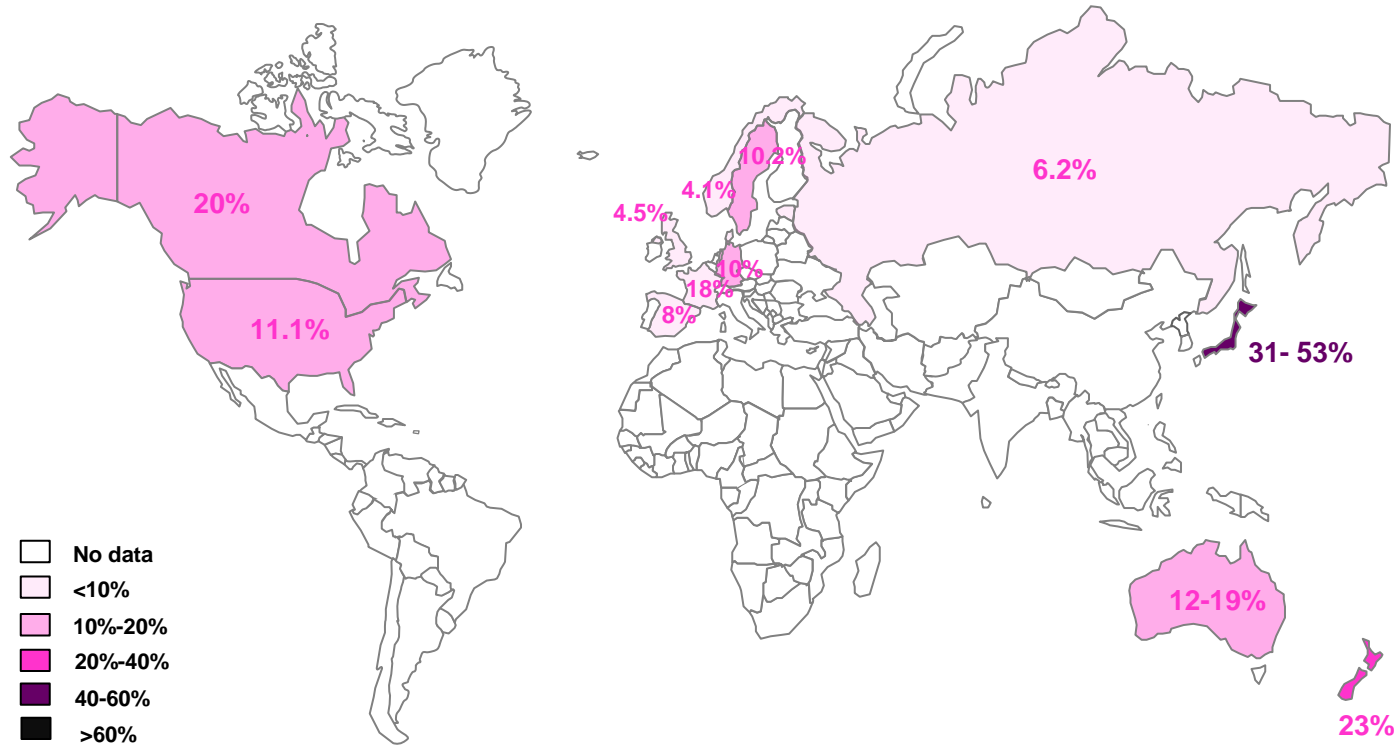
- Recommended treatment for complicated and macrolide-resistant *M. genitalium* infections
 - Moxifloxacin 400 mg od 7-10 days
(Jensen et al. JEADV 2016)



- Emergence of clinical acquired resistance to MXF
 - by mutations in the FQ target (topoisomerase IV)
 - both *in vitro* and clinical resistance
 - ranging from 4.5% (UK) to 50% (Japan)
 - **17.8%** in France in 2018, vs 7.7% in 2017



Prevalence of fluoroquinolone resistance-associated mutations



Bissessor Clin Infect Dis 2015; Deguchi, Clin Infect Dis 2016; Dumke, DMID 2016; Kikuchi J Antimicrob Chemother 2014; Le Roy Emerg Infect Dis 2016; Pond Clin Infect Dis 2014; Shipitsina PLoS one 2017; Couldwell Int J STD and AIDS 2013; Gesink Can family Physian 2016; Tagg J Clin Microbiol 2013; Murray Emerg Infec Dis 2017; Barbera Sex Transm infect 2017; Anderson, J Clin Microbiol 2017, Unemo, Clin Microbiol Infect 2017; Béb  ar C, French National Center for STI report, 2018.

Dual class resistance Macrolides AND fluoroquinolones

- Prevalence of dual resistance

- France : **10.9% in 2018** vs 7.5% in 2017, mainly in males
- Australia : 8.6%
- Japan : 17-30%



- Mainly due to successive treatment failures of macrolides then fluoroquinolones
- Tremendous clinical implications

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Emerging sex disease MG 'could become next superbug'

By Michelle Roberts

Health editor, BBC News online

🕒 11 July 2018



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Conclusion

- **Should we fear AMR for bacterial STIs?** Yes but..
- **Distinct situations**
 - ***N. gonorrhoeae*** and ***M. genitalium*** evolving into so called superbugs ->untreatable ??
(Jensen and Unemo Nature Rev Urol 2017)
 - By contrast ***C. trachomatis*** remains susceptible to many antimicrobials
 - **Syphilis** remains S to the 1st-line drug but there is some concern with azithromycin (2nd-line drug)

The Lancet Infectious Diseases Commission

STIs: challenge ahead, Unemo et al, Lancet Infect Dis, 2017;17:e235-79

Acknowledgments

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for bacterial STIs



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