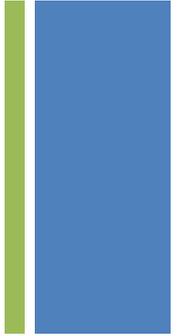
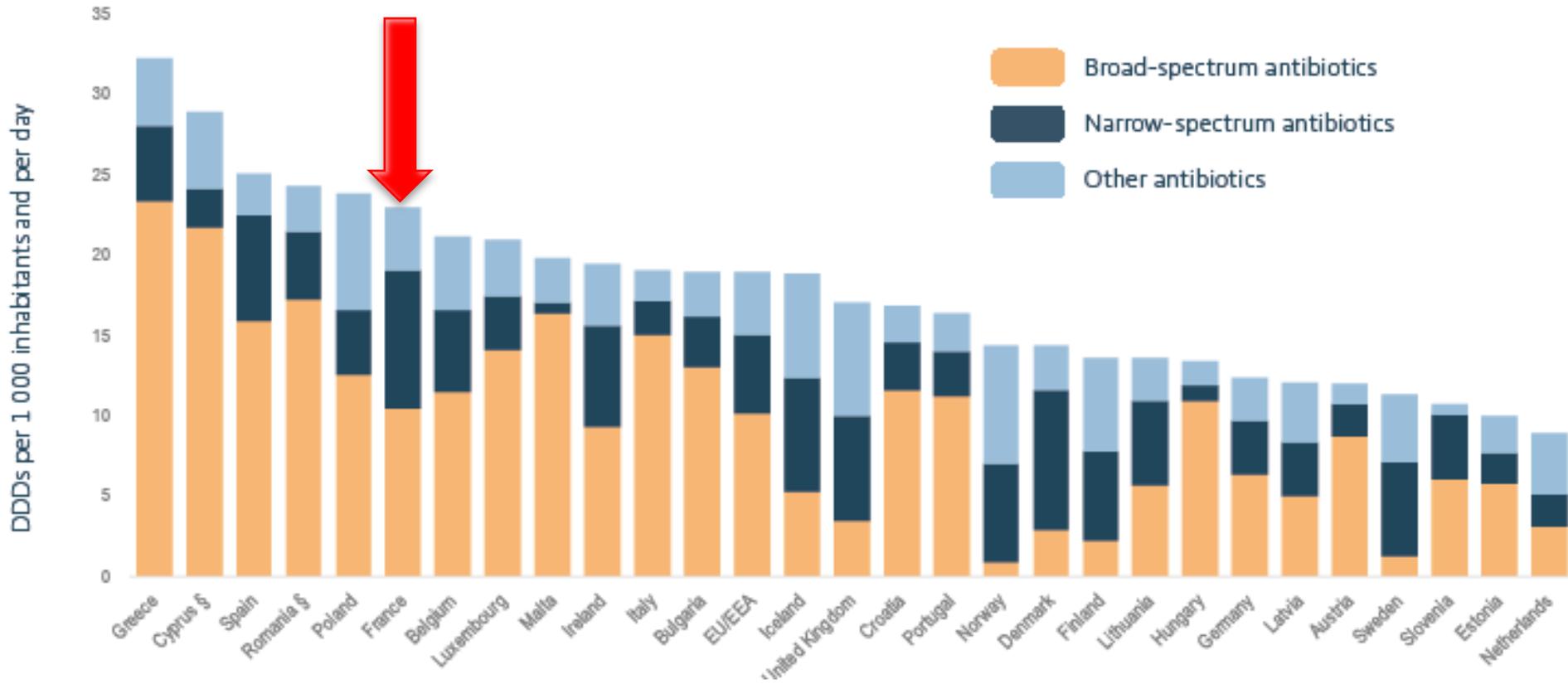
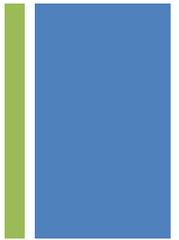


Antibiorésistance et IST

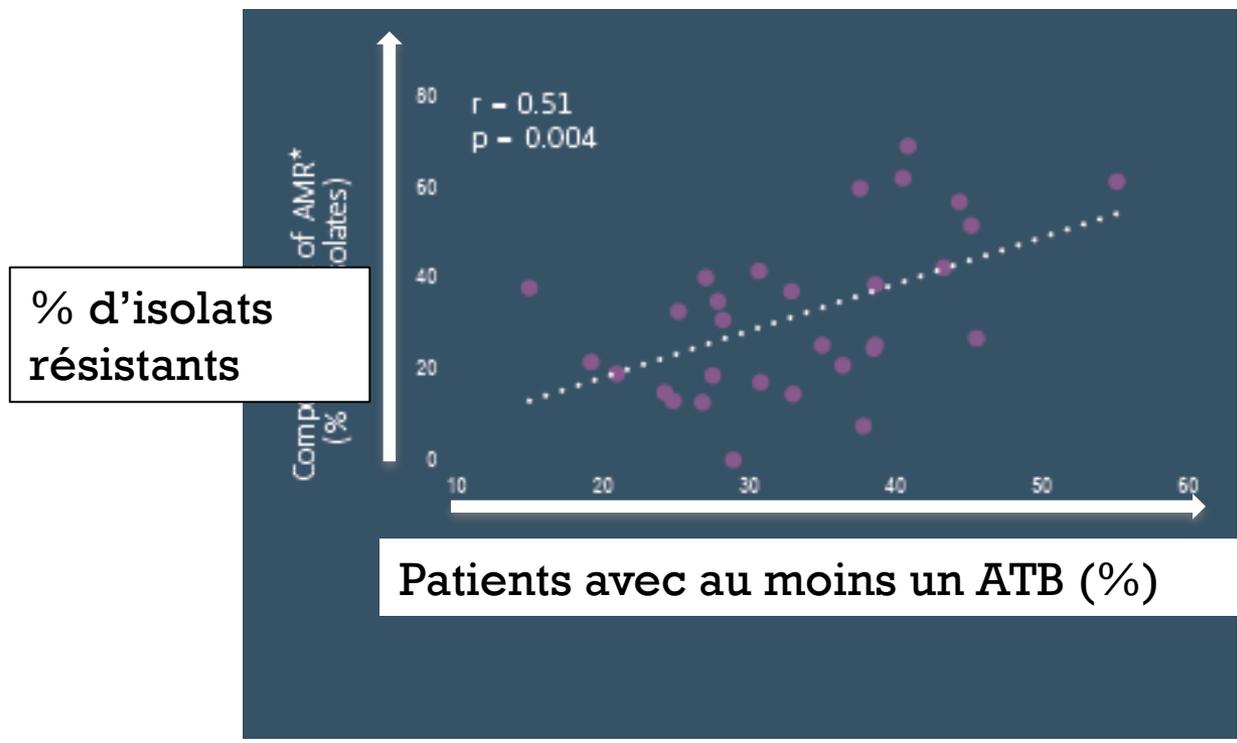


- Antibiorésistance, généralités
- IST, épidémiologie et résistances
 - Chlamydia
 - Gonocoque
 - Mycoplasme



Consumption of antibiotics* in the community, EU/EEA†, 2017

Figure 3. Associations between a composite index of AMR* and various determinants of AMR in European acute care hospitals (each dot represents a country)



Prescription d'ATB = augmentation des BMR



Antibiotiques



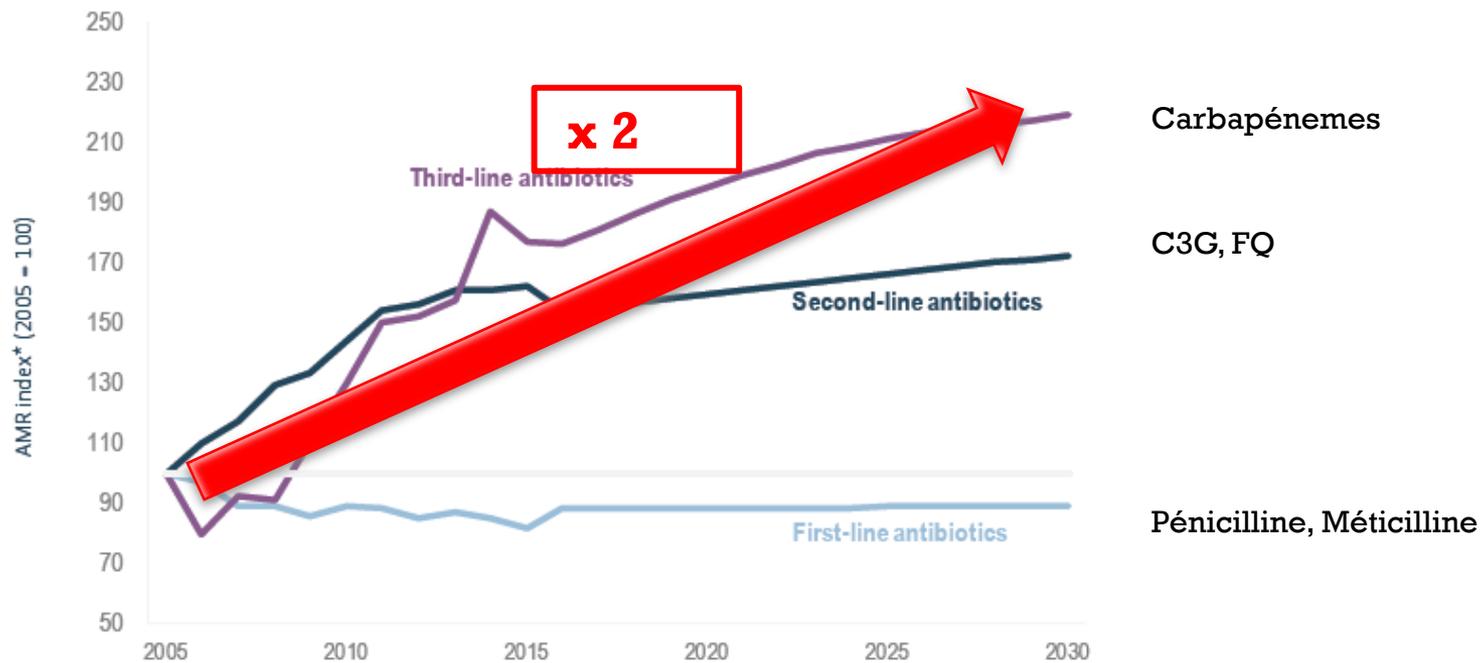
Résistance

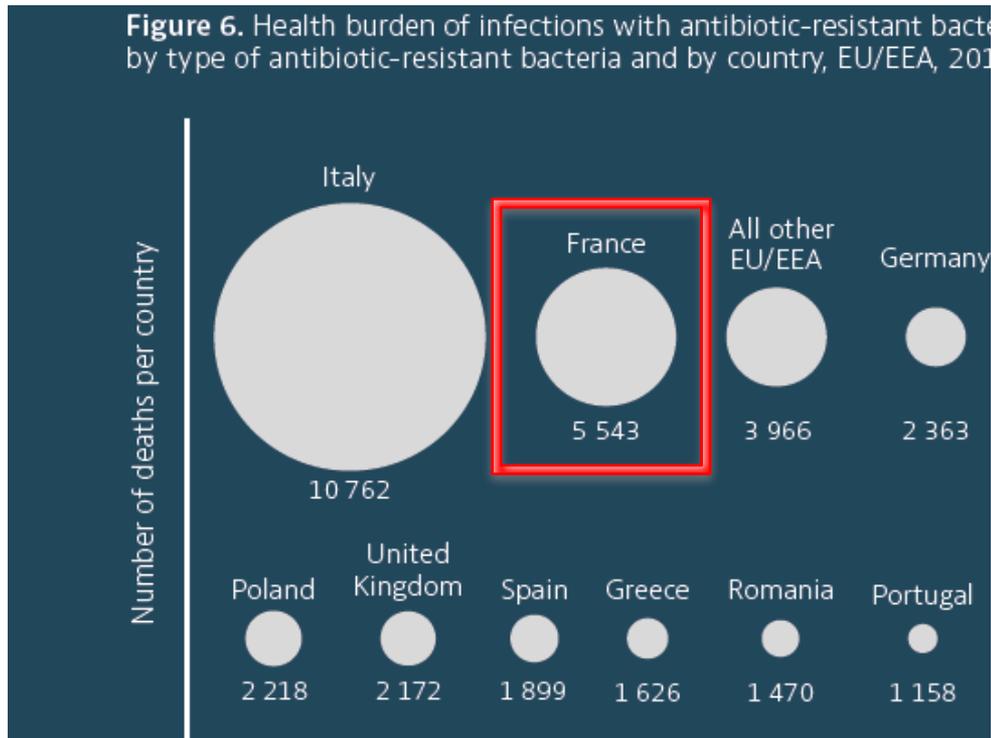


Antibiotiques à large spectre
(2ème, 3ème ligne)



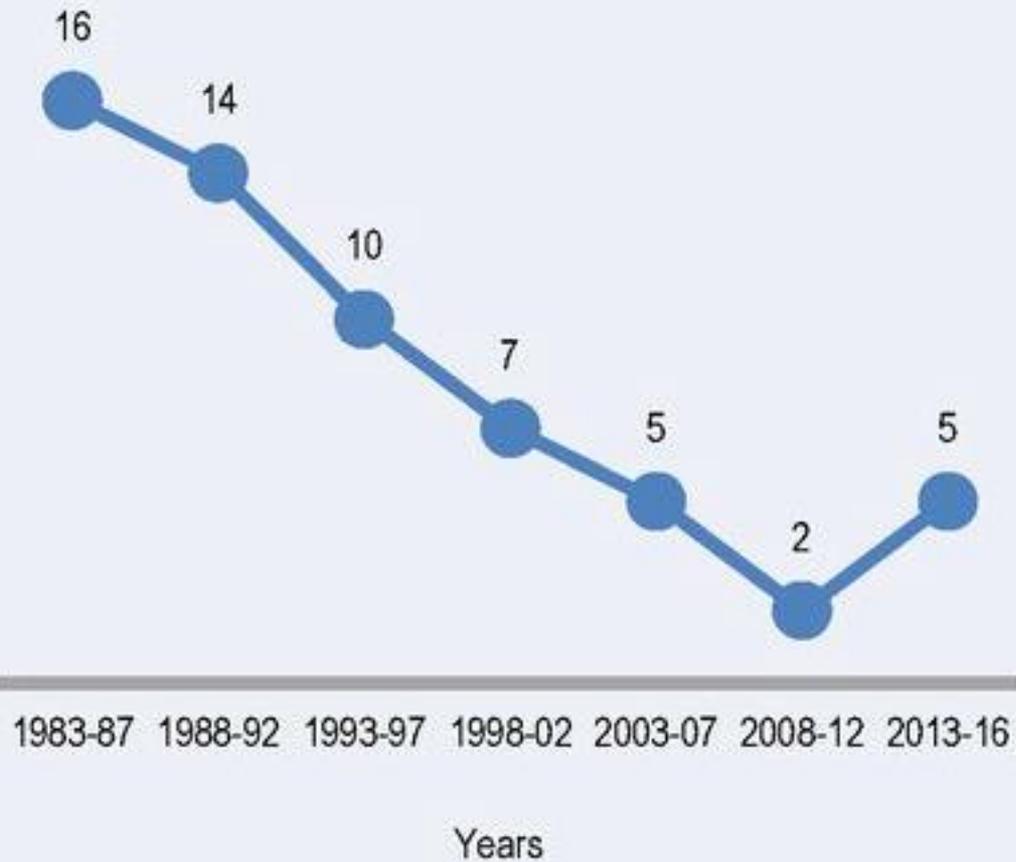
Résistance





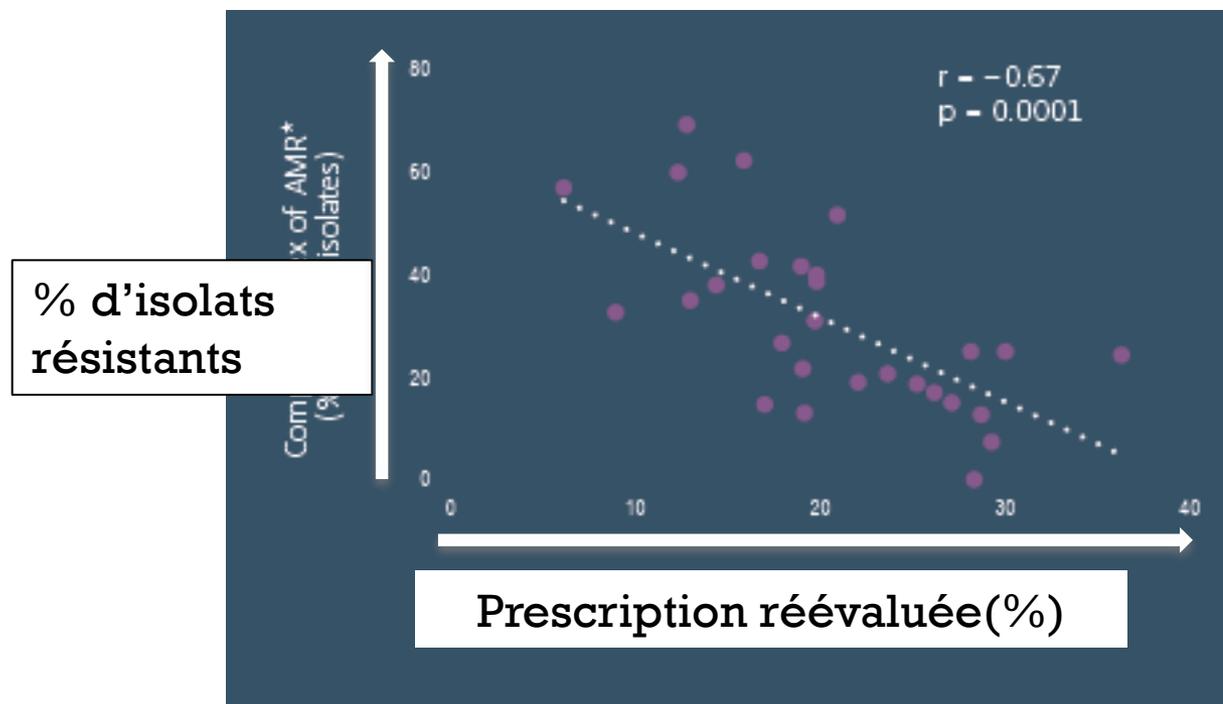
2015 : > 5000 décès liés aux BMR en France

Number of new antibiotics approved by the FDA

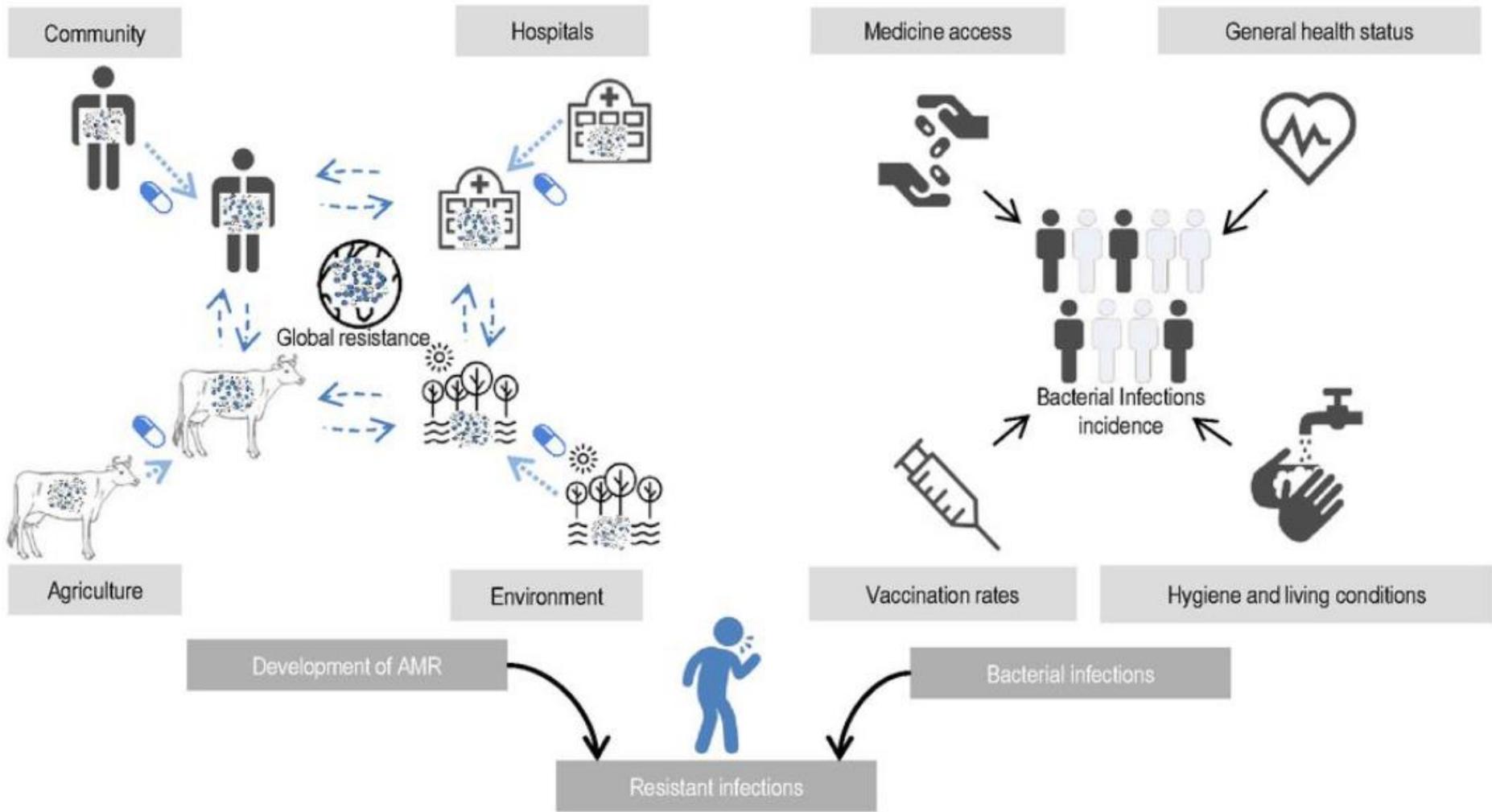


Source: OECD, WHO, FAO and OIE (2017_[19]).

Figure 3. Associations between a composite index of AMR* and various determinants of AMR in European acute care hospitals (each dot represents a country)



Réévaluation systématique du traitement = diminution des BMR



+ Recommandations OCDE 2019 pour diminuer antibiorésistance

■ Hôpital

- Promotion de l'hygiène hospitalière et individuelle
- Programme d'antibioréférence

■ Ville

- Prescription retardée (attente documentation microbio)
- Mise à disposition de TDR
- Campagnes médiatiques pour le public

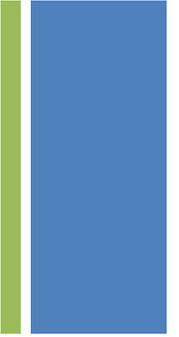


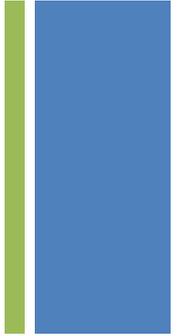
Réduction mortalité liée aux BMR et
de leur impact économique



Et les IST dans tout ça ?

+ Chlamydia



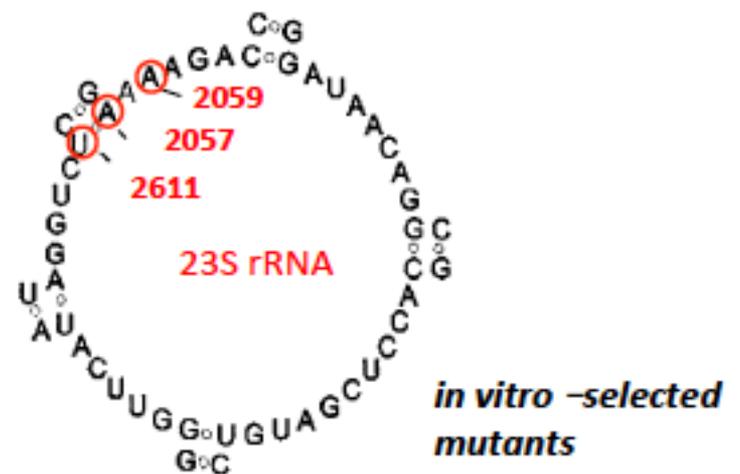
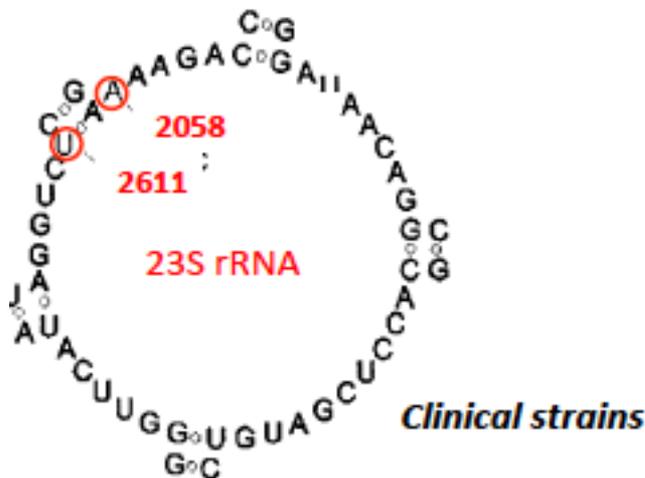


- Traitement recommandé (WHO 2016, IUSTI 2015, Recommandations SFD 2016)
 - Infections non compliquées
 - Azithromycine 1g dose unique
 - Ou Doxycycline 100mg x2 par jour pendant 7 jours
 - *Alternatives: tétracyclines, FQ, Erythromycine*
 - Infections rectales
 - Doxycycline 100mg x2 par jour pendant 7 jours
 - LGV
 - Doxycycline 100mg x2 par jour pendant 21 jours

+ Résistances

■ Macrolides

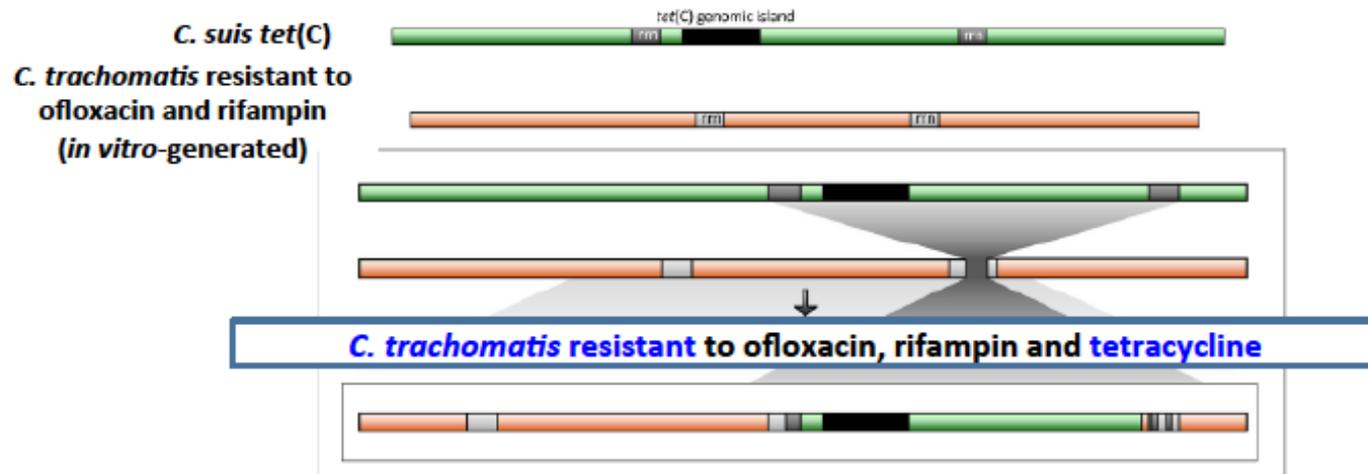
- Résistances acquises : très rare in vivo
 - Quelques cas avec mutations dans la cible ribosomale des macrolides
- Résistances possibles in vitro si exposition à des concentrations subinhibitrices d'antibiotiques



+ Résistances

■ Cyclines

- Pas décrit in vivo
- Resistances décrites chez une espèce porcine (pompe à efflux)
 - Transfert horizontal de gène entre espèce porcine et *C. trachomatis*



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

+ Résistances

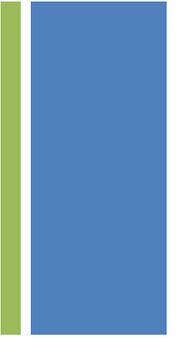
- Fluoroquinolones
 - Pas décrit en clinique
 - Mais décrit in vitro => mutations dans la DNA Gyrase

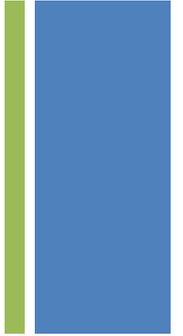
TABLE 2. Antibiotic susceptibilities of the reference strain and fluoroquinolone-resistant mutants of *C. trachomatis* L2

| 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.

+
Gonocoque



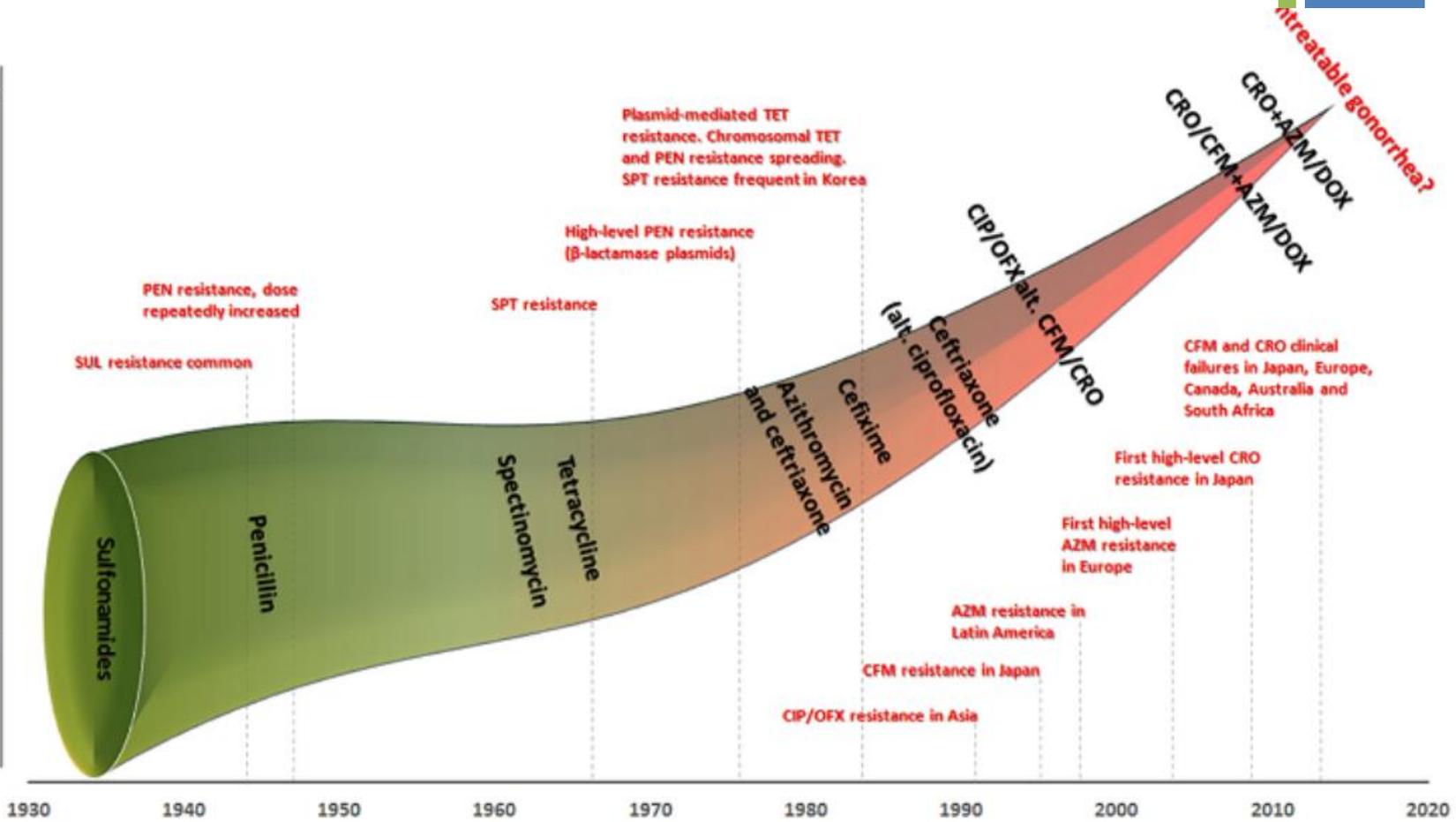


- Traitement minute empirique de première ligne si infection génitale non compliquée (WHO 2016, IUSTI 2012, Recommandations SFD 2016)
 - Ceftriaxone 250-500mg + Azithromycine 1-2g
 - *Alternatives: Azithro 2g, Ceftriaxone 500mg dose unique, Gentamicine 240mg dose unique, Ciprofloxacine 500mg dose unique*



Main resistance determinants

- Novel *penA* mosaic alleles (CRO resistance)
- 23S rRNA/*erm+mefA* (AZM resistance)
- penA* mosaic allele (CFM resistance)
- gyrA+parC* (CIP resistance)
- tetM* (TET resistance)
- bla_{TEM-1}* (*bla_{TEM-135}*) (PEN resistance)
- rpsJ* (*mtrR+penB*) (TET resistance)
- 16S rRNA/*rpsE* (SPT resistance)
- penA* (*mtrR+penB+ponA1*) (PEN resistance)
- folP* (SUL resistance)



Super Bug Status!

Figure 1. Percentage of resistant *Neisseria gonorrhoeae* by antimicrobial and year, Euro-GASP, 2009–2017

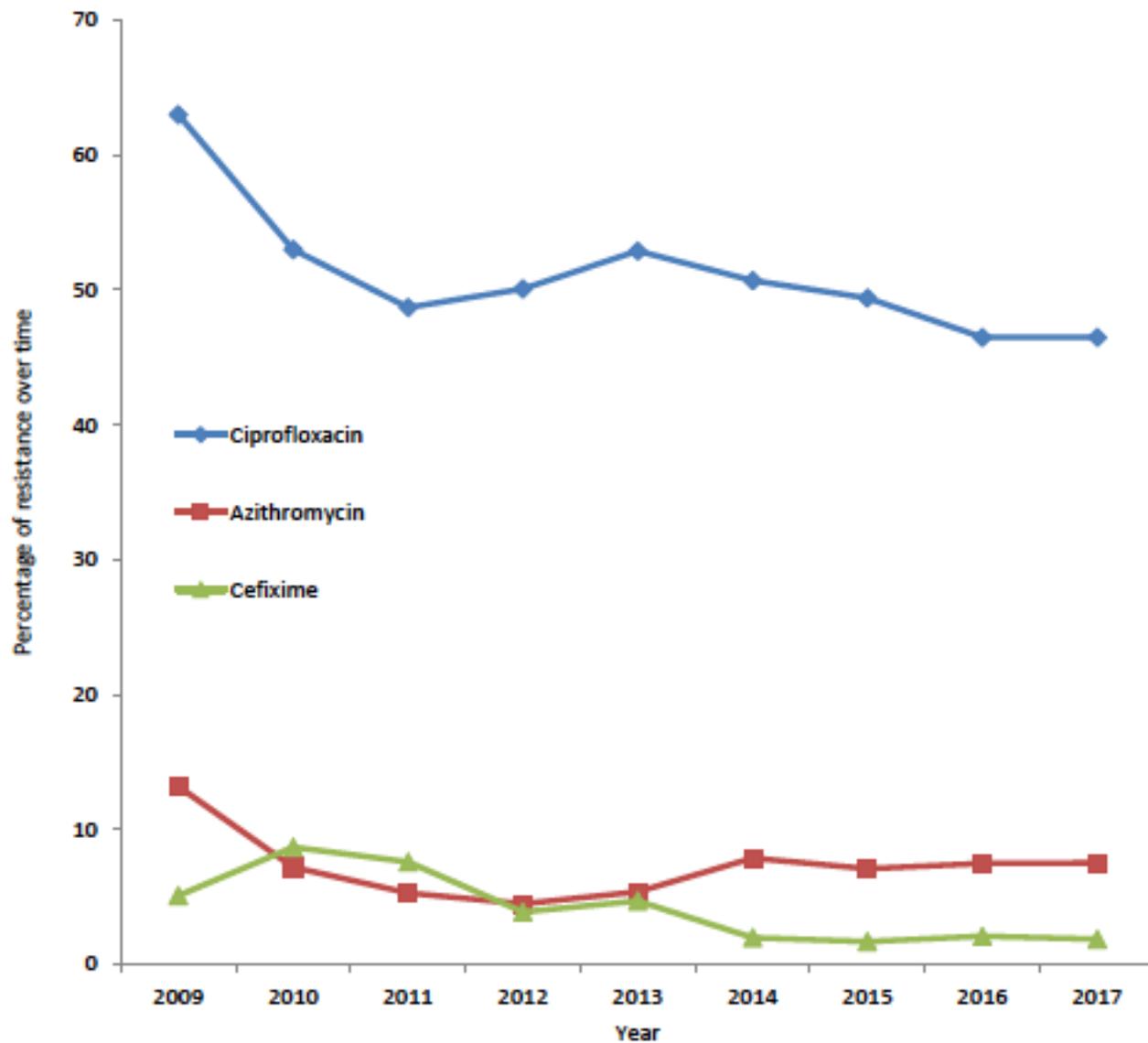
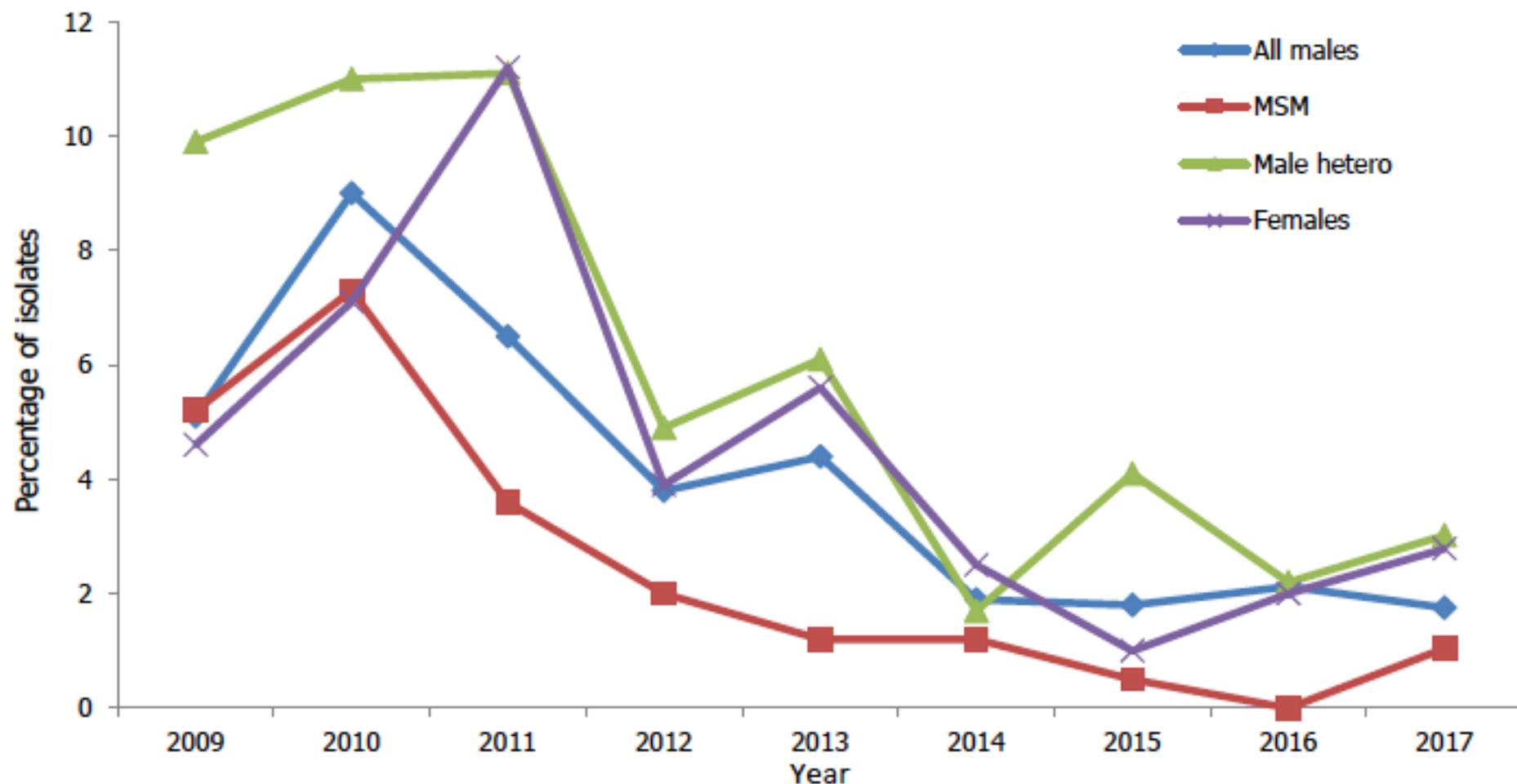


Figure 3. Percentage of isolates with cefixime resistance by gender and male sexual orientation, Euro-GASP, 2009–2017



No isolates displayed ceftriaxone resistance in 2017 or 2016 compared with one isolate in 2015, five in 2014 and seven in 2013 (Figure 4). The MIC distribution for ceftriaxone in 2017 shows a significantly higher proportion of more susceptible gonococcal isolates ($\text{MIC} \leq 0.016 \text{ mg/L}$) compared with 2016 ($p < 0.003$).

Map 1. Proportion of gonococcal isolates with cefixime resistance by country, EU/EEA, 2017

- No cefixime resistance
- Cefixime resistance <5%
- Cefixime resistance \geq 5%



- Liechtenstein
- Luxembourg
- Malta

Mécanismes de résistance

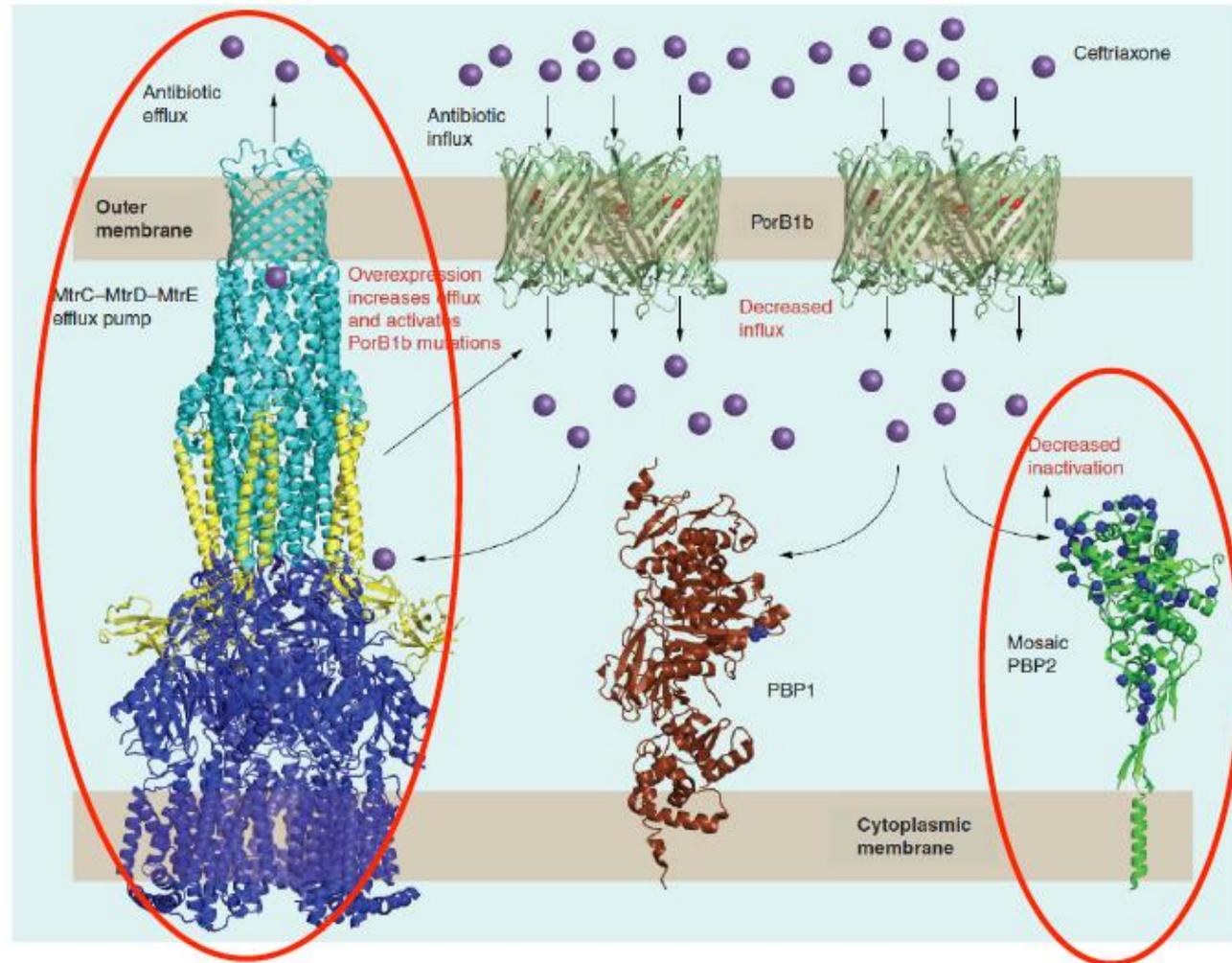


Mosaic *penA* gene

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

- **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 (*Tn916* on a plasmid)

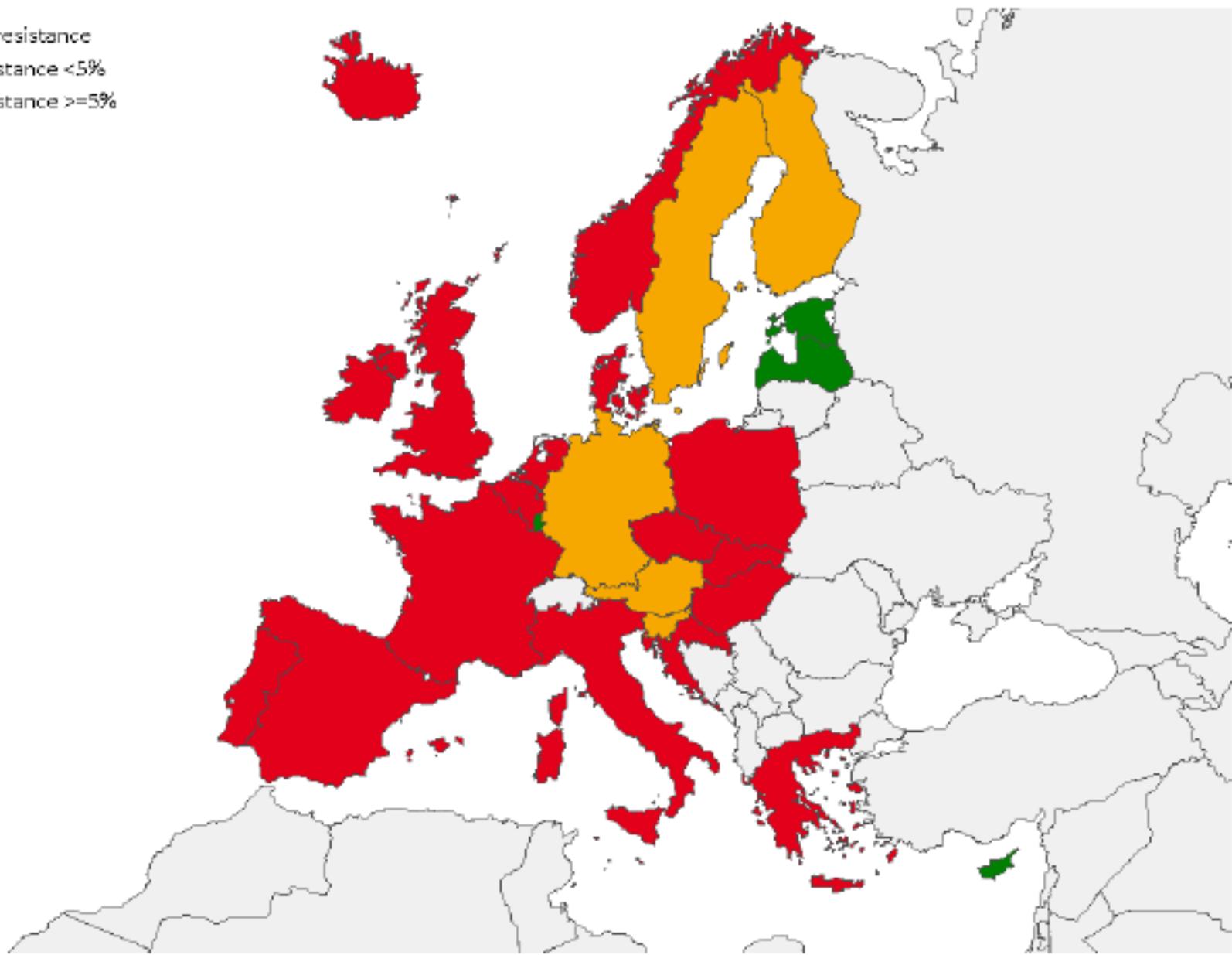
Unemo et al, Future Microbiol. 2012; Unemo and Jensen, Nat Rev Urol 2017; Wi et al, PloS Med 2017

Diapositive empruntée à Cécile Béabar, CNR IST bactériennes, Bordeaux

Map 2. Proportion of gonococcal isolates with azithromycin resistance by country, EU/EEA, 2017

- No azithromycin resistance
- Azithromycin resistance <5%
- Azithromycin resistance \geq 5%

- Liechtenstein
- Luxembourg
- Malta



Extensively drug-resistant (XDR) *Neisseria gonorrhoeae* in the United Kingdom and Australia

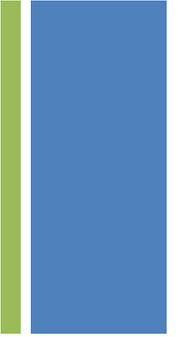
7 May 2018

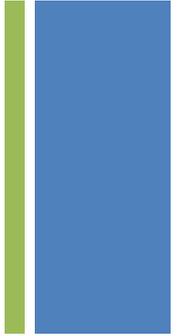
2018

3 cas de Gonocoque XDR = R-C3G et haut niveau de R à l'Azithromycine :

- 1 au RU
- 2 en Australie
- 2/3 retour de voyage d'Asie du SE
- 2 traités par Gentamycine, 1 par Ertapeneme

+ Mycoplasma genitalium





- Traitement recommandé pour les infections non compliquées (IUSTI 2016, SFD 2016)
 - Azithromycine 500mg J1 puis 250mg/jour J2-J5
 - *Alternative : Josamycine 1,5-2g/j 10 jours*
 - 2nde ligne: MXF 400mg/j 7-14 jours
 - 3eme ligne: Doxycycline 200mg/j 14 jours
 - Efficacité 30%

+ Résistances

■ Macrolides

- Mutation dans la cible ribosomale
- Possiblement à cause de l'usage important d'Azithromycine 1g
- Azithro 1g = 1,5g (CID 2017) mais étude rétrospective

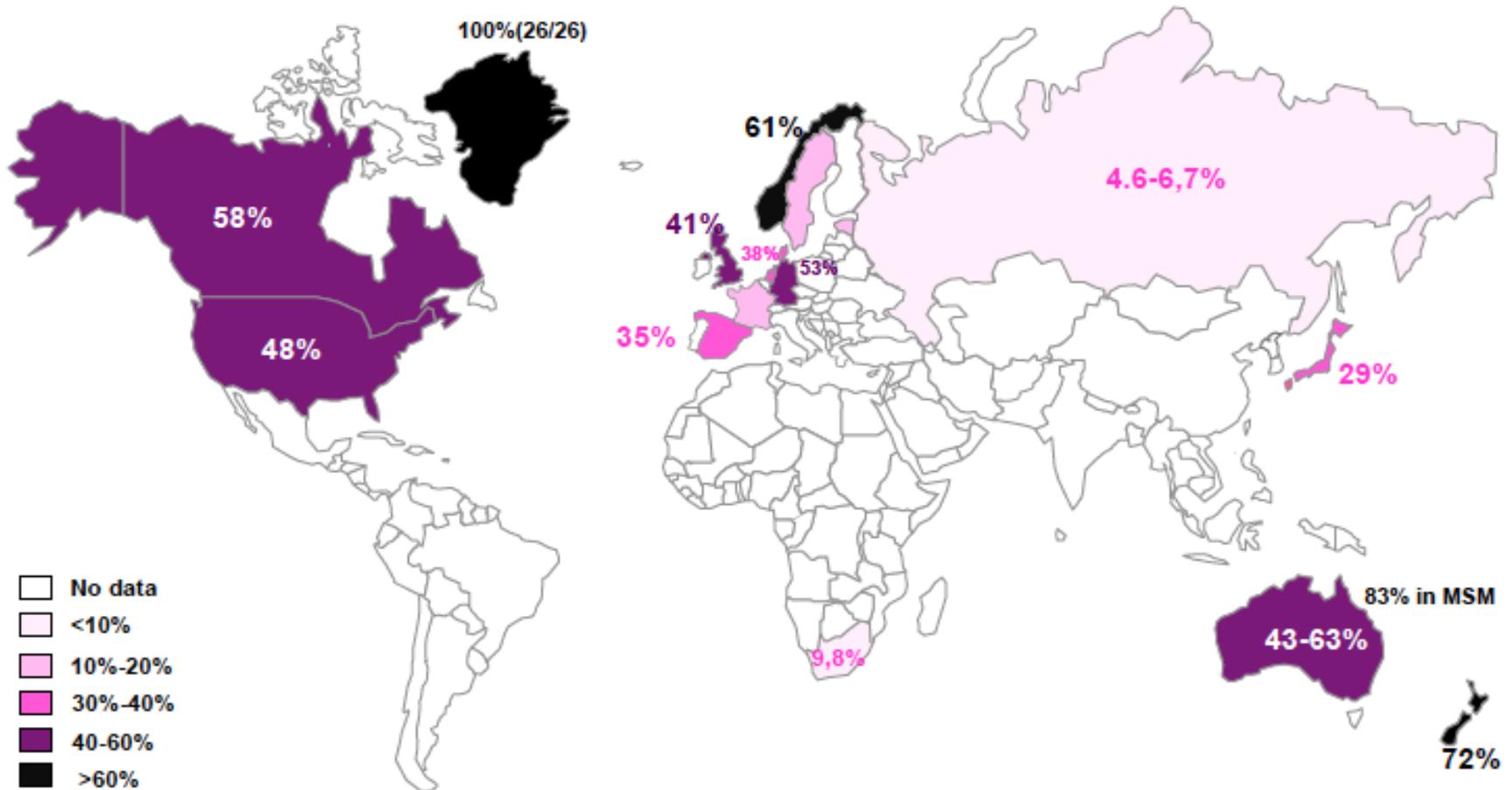
Azithromycin 1.5g Over 5 Days Compared to 1g Single Dose in Urethral *Mycoplasma genitalium*: Impact on Treatment Outcome and Resistance

Tim R. H. Read,^{1,2} Christopher K. Fairley,^{1,2} Sepehr N. Tabrizi,^{3,4,5} Melanie Bissessor,^{1,2} Lenka Vodstrcil,² Eric P. F. Chow,^{1,2} Mieke Grant,² Jennifer Danielewski,^{3,5} Suzanne M. Garland,^{3,4,5} Jane S. Hocking,⁶ Marcus Y. Chen,^{1,2} and Catriona S. Bradshaw^{1,2}

■ Fluoroquinolones

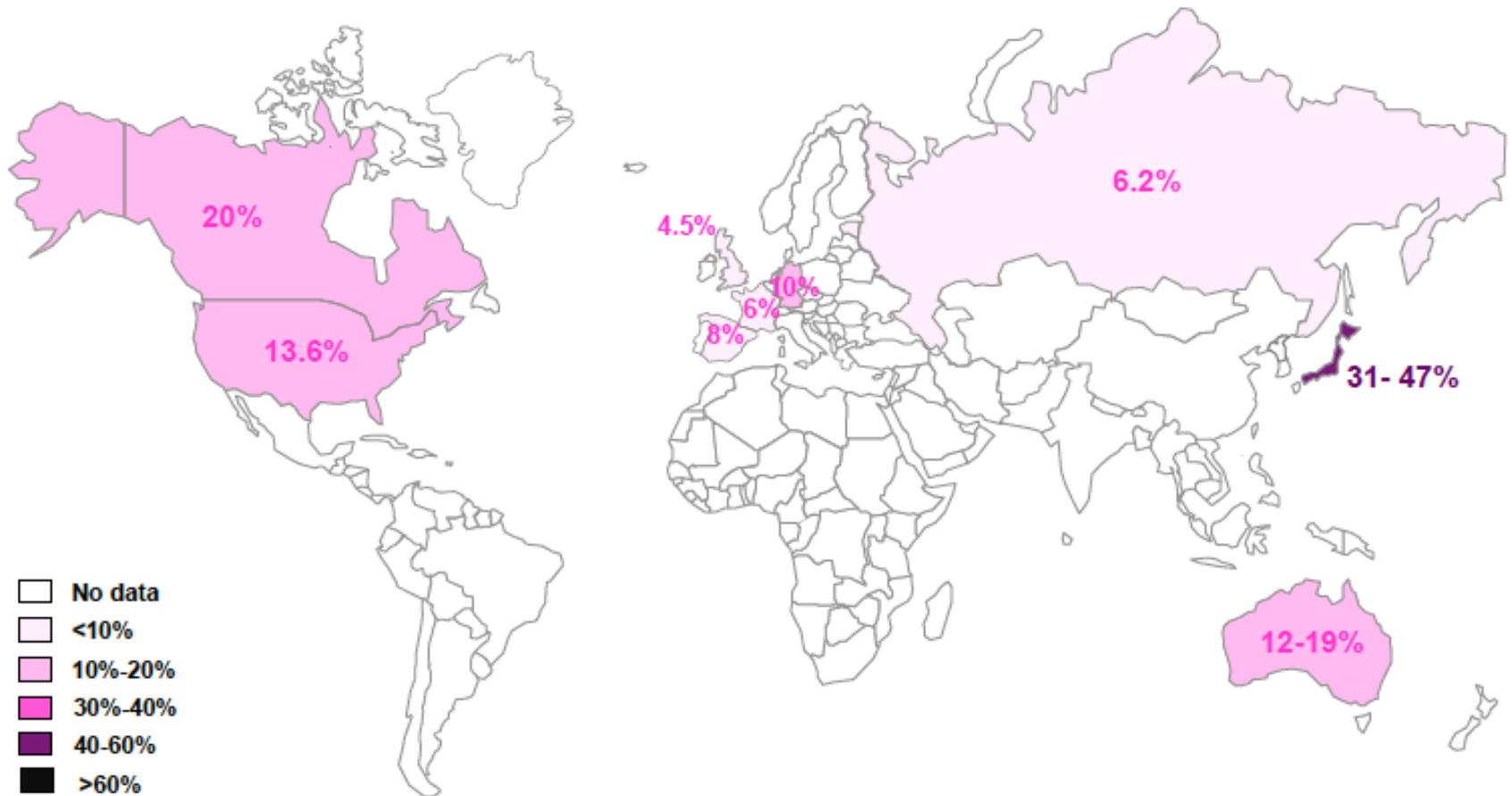
- Mutation de la cible = topoisomérase IV

Prevalence of macrolide resistance in *M. genitalium*



Anagnius, 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; Shipitsina, Plos One, 2017; Basu, J. Clin. Microbiol. 2017; Tabrizi, J. Clin. Microbiol. 2017; Barbera, Sex. Transm. Dis. 2017; Dumke, Diagn Microbiol infect Dis, 2016.

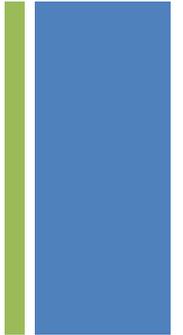
Prevalence of fluoroquinolone resistance in *M. genitalium*



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 Physician 2016; Tagg J Clin Microbiol 2013; Murray Emerg Infec Dis 2017; Barbera Sex Transm infect 2017



Conclusion



- Des situations distinctes
 - Syphilis et *C.trachomatis* posent peu de problèmes en termes de résistance
 - *N.gonorrhoeae* et *M.genitalium* beaucoup plus
 - Résistances = augmentation de la prévalence et des complications (Unemo et Jensen, Nature Rev Uro, 2017)
- ⇒ Monitoring des résistances essentiel
- ⇒ Connaissance des protocoles thérapeutiques
- ⇒ Lutte contre l'antibiorésistance