

Gonokocker – resistenssituation, genetik och respons för att möta “obehandlingsbar” Gonorrhé?

Magnus Unemo, PhD, Assoc. Professor

Head of WHO Collaborating Centre for Gonorrhoea and other STIs
Swedish Reference Laboratory for Pathogenic Neisseria
Department of Laboratory Medicine, Microbiology



Örebro University Hospital, Sweden

WHO`s global incidence estimates of non-viral, treatable STIs (million adults, 2005)

Gonorrhoea – Major Public Health concern!

1. High incidence (106 million 2008!)
2. Severe complications, incl. PID, infertility, ectopic pregnancy, increased HIV transmission
3. High cost – especially calculated as “disability-adjusted life years” (DALY; Ebrahim. STI. 2005)
4. Suboptimal diagnostics, case reporting, surveillance in many countries ⇒ incidences?
5. High antimicrobial resistance (AMR) and NO AMR testing before treatment mainly worldwide!

Chlamydia

Gonorrhoea

Syphilis

Trichomoniasis

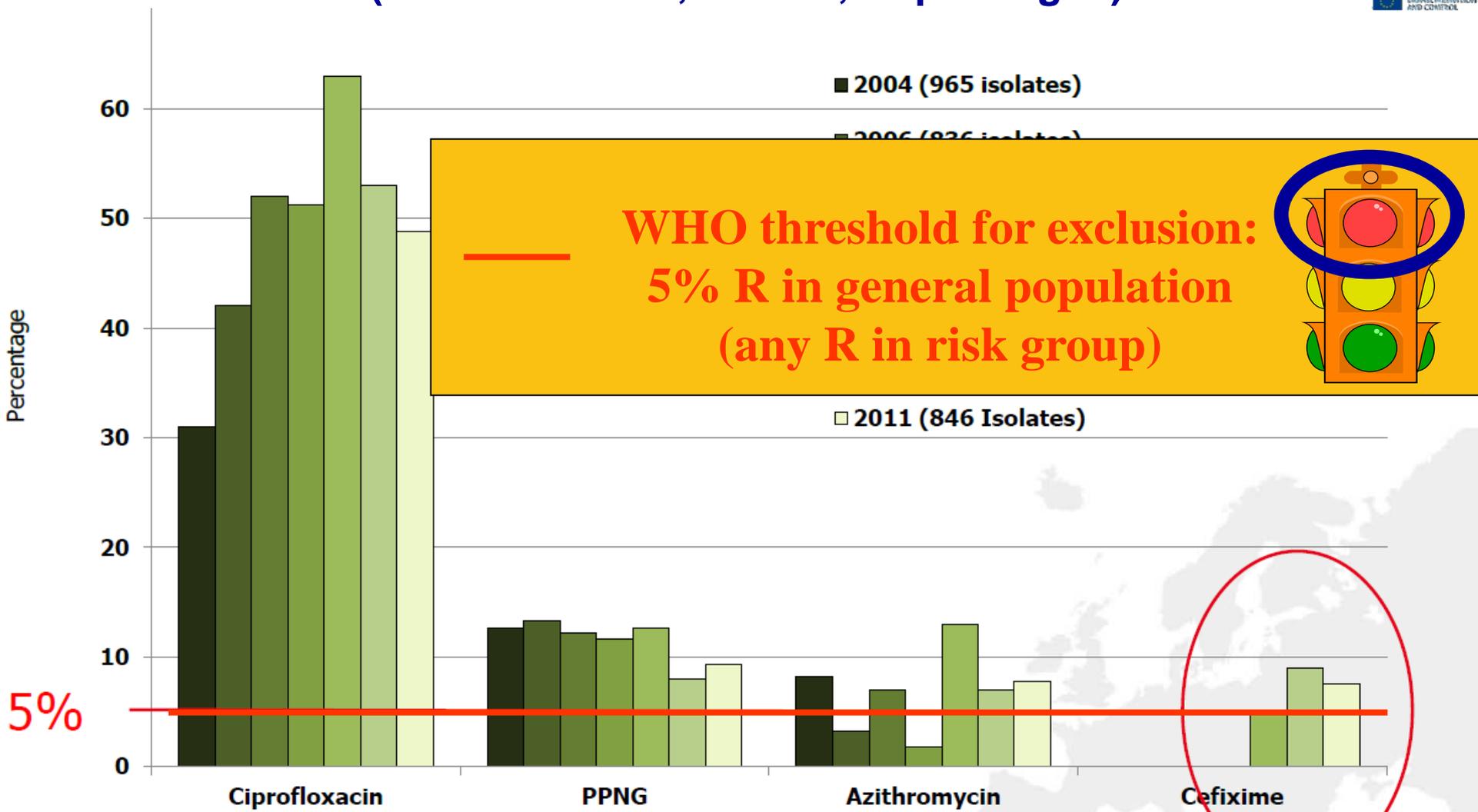
Total

Need to be considered

- **Empirical treatment** (informed by national/international AMR surveillance) **without any in vitro AMR data available!**
- **Resistance**, due to mainly all known resistance mechanisms, **developed to all introduced antimicrobials!**
- **Emergence of AMR in GC mainly in Asia and mostly due to transformation and subsequent recombination?**
- **Successful AMR GC clones then spread worldwide!**
- **Possible to model, predict and affect this spread, which is not only due to antimicrobial selective pressure?**

Overall % resistant *N.gonorrhoeae*, 2004-2011

EURO-GASP (ECDC: London, Örebro, Copenhagen)



5%

Spectinomycin - no resistance

Ceftriaxone – no resistance

Antibiotic resistance rates (%) and beta-lactamase production of Swedish *Neisseria gonorrhoeae* strains 2005-2011.

	2005 (n=497)	2006 (n=352)	2007 (n=406)	2008 (n=447)	2009 (n=384)	2010 (n=618)	2011 (n=805)
Beta-lactamase pos.	23	30	30	28	44	29	23
Ampicillin	23	30	30	28	44	31	24
Cefixime	0	0	<1	1	5	6	8
Ceftriaxone	0	0	0	<1	0	2	2
Azithromycin	<1	5	7	13	6	12	11
Ciprofloxacin	49	61	70	63	75	56	55
Spectinomycin	0	0	0	0	0	0	0

Magnus Unemo, Hans Fredlund, Per Olcén. SWEDRES 2012



Dwindling treatment options for *Neisseria gonorrhoeae*

1943-mid 1980s

Penicillins

Tetracyclines

Quinolones (norfloxacin, ciprofloxacin)

Aminoglycosides (gentamicin, kanamycin)

Macrolides (azithromycin)

Spectinomycin (Resistance selection! Availability?)

Cephalosporins (ceftriaxone, cefixime)

2011: Decreased susceptibility to cefixime ($\geq 0.25\text{mg/L}$)



Cefixime treatment failures

- Previously, verified treatment failures only published from Japan (since 2003)!
- **2010: First treatment failures, strictly verified using WHO criteria, in Europe (Norway)!**
(Unemo, et al. Euro Surveill. 2010)!



2011: Decreased susceptibility to cefixime ($\geq 0.25\text{mg/L}$)

- No decreased susceptibility
- < 5%
- 5-15%
- > 15%
- Not rep

Cefixime treatment failures

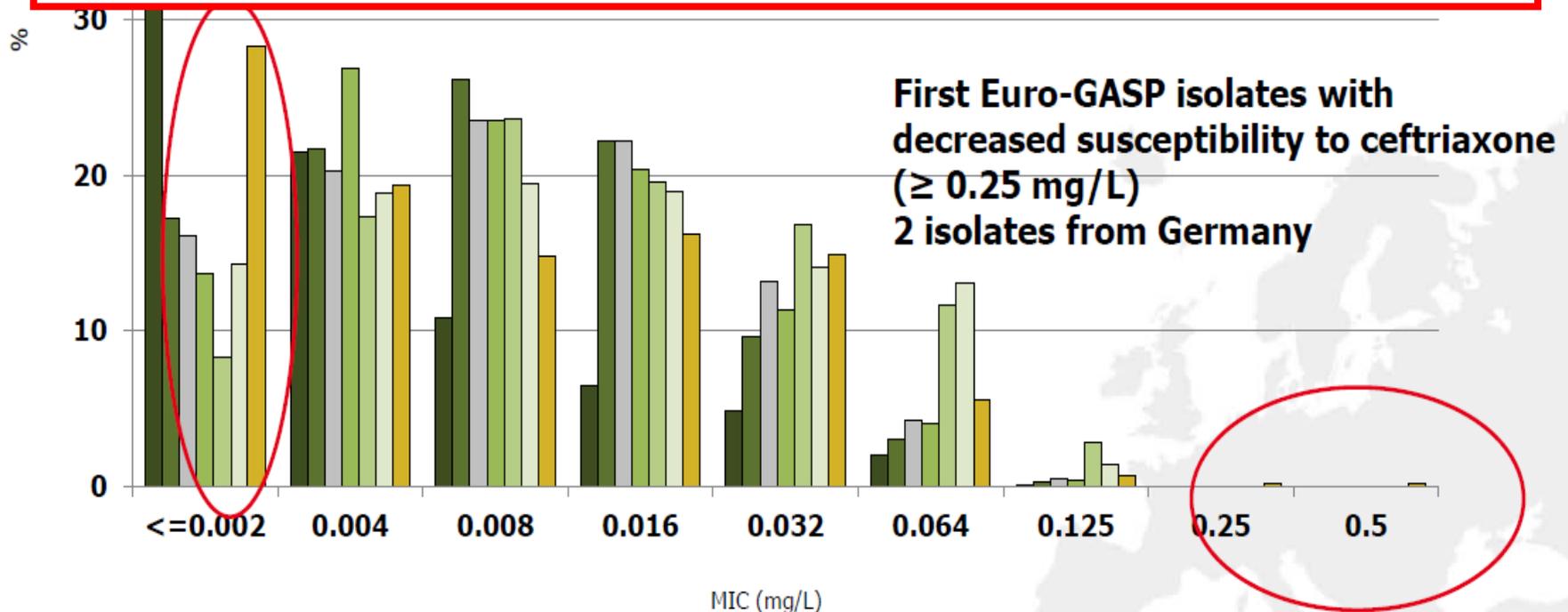
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- 2011: Treatment failures published from the UK (Ison, et al. Euro Surveill. 2011), Austria (Unemo, et al. Euro Surveill. 2011) and France (Unemo, et al. AAC. 2011)!
- **Level of treatment failures unknown - MONITOR!**

- Non-visible
- Luxembourg
 - Malta

Distribution of MIC for ceftriaxone, 2004-11 (9-20 European countries)

Ceftriaxone

- Susceptibility decreasing globally!
- Confirmed treatment failure of pharyngeal gonorrhoea with ceftriaxone in Sweden (Unemo, et al. Euro Surveill. 2011)
- Pharyngeal case from Slovenia under verification!



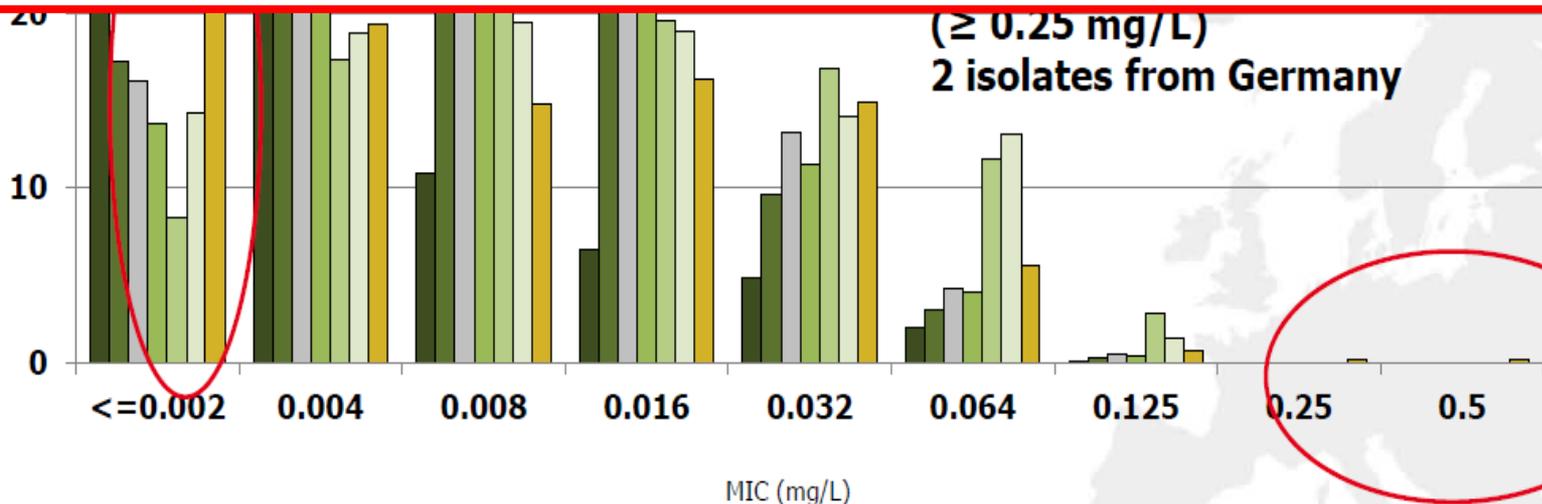
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(Ohnishi, Golparian, Shimuta, Saika, Hoshina, Iwasaku, Nakayama, Kitawaki, and Unemo. AAC. 2011)!



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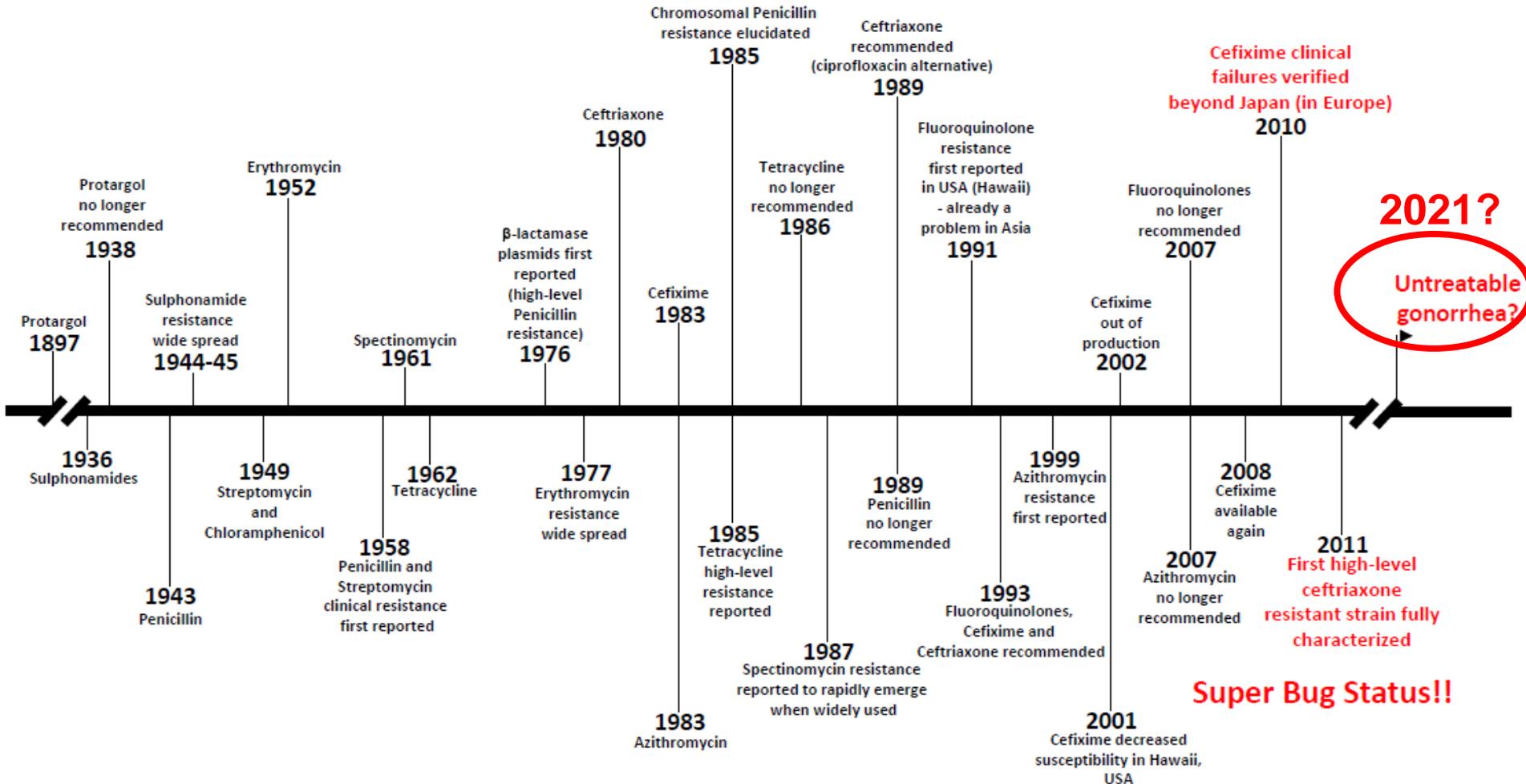


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- **F89 (MLST ST1901): Highly resistant strain (MIC=1-2 mg/L) confirmed in France - XDR!** (Unemo, Golparian, Nicholas, Ohnishi, Gallay, Sednaoui. AAC. 2011)!

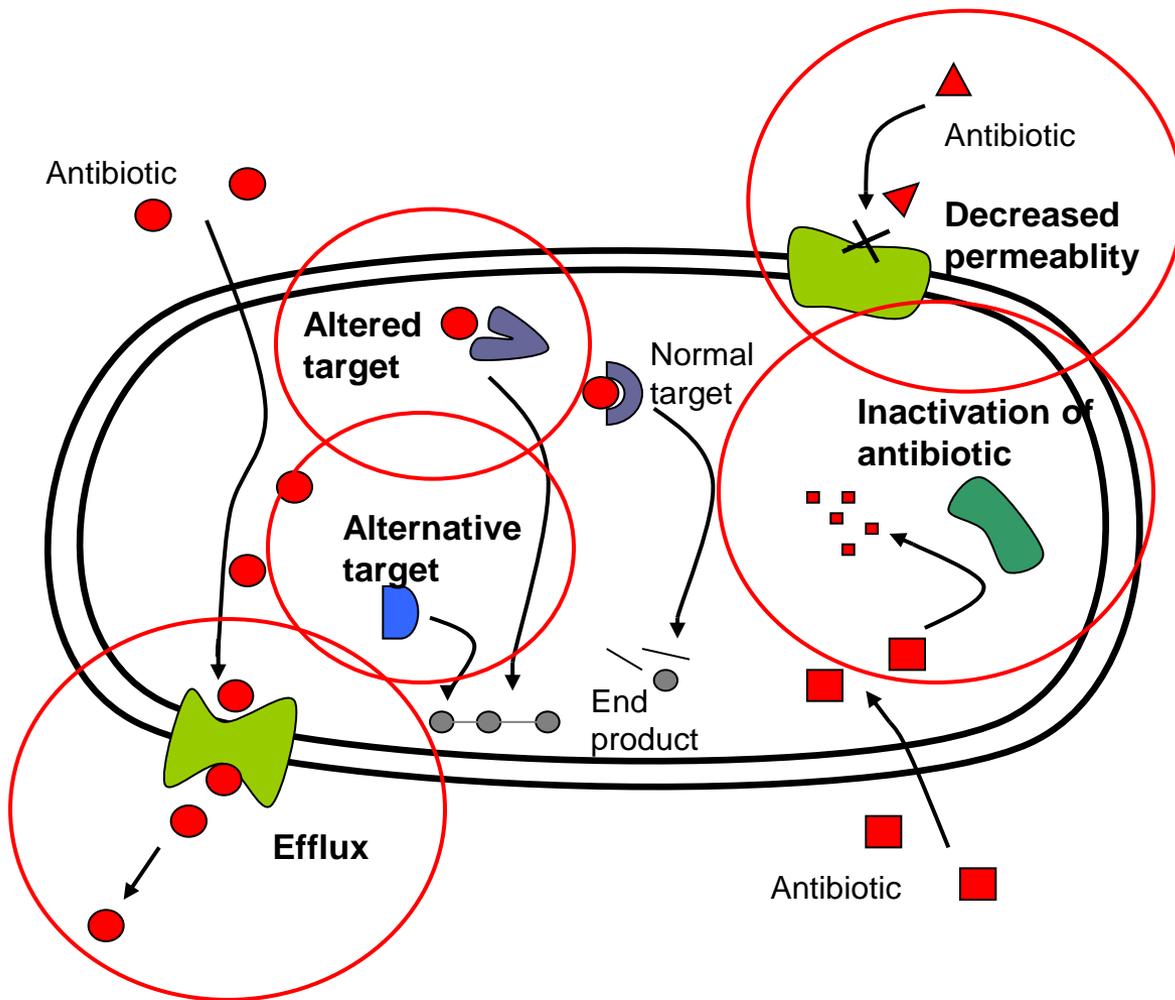
Gonorrhoea may become untreatable!

Introduced treatment and emergence of resistance – only 1-2 decades needed for international spread of AMR?



Super Bug Status!!

Mechanisms for antimicrobial resistance in bacteria



Reduced uptake of antimicrobial (porins)

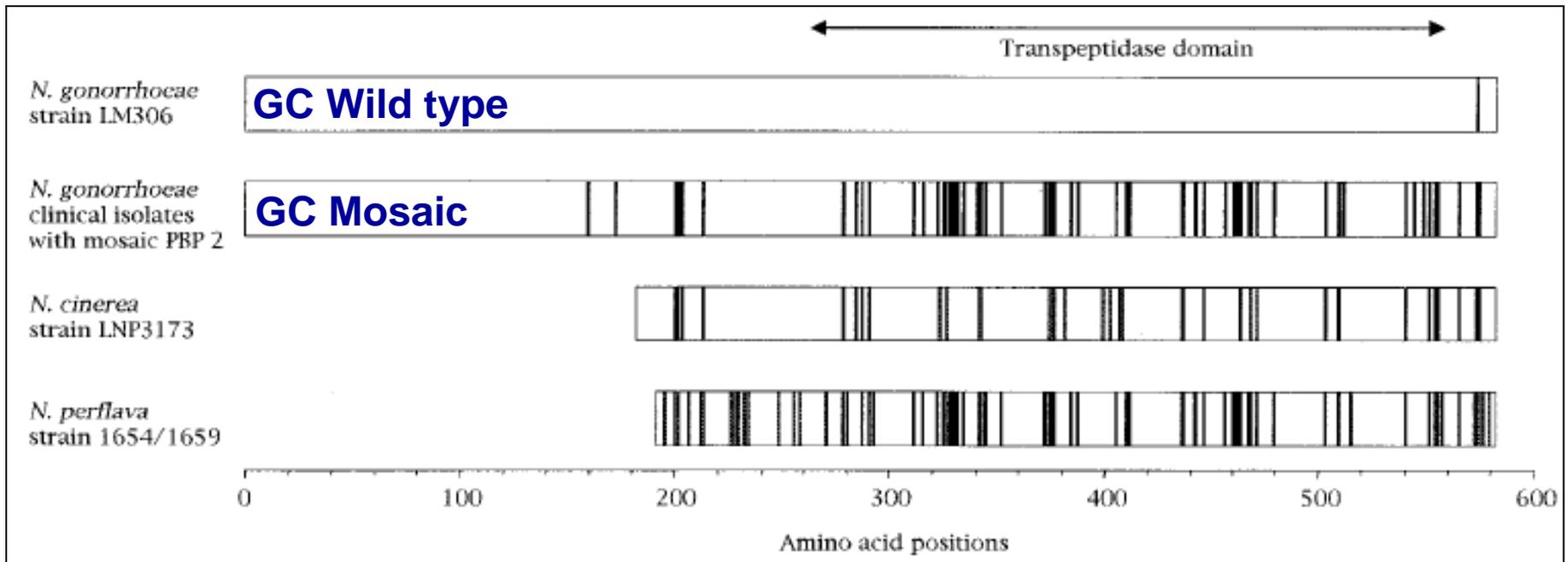
Increased export of antimicrobial (efflux)

Inactivation or modification of target

Alternative target

Inactivation or modification of antimicrobial

penA mosaic gene (encoding mosaic penicillin-binding protein 2) in cefixime resistant isolates



Ito, et al. AAC. 2005

The main resistance mechanism, marker for monitoring, but not the whole story!

“WHO global initiatives to meet the public health challenges of emergence of untreatable gonorrhoea”

(Tapsall J, Ndowa F, Lewis D, Unemo M.
Expert Rev Anti Infect Ther. 2009)

- **New definitions** (multi-, extensively-, pan-drug-resistance; verified treatment failures, etc)
- **Holistic views and actions:** improved prevention, diagnostics, treatment; use and quality of antimicrobials; gonorrhoea prevalence and control,
- **Enhanced global quality assured surveillance of AMR (2008 WHO strains (Unemo et al. JAC. 2009) distributed worldwide) and treatment failures crucial globally!**

WHO Global Gonococcal Antimicrobial Surveillance Programme (GASP)



(Tapsall J, Ndowa F, Lewis D, Unemo M. ERAIT. 2009)



Important additional actions

- **AWARENESS**; more frequent use of test-of-cure, tracing and treatment of **sexual contacts**, and special attention on **pharyngeal gonorrhoea**!
- **Elucidate genetic determinants for resistance extended-spectrum cephalosporins, and their relation to MIC and treatment outcome!**
- **Understanding of internationally (nationally) spread resistant strains – GC population dynamics!**
- **WHO Global (Regional and National!) Action Plan (clinical, microbiological, epidemiological components)!**



GLOBAL ACTION PLAN
TO CONTROL THE SPREAD AND IMPACT OF
ANTIMICROBIAL RESISTANCE IN *NEISSERIA*
GONORRHOEAE

(WHO 2012;
Launch 6th June: Ndowa N, Lustinarasimhan M, Unemo M;
STI Editorial)

DEPARTMENT OF REPRODUCTIVE HEALTH AND
RESEARCH
WORLD HEALTH ORGANIZATION

ECDC SPECIAL REPORT

Response plan to control and manage the threat of multidrug-resistant gonorrhoea in Europe

(ECDC 2012;

Launch 4th June; Eurosurveillance:
van de Laar M, Spiteri G, Bignell C, Cole M,
Hoffmann S, Ison C, Unemo M)



Crucial research area!!!

Future prevention and/or treatment of gonorrhoea

- **Single or combinations of "old" or new antimicrobials OR other compounds in vitro and in vivo clinical trials!**
- Single or dual antimicrobial therapy?
- Gentamicin? (Chisholm, et al. JAC. 2011)
- Solithromycin? (Golparian, et al. AAC. 2012)
- Ertapenem? (Unemo, et al. AAC. 2012)

Or rely on old prevention posters?



Prevention poster
USA 1943