Résistance bactérienne au cours des Infections Sexuellement Transmissibles

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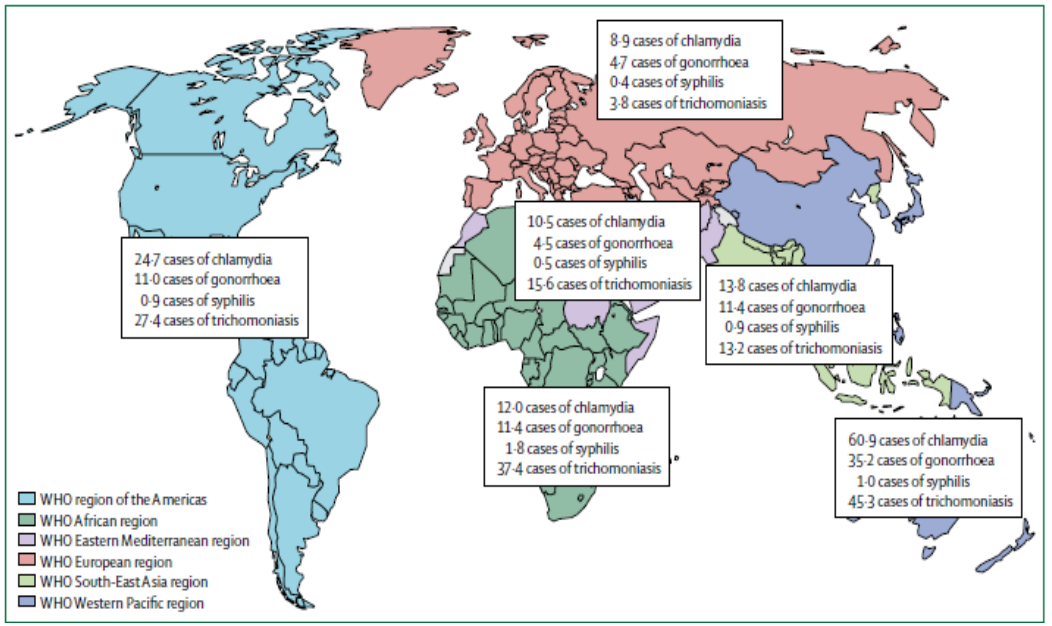
INTRODUCTION

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

- ***Chlamydia*** 131million
- ***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
- Focus on bacterial STIs: ***C. trachomatis, N. gonorrhoeae, T.***

Chlamydia trachomatis

- **Obligate intracellular** bacterium
- **Recommended treatment (WHO guidelines 2016, IUSTI Europe 2015, MMWR Recommend Rep 2015)**

✓ **uncomplicated urogenital infections**

1st-line: **azithromycin** 1g orally in a single dose

or **doxycycline** 100 mg orally twice daily for 7 days

Alternative regimens: tetracycline or erythromycin or fluoroquinolone (ofloxacin or levofloxacin)

✓ **rectal infections**

doxycycline 100 mg orally twice daily for 7 days

✓ **lymphogranuloma venereum (LGV)**

doxycycline 100 mg twice daily for 21 days

Chlamydia trachomatis

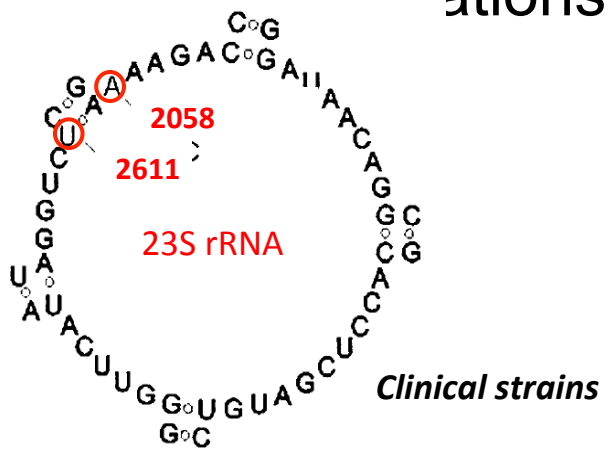
Acquired AMR in patients : very rare

- **Macrolides**

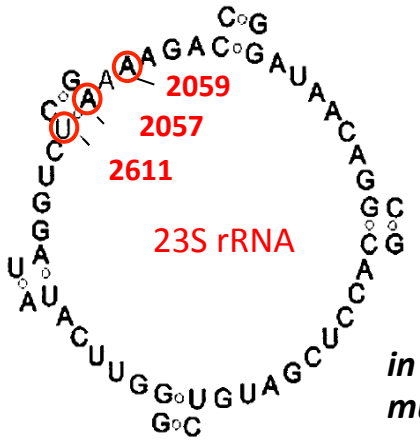
- **Resistance** described among **4** *C. trachomatis* **clinical strains**

-> **mutations** in the macrolide **ribosomal** target (23S rRNA gene and L4/L22 ribosomal proteins)

- ***In vitro*-resistant mutants** selected after exposition to subinh[illegible]rations of macr[illegible]



Clinical strains



in vitro –selected mutants

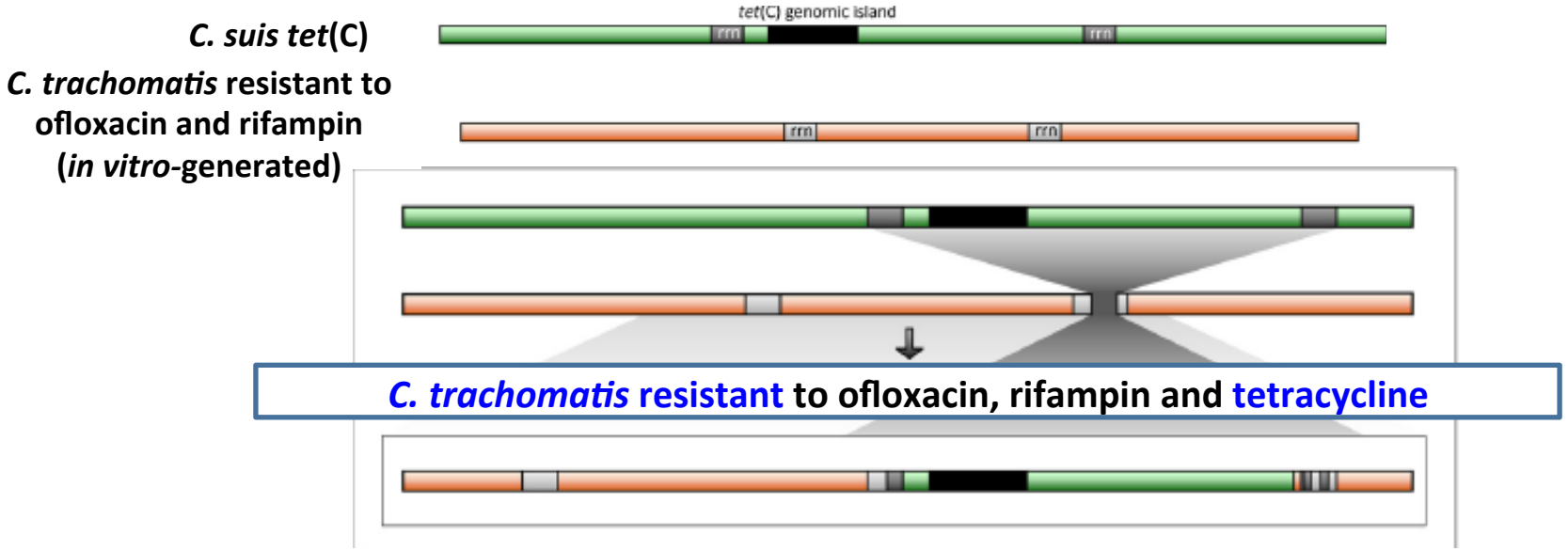
Misyurina et al, Antimicrob Agents Chemother, 2004; Binet et al, Antimicrob Agents Chemother, 2007; Zhu et al, Andrologia, 2010

Chlamydia trachomatis

- **Tetracyclines**

- **No** resistance described among *C. trachomatis* **clinical strains**
- Resistance described in a porcine species, ***Chlamydia suis***, via an efflux pump *tet*(C) gene within a genomic island

- ***In vitro***: horizontal gene transfer demonstrated between *C. suis* and *C. trachomatis*



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

Chlamydia trachomatis

- **Fluoroquinolones**

- **No** resistance described among *C. trachomatis* **clinical strains**
- ***In vitro* -resistant mutants** selected after exposition to subinhibitory concentrations of FQs

-> mutations in **the FQ enzyme targets (DNA gyrase)** leading to high MIC increases

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

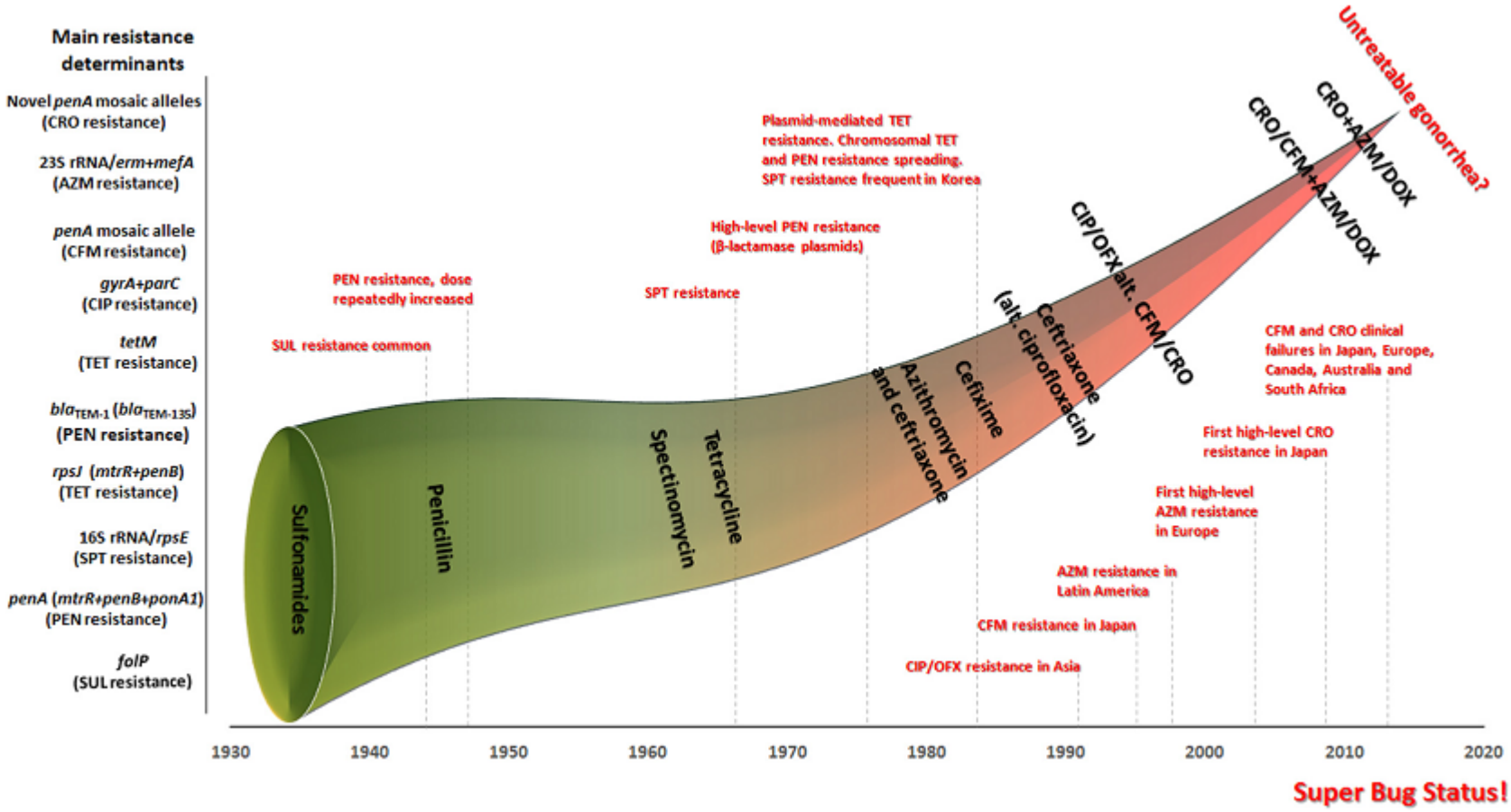
Strain	Selecting agents	MIC (μg/ml)[a]						
		OFX	SPX	PFX	CFX	NFX	ERY	DOX
Reference	None	1	0.03	2	1	12	0.4	0.05
L2-OFXR	Ofloxacin	64	32	32	32	96	0.4	0.05
L2-SPXR	Sparfloxacin	32	32	32	16	48	0.4	0.05

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

Dessus-Babus et al., Antimicrob Agents Chemother, 1998

Neisseria gonorrhoeae

History of discovery and recommended antimicrobials, evolution of resistance in *N.gonorrhoeae* since 1930



Unemo, Clin Microbiol Rev 2014, 27:587

Neisseria gonorrhoeae

- **Super bug status**
  XDR isolates with high-level resistance to all ESCs and other antimicrobials available : 3 isolates described in Japan, France and Spa

ECDC, 2012

- **Empirical 1st-line treatment for uncomplicated gonorrhoea (WHO, Europe, USA)**
  Dual antimicrobial therapy : **ceftriaxone 250-500 mg + azithromycin 1–2 g**

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.

Number of countries in different WHO regions reporting gonococcal isolates with resistance to azithromycin and ciprofloxacin, and decreased susceptibility or resistance to ESCs (cefixime and/or ceftriaxone), 2009-2014

Resistance of gonococcal isolates to antimicrobials	WHO regions							Countries (%) reporting resistance/ decreased susceptibility
	Africa	Americas	Eastern Mediterranean	Europe	Southeast Asia	Western Pacific	Total	
ESCs								
Countries reporting	9	16	3	27	6	16	77	
≥5% resistance[a]	1	0	0	15	4	6	26	51 (66%)
<5% resistance	2	6	0	8	1	8	25	
Full susceptibility	6	10	3	4	1	2	26	
Azithromycin								
Countries reporting	3	7	1	26	6	15	58	
≥5% resistance[a]	3	2	0	21	1	2	29	47 (81%)
<5% resistance	0	4	0	3	4	7	18	
Full susceptibility	0	1	1	2	1	6	11	
Ciprofloxacin								
Countries reporting	8	16	1	26	6	15	72	
>90% resistance[b]	0	1	1	3	4	5	14	70 (97%)
≥5% resistance[a]	6	14	0	23	2	7	52	
<5% resistance	0	1	0	0	0	3	4	
Full susceptibility	2	0	0	0	0	0	2	

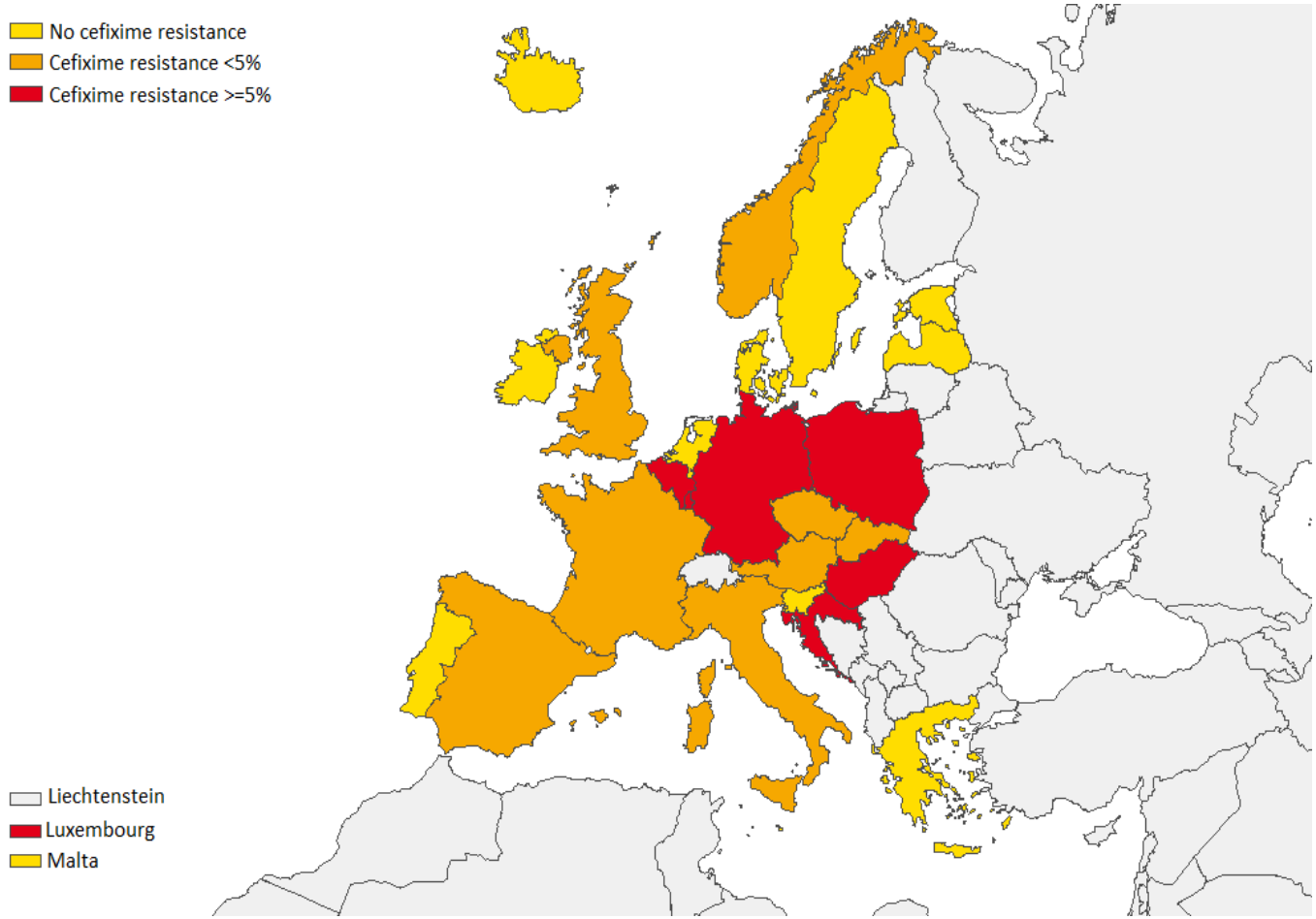
[a] Resistance level at which WHO recommends that the use of an antimicrobial in empiric treatment is discontinued.

[b] An arbitrary resistance level was included to show that the resistance levels to ciprofloxacin are extremely high in many parts of the world, particularly in the WHO Southeast Asian Region and Western Pacific Region.

ESC, Extended-spectrum cephalosporins; WHO, World Health Organization

https://doi.org/10.1371/journal.pmed.1002344.t001 Wi et al. (2017) PLOS Medicine 14(7): e1002344.

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

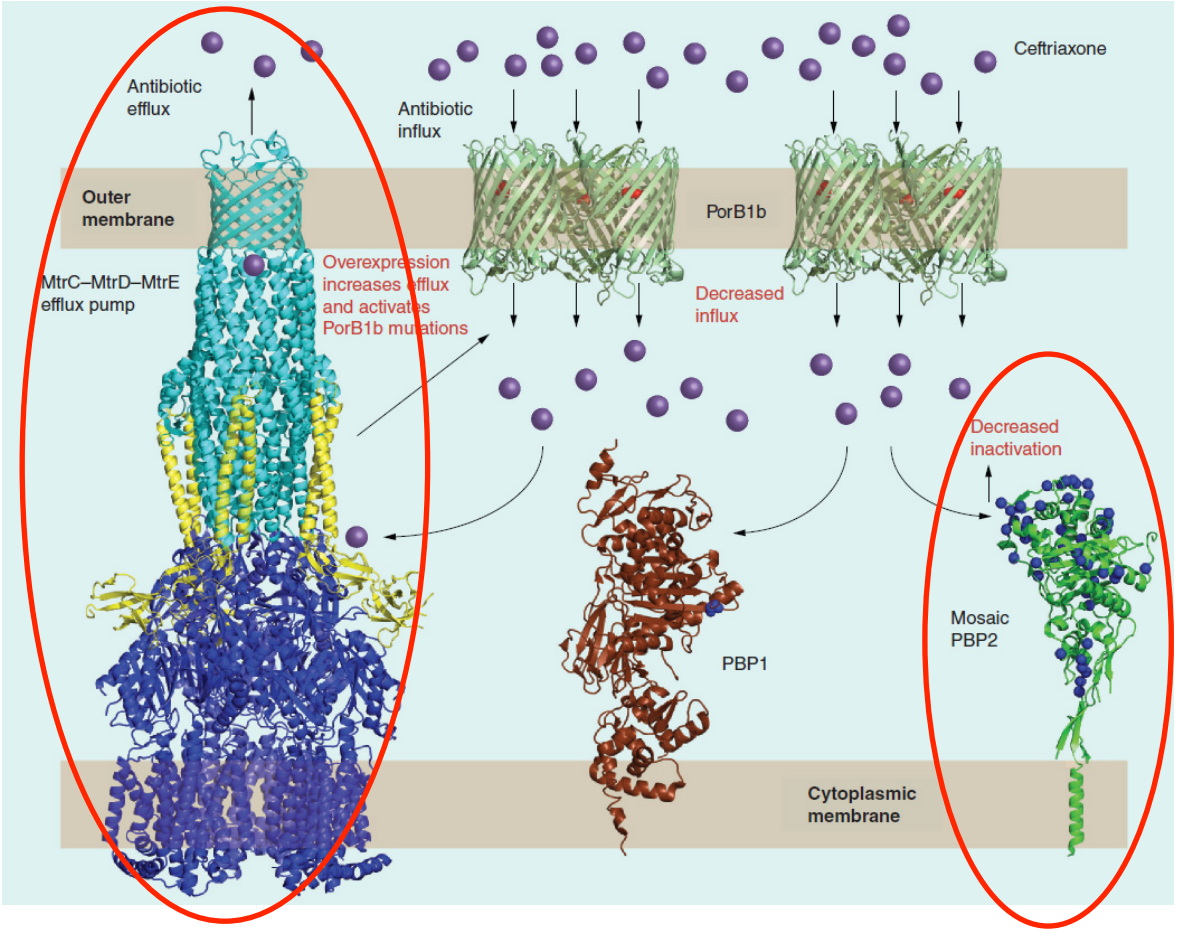


Neisseria gonorrhoeae

- **Main mechanisms of resistance to ESCs:**

Mosaic *penA* gene
Alteration of PBP2, the lethal target for ESCs

Hyperexpression of the MtrCDE efflux pump
Enhanced efflux & decreased influx of ESCs



Unemo et al, Future Microbiol. 2012

Neisseria gonorrhoeae

- **Azithromycin 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%

High-level resistance mainly caused by mutations in the macrolide target (23S rRNA gene)

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

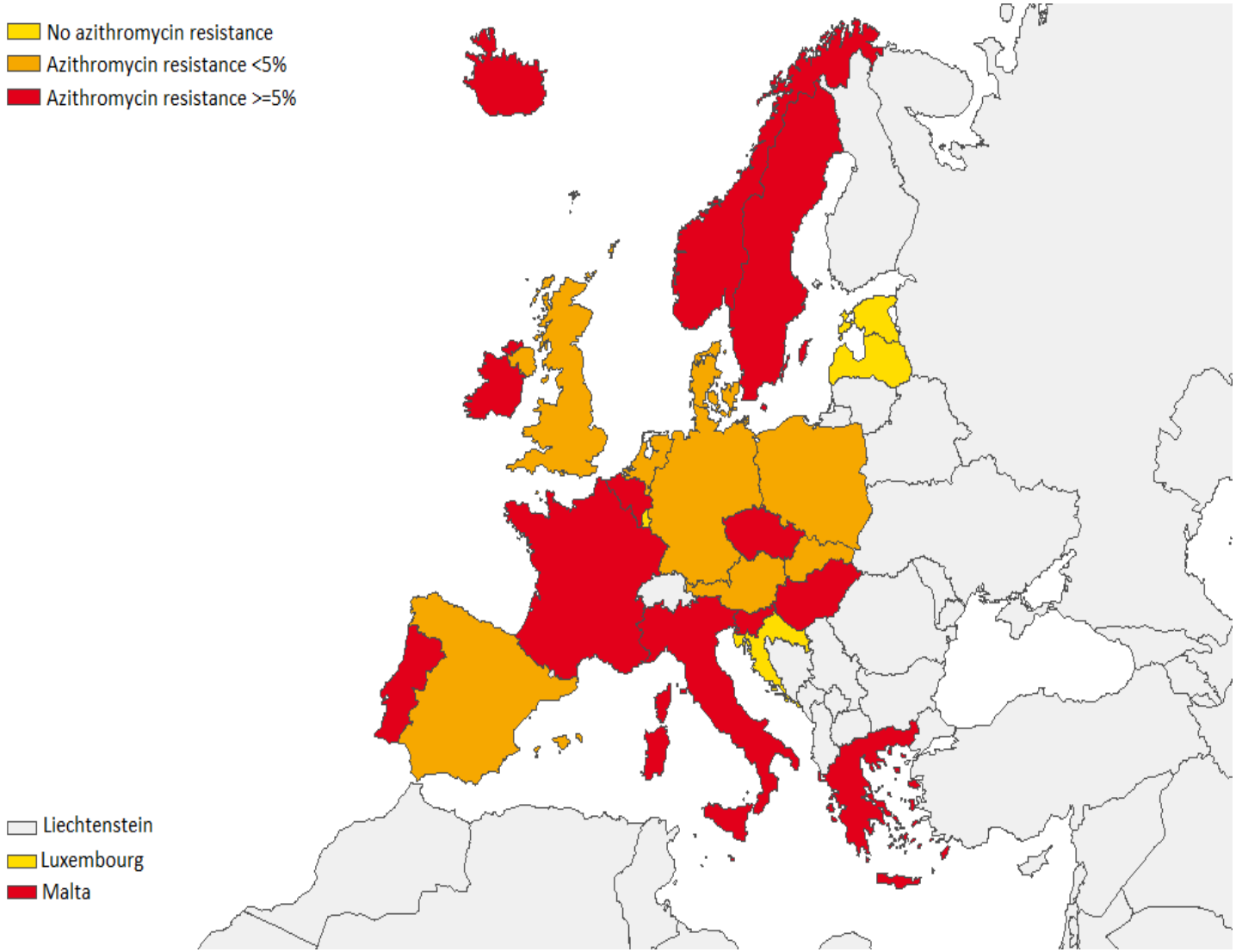
Mutations in the FQ enzyme targets (DNA gyrase) leading to high MIC increases

- **Tetracycline resistance > 50%**

High-level resistance mainly caused by the *tet*(M) gene carried on a mobile element (Tn*916* on a plasmid)

Unemo et al, Future Microbiol. 2012; Unemo and Jensen, Nat Rev Urol 2017; Wi et al, PloS Med 2017

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



Treponema pallidum

- 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

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- **Alternatives**: doxycycline, ceftriaxone or azithromycin
  - No clinical AMR to **tetracyclines** confirmed
  - AMR described for **macrolides (azithromycin)**

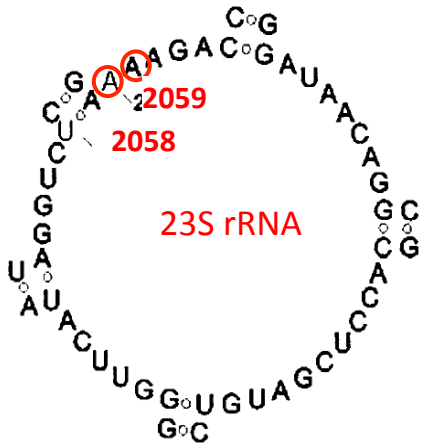
Janier et al, JEADV 2014; Workowski, et al. MMWR Recommend Rep 2015; Stamm LV, Epidemiol Infect 2015; Stamm LV Microbial Cell 2016

Treponema pallidum

- **High prevalence of azithromycin resistance**

In 1977, 1st case of clinical failure following azithromycin treatment for syphilis → mutation in the 23S rRNA **ribosomal target** (A2058G+++)

Clinical resistance: France (74%), UK (66%)
Australia (84%), USA (80%)
China (100%)



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Mycoplasma genitalium

- **Tetracyclines: low eradication rate for *M. genitalium* clinically**
  - 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

REVIEW ARTICLE

2016 European guideline on *Mycoplasma genitalium* infections

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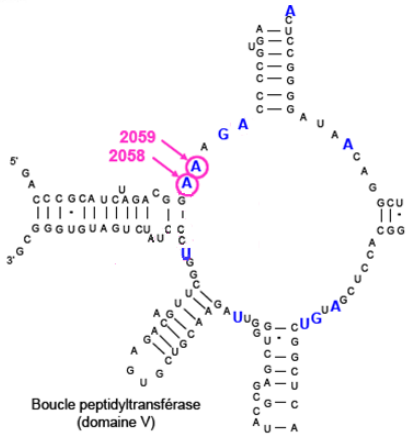
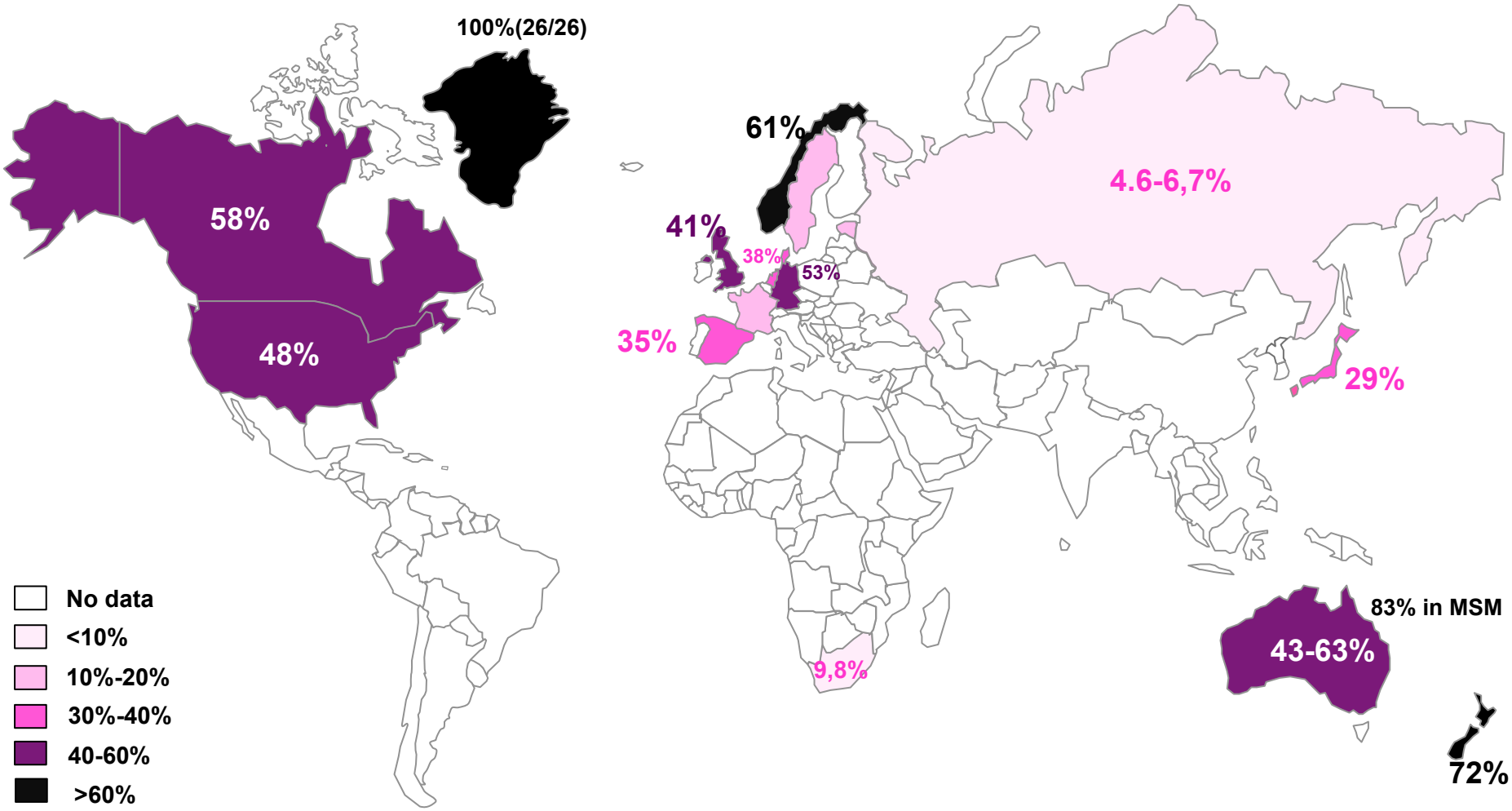
- Clinical acquired resistance to macrolides
  - by mutations in the macrolide target (23S rRNA)
  - most likely caused by azithromycin 1g single dose



Prevalence of macrolide resistance in *M. genitalium*



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Mycoplasma genitalium

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

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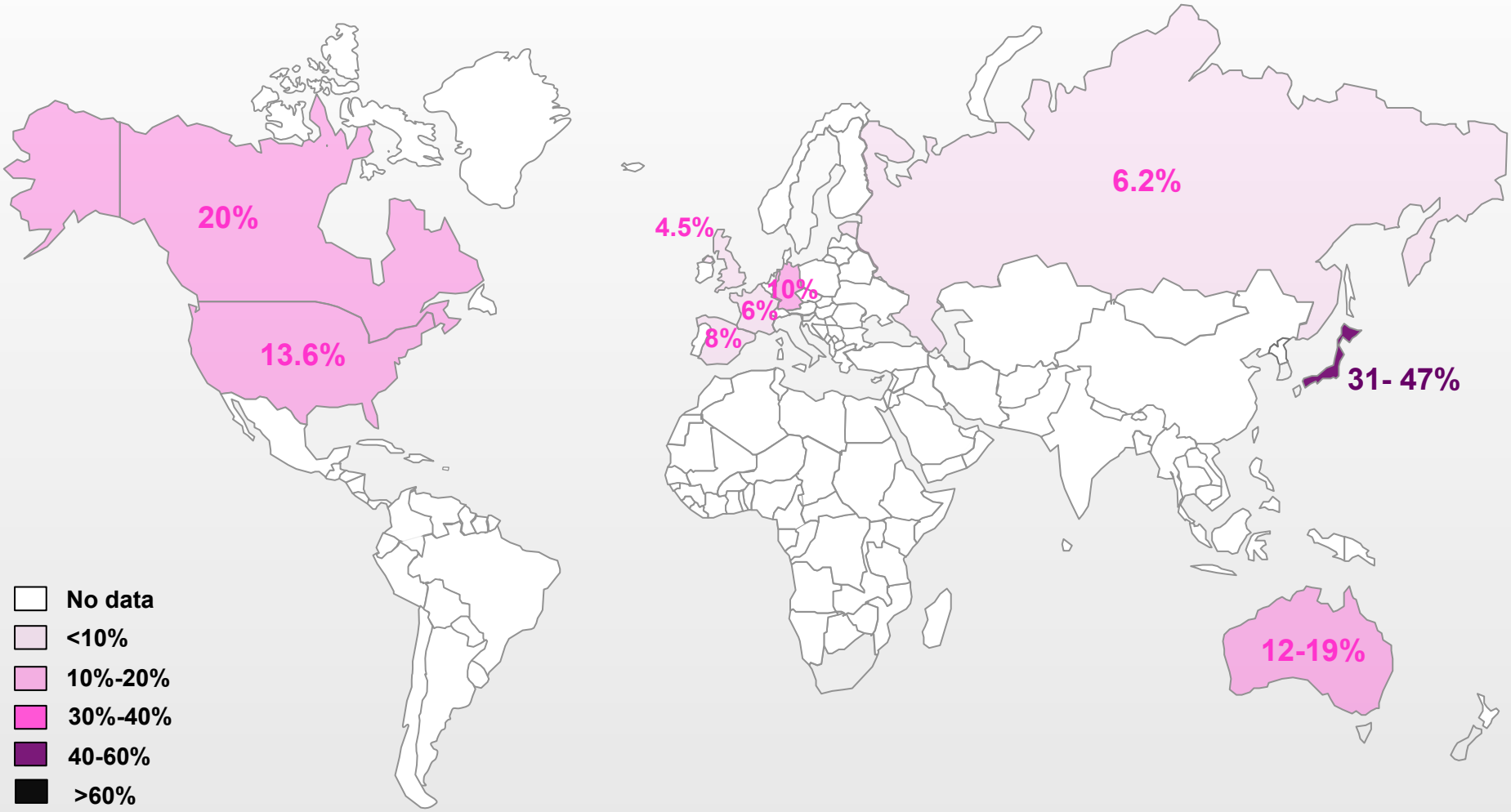
- **Emergence of clinical acquired resistance to MXF**
  - by mutations in the FQ target (topoisomerase IV)
  - both *in vitro* and clinical resistance
  - ranging from 4.5% (UK) to 47% (Japan)

Jensen and Bradshaw BMC Infect Dis 2015, Jensen and Unemo Nature Rev Urol 2017

Prevalence of fluoroquinolone resistance in *M. genitalium*



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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

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