Société belge d'infectiologie et de microbiologie clinique
Belgische vereniging voor infectiologie en klinische microbiologie

Resistance in sexually transmitted infections

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Plan

- Scope of the problem
- Gonorrhea
- Chlamydial infections
- Syphilis
- Other STI


STOCKHOLM - SWEDEN
25 - 27 MARCH 2009
EUROPEAN
HIV DRUG RESISTANCE
WORKSHOP
From basic science to clinical implications

Resources

- CDC/Division of STD Prevention

http://www.cdc.gov/std/

- STD Treatment Guidelines – Updates

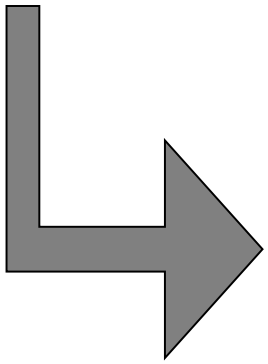
  http://www.cdc.gov/std/treatment/

- The Practitioner's Handbook for the Management of Sexually Transmitted Disease

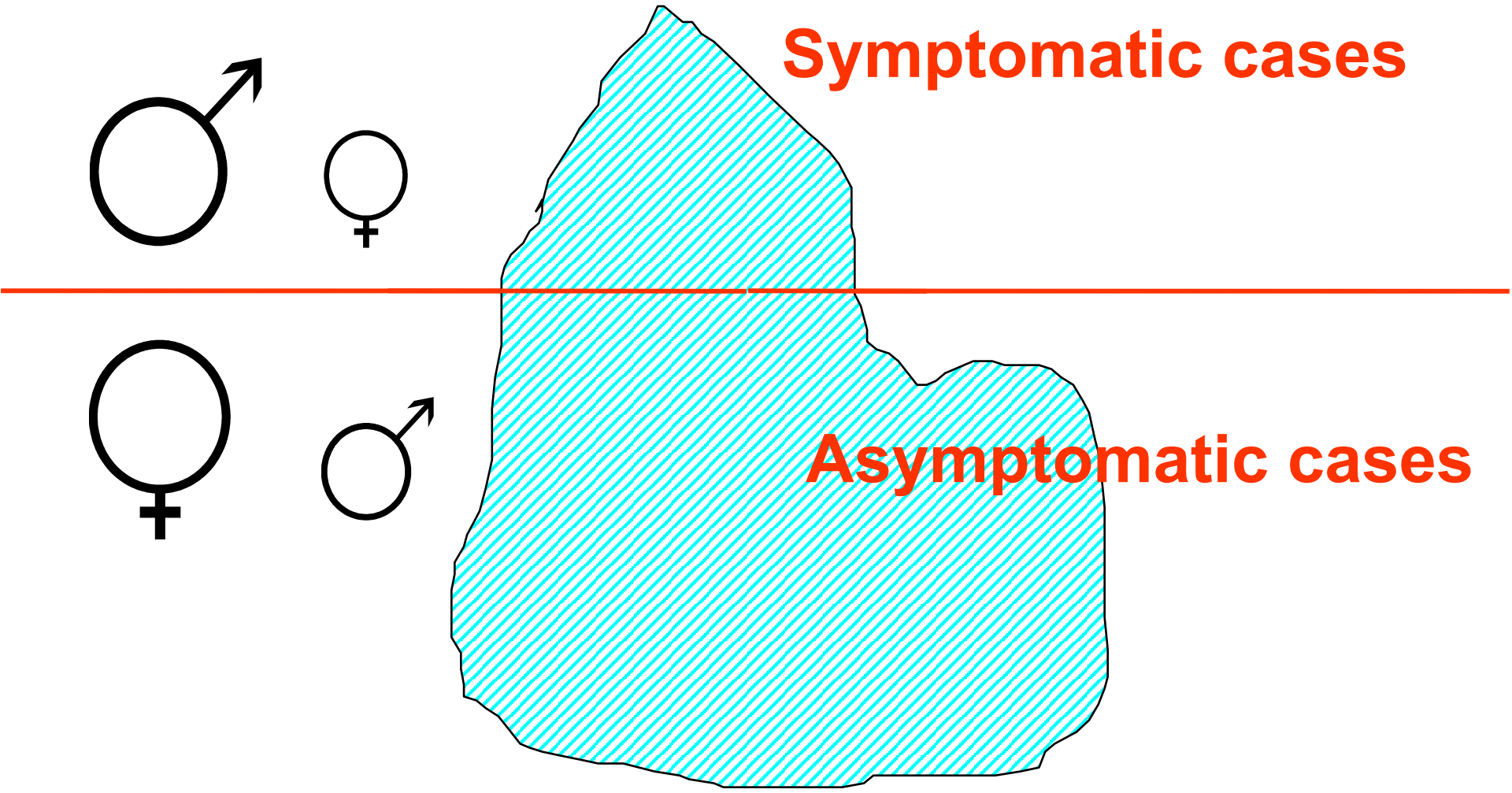
http://depts.washington.edu/nnptc/online_

Scope of the problem

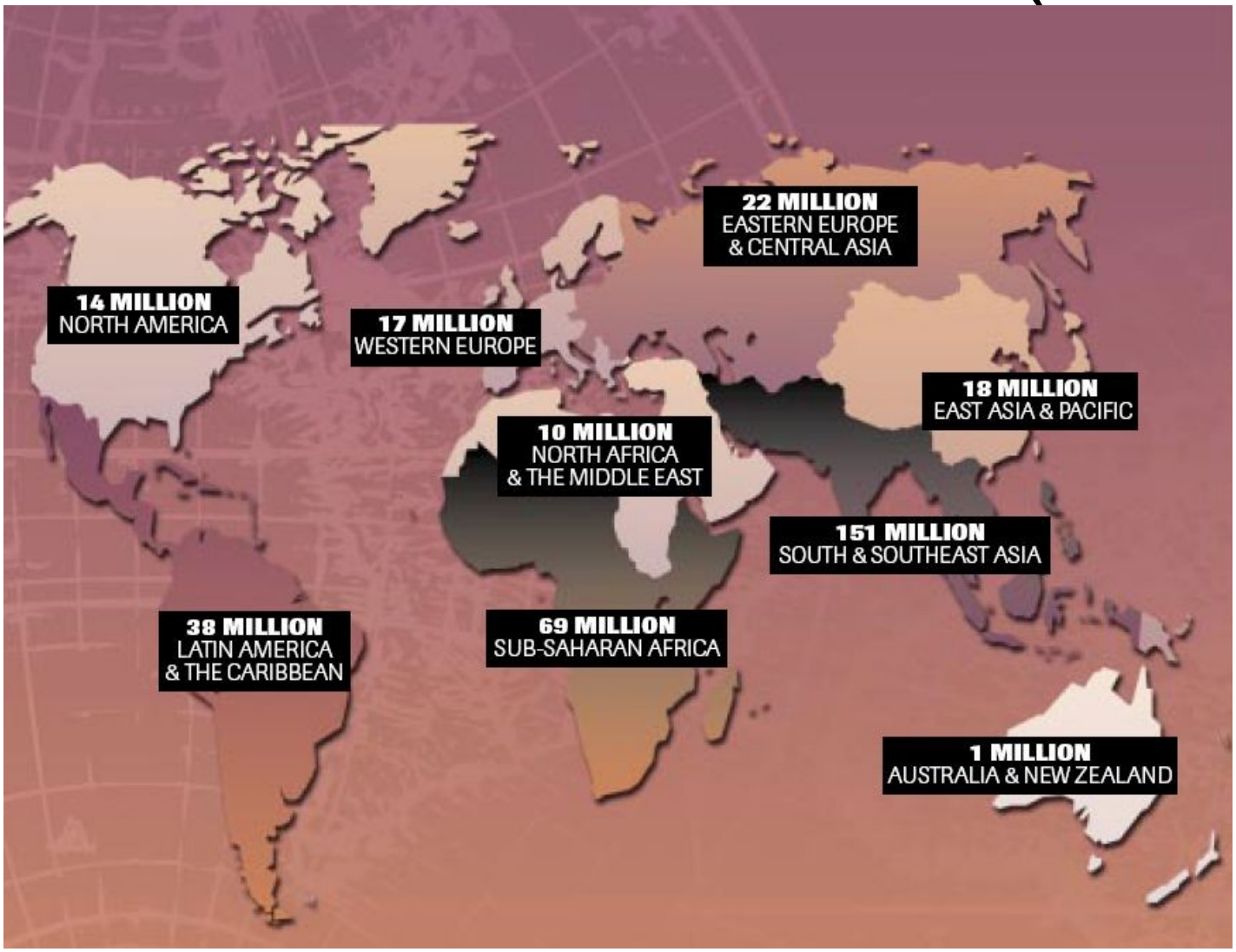
- Global Public Health Problem
- Often asymptomatic
- Interactions with HIV epidemic
- Complications



- **Infertility**
- **Obstetrical complications**
- **Cancers**

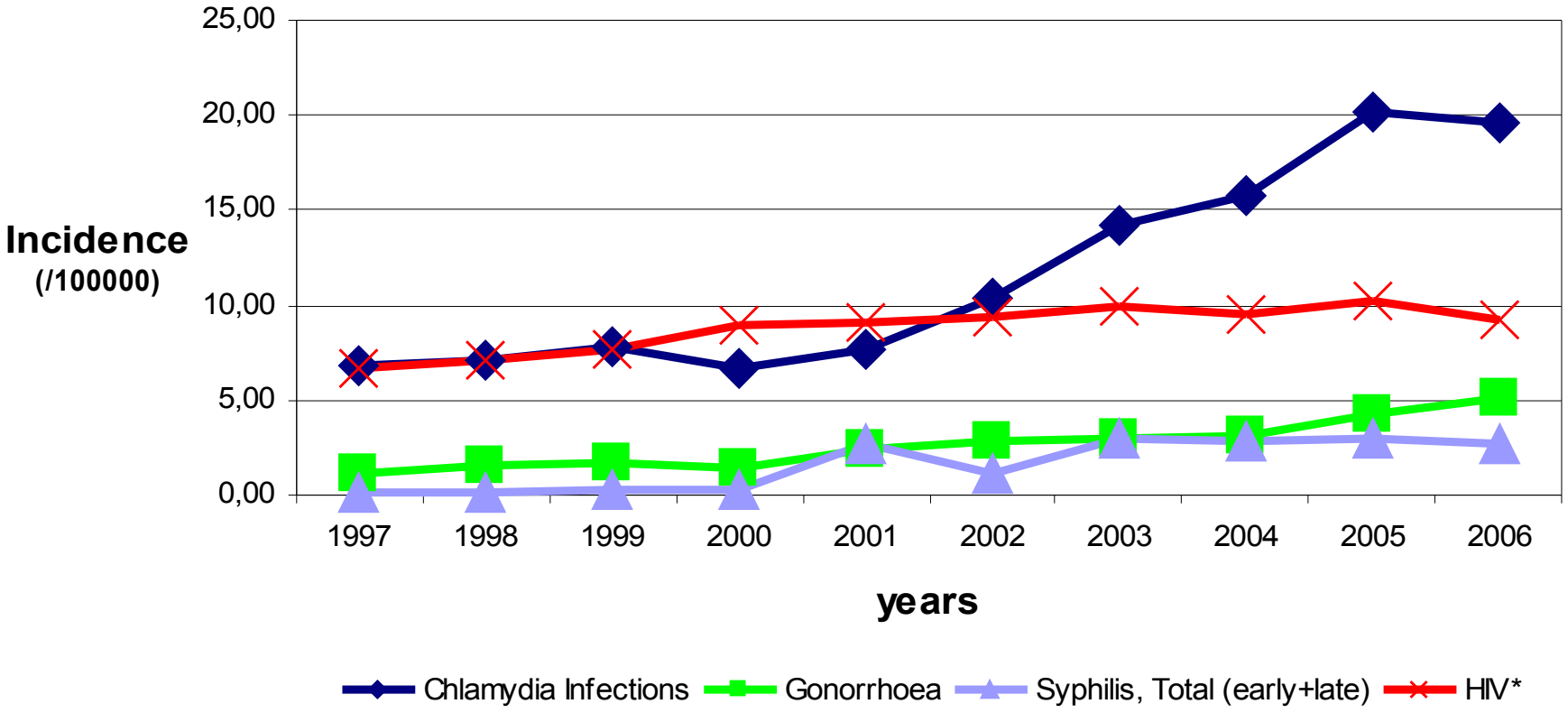

Symptomatic cases
Asymptomatic cases

New cases of curable STI (1999)



Source: WHO, “Global Prevalence and Incidence of Selected curable STI’s: overview & Estimates” 2001

Incidence rate of several STI in Belgium



Source: centralized information system for infectious diseases (CISID), WHO regional office for Europe

STI classification: by organisms

Bacteria	Viruses	Other
Transmitted predominantly by sexual intercourse		
N. gonorrhoeae	HIV	Trich. Vaginalis
C. trachomatis	HSV-2	Phthirus pubis
T. pallidum	HPV	
H. ducreyi	Hep. B virus	
C. granulomatis		
U. urealyticum		
Sexual transmission not well defined/ not predominant mode		
G. vaginalis	CMV	Candida albicans
group B Strepto.	HCV	Sarcoptes scabei
	HSV-1	
	EBV	
	HHV-8	
Transmitted by sexual contact involving oral-fecal exposure		
Shigella spp.	HAV	Giardia lamblia
Campylobacter spp.		E. histolytica

Adapted from Harrison's Principle of Internal Medicine 17th edition

STI Classification: by syndromes

Genital Ulcers:

- T. pallidum
- Lymphogranuloma venereum
- Herpes infection
- Chancroid
- Granuloma inguinale

Urethritis/Cervicitis:

- C. trachomatis
- N. gonorrhoeae
- others

Pelvic Inflammatory Disease:

- C. trachomatis
- N. gonorrhoeae
- Bacterial vaginosis
- Group B strepto.
- M. genitalium

Vaginal discharge:

- Bacterial vaginosis
- T. vaginalis
- C. albicans

Antibiotic resistance

is the ability of a microorganism to withstand the effects of antibiotics.

(Wikipedia, the free encyclopedia)

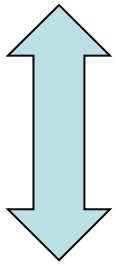
Factors Contributing to Resistance

- Insufficient drug access & counterfeit drugs
- Incorrect diagnosis
- Inadequate prescription
- Advertising for drugs
- Lack of education
- Food production & Modern farming
- …

http://www.who.int/infectious-disease-report/2000/index.html

Syndromic approach of STI

"Identify all possible STDs that can cause symptoms and give recommended treatment based on epidemiological and laboratory data specific to the country/region."



Etiological approaches

Syndromic approach of STI

"Identify all possible STDs that can cause symptoms and give recommended treatment based on epidemiological and laboratory data specific to the country/region."

<u>4 major clinical syndromes:</u>

- Genital ulceration
- Urethral discharge
- Abnormal vaginal discharge
- Lower abdominal pain in women

Advantages:

- Simplified approaches to diagnosis
- Allow to tackle rapidly mixed infections
- Immediate treatment

Disadvantages:

- Treat as many patients as possible (sensitivity) vs. Over-treating (specificity)
- Resistance?

Gonorrhoea

1

2

3

4

Credits: 1 & 2 Seattle STD/HIV Prevention Training Center at the University of Washington 3& 4 CDC Public Health Image Library

Resistance to N. Gonorrhoea

- Natural resistance
- Acquired resistance
  - Chromosomally mediated
  - Plasmid mediated

The development of antibiotic resistance to N gonorrea is parallel to the history of antibiotics development.

- *2000 B.C. – Here, eat this root*
- *1000 A.D. – That root is heathen. Here, say this prayer.*
- *1850 A.D. – That prayer is superstition. Here, drink this potion.*
- *1920 A.D. – That potion is snake oil. Here, swallow this pill.*
- *1945 A.D. – That pill is ineffective. Here, take this penicillin.*
- *1955 A.D. – Oops....bugs mutated. Here, take this tetracycline.*
- *1960-1999 – 39 more "oops"...Here, take this more powerful antibiotic.*
- *2000 A.D. – The bugs have won! Here, eat this root.*

Anonymous,

source: http://www.who.int/infectious-disease-report/2000/index.html

Plasmid mediated resistance to penicillin

- NGPP: N. gonorrhoea penicillinase producing
- First description in 1976
- High-level resistance (MIC: 2 to 128 µg/ml)
- Beta-lactamase type TEM-1
- Easy to detect

Plasmid mediated resistance to tetracyclin (NGRT)

- NGRT: N. gonorrhoea resistant to tetracycline
- High-level resistance (MIC ≥ 16 µg/ml)
- Appeared for the first time in 1985 in the US (Eastern Coast)
- Transposon
- Frequent association with plasmid coding for beta lactamase

Chromosomal resistance to penicillin

- Chromosom mediated resistant N. gonorrhoea (CMRNG)
- Harder to investigate
- Require MIC determination
- Broad spectrum of resistance from decreased sensibility to true resistance.
- Appears slowly
- Often combined resistance
- Currently increasing

Chromosomal resistance to tetracyclin

- Resistance MIC ≥ 2 µg/ml.
- Usually associated with chromosomal resistance to penicilline

Chromosomal resistance to fluoroquinolons

- Appeared for the first time in Asia in the 90's
- Decreased sensibility to ciprofloxacin ($0.125 \leq MIC < 1\mu g/ml$) or resistance ($MIC \geq 1\ \mu g/ml$)
- Cross-resistance to all fluoroquinolons

Chromosomal resistance to 3rd generation cephalosporins

- C3G are resisting very good to the penicillinase.
- Resistance if MIC > 0.5 µg/ml
- Sporadic clones described in Asia, Africa and Europe.

Chromosomal resistance to spectinomycin

- High level resistance if MIC ≥ 128 µg/ml
- Resistances are unfrequent in Europe

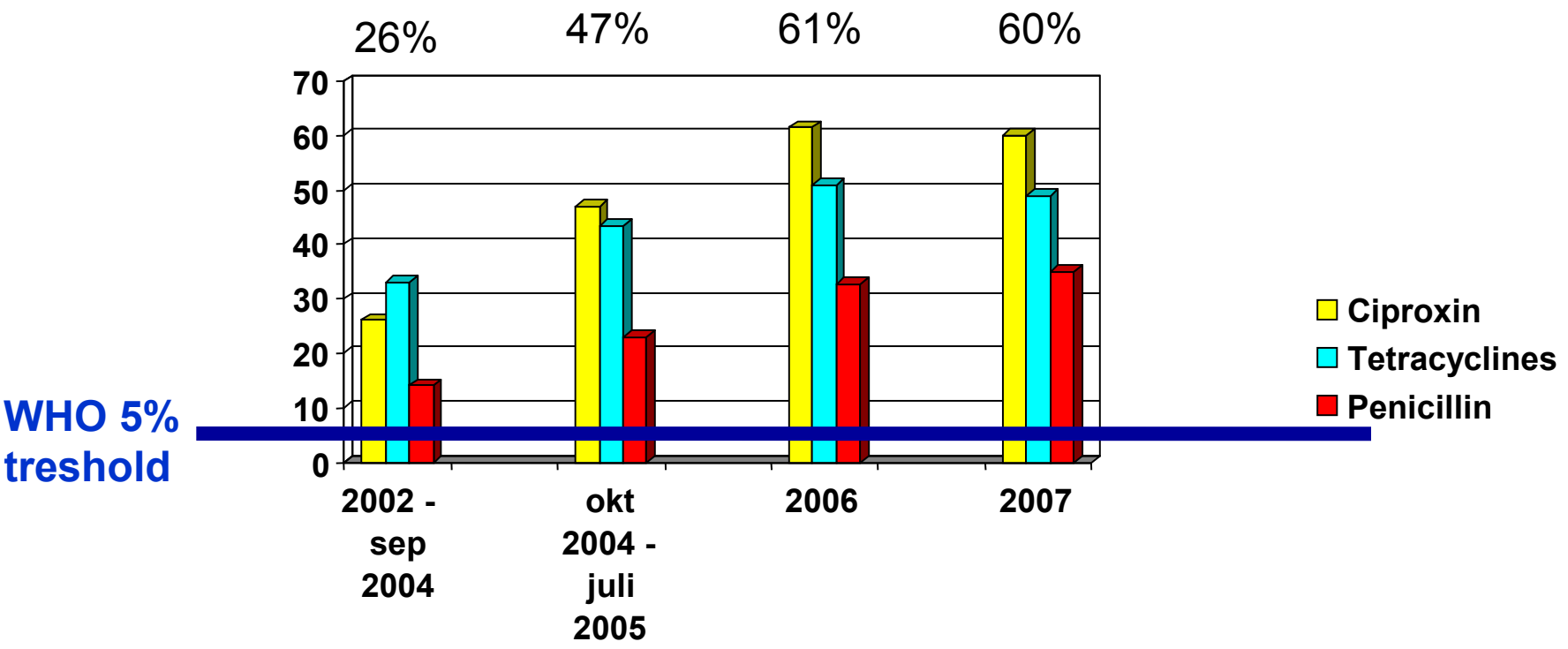
N. gonorrhoea resistance in Belgium

- Number of isolates tested in 2007: 494
  - From 69 laboratories
  - Gender of patients
    - 430 males
    - 59 females
    - unknown: 5

Source: Institute of Tropical Medicine & Institute of Public Health

N. gonorrhoea resistance in Belgium

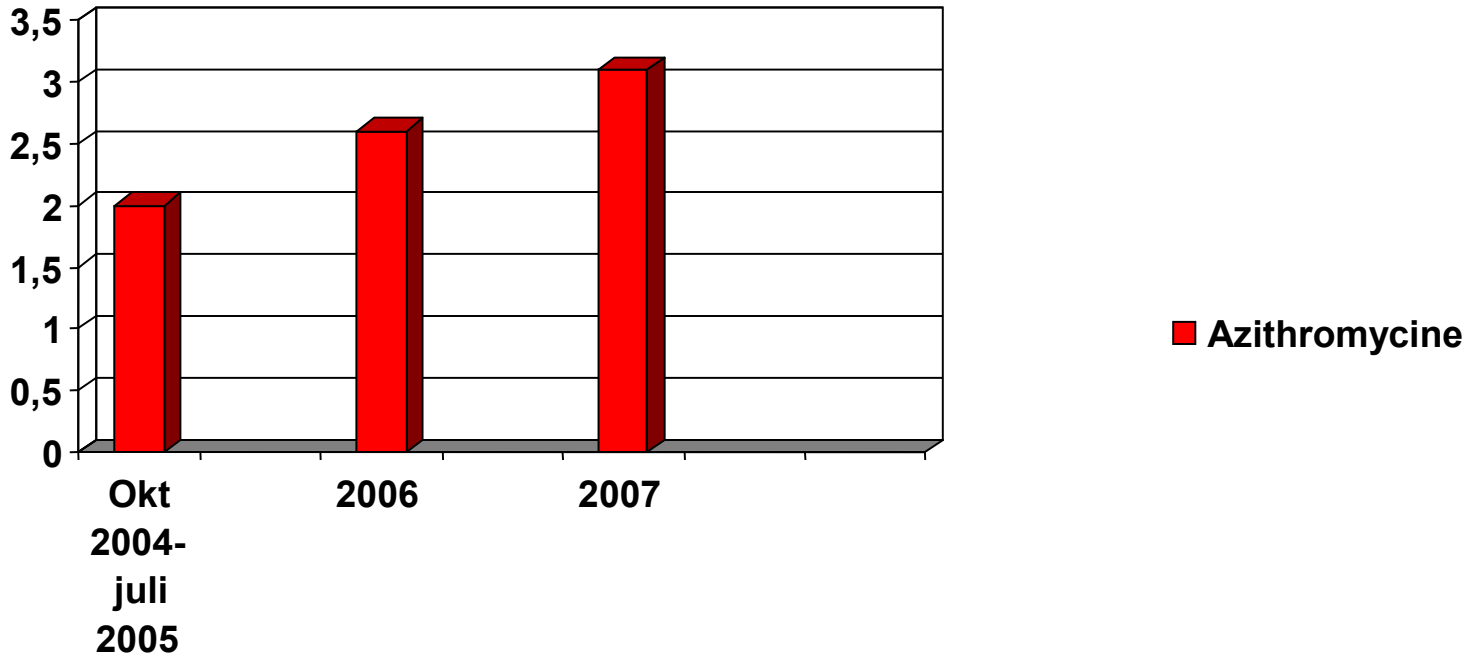
WHO "Do not give antibiotic for gonorrhoea therapy if resistant > 5% of strains"



Data: Institute of Tropical Medicine & Institute of Public Health

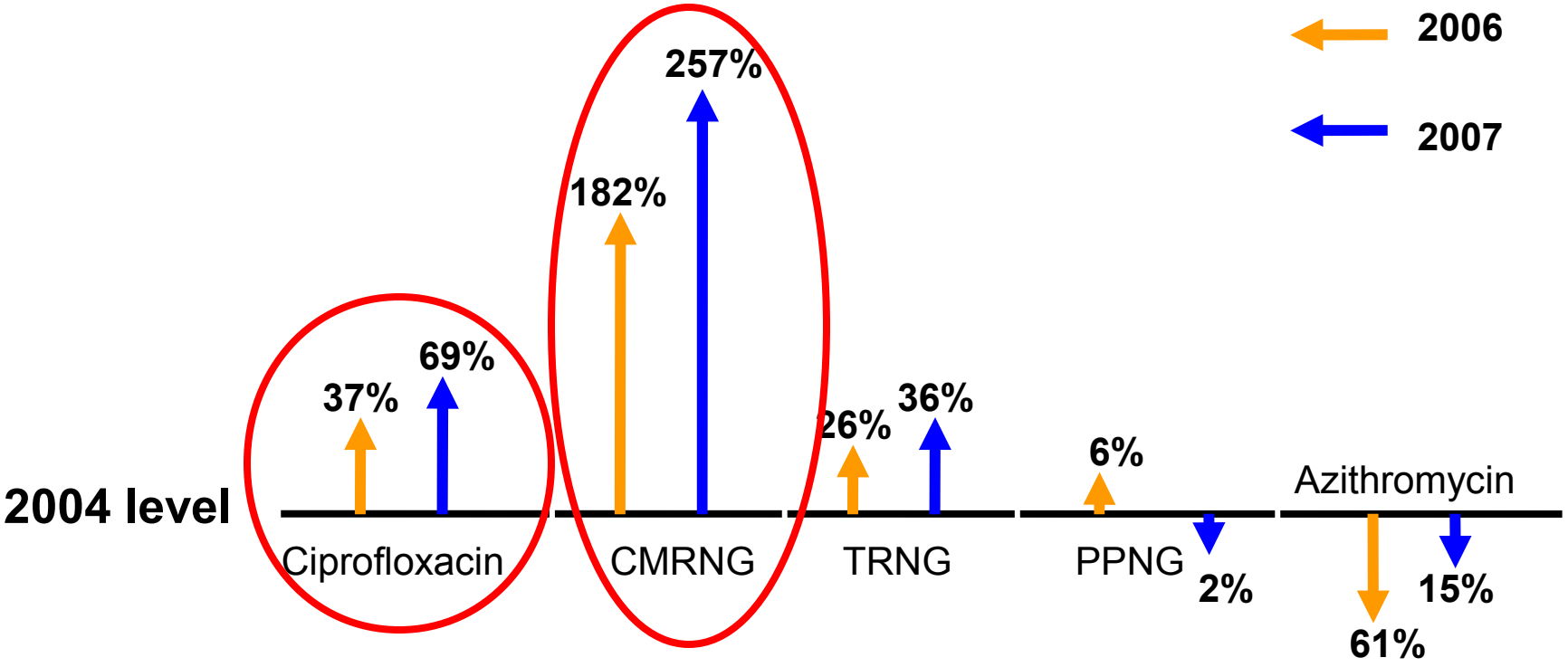
N. gonorrhoea resistance in Belgium

WHO 5% treshold



Data: Institute of Tropical Medicine & Institute of Public Health

Progression of antimicrobial resistance in Europe

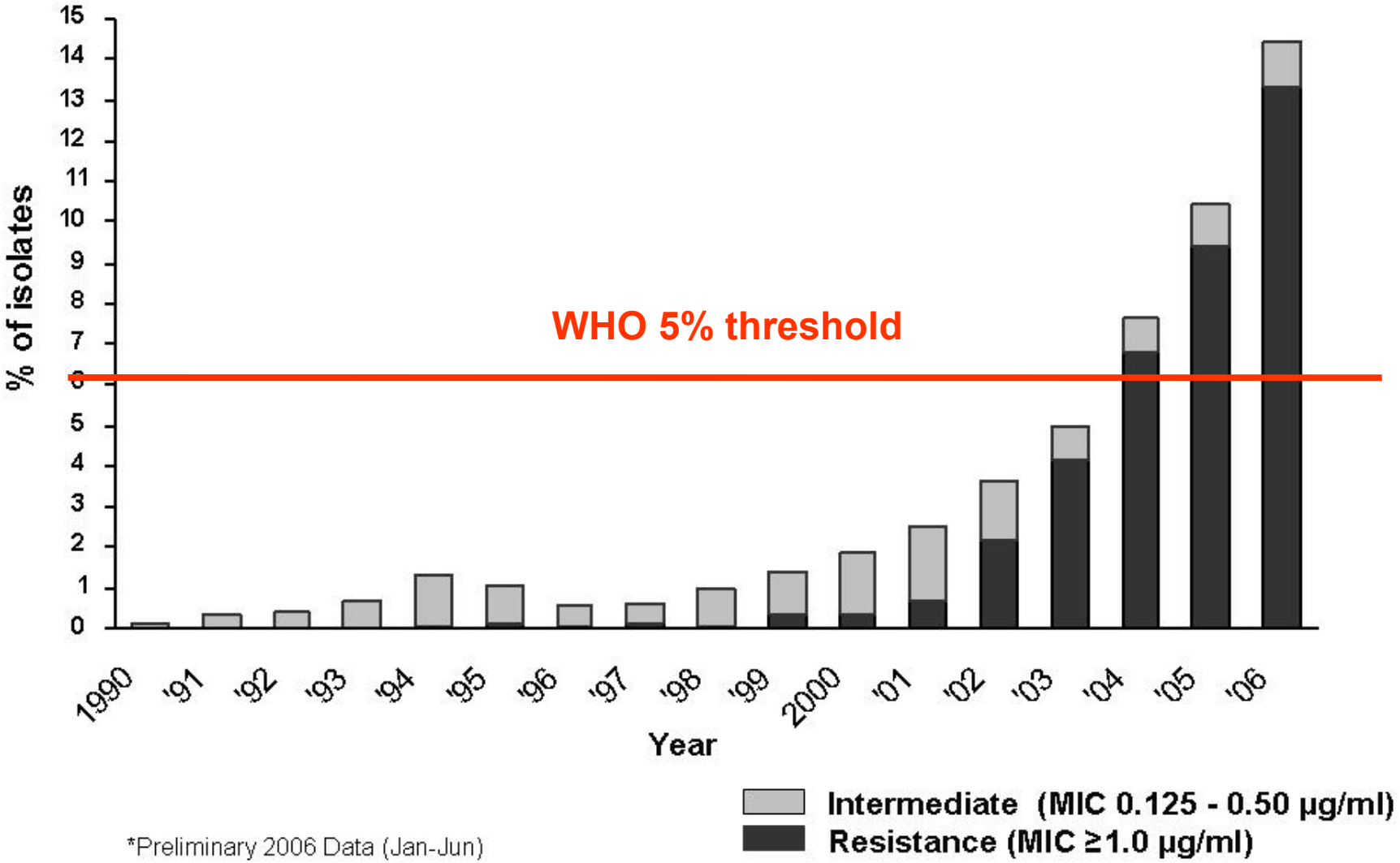


2004: 965 strains tested (12 countries)
2006: 837 strains tested (10 countries)
2007: 1409 strains tested (16 countries)

ESSTI
EUROPEAN SURVEILLANCE OF SEXUALLY TRANSMITTED INFECTIONS

Ciprofloxacine resistance

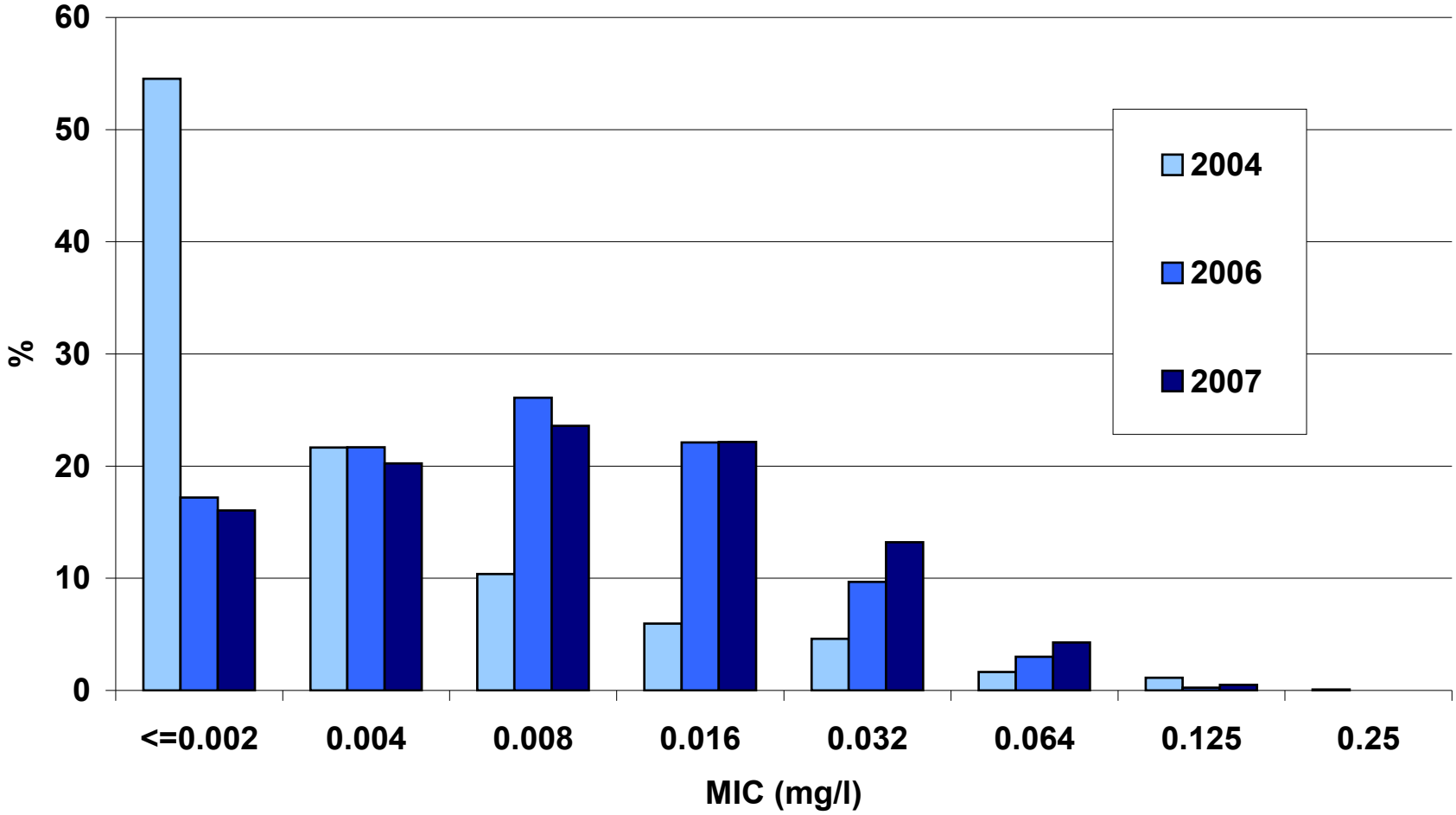
US situation



*Preliminary 2006 Data (Jan-Jun)

Yee et al ISSTDR-conference 2007 Poster 448

Shift in Ceftriaxone MIC



ESSTI
EUROPEAN SURVEILLANCE OF SEXUALLY TRANSMITTED INFECTIONS

Resistance to cephalosporin

Alarming case report from Seattle:

♂, 37y, asymptomatic

Culture pharynx positive N Gonorrea

R/ Cefpodoxime per os 400 mg

Roberts MC, ISSTDR. Poster 094

Resistance to cephalosporin

- Controle on day 27 & 47
  → Pharynx gono-culture still positive!!
  - Re-infection?
  - Treatment failure?

- **Analyse of the 3 Neisseria gonorrhoea strains**
  - Strains were identical
  - Resistant to
    - Penicillin
    - Tetracyclin
    - Ciproxin
    - Azitromycin
  - Reduced susceptibility:
    - Cefpodoxim

N. *gonorrhoeae* with genetic polymorphisms

Link with expanded-spectrum Cephalosporin reduced susceptibility

- Sweden, n = 16 (US, UK, Sweden)
- *penA* gene
  - Codes for penicillin binding protein 2 (PBP 2)

Magnus Unemo et al.: Antimicrob Agents Chemother 2007

N. *gonorrhoeae* with genetic polymorphisms

Link with expanded-spectrum Cephalosporin reduced susceptibility

- 'New' allele *penA* gene: mosaic allele
  - Reduced penicillin binding
  - Reduced sensitivity cefixime
  - (And to a lesser degree also to ceftriaxone)

  - Hypothesis origin 'new' allele:

→Recombination between commensal & pathogenic Neisseria strains

Consequences for diagnosis

- PCR:
  - Easy to perform
  - Rapid
  - Probably better for anal and throat samples
- Culture
  - Resistance assay

Chlamydia

Epidemiology of Chlamydia

- Incidence: 0.2/1000 pers./year
- Most frequently reported STD in developped world
- Rates 4x higher in females
- Frequently asymptomatic
- High prevalence of co-infection in partners (>50%)

Clinical picture Chlamydial infections

1. Urethritis, epididymitis, proctitis, cervicitis, salpingitis (PID).
2. Lymphogranuloma venereum (Chlamydia trachomatis L1, L2, L3)

3. Trachoma, inclusion conjunctivitis

Treatment of chlamydial infection

- Azithromycine
- Doxycycline
- (fluroquinolones)

No evidence of resistance

Syphilis

Credits: Seattle STD/HIV Prevention Training Center at the University of Washington

Treatment of Syphilis

Benzathine Penicillin G

Alternatives:

- Doxycycline
- Ceftriaxone
- Azithromycine
- Tetracycline

What about azithromycin?

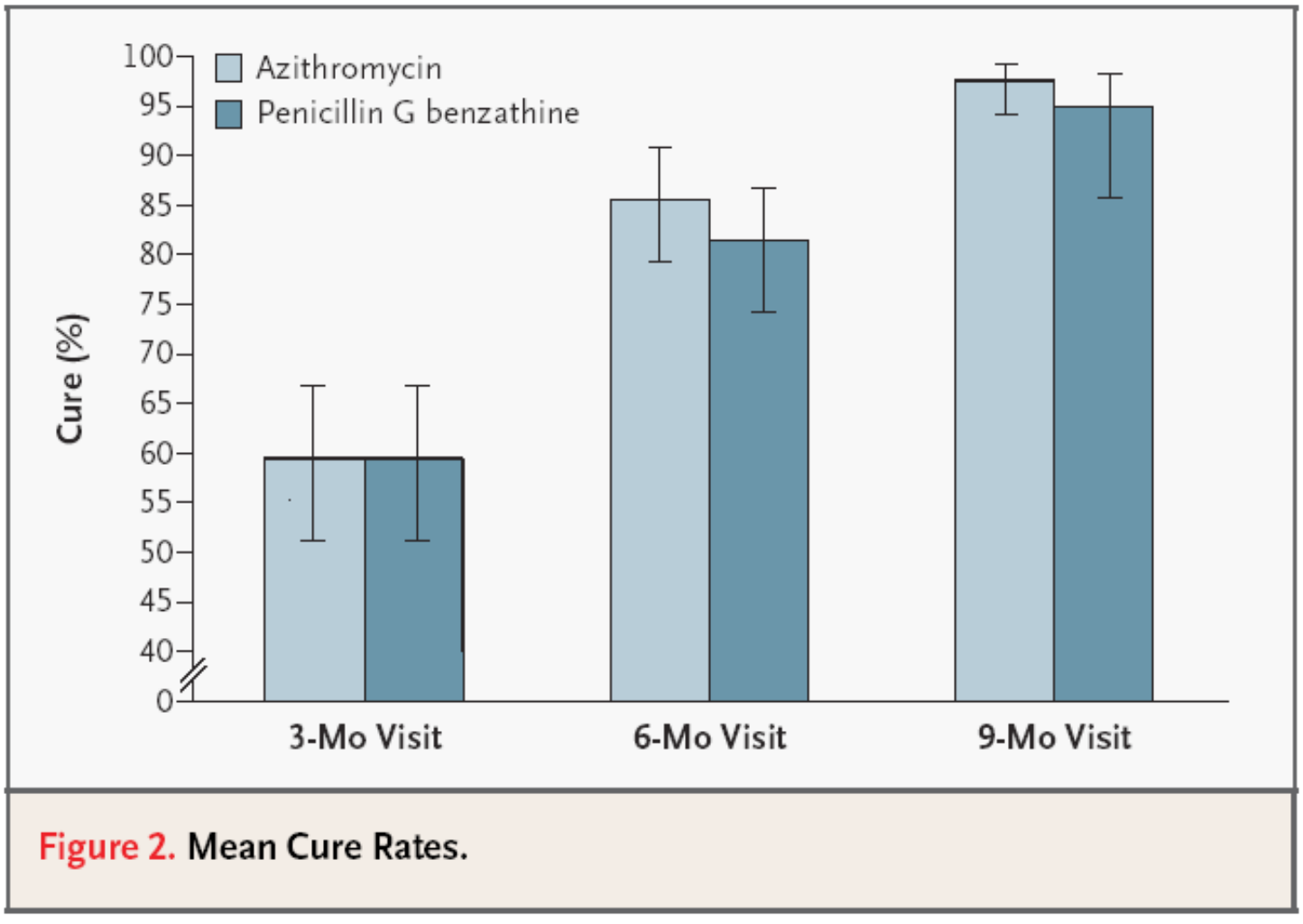


Figure 2. Mean Cure Rates.

Source: G. Riedner. N Engl J Med 2005 (Mbeya Tanzania)

This is a seducing treatment…

- Equivalent effectiveness to penicillin
- Single dosis treatment
- No injection
- Potentially active against:
  N. Gonorrhoea
  H. ducreyi
- “Patient delivered partner therapy”

But

Resistance of T. pallidum against azithromycine is on the rise!

- Described first in 2004[1] (but has been reported as back as 1985[2])
- San Francisco, Seattle, Baltimore, Dublin
- Mutation in the 23S ribosomal RNA genes

  → A2058G mutant strain
- Result of selection pressure rather than spread of single mutant strain

1. Lukehart SA NEJM 2004. 2. Stapleton JT Rev Infect Dis 1985

Penicilline remains the cornerstone in syphilis treatment

Potential threats for penicillin resistance

1.Presence of plasmid DNA in T.pallidum[1]

→ plasmid resistance not yet reported

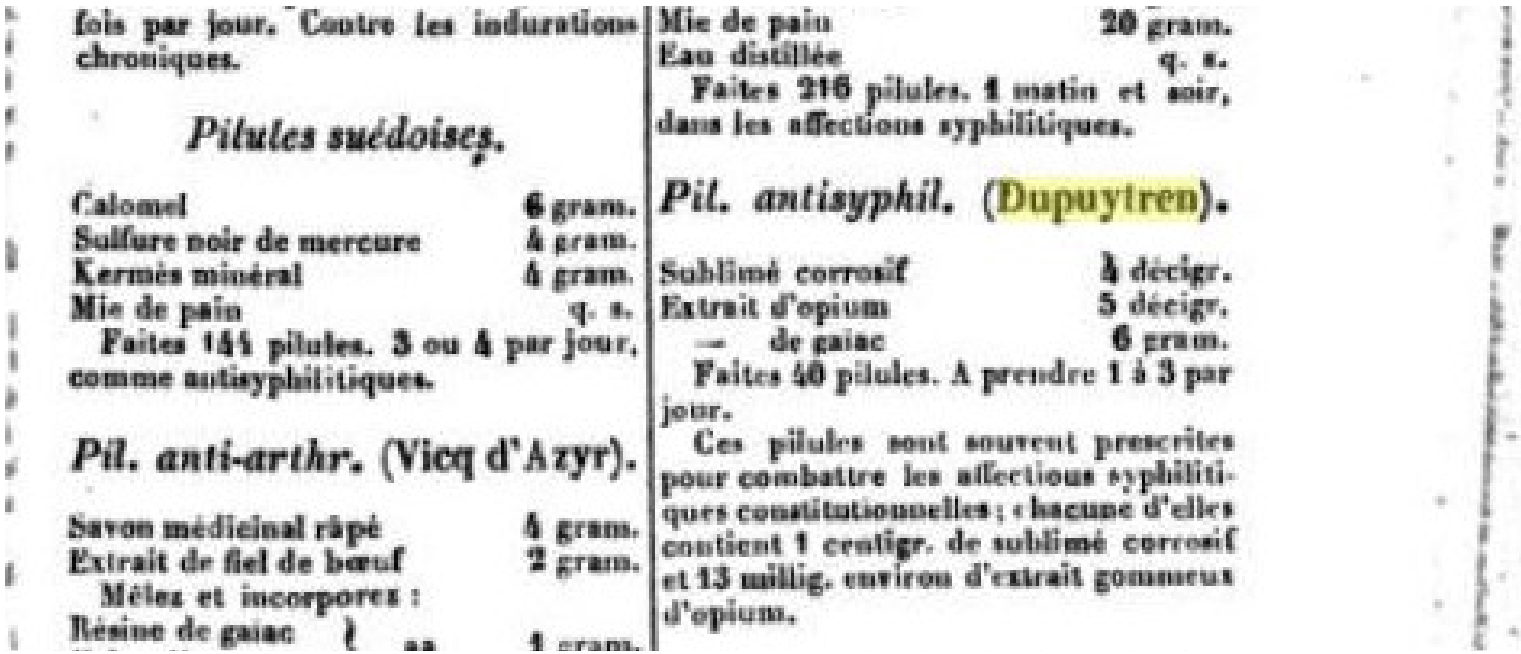
2. Membran bound protein Tp47 [2]

- β-lactamase activity
- Penicillin binding protein

A mutant that would overcome product inhibition for β-lactamase activity may become resistant to penicilline

1. Norgard MV Science 1981 2. Cha JY J Biol Chem 2004

What if penicillin treatment fail?



fois par jour. Contre les indurations chroniques.

Pilules suédoises.

Calomel	6 gram.
Sulfure noir de mercure	4 gram.
Kermès minéral	4 gram.
Mie de pain	q. s.

Faites 144 pilules. 3 ou 4 par jour, comme antisyphilitiques.

Pil. anti-arthr. (Vicq d'Azyr).

Savon médicinal râpé	4 gram.
Extrait de fiel de bœuf	2 gram.

Mêlez et incorporez :

Résine de gaiac	1 gram.
Mie de pain	20 gram.
Eau distillée	q. s.

Faites 216 pilules. 1 matin et soir, dans les affections syphilitiques.

Pil. antisyphil. (Dupuytren).

Sublimé corrosif	4 décigr.
Extrait d'opium	5 décigr.
— de gaiac	6 gram.

Faites 40 pilules. A prendre 1 à 3 par jour.

Ces pilules sont souvent prescrites pour combattre les affections syphilitiques constitutionnelles ; chacune d'elles contient 1 centigr. de sublimé corrosif et 13 millig. environ d'extrait gommeux d'opium.

In « Nouveau formulaire magistral » A. Bouchardat, Paris 1886

How will we detect resistant strains?

- Clinical
- Serological
- Molecular tests
  - DNA sequencing
  - PCR tests

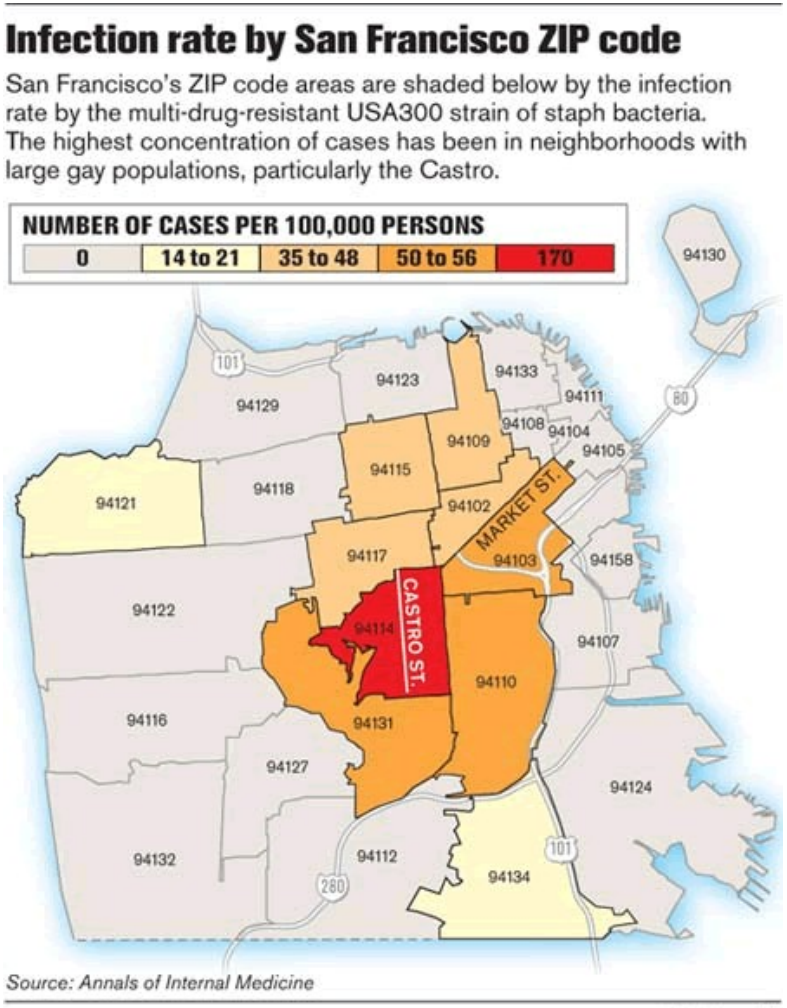
MRSA

CA-MRSA in gay men

- San Francisco (survey 9 hospital en 2 outpatients' depts)[1]
  - Incidence CA-MRSA 26/100.000
  - Single clone USA 300
  - Multidrug resistant (clindamycine en mupirocine R)
  - MSM: RR 13.2
  - HIV+ no independent risk factor
  - Esp. SSTI (genitals) → MRSA = SOA
- New York (retrospective, 100 MSM met CA-MRSA)[2]
  - 70% HIV+, 90% CD4 > 200
  - Multi drug resistant (clindamycine R 75%, cotrimoxazole S)
  - Recurrence ~druggebruik
  - ? Protective effect of co-trimoxazole?
- Kinky scene, skin abrading sex, drug use, history of STD's

1. Diep BA, Arch Int Med 2008; 2. Shastry, Arch Int Med 2007

CA-MRSA in San Francisco



http://www.hivandhepatitis.com/recent/2008/011808_a.html

CA-MRSA and HIV infection

- Increasing incidence since 2000 and up to 18 x higher than in general population
- 21% recurrent infections
- > 80% skin & soft tissue infections (genital area)
  - < 10% bacteraemia
  - > 90% of all SSTI caused by CA-MRSA
- Most isolates S for clindamycin, CTX, tetracyclin

CA-MRSA and HIV infection

- Health care associated risk factors
  - Hospitalisation < 6 m, use of b-lactam antibiotics, previous MRSA
- Other risk factors
  - Low CD4, high VL
  - recent STD (syfilis), use of drugs, sauna
- Protecting factors
    - Co-trimoxazole (OR 0.2)
    - Consistent condom use (OR 0.1)

Herpes simplex infections

Herpes simplex virus

- Tropism

  HSV I → oral

  HSV II → genital

- Latency in the sensory nerve ganglion
- Symptomatic recurrence &/or asymptomatic shedding.

Acyclovir & co.

- Activation by phosphorylation (thymidine kinase)
- Inhibition viral DNA polymerase

Acyclovir resistant HSV:

- No evidence of sexual transmission
- Less/not virulent outside the context of severe immunesuppression

Take Home Messages

- Gonorrhoea
  - Growing resistances
- Chlamydial infections
  - No resistance registered yet
- Syphilis
  - Increasing azitromycin resistance
  - Potential for penicillin resistance
- MRSA : emerging STD
- H. simplex:
  - no evidence of sexual transmission of resistant strains
- Importance to document resistance

Resistance to use condoms