ESGMI ESCMID STUDY GROUP FOR MYCOPLASMA INFECTIONS
European Society of Clinical Microbiology and Infectious Diseases

The International Organization for Mycoplasmology
Dedicated to the study of the Mollicutes

Les mycoplasmes urogénitaux : des agents d'IST ?

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USC EA 3671 Mycoplasmal and chlamydial infections in humans
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December 1st 2017

université de BORDEAUX

INRA SCIENCE & IMPACT

CHU Hôpitaux de Bordeaux

Characteristics of mycoplasmas

- **Smallest free-living eubacteria (500 to 2200 kbp)**
- **Lack of cell wall (« *Mollis cutis* » or Mollicutes)**
- **18 human species: respiratory or urogenital tract**
- **5 human pathogenic species:**

- *M. pneumoniae* → respiratory tract infections

- *M. hominis*
- *U. urealyticum*
- *U. parvum*
- *M. genitalium*

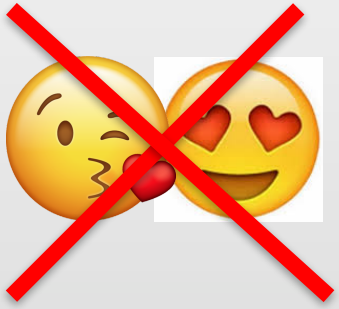
} **urogenital tract infections**
Sexually transmitted infections (Mg)

Ureaplasma spp. and *M. hominis*

- **Commensals of the urogenital tract**
  - **More frequent in women**
  - ***Ureaplasma* spp. (30%) >> *M. hominis* (<10%)**
  - **Variable according to different parameters**
    - ✓ age, sexual activity, race, pregnancy, socio-economic level

- **Opportunistic pathogens**
  - **Challenge to interpret their presence in the lower genital tract**

- **Not IST agents**



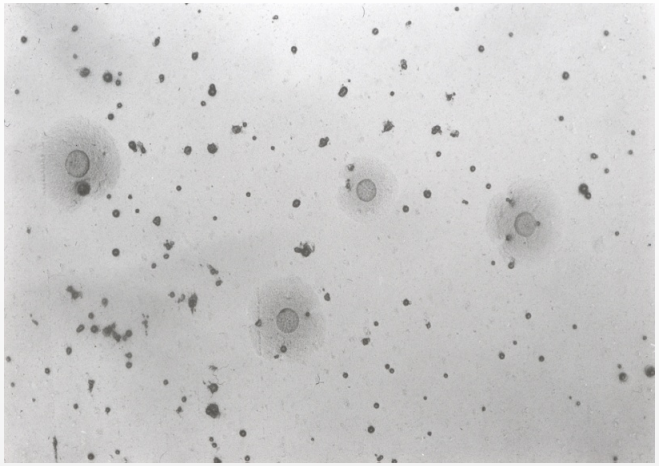
Mycoplasmal urogenital infections

Disease	*M. hominis*	*Ureaplasma* spp.	*M. genitalium*
Male genital disease			
Nongonoccocal urethritis	-	+	+
Epididymitis, prostatitis	-	±	±
Gynecologic infections			
Bacterial vaginosis	+	-	±
Cervicitis	-	-	+
PID	+	-	+
Adverse pregnancy outcomes	+	+	±
Neonatal infections	±	+	?
Extragenital infections	+	+	±

+, Confirmed association
±, Non confirmed association
-, No association
?, Unknown

Laboratory detection

- **Culture : *M. hominis* and *Ureaplasma* spp.**
  - Agar or liquid broth
  - Commensal ➔ Quantitative cultures required



Specimens	Threshold
Sterile sites or specimens	No threshold Detection = infection
Men	
Urethral specimens, sperm	U ≥ 10^4 CCU/ml
1er void urines	U ≥ 10^3 CCU/ml
Women (cervico-vaginal specimens)	- Mh ≥ 10^4 CCU/ml - U : no threshold, detection non significant
Neonates	
Endotracheal specimens	U ≥ 10^4 CCU/ml

U, *Ureaplasma* spp. Mh, *M. hominis; CCU,color changing unit*

- **PCR : specimens from sterile sites**
  - Higher sensitivity

Urogenital mycoplasmas and antibiotics

- **Intrinsic resistance related to:**

  - the *Mollicutes* class: ATB targeting the cell wall (β-lactams, glycopeptides, fosfomycin) and rifampicin (mutation in *rpoB* gene)

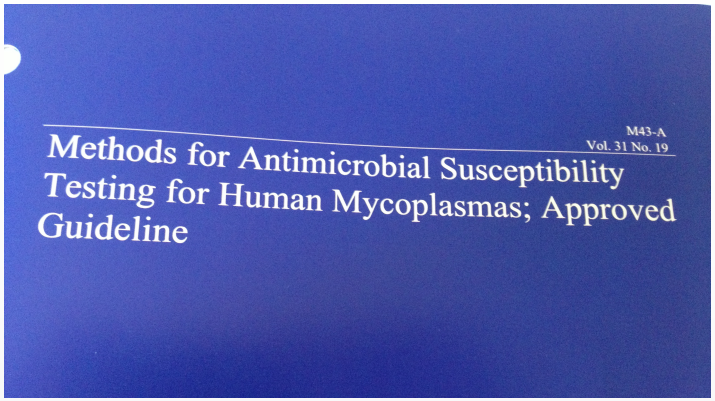
  - certain species and macrolides and related ATB:
  - ✓ ***M. hominis* resistant to 14- and 15-membered macrolides**
  - ✓ ***Ureaplasma* spp. resistant to lincosamides**

- **Active antibiotics**

  - Macrolides and related ATB: macrolides, lincosamides, streptogramin combinations, ketolides (MLSK)
  - Fluoroquinolones
  - Tetracyclines

Antibiotic susceptibility testing

- **Phenotypic techniques**
  - Broth microdilution
  - Agar dilution
  - E- tests (*M. hominis*)



- **CLSI recommendations**
  M43-A 31(19), 2011

- **In routine, commercialized kits**
  ***M. hominis*, *Ureaplasma* spp. only**

- **Molecular techniques** to detect tetracycline, fluoroquinolone or macrolide resistance

Acquired resistance to antibiotics in *Ureaplasma* spp. and *M. hominis*

- ✓ **Resistance to tetracyclines +++**
  - **acquisition of *tet*(M) gene**
  - **15 % Mh, 7,5 % U (France, 2010-2015)**

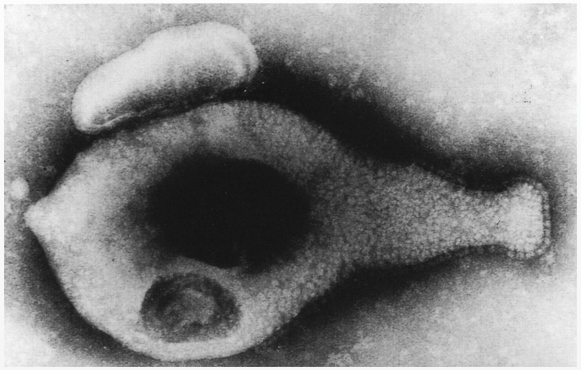
- ✓ **Resistance to macrolides**
  - **Mutations in domain V of 23S rRNA**
  - **Very rare cases in Mh and U**

- ✓ **Resistance to fluoroquinolones**
  - **mutations of gyrase and topoisomerase IV genes**
  - **Patients previously treated by FQ**
  - **3 % Mh and 1% U (France, 2010-2015)**

Meygret et al. oral communication, RICAI 2017

Mycoplasma genitalium

- **1980: *Mycoplasma genitalium* isolated from 2 of 13 men with nongonoccocal urethritis (NGU)**
  - **Very slow growth (>50 days)**
  - **Very few isolates available**



Tully, Int J Syst Bacteriol 1983

- **1990's: development of PCR assays**

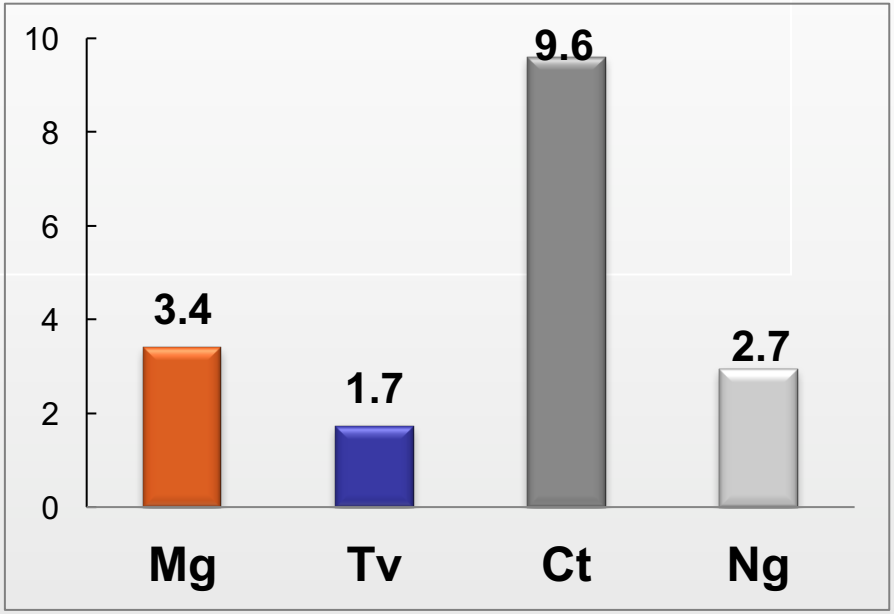
- **1995: smallest genome known (580 kbp, 485 genes)**
  - **The 2nd bacterial genome fully sequenced (Himmelreich, 1995)**
  - **Minimal requirements of life, concept of minimal cell**

Tully Lancet 1981

M. genitalium prevalence

- **Community-based populations 1–3%**
  - **Carriage frequently asymptomatic**
- **STI testing centers populations (high risk) 4 – 38%**
- **Prevalence in France 2014-2015**

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



Pereyre *et al.* Clin. Microbiol. Infect. 2016

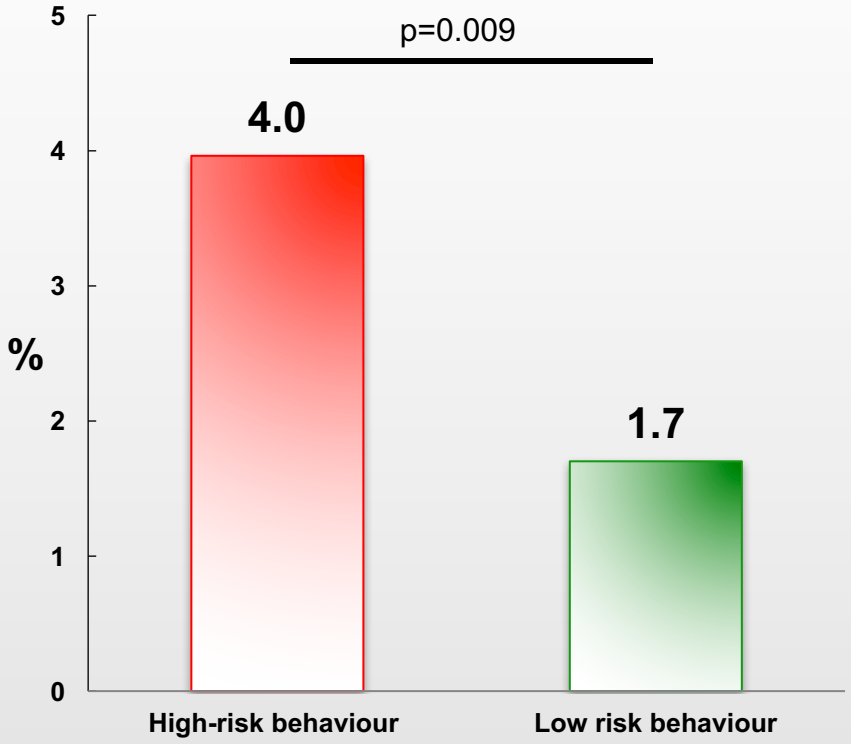
Anderson Sex Transm Infect 2007; Baczynska Syst Biol Reprod Med 2008; Cohen Sex Transm Dis 2007; Jensen J Eur Acad Dermatol 2013; Manhart Am J Public Health 2007; Clin Infect Dis 2011; Oakeshott Clin Infect Dis 2010; Peuchant Diagn Microbiol Infect Dis 2015; Svenstrup BMJ Open 2014; Walker Clin Infect Dis 2013

M. genitalium prevalence in France

- **By sample collection sites**

Urogenital specimens submitted for *C. trachomatis* and *N. gonorrhoeae* detection in France 2014-2015

STI centres
Abortion centres
Family planning centres
Penitentiary centres



Gynaecologic practices
Obstretric practices
Reproduction centres

Pereyre *et al.* Clin. Microbiol. Infect. 2016

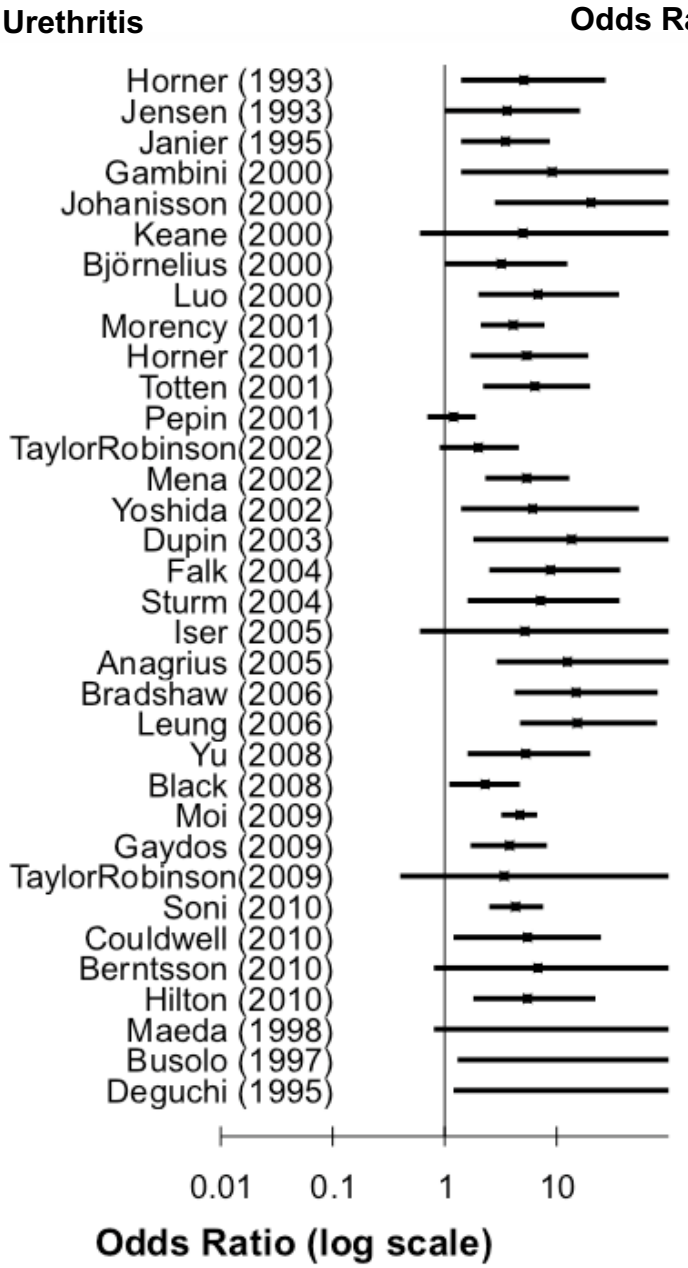
M. genitalium: disease association

Men	Women
Non gonococcal urethritis (NGU)	Urethritis
Balanoposthitis	Cervicitis
Epididymitis Prostatitis	Endometritis, Salpingitis (PID)
Proctitis (MSM)	Adverse pregnancy outcomes
	Female infertility
	Increased HIV transmission

Association between *M. genitalium* and male NGU

34 studies
1993-2010
Europe, America, Asia, Oceania

Pooled OR = 5.5
(4.3-7.0)



2nd cause of NGU after *C. trachomatis*

Manhart et al, Clin Infect Dis 2011

M. genitalium: disease association

Men	Women
Non gonococcal urethritis (NGU)	Urethritis
Balanoposthitis	Cervicitis
Epididymitis Prostatitis	Endometritis, Salpingitis (PID)
Proctitis (MSM)	Adverse pregnancy outcomes
	Female infertility
	Increased HIV transmission

Association between *M. genitalium* and female disease
Meta-analysis 1980-2014

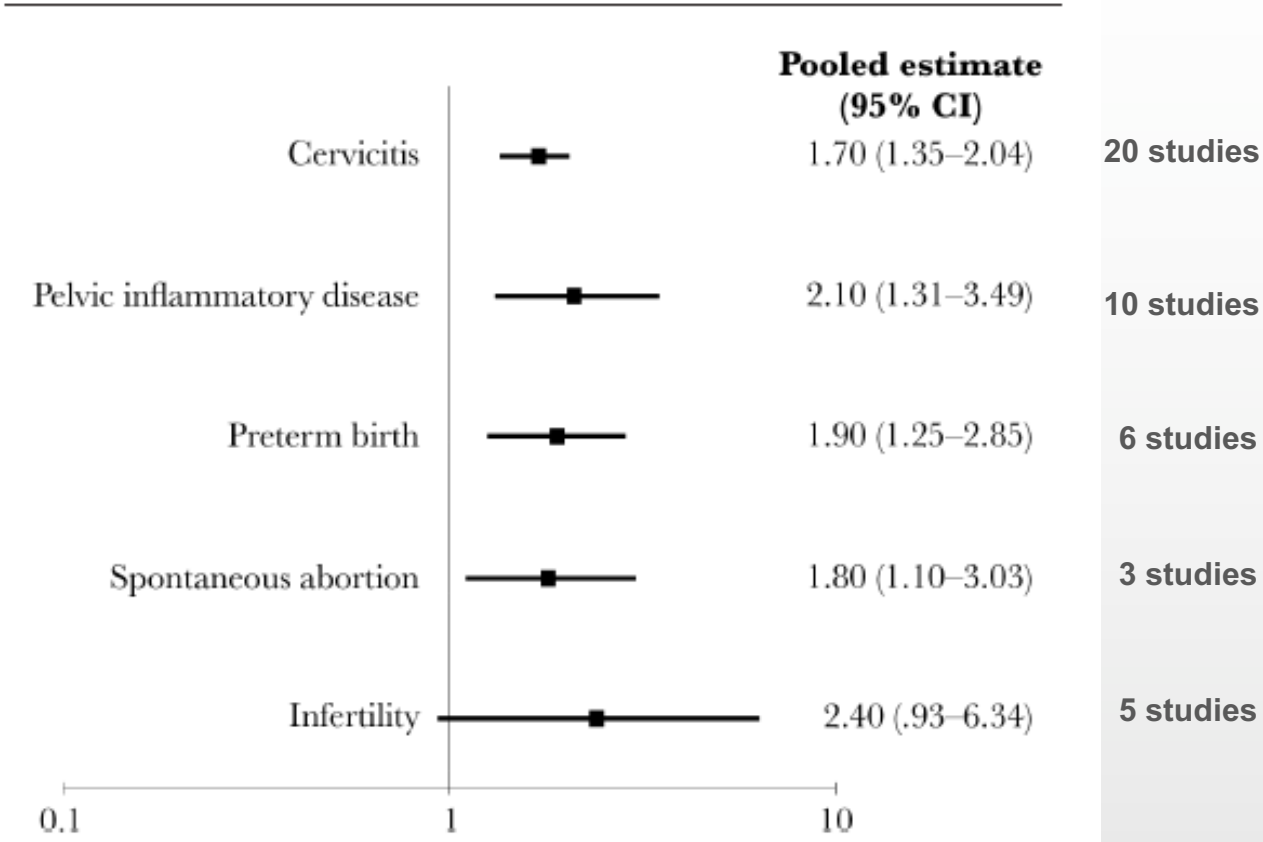
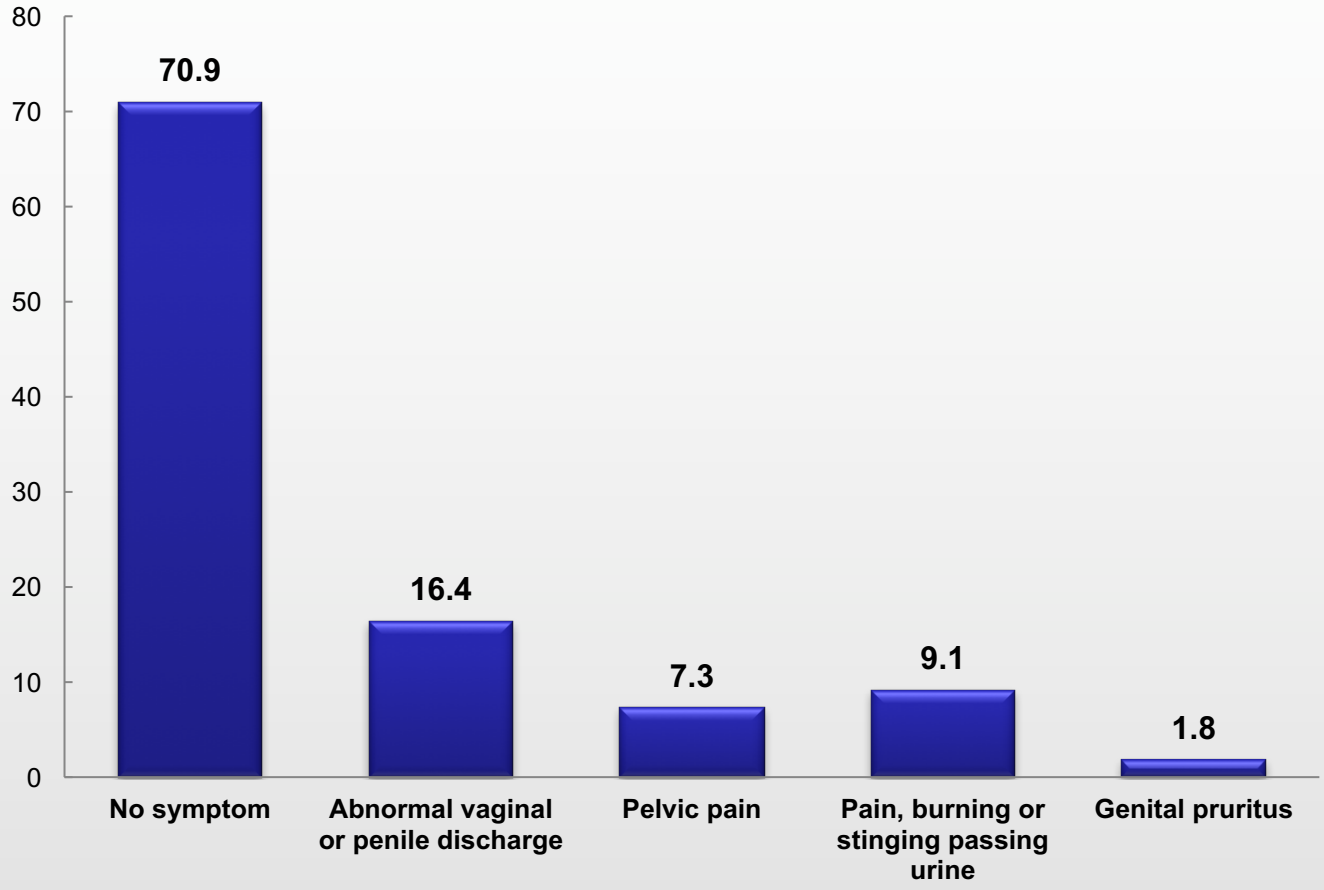


Figure 1. Summary effect sizes from meta-analysis of the association between *Mycoplasma genitalium* infection and 5 female reproductive tract disease syndromes Adapted from Lis et al [7]. Abbreviation: CI, confidence interval.

Lis et al, Clin Infect Dis 2015; Wiesenfeld J. Infect. Dis 2017

Clinical symptoms in *M. genitalium* infections

***M. genitalium*-positive urogenital specimens submitted for *C. trachomatis* and *N. gonorrhoeae* detection in France 2014-2015**



Pereyre Clin. Microbiol. Infect. 2016

An STI agent

- **Sexually transmission is established**
  - **Among heterosexual contacts, women are twice as likely as men to be infected** (aOR=2.18, *Slifirski, Emerg. Infect. Dis. 2017*)
  - **Transmission is probably lower than that for *C. trachomatis***
    - ✓ *Consistent with lower infectious load of Mg*
    - ✓ *men with symptomatic NGU may be more infectious than men with asymptomatic infection*

- **Among MSM, rectal infection is more common than urethral infection**
  - **MSM: rectal positivity: 42% *vs* urethral positivity : 8%** (*Slifirski, Emerg. Infect. Dis. 2017)*

- **Transmission through oral sex is likely to be rare**
  - **as carriage of Mg in the oropharynx is not frequent**

Horner, J infect Dis 2017; Slifirski, Emerg Infect Dis, 2017

Diagnostic of *M. genitalium* infections

- **Only direct diagnosis,** **no serology kit commercialized**

- **Culture extremely fastidious** **(co-culture with Vero cells required)**
  No routine MIC determination

- **Nucleic acid amplification tests:**

  - A lot of in-house PCRs, real-time PCR ++, TMA

  - MgPa adhesin gene (*mgpB*), 16S rRNA

  - Monoplex and multiplex tests commercialized, some CE-marked

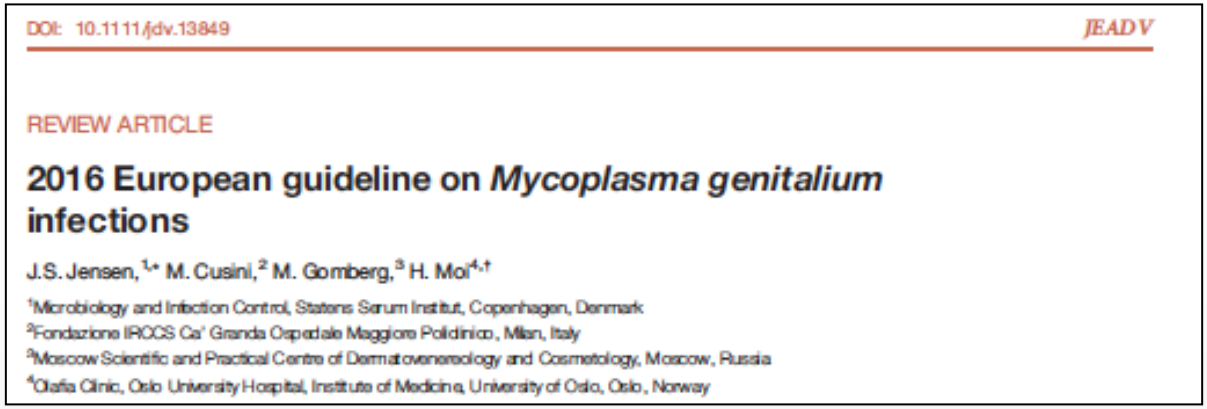
Hamasuna J Clin Microbiol 2007; Jensen J Clin Microbiol 2004; Le Roy J Microbiol Methods 2012, 2014;
Lee J Infect Chemother 2012; Lillis J Clin Microbiol 2011; Wroblewsky J Clin Microbiol 2006; Tabrizi J Clin Microbiol 2016;
Munson J Clin Microbiol 2016

Commercially available mono and multiplex NAATs for *M. genitalium*

Manufacturer	Kit	Technique	Pathogens targeted
Hologic	*Mycoplasma genitalium* Aptima assay	TMA	*M. genitalium*
Roche/TIB MolBiol	LightMix *Mycoplasma genitalium*	qPCR	*M. genitalium*
Progenie molecular	MYGE-U, MYGE-G	qPCR	*M. genitalium*
SpeedX	ResistancePlus MG	qPCR	*M. genitalium* and macrolide resistance
BioGX (BD MAX)		qPCR	*M. genitalium* and urogenital mycoplasmas
Diagenode	S-DIAMGTV	qPCR	*M. genitalium, Trichomonas vaginalis*
Fast-track Diagnostics	Several kits	qPCR	*M. genitalium* and several STI pathogens and urogenital mycoplasmas
Sacace	Several kits	qPCR	*M. genitalium* alone or multiplexed with several STI pathogens and/or urogenital mycoplasmas
Seegene	Several kits	qPCR	*M. genitalium* and several STI pathogens and urogenital mycoplasmas

- No reimbursement
- Need for external quality assessment programs

Indication for Mg testing



DOI: 10.1111/jdv.13849 JEADV

REVIEW ARTICLE

2016 European guideline on *Mycoplasma genitalium* infections

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[1]Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark
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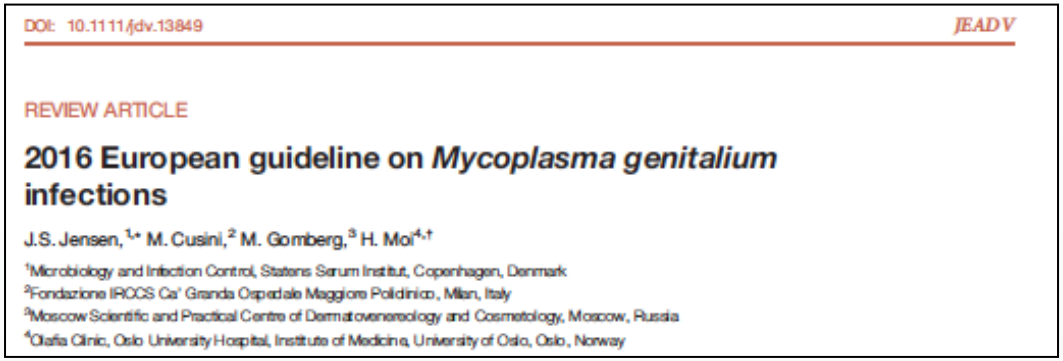
[3]Moscow Scientific and Practical Centre of Dermatovenerology and Cosmetology, Moscow, Russia
[4]Olafia Clinic, Oslo University Hospital, Institute of Medicine, University of Oslo, Oslo, Norway

Symptoms

- Symptoms or signs of urethritis in men
- Mucopurulent cervicitis
- Cervical or vaginal discharge with risk factor of STI
- Intermenstrual or post coidal bleeding
- Acute pelvic pain and/or PID
- Acute epididymo-orchitis in a male <50 yo

Indication for Mg testing



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

Symptoms

Risk factors

- Symptoms in a regular sexual partner

- Persons with high-risk sexual behavior (<40 yo, >3 new sexual contacts in the last year)

The public health value of testing asymptomatic persons for Mg has not been established. Decision on testing should be informed by local epidemiology when available

- Sexual contact of persons with STI or PID, with Mg-infected persons

- Before termination of pregnancy or other procedures, that break the cervical barrier

- Regular testing of MSM including anal sampling

M. genitalium and tetracyclines

- **Relative potency *in vitro***

MIC ranges (µg/ml)

Antibiotics	***M. genitalium***	***M. hominis***	***Ureaplasma* spp.**
Tetracyclines			
Doxycycline	≤0.01-0.3	0.1-2	0.02-1
Minocycline	≤0.01-0.2	0.03-1	0.06-1

- **BUT, low eradication rate**
  - **Microbiological cure : between 30 and 40 %**

Pereyre, Antimicrob. Chemother. Vaccines, 3rd edition, 2016; Jensen J Eur Acad Dermatol Venereol. 2016

M. genitalium and macrolides

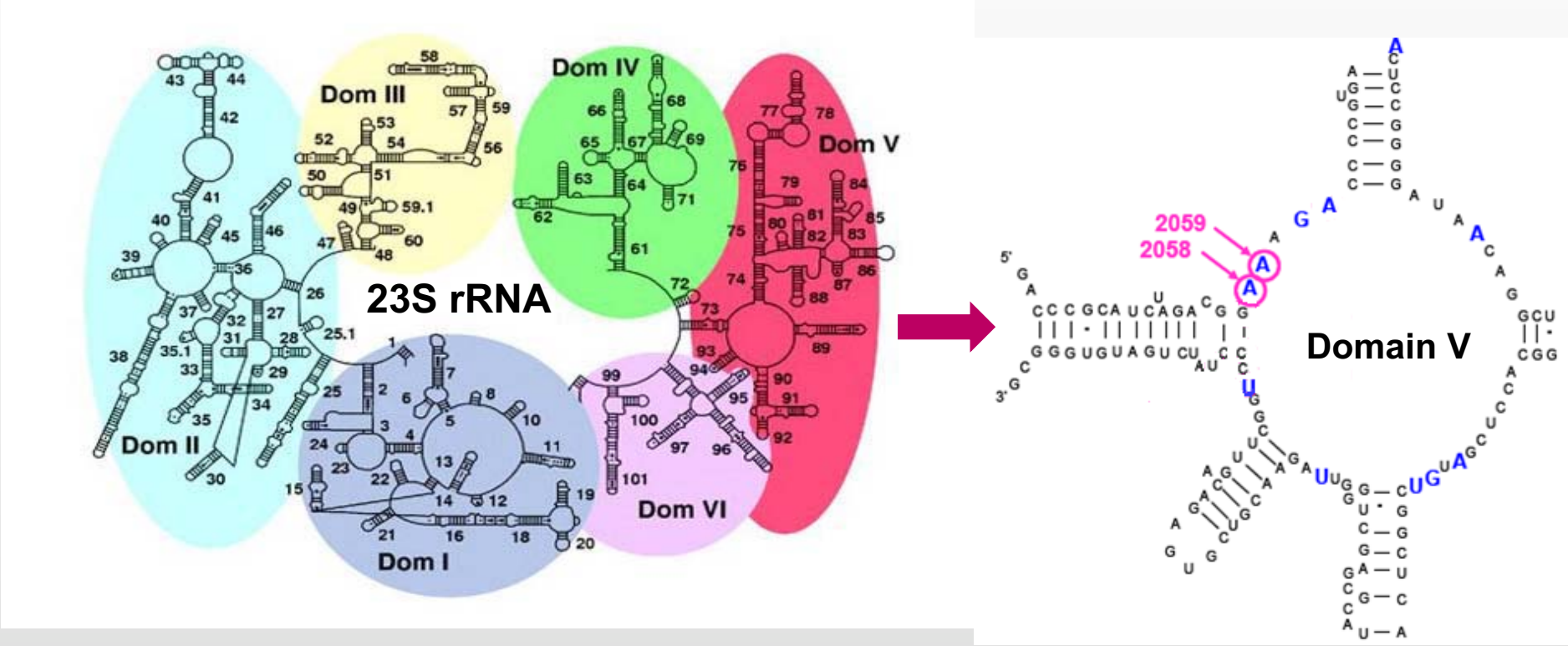
- **Low MICs**

Antibiotics	*M. genitalium*	*M. hominis*	*Ureaplasma* spp.
MLSK group			
Erythromycin	≤0.01	32->1 000	0.02-16
Roxithromycin	<0.01	>16	0.1-2
Clarithromycin	≤0.01-0.06	16->256	≤0.004-2
Azithromycin	≤0.01-0.03	4->64	0.06-4
Josamycin	0.01-0.02	0.05-2	0.03-4
Clindamycin	0.2-1	≤0.008-2	0.2-64
Pristinamycin	≤0.01-0.02	0.1-0.5	0.1-1
Quinupristin/ Dalfopristin	0.05	0.03-2	0.05-0.5
Telithromycin	≤0.015	2-32	≤0.015-0.25
Solithromycin	≤0.000000063-0.000125	0.002-0.008	0.002-0.063

Pereyre, Antimicrob. Chemother. Vaccines, 3rd edition, 2016

Macrolide resistance in *M. genitalium*

- **Mutations in domain V of 23S rRNA**
  - **Single operon encoding 16S and 23S rRNA**
  - **A2058G**/C/T, **A2059G**/C/T (***E. coli*** **numbering)**



Detection of macrolide resistance-associated mutations

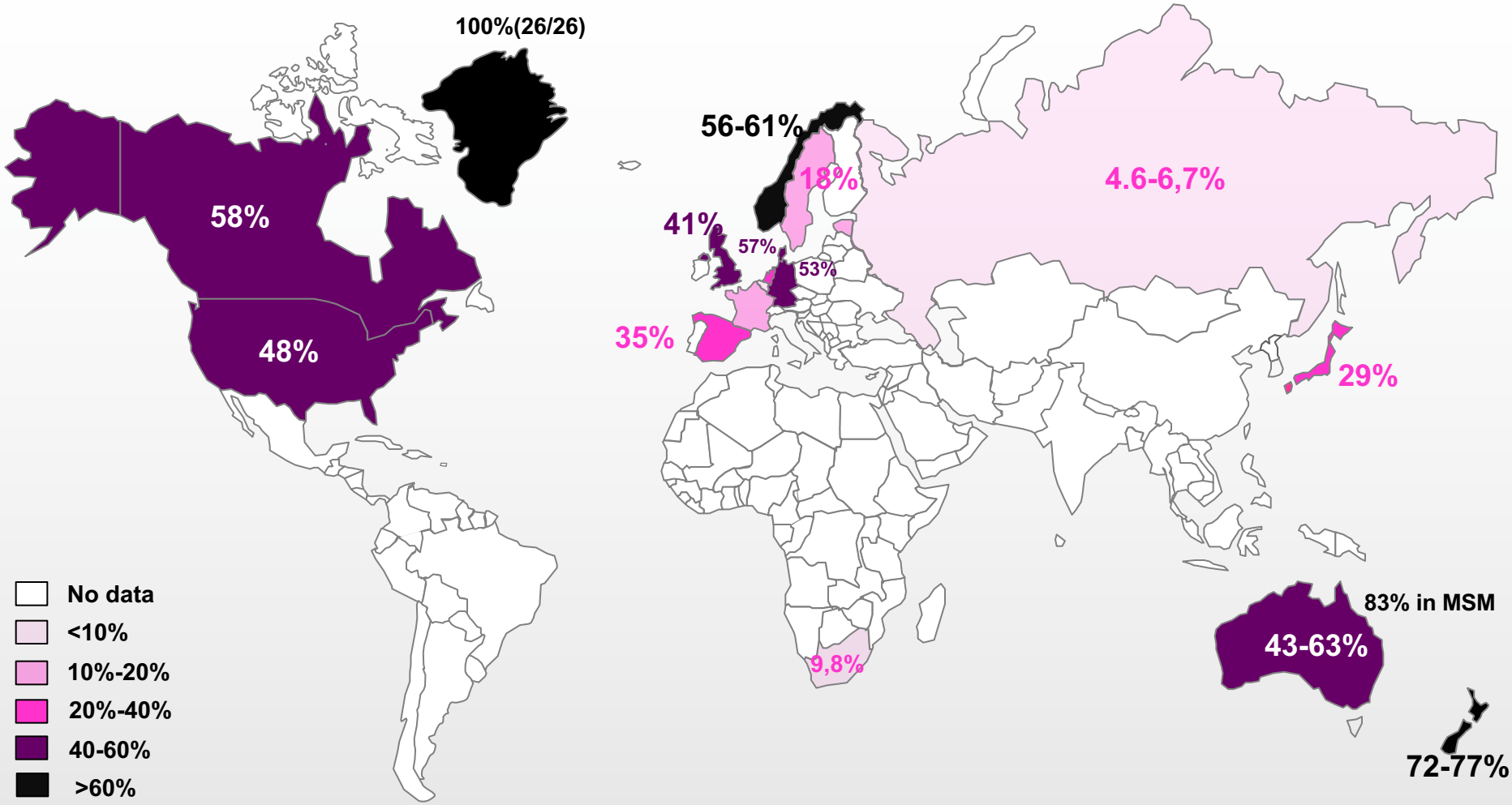
- **Amplification and 23S rRNA sequencing**
  - **Time-consuming, not adapted to routine**

- **In-house methods**
  - **FRET real-time PCR** (Touati *et al.* J. Clin. Microbiol. 2014)
  - **HRM (High Resolution Melting curve analysis)** (Twin *et al.* PloS One 2012)
  - **PCR and pyrosequencing** (Salado-Rasmussen *et al.* Clin. Infect. Dis. 2014)
  - **Taqman PCR** (Wold *et al.* J. Eur. Acas. Dermatol. Venereol. 2015), (Kristiansen *et al.* J. Clin. Microbiol. 2016)
  - **Single probe PCR and melting curve analysis** (Gossé *et al.* J. Clin. Microbiol. 2016)

- **Commercial kits**
  - **ResistancePlus™ MG kit (SpeeDx, Australia) : multiplex real-time PCR**

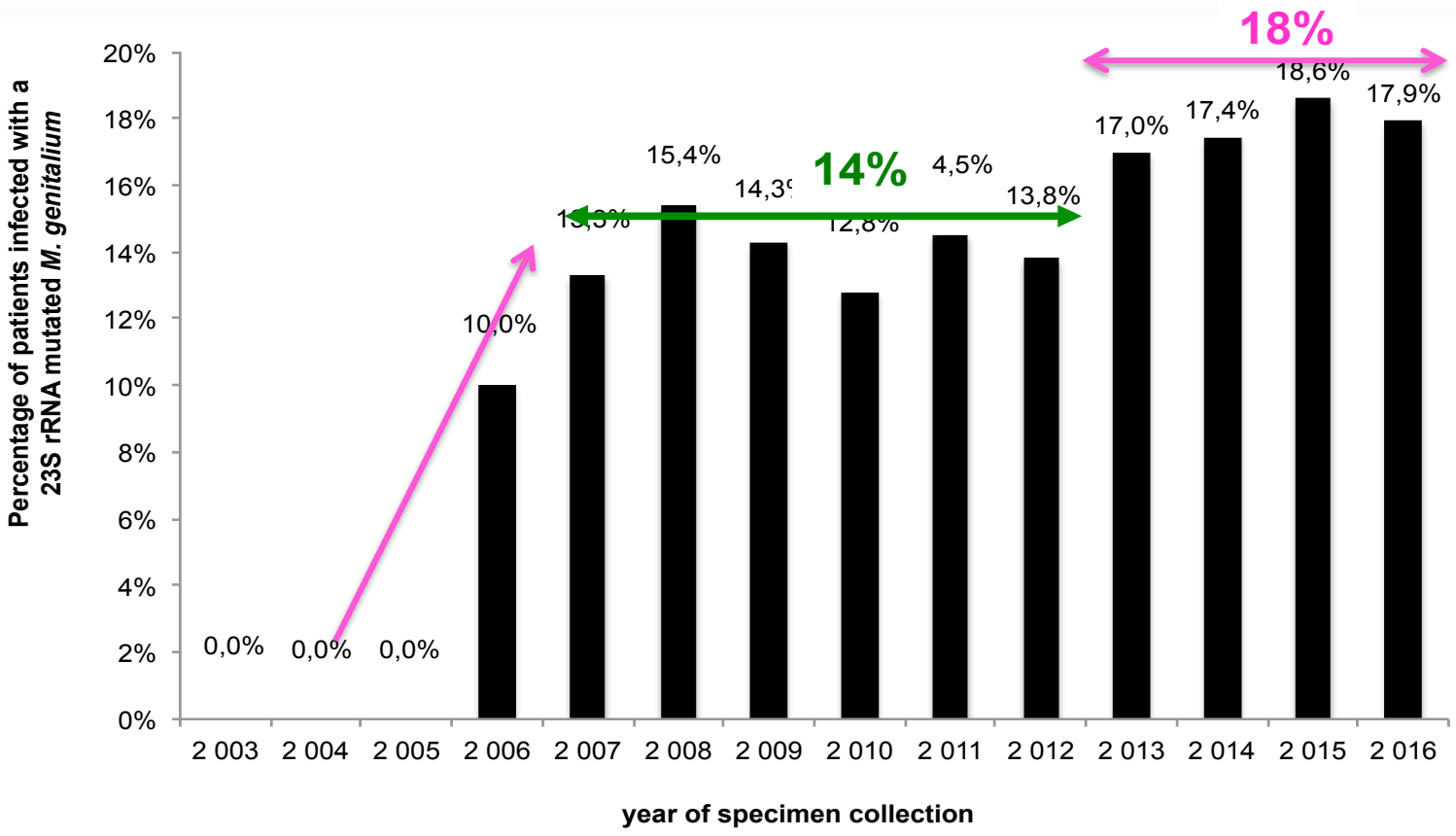
Detection of Mg and 5 mutations (Le Roy, J. Clin. Microbiol. 2017)

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; 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.

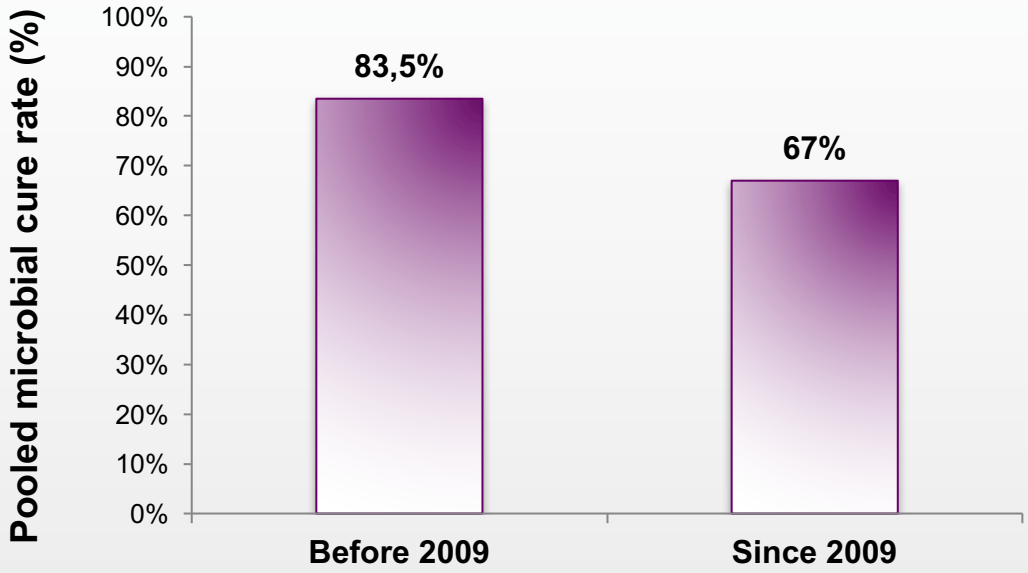
Macrolide resistance in *M. genitalium*
Bordeaux, France



Chrisment et al. J. Antimicrob. Chemother. 2012; Touati et. al, J. Clin. Microbiol. 2014; Le Roy, Emerg. Inf. Dis, 2016

M. genitalium treatment studies : Azithromycin 1g

- **Meta-analysis on the efficacy of AZM 1g for Mg treatment** *(Lau Clin. Infect. Dis. 2015)*
  21 studies, 1490 participants, mostly male NGU



- **AZM 1g single dose is no more the the 1st line treatment**
  - ➔ Therapeutic failure if patient infected with a mutated strain
  - ➔ **Selection of resistant mutants <u>during</u> AZM treatment**

Björnelius Sex Transm Infect 2008; Manhart Clin Infect Dis 2013; Mena Clin Infect Dis 2009; Schwebke CID 2011, Sena J Infect Dis 2012; Stamm Sex Transm Infect 2007; Lau Clin Infect Dis 2015; Horner Clin Infect Dis 2015; Jensen BMC Infect Dis 2015

M. genitalium treatment studies : Azithromycin 1.5 g/5 days

- **Extended 1.5 g AZM (500 mg d1, 250 mg d2-4)**

  85% effective and associated with lower risk of inducing AZM R

  Anagrius PLoS One 2013, Bjornelius Sex Transm Infect 2008, Falk J Antimicrob Chemother 2015, Gundevia STI 2015

- **Patients failing azithromycin 1g single dose cannot be treated successfully with extended 1.5 g AZM**

  Jernberg Sex Transm Infect 2008, Jensen Clin Infect 2009

- **Moxifloxacin 400 mg for 7-10 d in case of AZM failure… but…**

  Jensen JEADV 2016, Horner, STD and AIDS, 2016; www.cdc.gov/std/tg2015

M. genitalium and fluoroquinolones

- **Only moxifloxacine has low MICs**

Antibiotics	*M. genitalium*	*M. hominis*	*Ureaplasma* spp.
Fluoroquinolones			
Ciprofloxacin	2	0.1-4	0.1-16
Ofloxacin	1-2	0.1-4	0.2-4
Levofloxacin	0.5-1	0.1-2	0.2-2
Moxifloxacin	0.03-0.06	0.06-0.125	0.125-1
Sitafloxacin (Japan only)	0.125		

Deguchi, J Infect Chemother 2014; Pereyre, Antimicrob. Chemother. Vaccines, 3rd edition, 2016

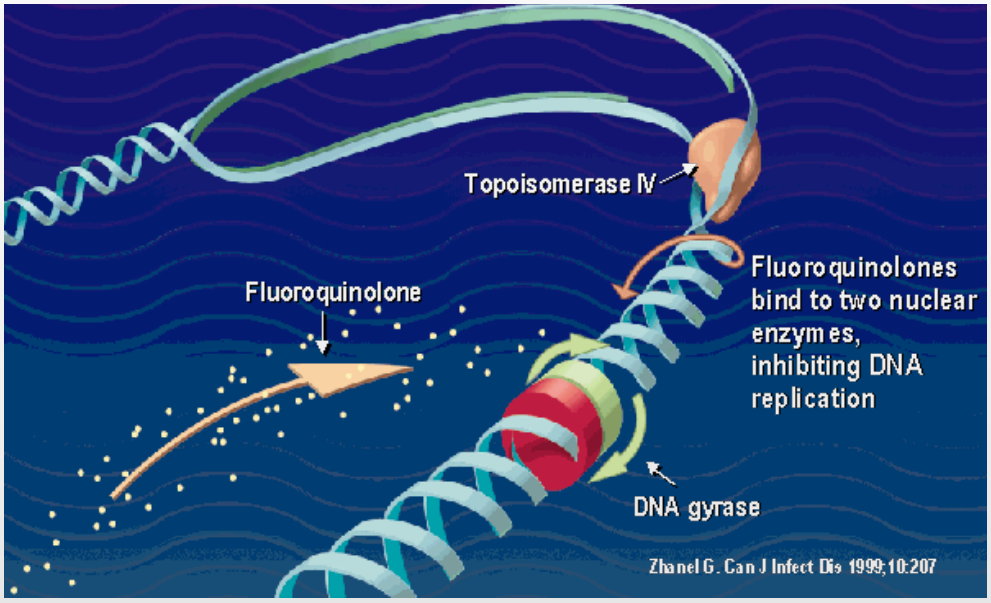
Fluoroquinolone resistance in *M. genitalium*

- **Mutations in the bacterial target genes of fluoroquinolones**

  - Most frequent mutations in *parC* (Topoisomerase IV)

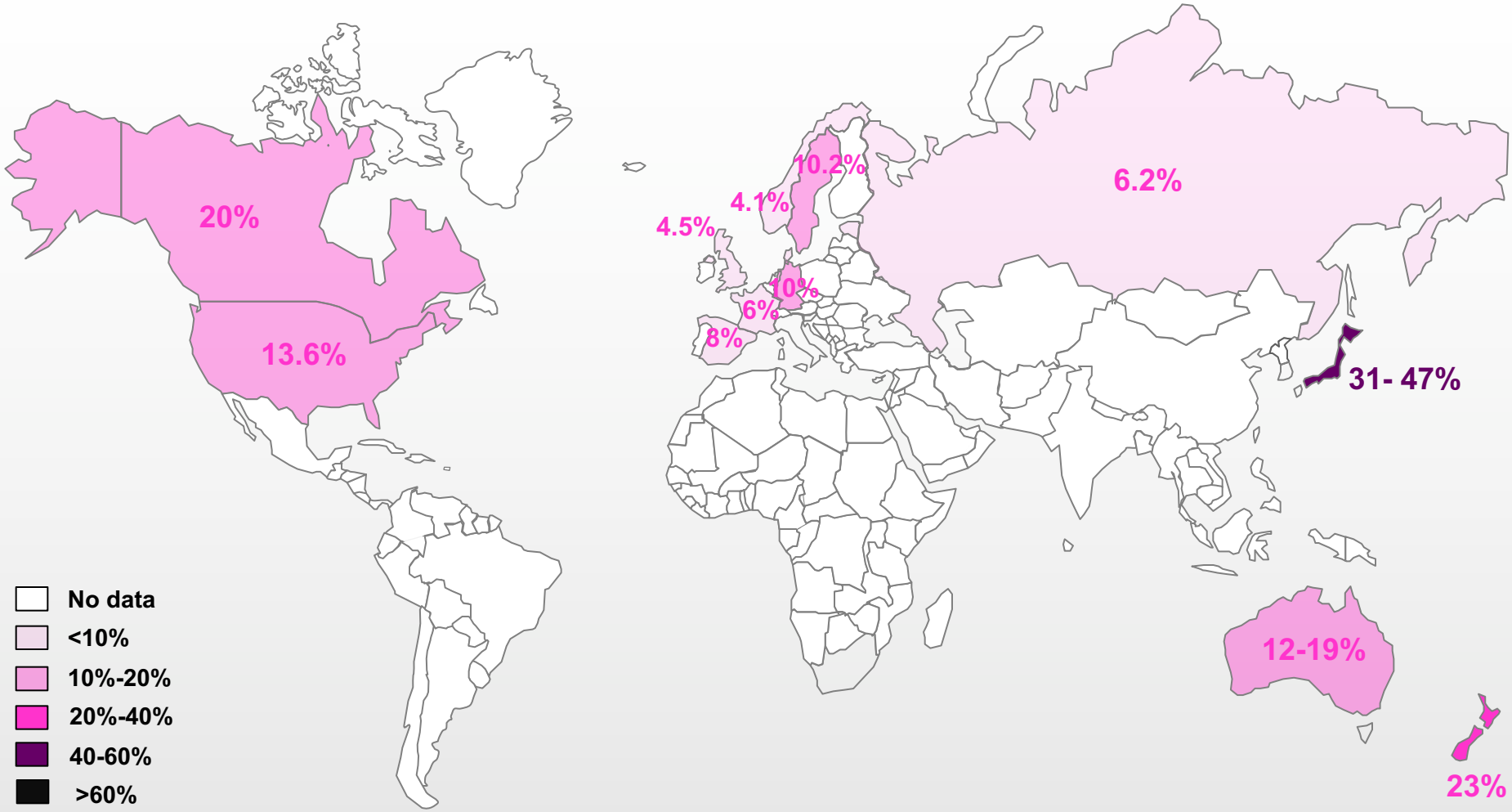
  Primarily Ser83 and Asp87

  - A few mutations in *gyrA* (DNA gyrase)



- Molecular detection only: amplification and sequencing of target genes

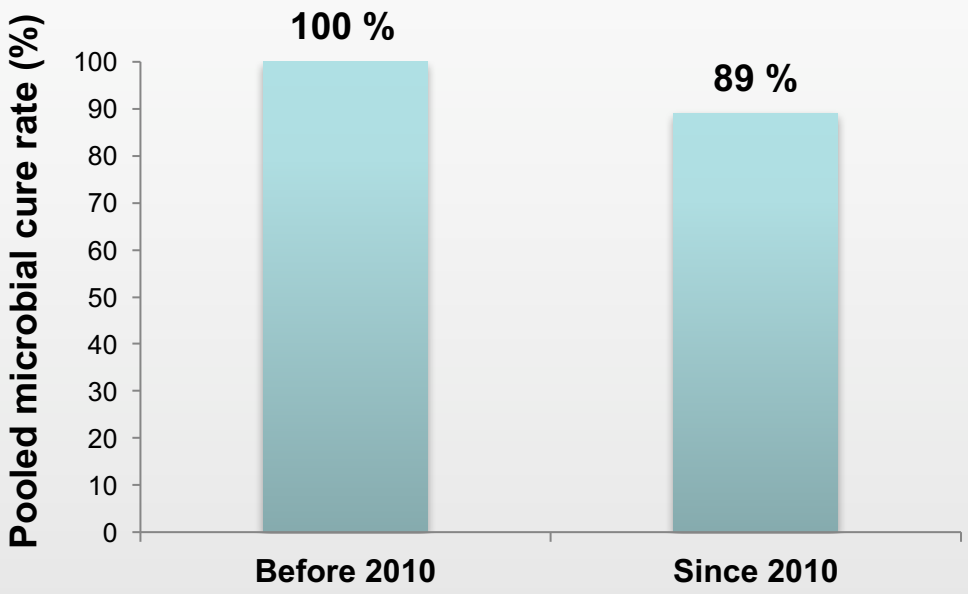
Prevalence of fluoroquinolone resistance-associated mutations



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.

M. genitalium fluoroquinolone treatment studies

- **Meta-analysis on the efficacy of moxifloxacin for *M. genitalium* treatment** *(Yi et al Int J STD AIDS 2017)*
  - **17 studies, 252 patients**



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JEADV 2016 DOI 10.1111/jdv.13849

IUSTI
INTERNATIONAL UNION AGAINST SEXUALLY TRANSMITTED INFECTIONS

- **Uncomplicated *M. genitalium* infection:**

- In the absence of macrolide resistance-associated mutations

Azithromycin 500 mg (day 1), then 250 mg (days 2-5)

Josamycin 500 mg 3 times daily - 10 days- IV

- Macrolide-resistant *M. genitalium* infection

- Second line treatment for persistent *M. genitalium* infection

Moxifloxacin 400 mg/d - 7 to 10 days

2016 European guideline on *Mycoplasma genitalium* infections

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- **Third-line treatment for persistent MG infection after AZM and MXF**
  - **Doxycycline 100 mg x2 daily for 14 days**
  - **Pristinamycin 1 g x4 daily for 10 days**

- **Complicated MG infection (PID, epididymitis)**
  - **Moxifloxacin: 400 mg - 14 days**

- **Test of cure: no earlier than 3 weeks after the start of antibiotic treatment**

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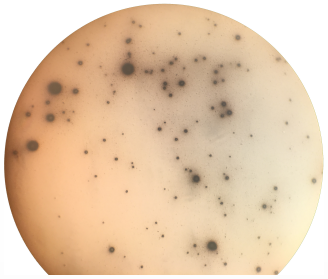
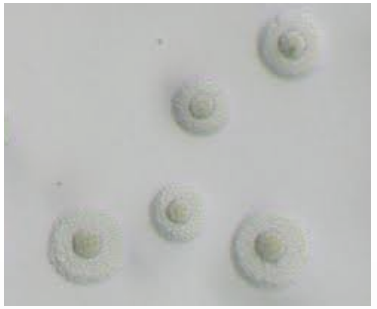
- All *M. genitalium*-positive test should be followed up with an assay capable of **detecting macrolide resistance-associated mutations**
- The extended azithromycin ttt after failure with 1g single dose will **NOT** eradicate *M. genitalium*



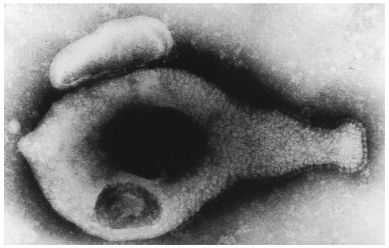
Take-home message



Ureaplasma spp. and *M.hominis* are NOT STI agents

- **Commensal of the urogenital tract**
  - **Quantitative culture to interpret their pathogenic role**
    - ***Ureaplasma* in men, *M. hominis* in women**
    - **Adverse pregnancy outcomes and neonates : both**
  - **PCR : specimens from sterile sites**
- **Antibiotic susceptibility testing**
  - **Commercialized kits, CLSI breakpoints**
- **Prevalence of resistance in France, 2010-2015**
  - **Tetracycline: 7.5% (U) to 15% (Mh)**
  - **Fluoroquinolones: 1% (U), 3% (Mh)**
  - **Macrolide : very rare**

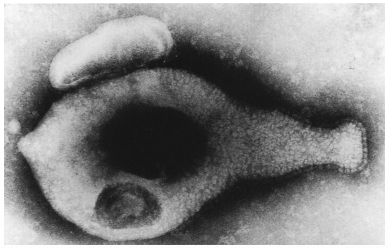
Take-home message



M. genitalium, a STI pathogen, has emerged!

- Male NGU, female cervicitis and PID
- Pauci-symptomatic infections
- Highest prevalence in high-risk sexual behavior patients +++
- Diagnostic : NAAT assays
  - Activity is predicted to increase (commercially available NAAT assays)
- Prevalence of resistance in France, 2015-2016
  - Tetracycline: no resistance but 70% treatment failure
  - Azithromycin: 18%
  - Moxifloxacin : 6%

Take-home message



- **1st-line treatment for uncomplicated *M. genitalium* infection**
  - Azithromycin 1.5 g on 5 days in absence of macrolide resistance
- **Moxifloxacin 400 mg/j 7-10 days in the other cases**
  - Under pressure
- **Always test of cure after 3-5 weeks**

⇒ Superbug? New XDR bacteria?

Might become untreatable in certain circumstances
Need for trials of combinations of registered drugs and new antimicrobial compounds

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