Emergence et impact clinique de la résistance aux antibiotiques chez *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, les mycoplasmes

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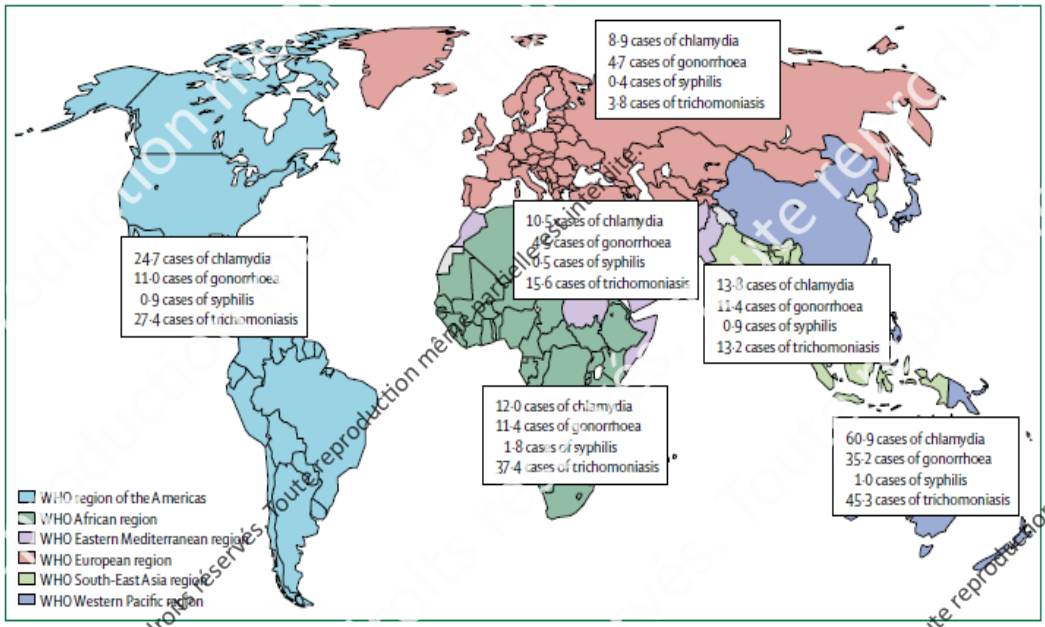
INTRODUCTION

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, M. genitalium and N. gonorrhoeae*

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

- **Macrolide** resistance described among 4 *C. trachomatis* clinical strains
- **No tetracycline** resistance described among *C. trachomatis* clinical strains but resistance described in a porcine species
- **No fluoroquinolone** resistance described among *C. trachomatis* clinical strains but *in vitro*-resistant mutants selected after exposition to subinhibitory concentrations of FQs

Misyurina et al, Antimicrob Agents Chemother, 2004; Binet et al, Antimicrob Agents Chemother, 2007; Zhu et al, Andrologia, 2010; Dugan et al., Antimicrob Agents Chemother, 2004; Suchland et al., Antimicrob Agents Chemother 2009; Jeffrey et al., BMC Microbiol 2013; Dessus-Babus et al., Antimicrob Agents Chemother, 1998

Chlamydia trachomatis

- Clinical failure in 10% patients

- In vivo evidence of **chlamydial persistence** (aberrant forms) -> failure to respond to antibiotic treatment
- **Heterotypic** resistance described in *C. trachomatis* (1-10% population expressed resistance): slower growth, entry into a stress response
- Anatomical sites like the **gastrointestinal site** protected from antibiotics -> reservoir
- Lack of treatment compliance, post-treatment reinfection

Sandoz and Rockey, Future Microbiol 2010
Borel et al, Curr Clin Micro Rpt 2016

Mycoplasma genitalium

- Tetracyclines: low eradication rate for *M. genitalium* clinically
  - Microbiological cure rate 22-45%
  - No acquired resistance described, reason ?
- Recommended treatment for uncomplicated *M. genitalium* infections
  - Azithromycin 500 mg (day 1), then 250 mg (days 2-5)

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REVIEW ARTICLE

2016 European guideline on *Mycoplasma genitalium* infections

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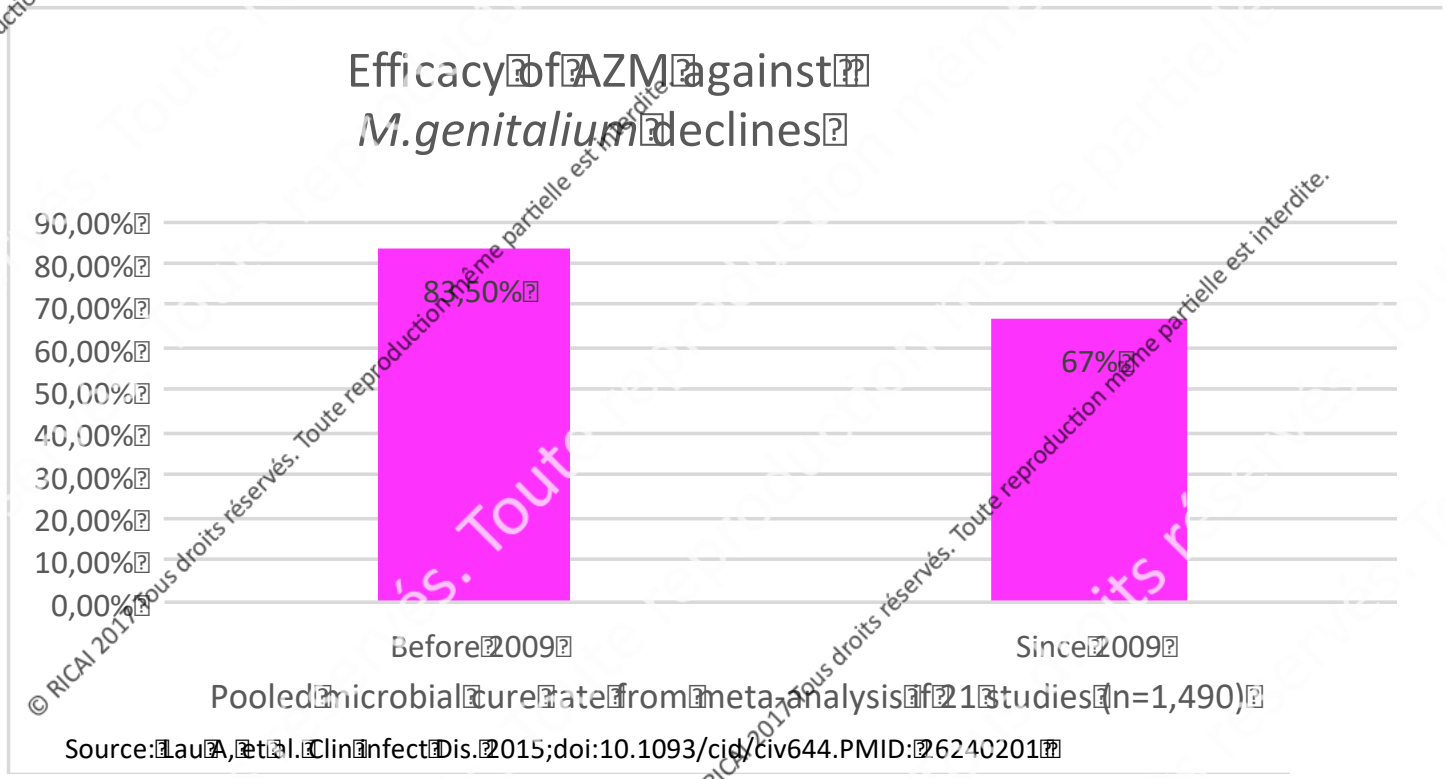
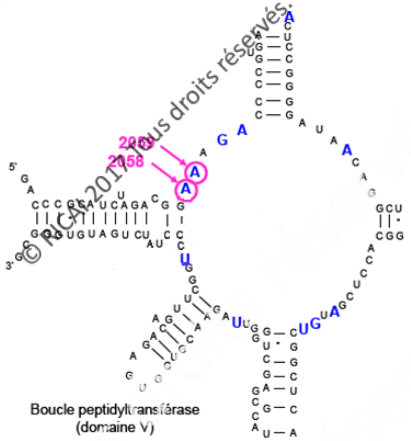
IUSTI
INTERNATIONAL UNION AGAINST SEXUALLY TRANSMITTED INFECTIONS

Mycoplasma genitalium

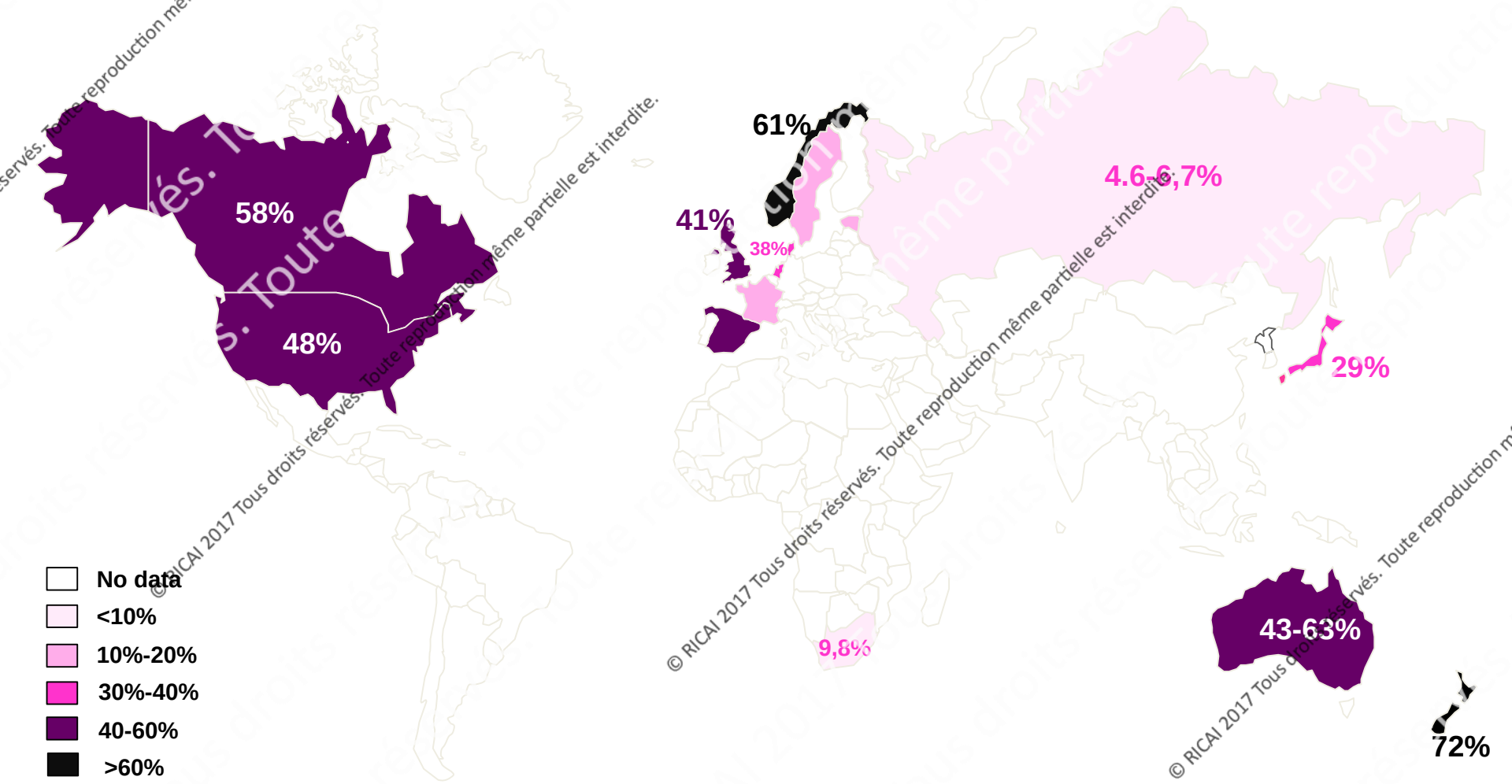
- **Metanalysis on the efficacy of AZM for Mg treatment**



- **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*



Anagrius, 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.

Consequence on NGU European guidelines (IUSTI 2016)

Clinical diagnosis of NGU

Doxycycline 100 mg bid for 7 days
Diagnostic testing for gonorrhoea, chlamydia and *M. genitalium*

***C. trachomatis* or no identified**

No additional testing or treatment in absence of persistent urethritis

Macrolide-S *M. genitalium*

Azithromycin 1.5g for 5 days

Macrolide-R *M. genitalium* pathogen

Moxifloxacin 400 mg for 7-10 days

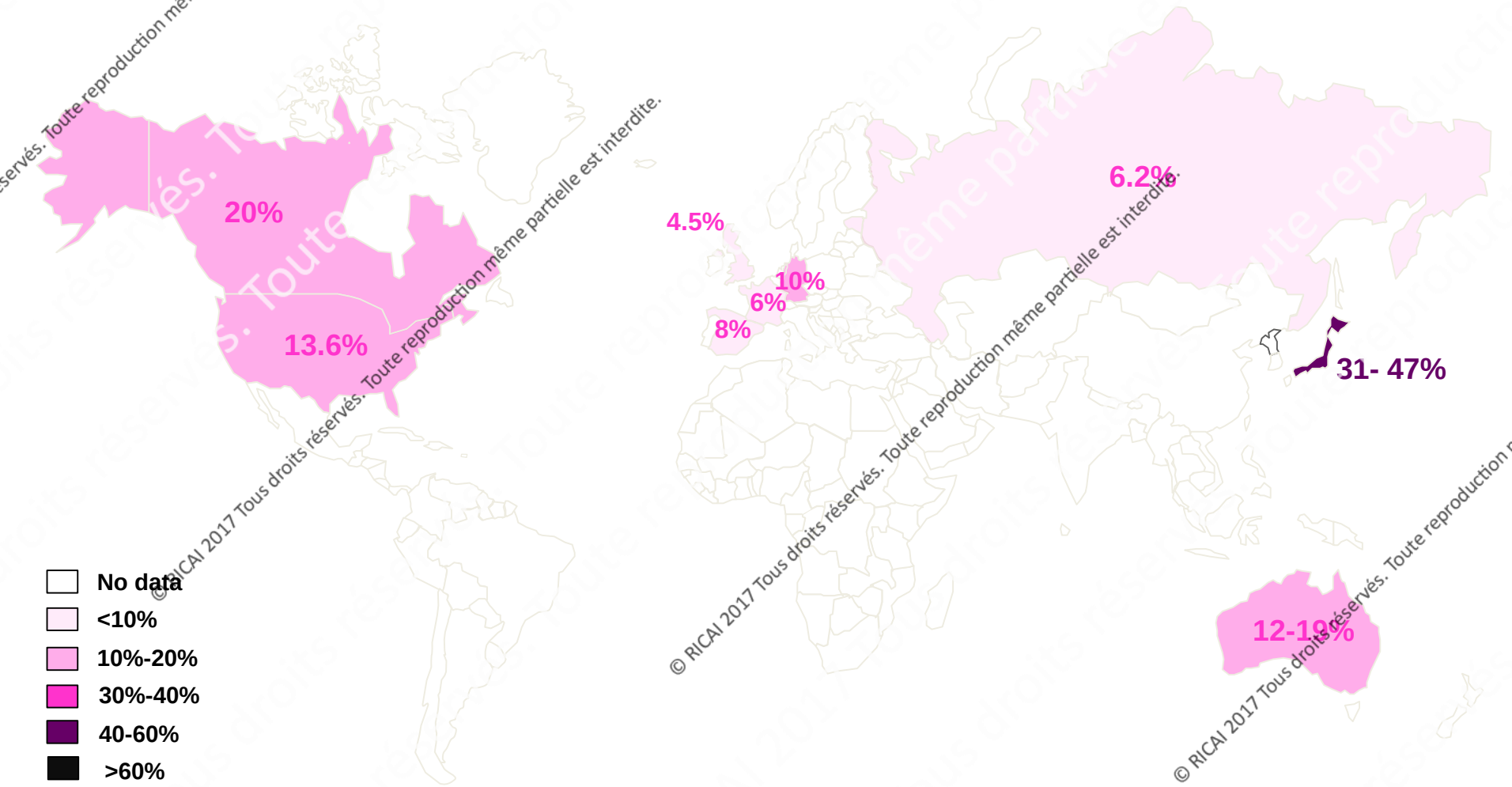
Mycoplasma genitalium

- **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 47% (Japan)

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

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

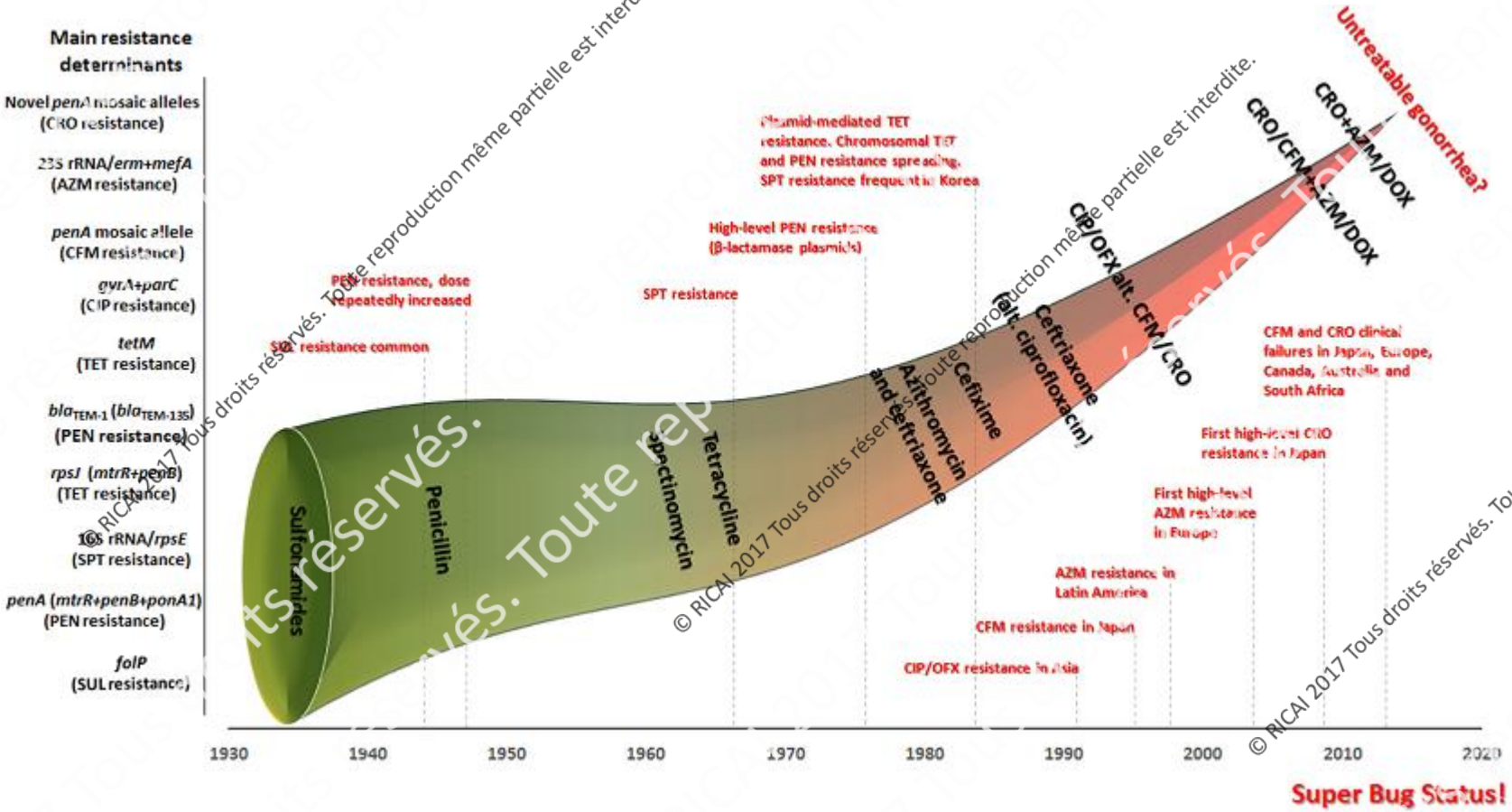
Neisseria gonorrhoeae

- Emergence and spread of antimicrobial resistance in *N. gonorrheae*
  - Horizontal gene transfer and subsequent recombination
  - Asymptomatic carriage in extragenital site for MSM
  - Inadequate monitoring of *in vitro* antimicrobial resistance, pharmacokinetics and pharmacodynamics and clinical efficacy of antimicrobials

Unemo and Shafer, Clin Microbiol Rev 2014

Neisseria gonorrhoeae

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



Unemo and Shafer, Clin Microbiol Rev 2014

Neisseria gonorrhoeae

- Empirical 1st-line treatment
  for uncomplicated gonorrhoea (WHO, Europe, USA)

  Dual antimicrobial therapy : **ceftriaxone 250-500 mg + azithromycin 1–2 g**

- Treatment failures with ESCs

  - **XDR isolates (superbugs)** with high-level resistance to all ESCs and other antimicrobials available. 3 isolates described in Japan, France, Spain

  - **1st treatment failure** to the recommended dual therapy published in 2016 in the UK

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; Fifer et al, N Engl J Med 2016

N. gonorrhoeae

- **Internationals failures of dual therapy for *N. gonorrhoeae***

Location	CTX / AZI Dose	MIC mg/L	Ng-MAST	Year	Country	Ref
Pharyngal*	500 mg /1g	0.25	ST12133	2014	Sweden	Fifer, 2016

Type of healthcare clinic (day of presentation)	Symptoms (signs)	Diagnostic test		MIC (mg/L)[a]		NG-MAST[b]	Treatment (day administered)
		Positive (type of sample)	Negative (type of sample)	*Ampicillin*	*Ceftriaxone*		
Primary (1)	Urethral discharge, dysuria, pharyngeal pain (inflammation in urethra and pharynx)	PCR (urine)	NA	NA	NA	NA	Amoxicillin Two daily doses of 750 mg, for 10 days, oral administration (first administered on day 1)
STI (12)	– (inflammation in pharynx)	Culture (pharyngeal)	Microscopy and culture (urethral) PCR (urine)	2	0.125	ST2958	Ceftriaxone One dose of 250 mg, intramuscular administration (day 26)
STI (36)	– (inflammation in pharynx)	Culture (pharyngeal)	NA	2	0.125	ST2958	Ceftriaxone One dose of 500 mg, intramuscular administration (day 43)
STI (50)	– (inflammation in pharynx)[c]	Culture (pharyngeal)	NA	2	0.25	ST2958	Ceftriaxone One dose of 1 g, intravenous administration (day 71)
STI (85 and 92)	– (–)	NA	Culture (pharyngeal)	NA	NA	NA	NA

Fifer *et al* 2016, New Engl J Med

Neisseria gonorrhoeae

- WHO global GASP, Euro-GASP and national GASP in USA, UK
  - global action plans
  - Quality-assured surveillance of gonococcal AMR and gonorrhea treatment failures

ECDC 2012

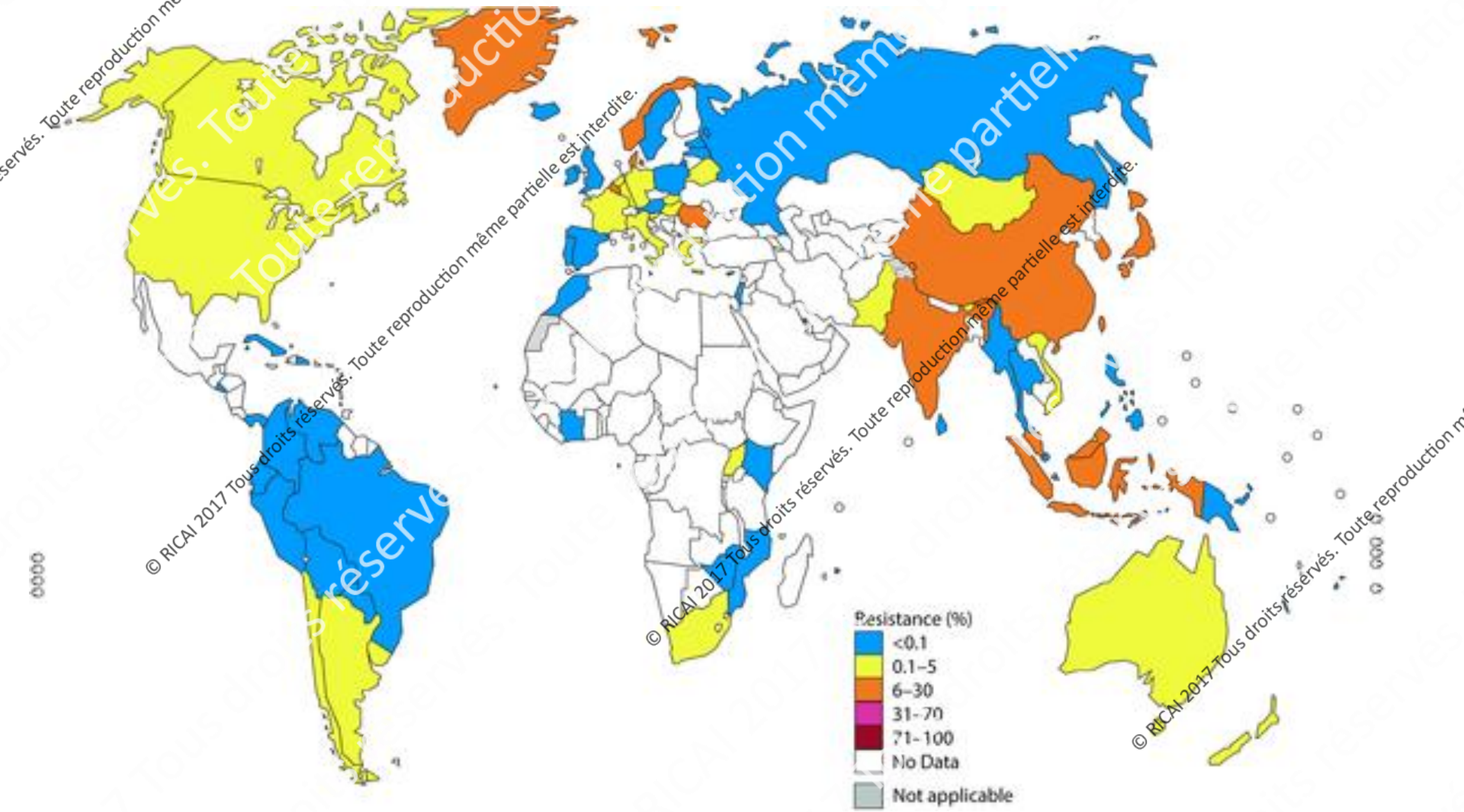
Number of countries in different WHO regions reporting gonococcal isolates with resistance to azithromycin and ciprofloxacin, and decreased susceptibility or resistance to ESCs (cefixime and/or ceftriaxone), 2009-2014

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 extended-spectrum cephalosporin (ESC) (cefixime and/or ceftriaxone) according to the 2014 WHO-GASP data



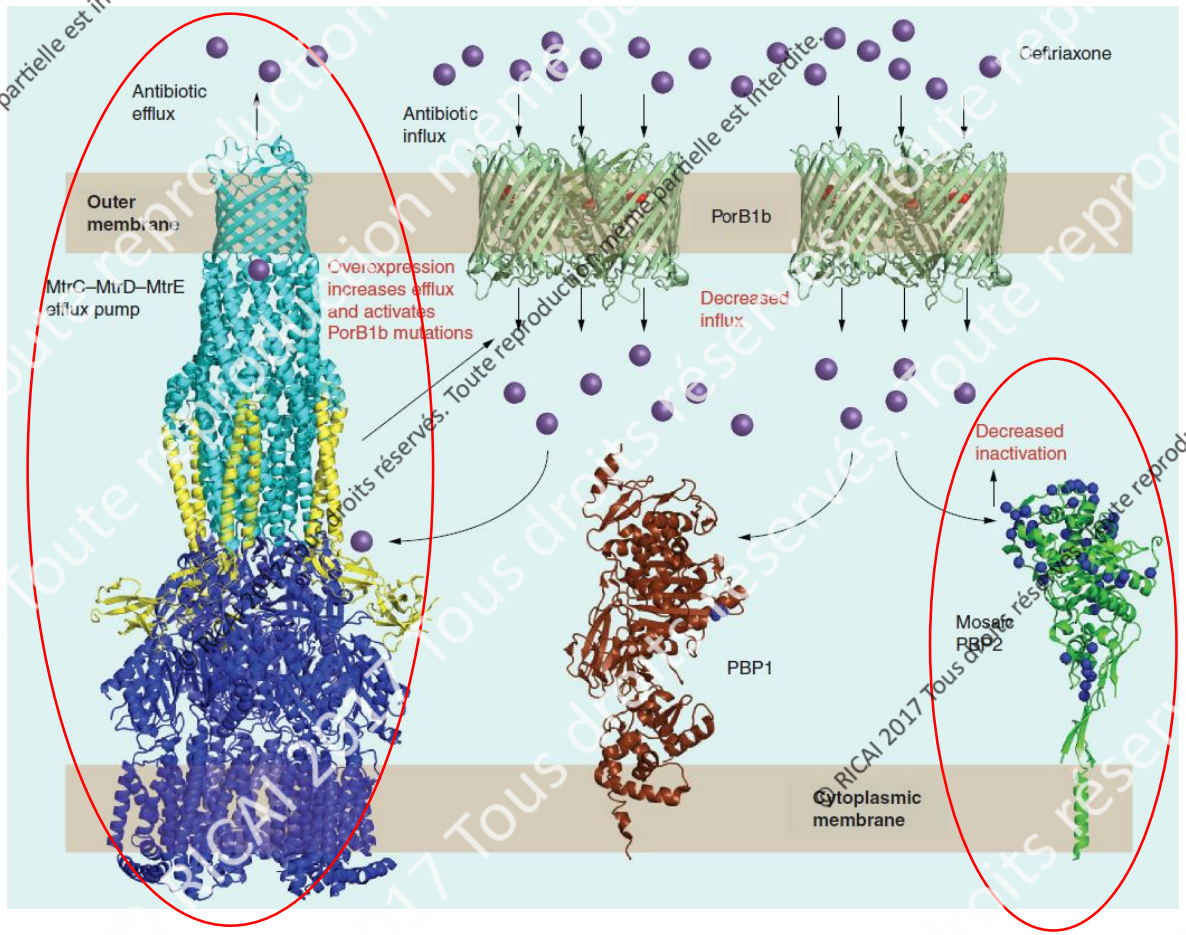
Wi et al. (2017) PLOS Medicine 14(7): e1002344.

Neisseria gonorrhoeae

- Main mechanisms of resistance to ESCs:

Mosaic PBP2 gene

Hyperexpression of the MtrCDE efflux pump



Unemo et al, Future Microbiol. 2012

Neisseria gonorrhoeae

- Azithromycin resistance: 2% - 8%

Europ EURO-GASP 2014 (n=1066) 21 countries	Australia 2015 n=5411	United States GISP 2014 (n=5093), 27 sites
7.9%	2.6%	2.5%

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

- Fluoroquinolone resistance: 30 % – 50 %

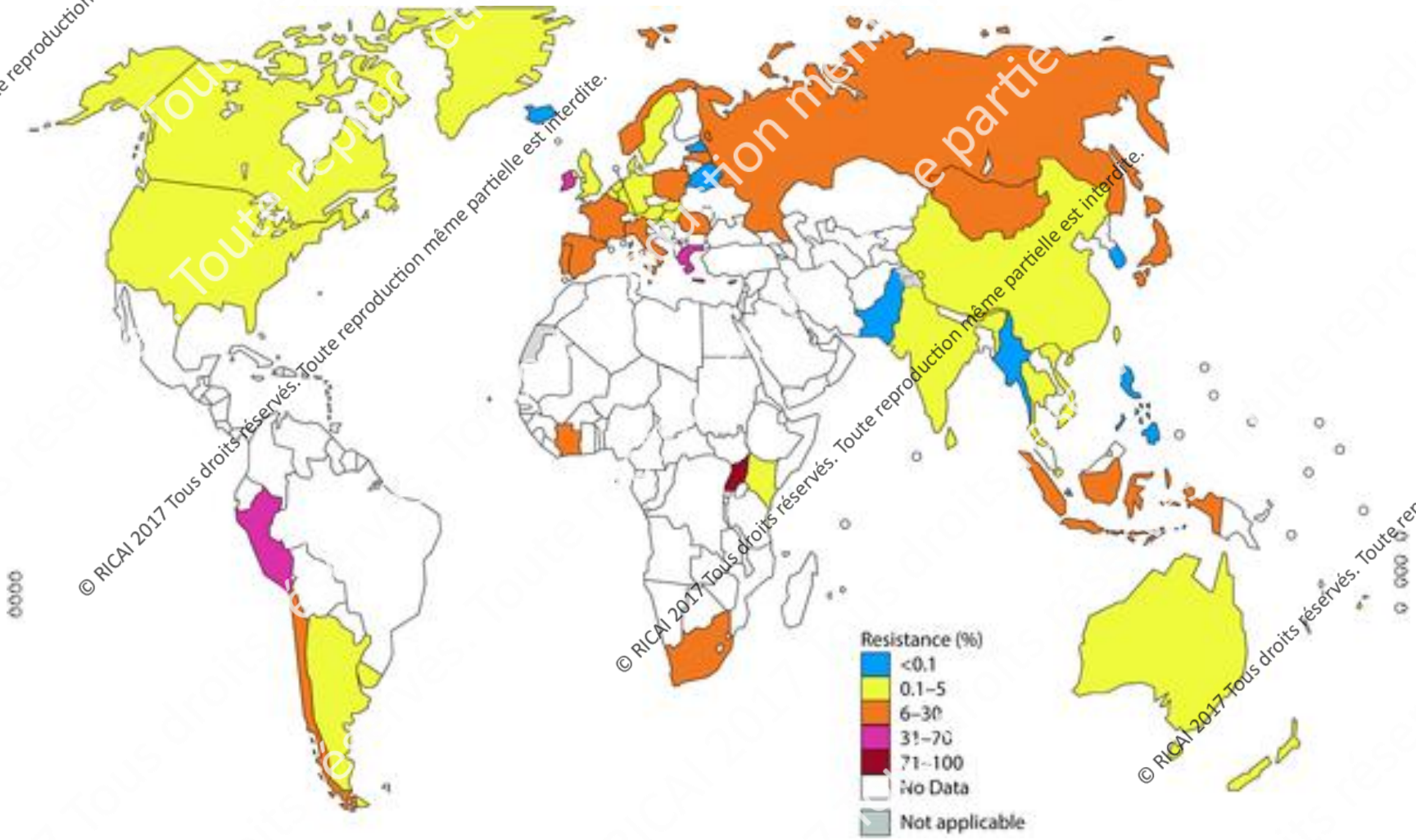
Mutations in the FQ enzyme targets (DNA gyrase) leading to high MIC increases

- Tetracycline resistance > 50%

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

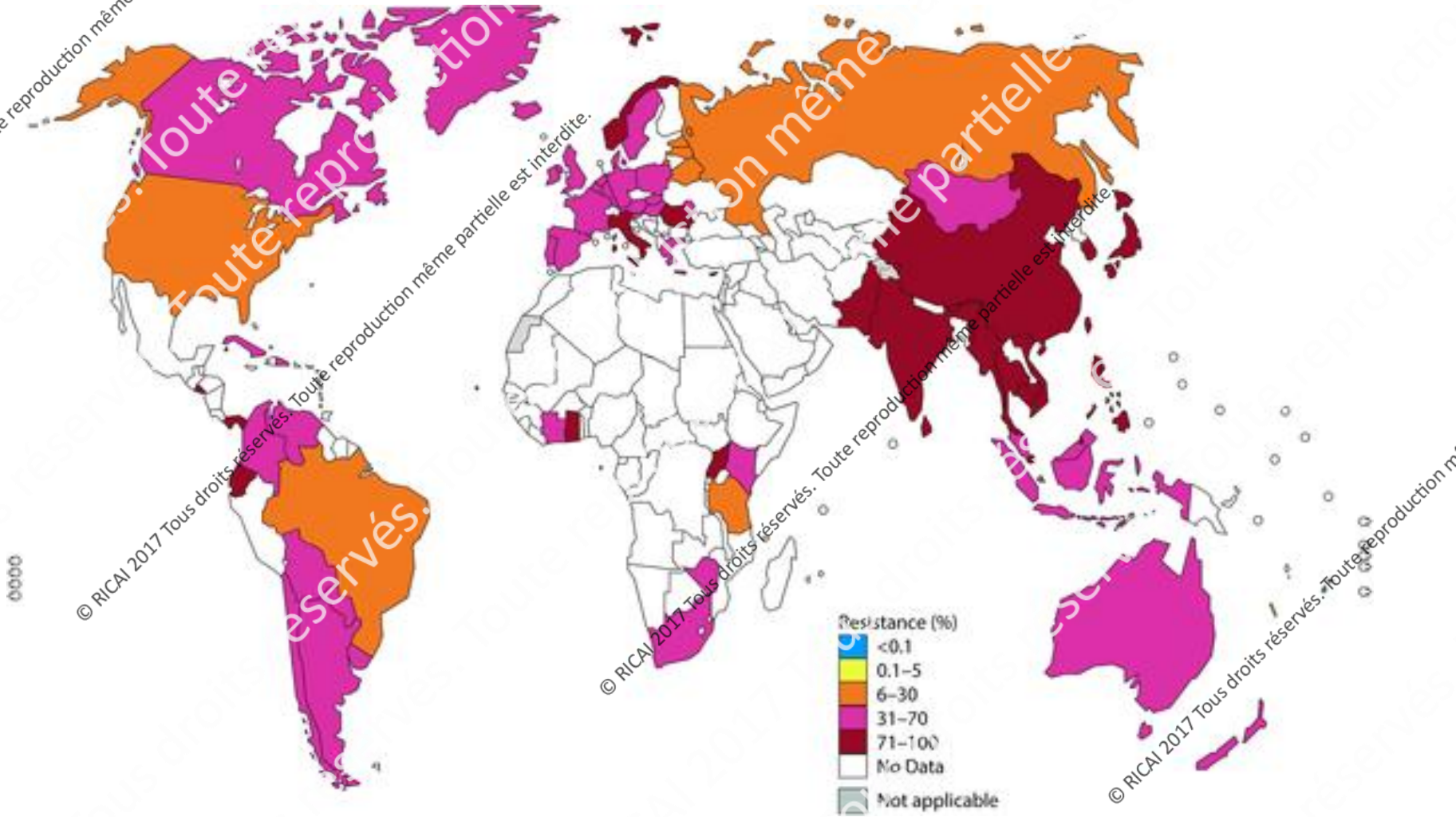
Unemo et al, Future Microbiol. 2012; Unemo and Jensen, Nat Rev Urol 2017; Wi et al, PloS Med 2017

Percentage (%) of isolates with resistance to azithromycin according to according to the 2014 WHO-GASP data



Wi et al. (2017) PLOS Medicine 14(7): e1002344.

Percentage (%) of isolates with resistance to ciprofloxacin **according to according to the 2014 WHO-GASP data**



Wi et al. (2017) PLOS Medicine 14(7): e1002344.

Conclusion

- AMR in STIs: 2 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
- Combination therapy: *N. gonorrhoeae*, *M. genitalium*?
- Rapid molecular AMR testing for simultaneous detection of *N. gonorrhoeae* and *M. genitalium* and their AMR should be developed -> immediate diagnosis, AMR surveillance and personalized treatment
- Future treatment needed

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

Acknowledgments

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  B. de Barbeyrac