





# Sexual Transmitted Infections and antibioresistance

### Dr Agnès LIBOIS



**Respect Innovation Engagement Solidarity Quality** 

# Plan

- Gonorrhea: last treatment?
- Mycoplasma genitalium: next untreatable STI? A case
- Extensively-drug resistant Shigella in MSM
- Actions:
  - Decrease antibiotic pressure:
    - Less testing in asymptomatic MSM
    - Vaccine against gonorrhea
    - Point-of-care for STI and better tools to determine resistance
  - Surveillance





Figure 1 • Estimation du nombre de diagnostics de chlamydia, de gonorrhée et de syphilis par 100 000 habitants, Belgique, 2015-2021



Source : laboratoires sentinelles IST - données INAMI pour les laboratoires sentinelles IST



# Gonorrhea: last available treatment





# Resistance of *N.gonorrhea* in Belgium: report 2022



National Reference Centre of Sexually Transmitted Infections (NRC-STI), Institute of Tropical Medicine, Antwerp, Belgium

Phenotypic susceptibility testing WGS for some isolates: depends on the available budget



Belgium.

Figure 4: Antimicrobial resistance (%) of Neisseria gonorrhoeae to azithromycin and ciprofloxacin from 2013 to 2022 in

740 isolates received Resistance ceftriaxone 13 cases since 2013, 0 in 2022

Figure 3: Antimicrobial resistance (%) of Neisseria gonorrhoeae to penicillin and tetracycline from 2013 to 2022 in Belgium.







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#### **Rapid communication**

Multidrug-resistant *Neisseria gonorrhoeae* isolate SE690: mosaic *penA-60.001* gene causing ceftriaxone resistance internationally has spread to the more antimicrobial-

susceptible genomic lineage, Sweden, September 2022

Daniel Golparian<sup>1</sup>, Nora Vestberg<sup>2</sup>, Wiktor Södersten<sup>3</sup>, Susanne Jacobsson<sup>1</sup>, Makoto Ohnishi<sup>4</sup>, Hong Fang<sup>2</sup>, Karin Haij Bhattarai<sup>2</sup>, Magnus Unemo<sup>1,5</sup> b

#### Woman 20 year

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Clara Maubaret<sup>1,2,3,\*</sup>, François Caméléna<sup>1,2,3,\*</sup> (), Manel Mrimèche<sup>1,2,3</sup>, Aymeric Braille<sup>2,3</sup>, Mathilde Liberge<sup>1,2,3</sup>, Mary Mainardis<sup>2,3</sup>, Clémence Guillaume<sup>4</sup>, Franck Noel<sup>5</sup>, Cécile Bébéar<sup>6,7</sup> (), Jean-Michel Molina<sup>8,9</sup>, Florence Lot<sup>10</sup>, Emilie Chazelle<sup>10</sup>, Béatrice Berçot<sup>1,2,3</sup> ()

A woman (no travel, one partner) and a heterosexual man (travel in SE Asia). Resistance to azithromycin, ceftriaxone, ciprofloxacine et tetracycline



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#### Rapid communication



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Sonja Pleininger<sup>1</sup>, Alexander Indra<sup>1</sup>, Daniel Golparian<sup>2</sup>, Florian Heger<sup>1</sup>, Stefanie Schindler<sup>1</sup>, Susanne Jacobsson<sup>2</sup>, Stefan Heidler<sup>3</sup>, Magnus Unemo<sup>2,4</sup>

Hetero man, travel to Cambodia, R à azithro, ceftriaxone, Cipro et tetracycline.



The Commonwealth of Massachusetts Executive Office of Health and Human Services Department of Public Health Bureau of Infectious Disease and Laboratory Sciences 305 South Street, Boston, MA 02130

MAURA T. HEALEY Governor KIMBERLEY DRISCOLI Lieutenant Governor Division of STD Prevention Tel: (617) 983-6940 Fax: (617) 887-8790 www.mass.gov/dph/cdc/std

MARY A. BECKMAN Acting Secretary

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MARGRET R. COOKE Commission

Tel: 617-624-6000 www.mass.gov/dph

CLINICAL ALERT January 19, 2023

#### MULTI-DRUG NON-SUSCEPTIBLE GONORRHEA IN MASSACHUSETTS

 A novel strain of multidrug-non-susceptible Neisseria gonorrhoeae with reduced susceptibility to ceffriaxone, cefixime, and azithromycin, and resistance to ciprofloxacin, penicillin, and tetracycline, has been identified in a Massachusetts resident. Although ceftriaxone 500 mg IM was effective at clearing infection for this case, this is the first isolate identified in the United States to demonstrate resistance or reduced susceptibility to all drugs that are recommended for treatment.

CHU Saint-Pierre MC Sint-Pieter



### **EGASP results**

Result of antimicrobial susceptibility testing, EGASP Surveillance 2015 - 2022					
	Thailand N=2170 %	Philippines N=1388 %	Cambodia N=181 %	Uganda N=151 %	Overall N=3897 %
% isolates with AMR to ceftriaxone (MIC > 0.125 mg/L )	0.0	0.0	17.1	0.0	0.8
% isolates with AMR to cefixime (MIC > 0.125 mg/L)	0.3	0.0	31.4	0.0	1.7
% isolates with AMR to azithromycin (above ECOFF, MIC > 1 mg/L)	0.2	0.0	6.9	0.0	0.5
% isolates with AMR to gentamycin (MIC > 16 mg/L (alert))	0.0	0.0	0.0	0.0	0.0
% isolates with AMR to ciprofloxacin (MIC > 0.06 mg/L)	95.5	88.8	91.0	100.0	93.3



## N. gonorrhea: WHO priority pathogen for AMR



The rapidly changing antimicrobial susceptibility of *Neisseria gonorrhoeae* has created problems in developing countries since the introduction of antibiotics. Because of the widespread resistance, older and cheaper antibiotics have lost their usefulness as treatment options. Drugs like penicillin, tetracycline and ciprofloxacin have been effective in the past, but now all of the 82 million cases of gonorrhoea detected each year are resistant to one or all of these. The last effective drug we have, ceftriaxone, already indicates increasing gonococcal resistance. Without new antibiotics, we will have no easy treatment options. This is a great concern that will have a major impact in disease control efforts.

The WHO Gonococcal Antimicrobial Surveillance Programme has been documenting the emergence and spread of antimicrobial resistance (AMR) in gonorrhoea and uses this to inform updated treatment guidelines. WHO has recently enhanced the global surveillance by developing standard surveillance protocols (EGASP).

#### Impact

### **82 million** new gonorrhoea cases

are resistant to one or several classes of antibiotics





### New treatment recommendations for Neisseria gonorrhoeae

The WHO recommends that national or local antimicrobial resistance data determine the choice of therapy when available. *Good practice statement (updated 2023)* 

For adults and adolescents (including pregnant individuals) with genital, anorectal or oropharyngeal gonococcal infections, the WHO suggests:

• ceftriaxone 1 g intramuscularly as a single dose.

If ceftriaxone is not available or refused, the WHO suggests:

• cefixime 800 mg orally and performing test of cure.

If test of cure is not possible or when oropharyngeal infection is diagnosed or is a potential concern, the WHO suggests:

• cefixime 800 mg orally plus azithromycin 2 g orally.

When resistance, allergy or availability of cephalosporins is a concern, the WHO suggests one of the following options:

- spectinomycin 2 g intramuscularly as a single dose plus azithromycin 2 g orally; or
- gentamicin 240 mg intramuscularly as a single dose plus azithromycin 2 g orally.

Conditional recommendation, low certainty in evidence of effects (updated 2023) World Health Organization

### nature

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NEWS 01 November 2023

### 'Groundbreaking': first treatment targeting 'super-gonorrhoea' passes trial

Antibiotic could turn the tide on drug-resistant form of the infection - if it's used wisely.

#### Ewen Callaway

Zoliflodacin oral



The bacterium *Neisseria gonorrhoeae* causes gonorrhoea, which is often symptomless. Credit: Kwangshin Kim/Science Photo Library

- inhibits DNA biosynthesis via inhibition of topoisomerase.
- Phase III: 930 people with Ng in South Africa, Thailand, United States, Belgium and Netherlands.
- zoliflodacin vs ceftriaxone+ azithromycin: same efficacy
- To be used in combination to avoid development of resistance??

Gepotidacin: Phase III RCT ongoing



## **Surveillance of gonorrhea resistance in Belgium**

- Phenotypic susceptibility testing : need a positive culture
- But diagnostic test in clinic: NAAT (send swab for culture and antibiogram to NRLab when possible)
- WGS for some isolates: depends on the available budget...

**Surveillance to intensify** 





## Mycoplasma genitalium: next untreatable STI?

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RESEARCH ARTICLE

2018

Prevalence of *Mycoplasma genitalium* in men with urethritis in a large public hospital in Brussels, Belgium: An observational, crosssectional study

Agnès Libois<sup>1</sup>\*, Marie Hallin<sup>2</sup>, Tania Crucitti<sup>3</sup>, Marc Delforge<sup>1</sup>, Stéphane De Wit<sup>1</sup>

Estimation of the real magnitude of antimicrobial resistance of *Mycoplasma* genitalium in Belgium by implementing a prospective surveillance programme

2022, 21 labs

Sanger sequencing of the 23SrRNA and *parC* gene 232 samples (63% women)

Prevalence Mg: 9% in Saint-Pierre in men with complaints of urethritis

- R macrolide: 55% (100 % MSM, 60% in MSW, 44% in women)
- R quinolone: 26% (no difference between group)

Irith De Baetselier et al. Accepted to Eurosurveillance.



# **Treatment of** *M.***genitalium**

- Doxycycline 2x100 mg for one week (decrease bacterial load) then moxifloxacine 400 mg/d 7 days.
- or doxycycline then azithromycin (1g then 500mg/j 3 days) if resistance testing available

CDC guidelines. MMWR / July 23, 2021 / Vol. 70 / No. 4

- Testing for azithro R unavailable in routine clinic in Belgium and seems USELESS in MSM.
- Doxy then azithro still recommended in Europe and Belgium if resistance testing not available.
- Test only if symptomatic! Problem of multiplex molecular assay





### • A case report

- Man 30 y, urethritis < M.Genitalium since december 2022. No reinfection possible.
- Several treatment without success
  - Doxycyclin 7j followed by azithromycin 1g for one day then 500 mg/d 3d.
  - Doxycyclin 100 mg 2x/j 7j followed by Moxifloxacin 7d
  - Doxycyclin 100 mg 2x/j 7j followed by Pristinamycin 1g 4x/d 10d
  - Minocyclin 100 2x/j 14 d

PCR confirmed resistance to azithromycin and quinolones

Mail to

Jørgen Jensen



### • Answer:

**"This type of patient is really giving us headaches.** I think you are doing the right thing by trying minocycline. It does actually seem to cure more patients than doxycycline even if doxy is given for longer courses.

I don't think **Culturing** would do much difference for this specific patient, but we try to isolate Mg from this type of problem

patients in order to have isolates from difficult-to-treat patients in order to evaluate alternative antimicrobials. However, it often **takes 3-6 months** before we have an isolate and can start susceptibility testing and that again takes one month.

I have seen a case report on chloramphenicol, but we have not tried it, as Danish physicians find it too risky to use. We have done in-vitro testing of thiamphenicol and it has some activity for a proportion of the strains but has not been used in vivo to my knowledge

For tinidazole/metronidazole there was a recent publication showing some activity in vitro, but my lab found much higher MICs than reported in that paper. You may, however **try it in combination with minocycline** – I would use metronidazole in the highest tolerable dose instead of tinidazole if the latter is difficult to source.

### I am sorry that I don't have a magic bullet





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JOURNAL ARTICLE ACCEPTED MANUSCRIPT

# Efficacy of sitafloxacin for *M. genitalium* in an era of increasing antimicrobial resistance **a**

Ranjit S Samra, Erica L Plummer, Lenka A Vodstrcil ∞, Ivette Aguirre, Emily J Clarke, Christopher K Fairley, Eric P F Chow, Catriona S Bradshaw ∞

Open Forum Infectious Diseases, ofad590, https://doi.org/10.1093/ofid/ofad590

- Sitafloxacin: quinolone available in Asia-Pasific region (not in Europe)
- Retrospective evaluation of efficacy of sitafloxacin regimens for macrolide-resistant *M.genitalium* at Melbourne Sexual Health Centre, Australia between January 2017-February 2022.
- Doxycycline followed by combined doxycycline + sitafloxacin.
- 229 patients, 80 % microbial cure (94 % if not previous failure on moxifloxacin and 69.5% cure if previous moxiflo failure)
- Benefit of incorporating relevant fluoroquinolone resistance markers into assays to assist clinical decision-making.



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# Extensively drug resistant *Shigella sonnei* increasing in MSM.

**Public Health** England Gram-negative pathogenic Enterobacterales ٠ Protecting and improving the nation's health ECDC Alert: January 22, 2022 ٠ 140 **SUSCEPTIBLE** RESISTANT Multi-drug resistant Shigella sonnei 120 cluster (CTX-M-27) probably associated •Carbapenems •Cephalosporins 100 with MSM •Colistine Macrolides 80 •Aminoglycosides 60 •Fluoroquinolones 40 20 0 2020 2021 2022\* Total S. sonnei XDR S. sonnei

Since 2023, National Reference Center: sequencing of all isolates.

#### RAG Recommandations:

- Inform
- Avoid quinolones and macrolides in MSM
- Develop a national STI plan

Inspired from a slide of Pieter-Jan Ceyssens (sciensano)





## What can we do?

- STI increasing and problem of resistance.
- Actions:
  - Decrease antibiotic pressure:
    - Less testing in asymptomatic MSM
    - Vaccine against gonorrhea
    - Point-of-care for STI and better tools to determine resistance
  - Surveillance



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**Decrease antibiotic pressure:** Less testing Ng/Ct in asymptomatic MSM

- Gonoscreen results
- Belgian PrEP guidance adapted
- Also in others MSM (not on PrEP)
- Follow up needed after implementation of this measure :
  - Number of symptomatic infections?
  - Number of infections in women?
  - Possible impact of doxyPEP?





## Decrease antibiotic pressure by decreasing number of infections: Vaccine against N.gonorrhea?

- *N.meningitidis and gonorrhea* are closely genetically related (80-90% homology)
- Potential efficacy from OMV (= outer membrane vesicles) containing meningoccal B vaccines against Ng
- MenB-FHbp vaccine: no effect Only Bexsero®
- Case control and observational studies: 2-dose effectiveness 32 to 46%
- Number of studies ongoing
- Waiting for definitive results of DOXYVAC

#### ORIGINAL STUDIES

### Meningococcus B Vaccination Effectiveness Against *Neisseria* gonorrhoeae Infection in People Living With HIV: A Case-Control Study

Raccagni, Angelo Roberto MD\*; Galli, Laura MSc<sup>†</sup>; Spagnuolo, Vincenzo MD<sup>†</sup>; Bruzzesi, Elena MD\*; Muccini, Camilla MD<sup>†</sup>; Bossolasco, Simona MD<sup>†</sup>; Ranzenigo, Martina MD\*; Gianotti, Nicola MD<sup>†</sup>; Lolatto, Riccardo MSc<sup>†</sup>; Castagna, Antonella MD\*,<sup>†</sup>; Nozza, Silvia MD<sup>†</sup>

#### Author Information⊗

Sexually Transmitted Diseases 50(5):p 247-251, May 2023. | DOI: 10.1097/OLQ.00000000001771

Abara WE, Bernstein KT, Lewis FMT and others. <u>Health vaccinee bias and MenB-FHbp</u> <u>vaccine effectiveness against gonorrhoea</u>. Sexually Transmitted Diseases 2023; volume 50, issue 6, pages e8 to e10.





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Home > Health and social care > Public health > Health protection > Immunisation > Meningococcal B vaccination for the prevention of gonorrhoea, JCVI advice: 10 November

#### 繱

Department of Health & Social Care

#### Independent report

### JCVI advice on the use of meningococcal B vaccination for the prevention of gonorrhoea

Published 10 November 2023

### For those at higher risk

It is important for individuals offered vaccination to understand that real world studies have estimated that the 4CMenB vaccine has between 32.7 to 42% effectiveness against gonorrhoea. Therefore, although vaccination would be expected to reduce the chance of becoming infected with gonorrhoea, it would not completely eliminate the possibility. Vaccinated individuals could expect to have some reduction in their own risk of contracting gonorrhoea, however the main benefit of a vaccination programme is expected to be at a community level with a significant reduction in the number of cases overall.



#### Meningococcal B vaccine

4CMenB is a 4-component serogroup B meningococcal vaccine that contains:

- 3 main Neisseria meningitidis proteins:
  - Neisseria heparin binding antigen (NHBA)
  - Neisserial adhesion A (NadA)
  - factor H binding protein (fHbp)
- meningococcal serogroup B outer membrane vesicles (OMVs)



# Decrease antibiotic pressure : Point-of-care for STI and better tools to determine resistance

- POC for:
- Diagnosis of Ng (avoid 2 antibiotics for empiric treatment)
- Detection R Cipro of Ng
- Detection R azithro (and quinolone) of *M. Genitalium*
- Molecular assays targeting resistance mutations can improve antibiotic stewardship and decrease empirical use.
- But not used in Belgium (not reimbursed)



• Also need increase molecular-based AMR surveillance program.



# Conclusion

- Increase STIs
- XDR bacterial STI: N. gonorrhea, M. Genitalium and XDR Shigella
- Actions:
  - Decrease antibiotic pressure:
    - Less testing for Ng/Ct in asymptomatic MSM
    - Vaccine against gonorrhea
    - Point-of-care for STI and better tools to determine resistance and decrease empirical use: need implementation and reimbursement
  - Surveillance

....and what will be the effect of doxyPEP on AMR?





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