NORTHWEST AIDS EDUCATION AND TRAINING CENTER

The Emerging Challenge Neisseria Gonorrhea Resistance: How Should Clinicians Respond?

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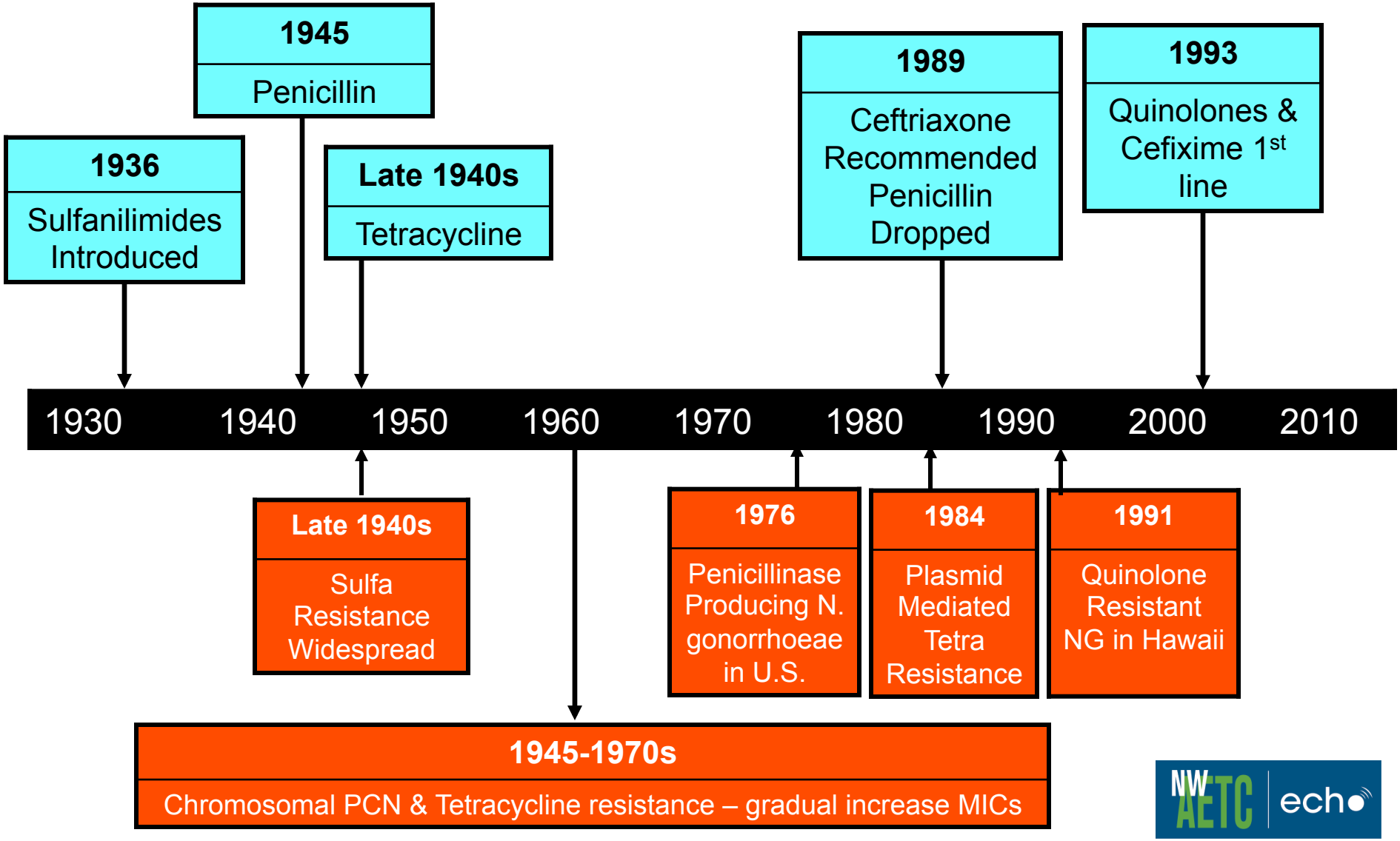
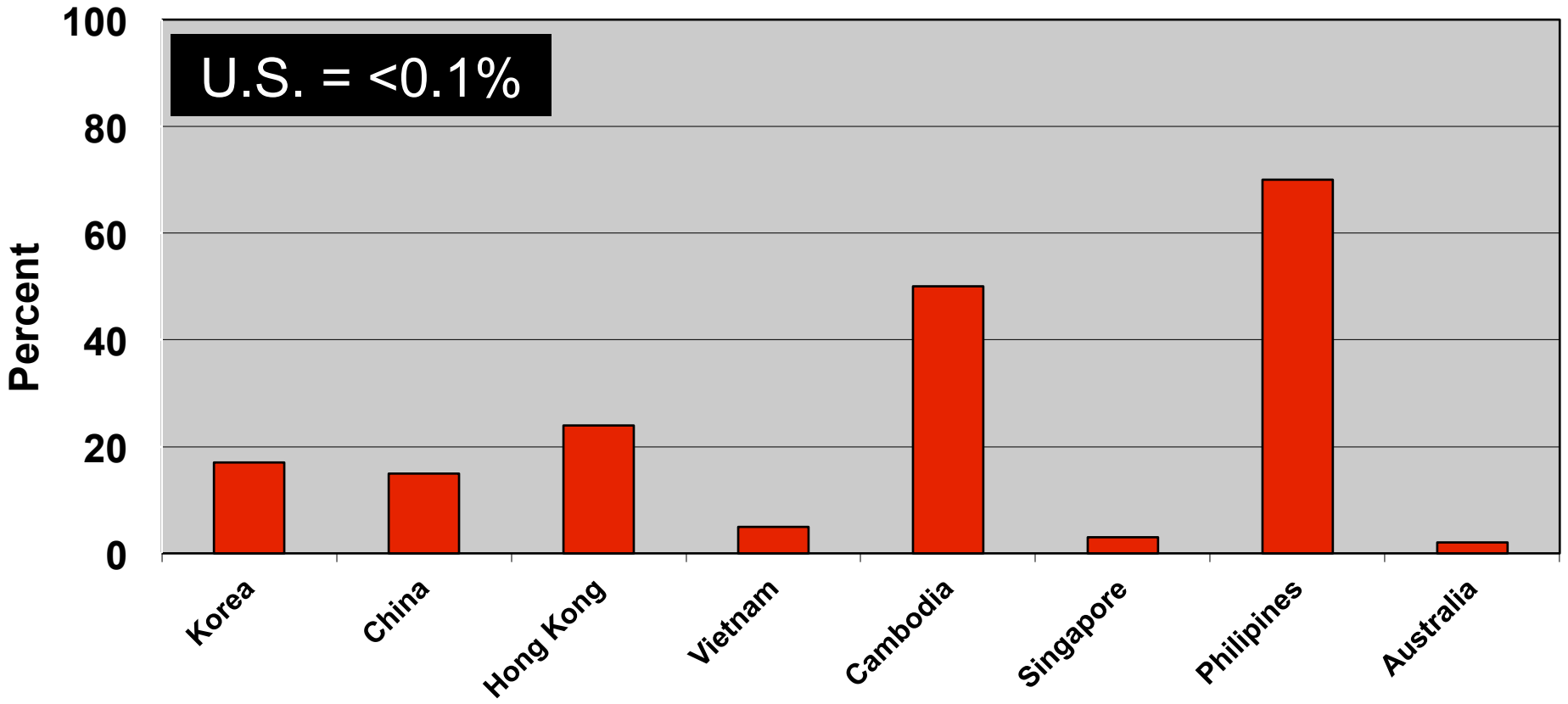
Overview

- Epidemiology of antimicrobial resistance and Neisseria gonorrhoeae
- Implications for Testing
- Implications for Treatment

Historical Perspective on *Neisseria gonorrhoeae* Antimicrobial Resistance in the United States

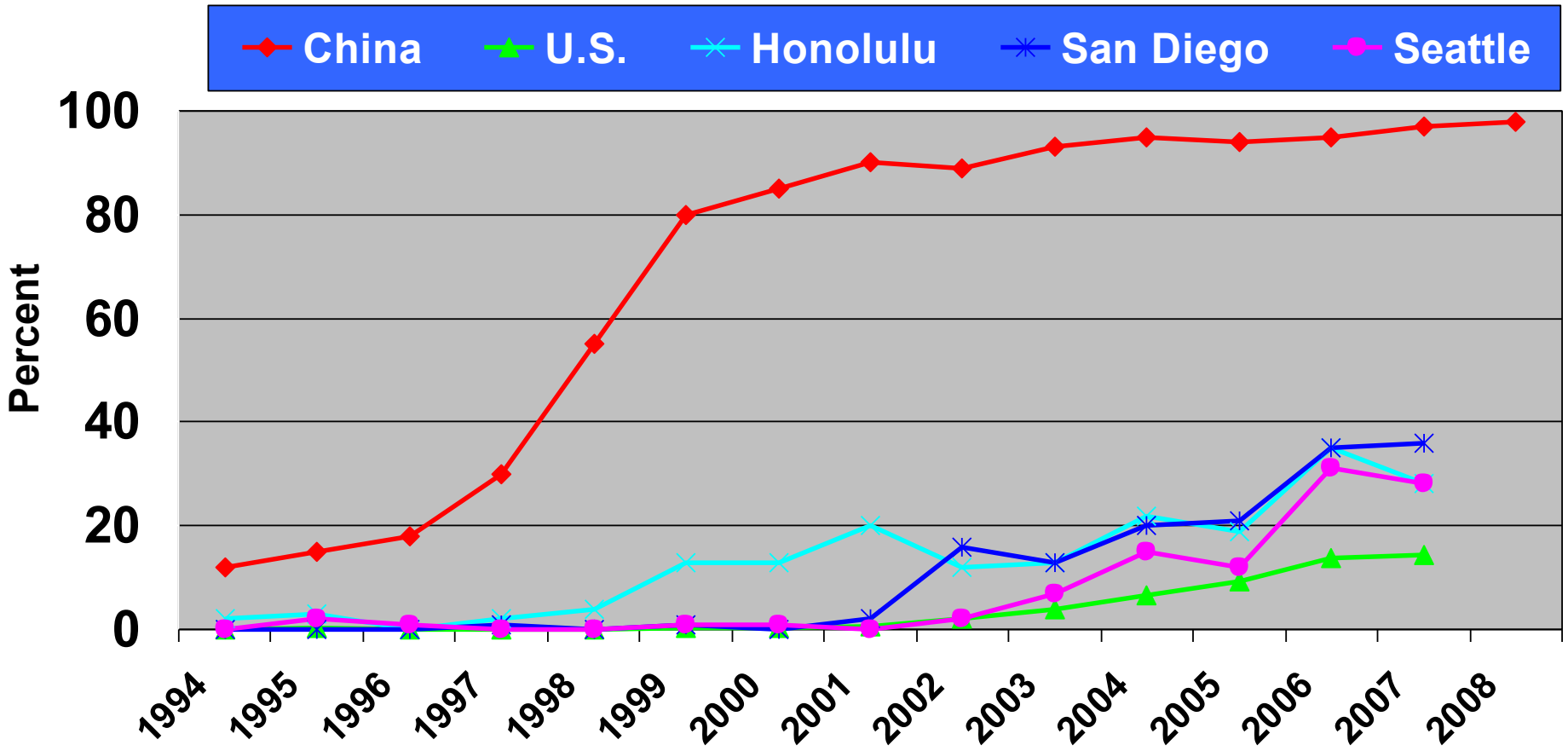


Prevalence of Quinolone Resistant *Neisserria gonorrhoeae*, 1996



Tapsall J. Anitmicrobial resistance in Neisseria gonorrhoeae 2001, WHO CDC 1998 GISP Report

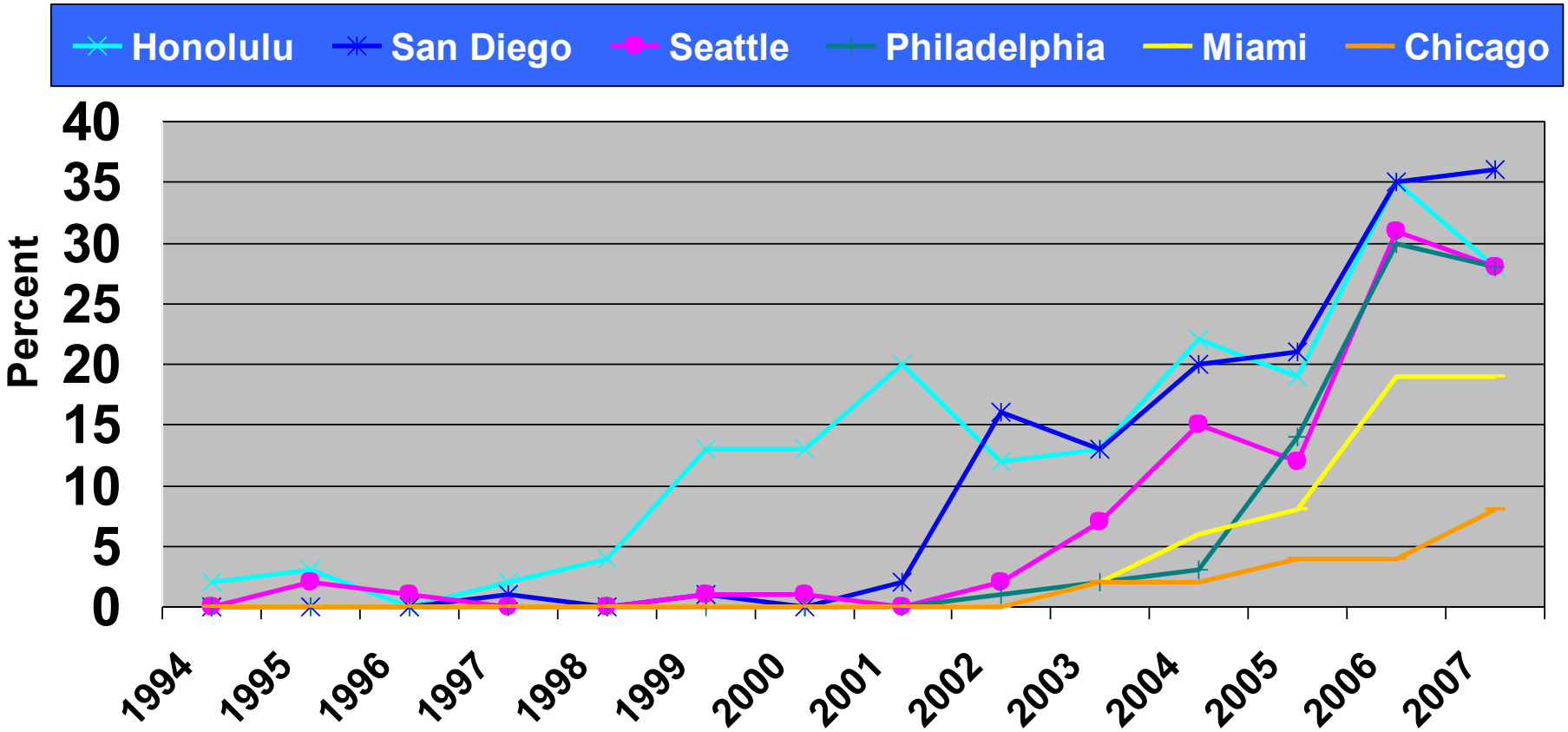
Trends in the Prevalence of Quinolone Resistant *Neisserria gonorrhoeae* in China and the U.S



QRNG= MIC≥1mg/l

Yue-Ping Yin, Chinese National STD Control Program CDC 1998 GISP Report

Trends in the Prevalence of Quinolone Resistant *Neisserria gonorrhoeae* in the U.S.

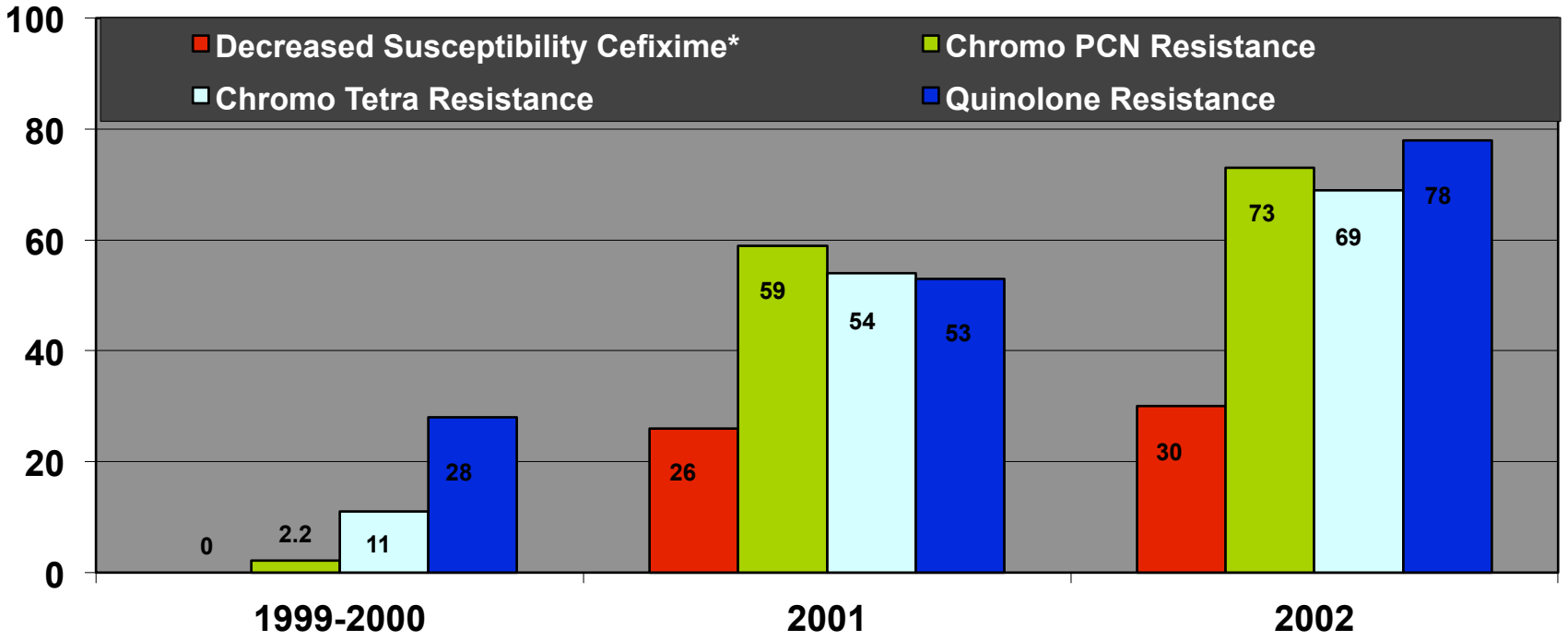


CDC GISP

Emergence of Decreased Susceptibility *N. gonorrhoeae* in Japan

2001 – Akesaka reports a case of treatment failure in a man with urethritis treated with cefdinir (MIC=1µg/ml)

Antimicrobial Resistance in *N. gonorrhoeae* in Central Japan 1999-2002

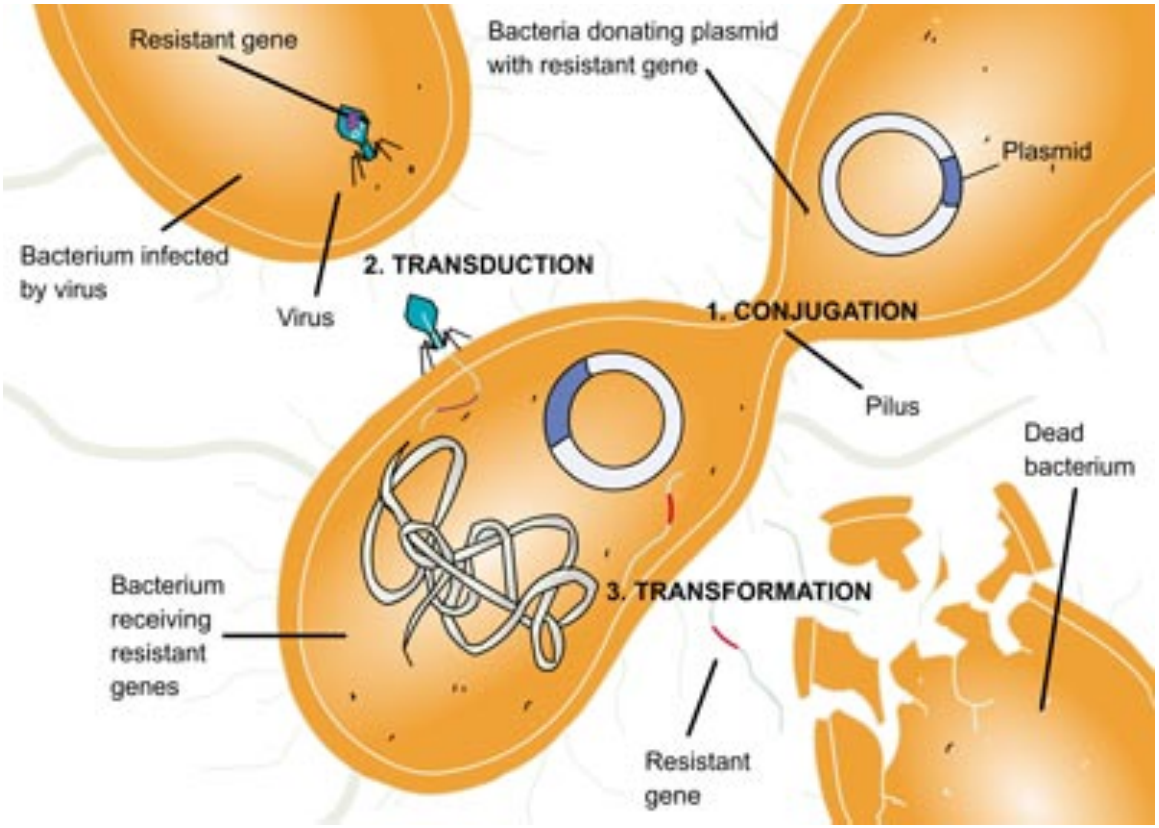


* Cefixime MIC ≥0.5 µg/ml

>99% isolates susceptible to ceftriaxone throughout period

Ito et al. Anti Agents Chemo 2004;48:3185

Bacterial Mechanisms for Horizontal Gene Transfer

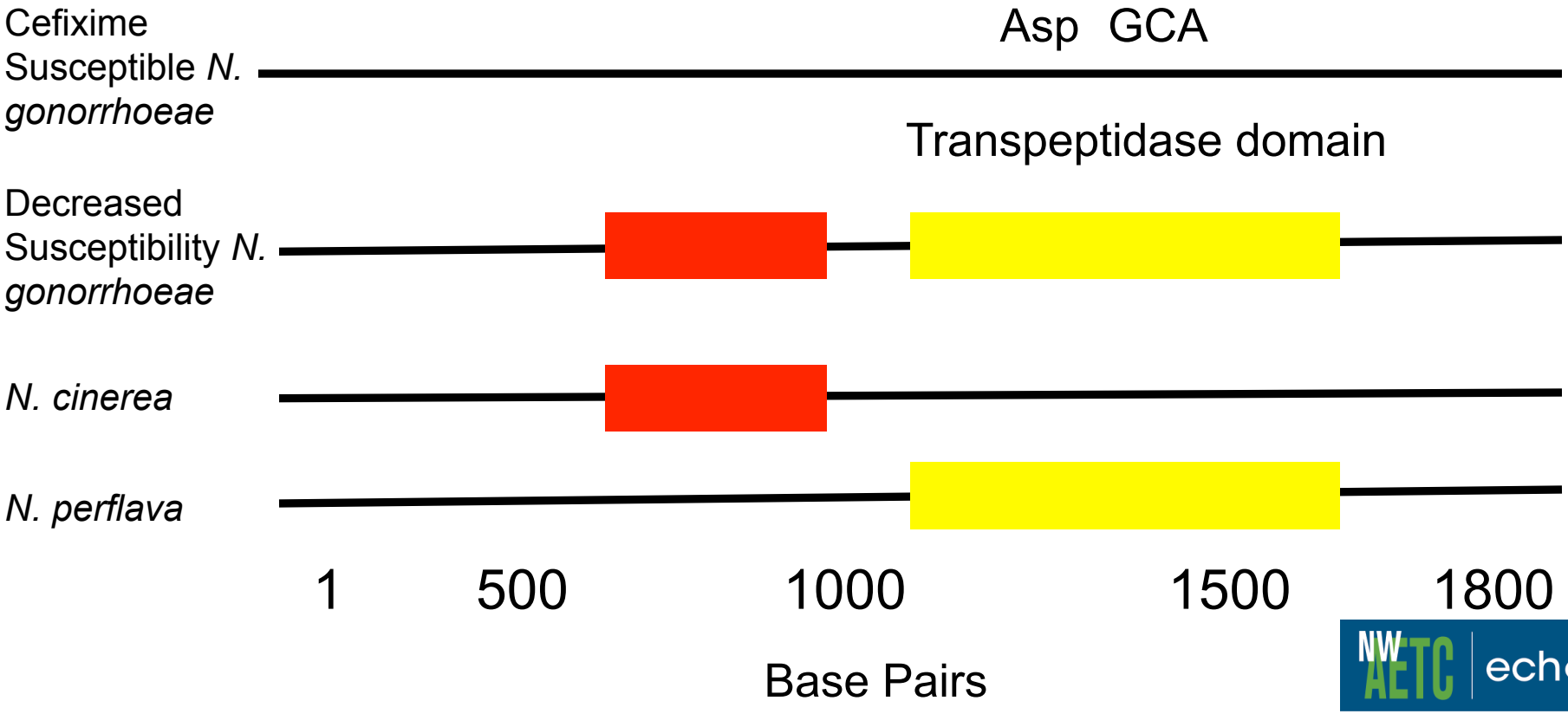


- **Conjugation**
  - Penicillinase producing NG (PPNG), high-level tetracycline resistance
  - Resistance obtained from other Gram negative bacteria
  - Not currently involved in decreased susceptibility to cephalosporins
- **Transformation**
  - Takes up DNA that has a genus specific 10 bp DNA uptake equence
  - Central role in changes in PenA gene (PBP2) and rising cephalosporin MICs

Mosaic-like Structure and Decreased Cephalosporin Susceptibility *N. gonorrhoeae*

2002 – Ameyama describes Mosaic-like structure of PBP-2 gene (*penA*)

- Contains fragments of PBP-2 from commensal *Neisseria* commonly found in the oro-pharynx (*N. cinerea, N. flavescens, N. perflava*, etc

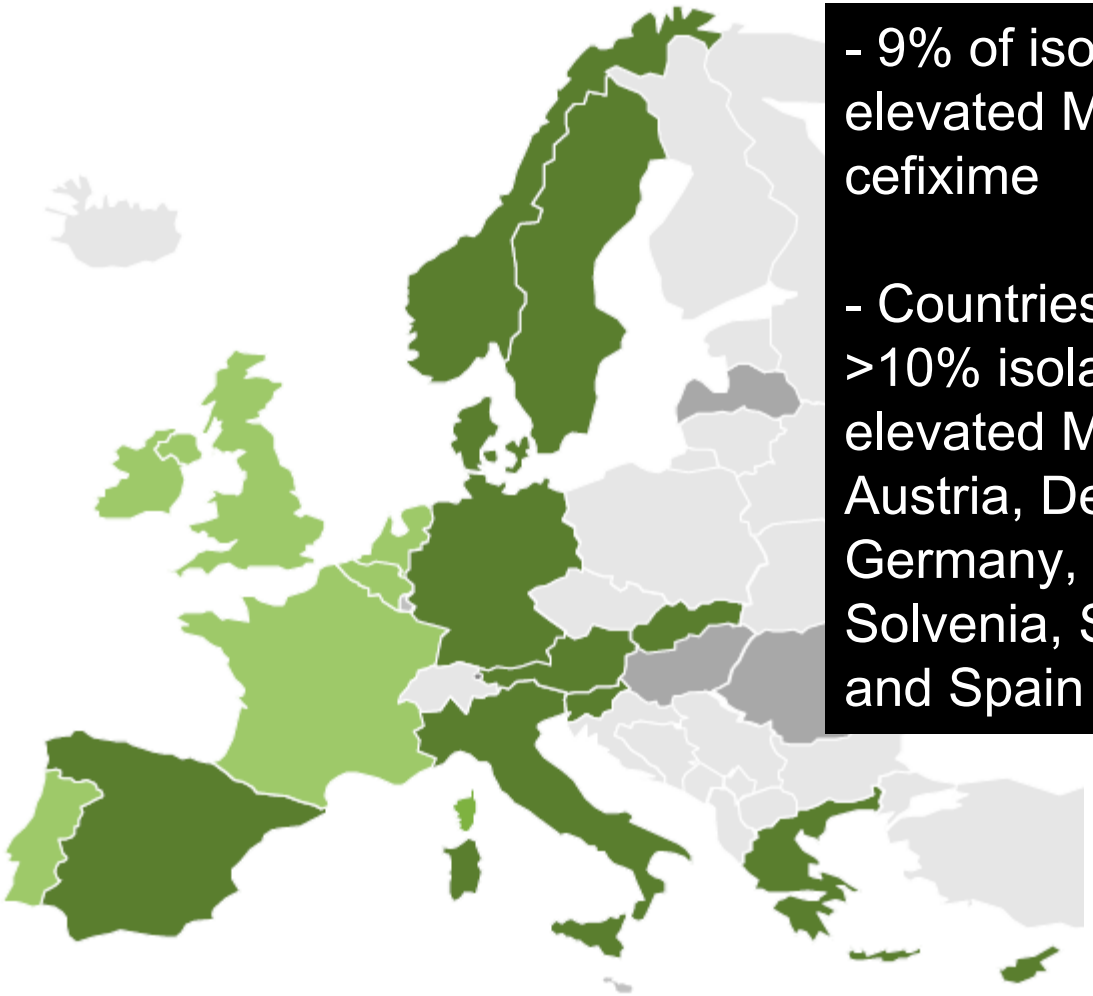


N. gonorrhoeae with Increased MICs (>.25µg/ml) to Cefixime in Selected European Countries: GASP 2010

Countries with no strains that exhibit decreased susceptibility to cefixime

Countries with strains that exhibit decreased susceptibility to cefixime (<5%)

Countries with strains that exhibit decreased susceptibility to cefixime (≥5%)



- 9% of isolates had elevated MICs to cefixime

- Countries in which >10% isolates had elevated MICS: Austria, Denmark, Germany, Greece, Solvenia, Slovakia and Spain

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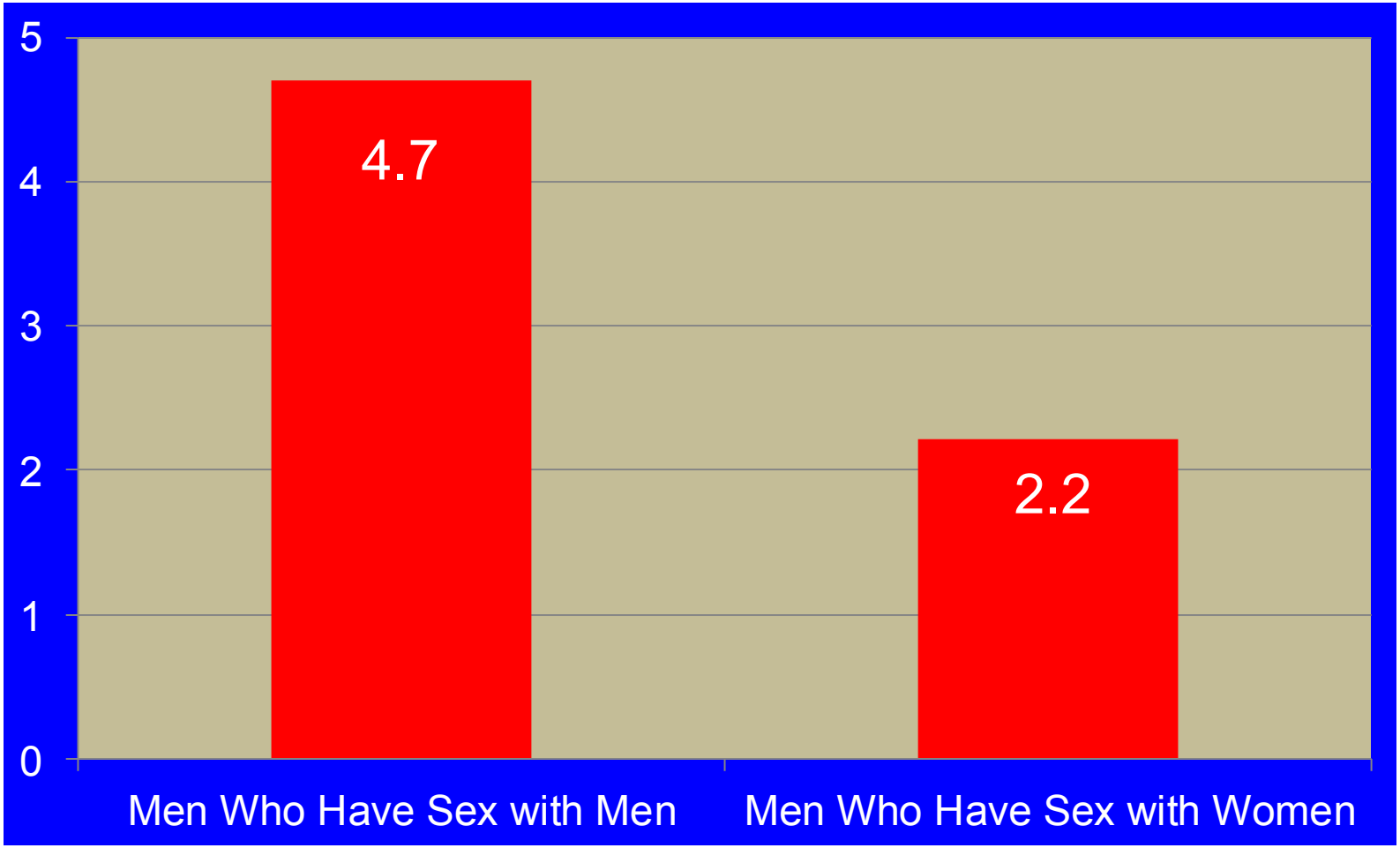
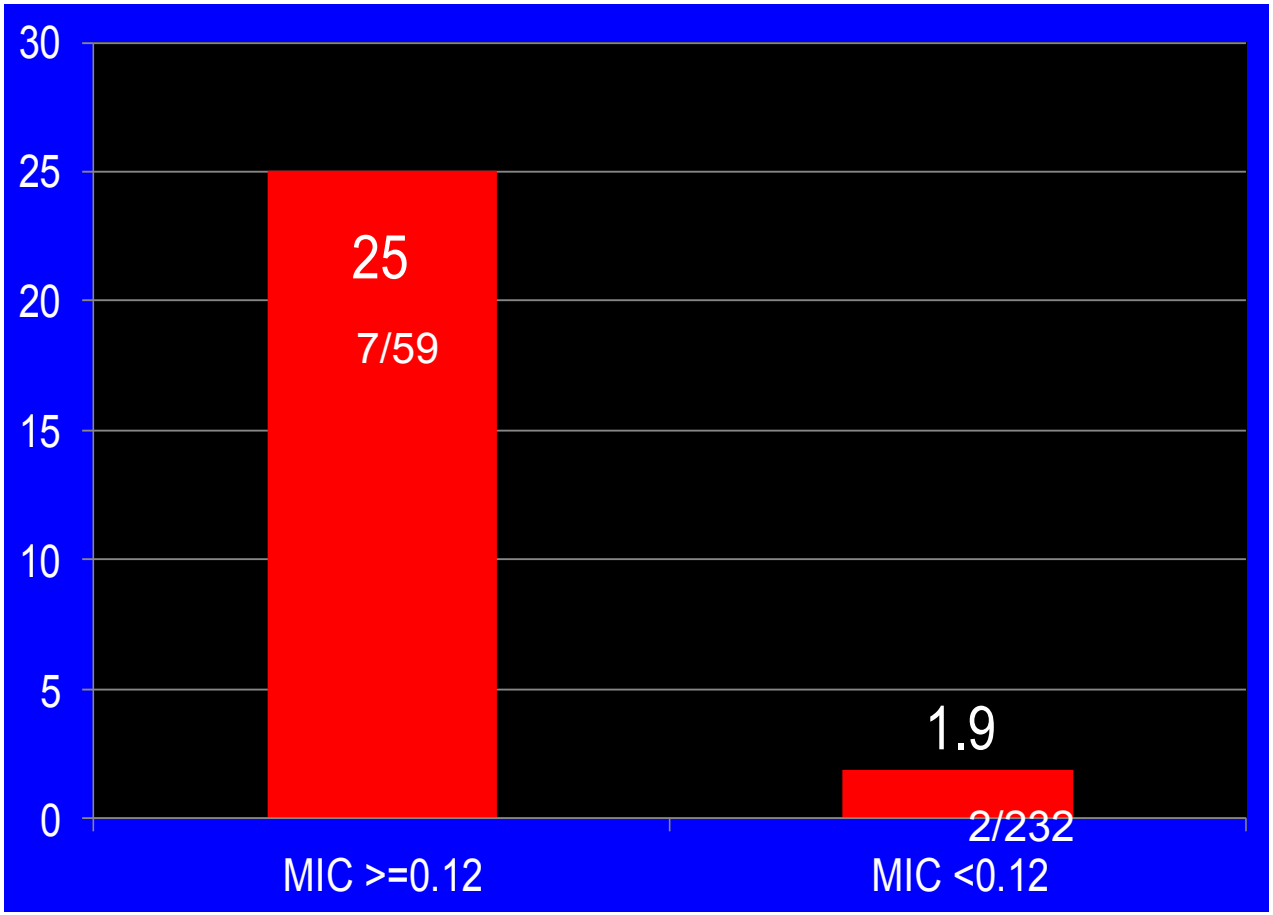
Percent of *Neisseria gonorrhoeae* Isolates With Elevated MICs (>0.25) to Cefixime in Western U.S. 2011, by Sexual Orientation



Kircaldy & GISP Collaborators

Treatment Failure in Persons Treated with Cefixime* in Toronto, 2010-11



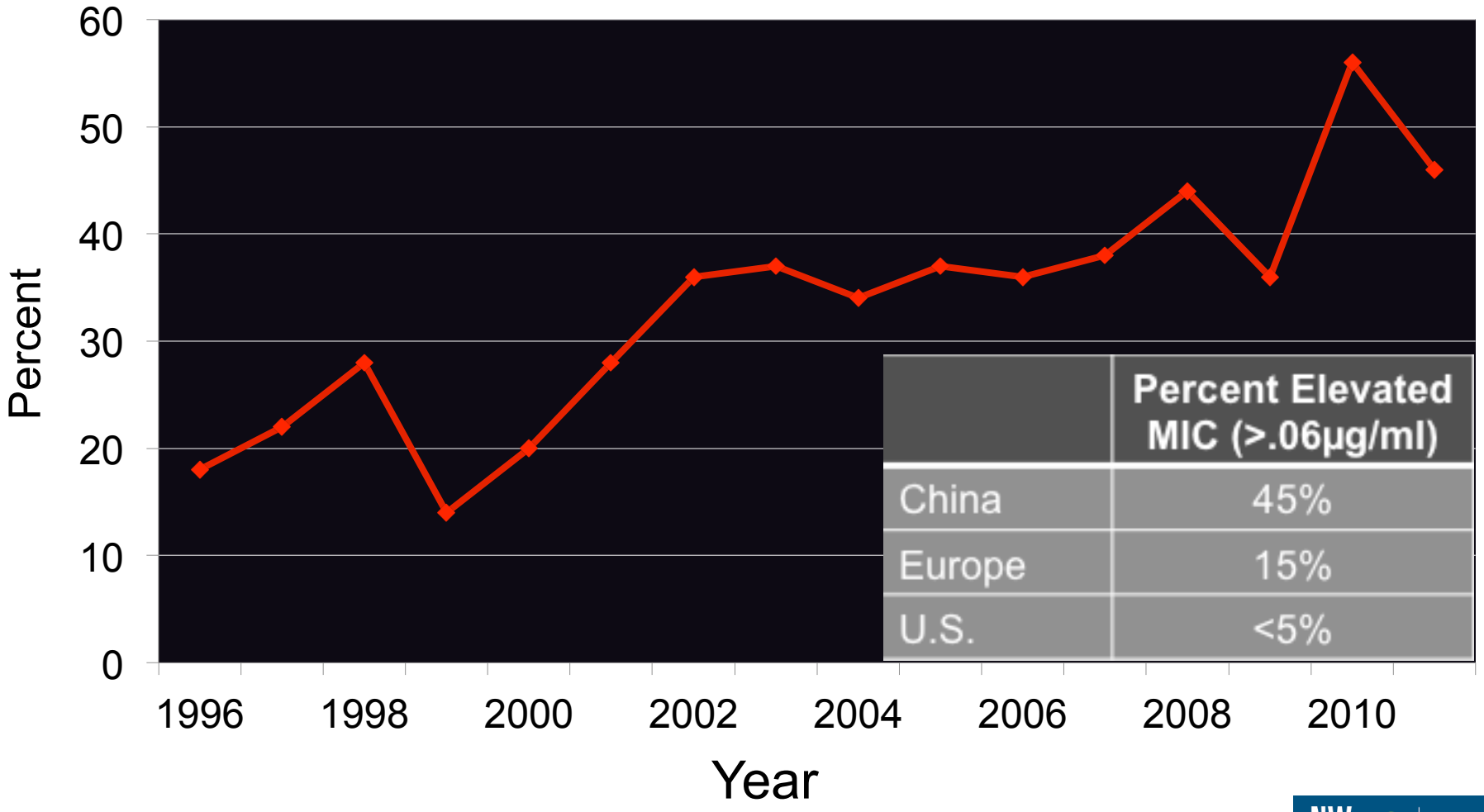
- **46% of patients underwent test-of-cure**
- **12% treatment failure if all persons with no test-of-cure were cured**

2011
Total US - 3% MIC ≥0.12
West
MSM – 8.5% MIC ≥0.12
MSW – 2.5% MIC ≥0.12

- 4/9 patients received dual therapy, 3 with doxy and 1 with azithro

Allen, VG. JAMA 2013

Intermediate Ceftriaxone Susceptibility *N. gonorrhoeae* in China, 1990-2009 (MIC 0.06-0.5 mg/l)



	Percent Elevated MIC (>.06µg/ml)
China	45%
Europe	15%
U.S.	<5%

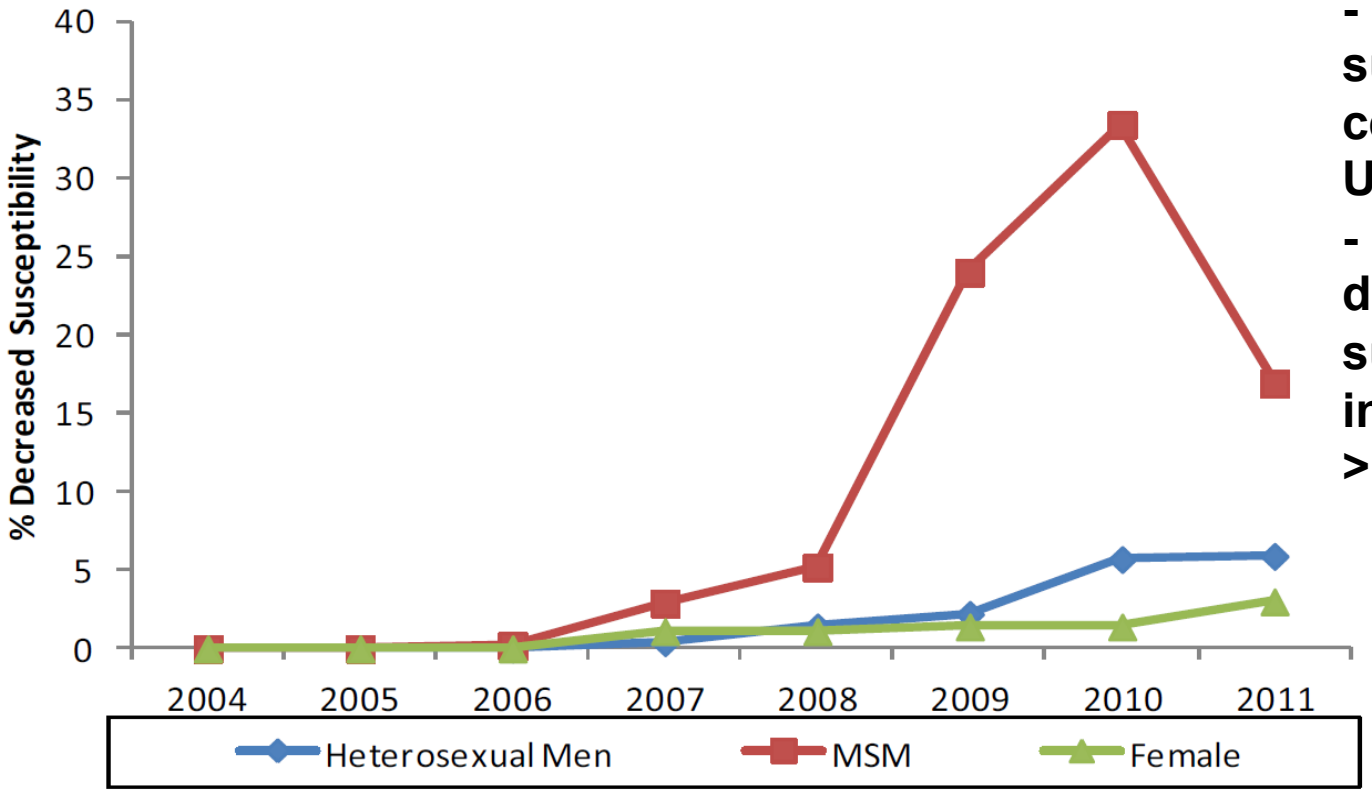
Yue-Ping Yin. Chinese CDC

Extensively Drug-Resistant *N. gonorrhoeae*

Author (Year)	Country	MSLT Type	Popula-tion	Ceftiaxone MIC (µg/ml)	Cefixime MIC (µg/ml)	Resistance Mechanism	Clinical
Ohnishi (2011)	Japan	ST7363 H041	♀ Sex Worker	2-4	8	PBP2 Mosaic, *mtrR, PenB*	Pharyngeal GC Cured Ceftriaxone – dose unknown
Unemo (2011)	France	ST1901 F89	MSM	1-2	4	PBP2 Mosaic + A501, *mtrR, PenB*	Urethral GC Failed Cefixime 200g x 2 Cured Gent 160mg IM
Camara (2012)	Spain	No MSLT but related to F89	2 MSM patients	1.5	1.5	PBP2 Mosaic + A501 *PenB*	Urethral & Rectal GC One pt cured with 7 days doxy, one with Azithro

Isolates appeared to be susceptible to Spectinomycin, Ertapenim, Meropenim, and Pip-Tazo.
French and Japanese strains were Azithro resistant (MIC=1)

N. gonorrhoeae with Increased MICs (>.125µg/ml) in the UK 2007-11



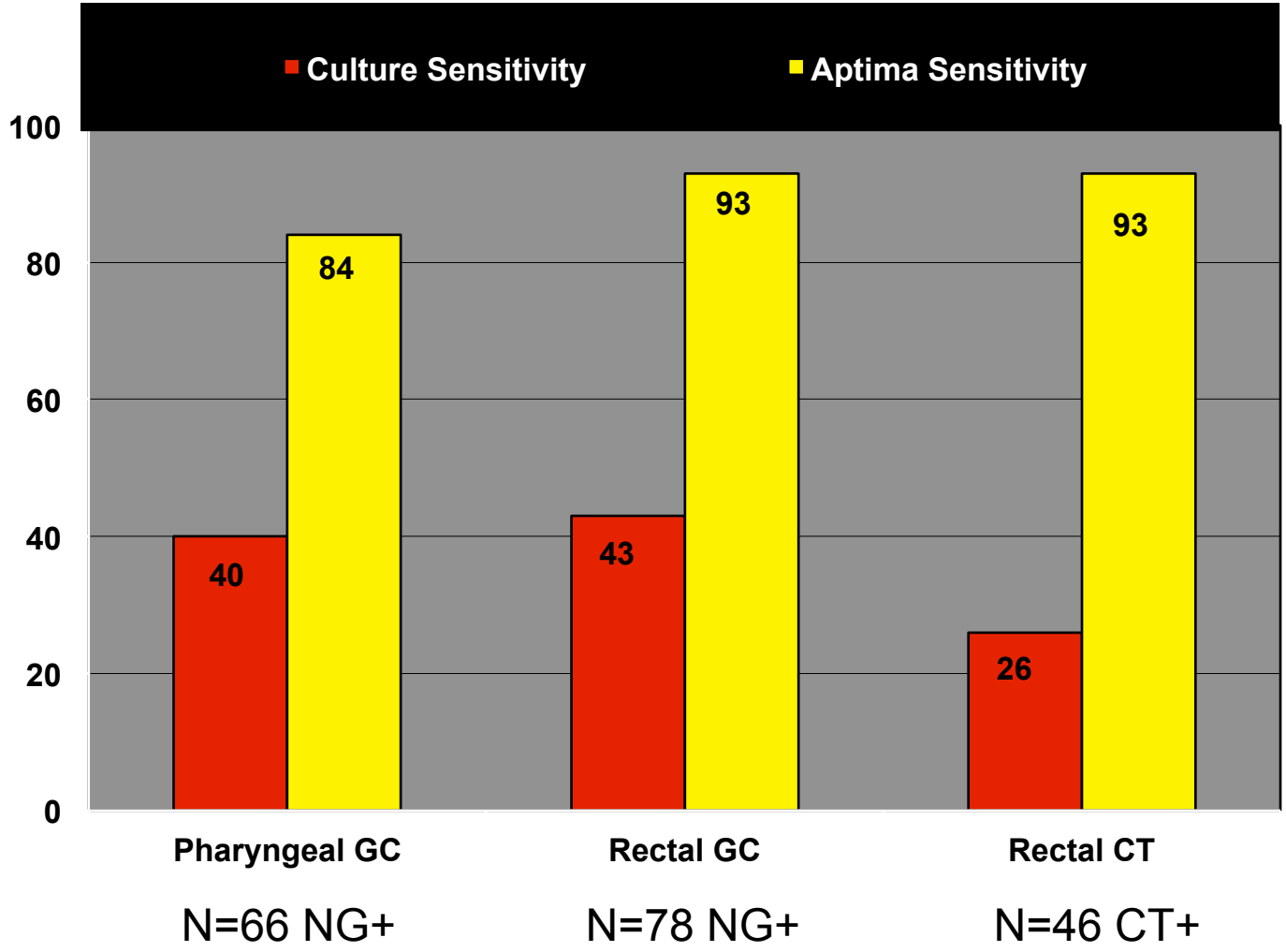
- Decreased susceptibility to cefixime stable in U.S. 1.2%
- No cefixime decreased susceptibility isolates in King County for >18 months 1/12-8/13

Source: Gonococcal Resistance to Antimicrobial Surveillance Programme (GRASP)

Challenges & Opportunities

- **Identify and treat the reservoir of asymptomatic infection – pharyngeal & rectal infections**
  - ~30-40% of women and MSM with urogenital infection have concurrent pharyngeal infections
  - ~8% of asymptomatic MSM without urethral infections in STD clinics have pharyngeal or rectal infections
  - Pharyngeal infections more difficult to treat due to relatively low concentrations of antibiotic

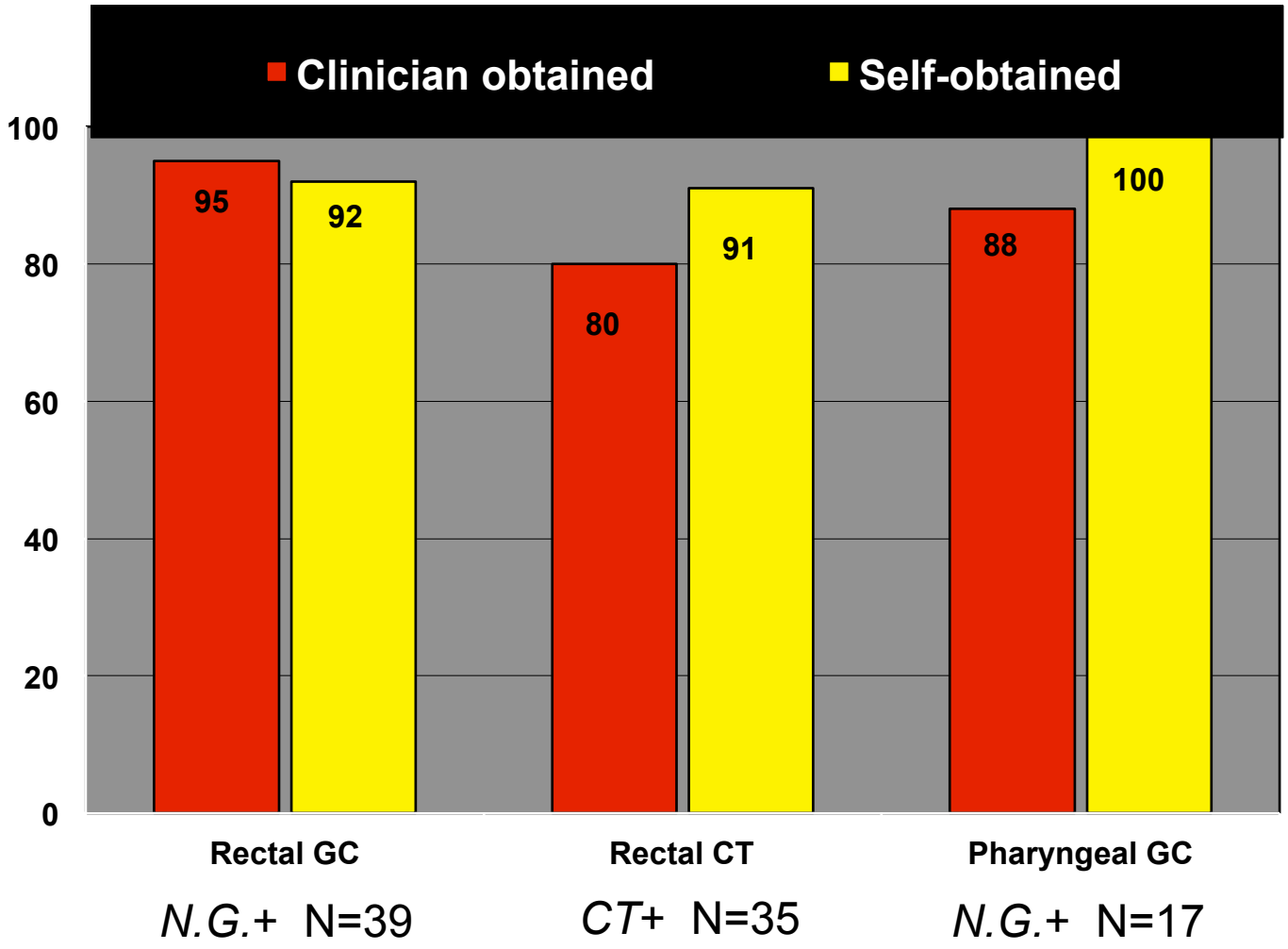
Nucleic Acid Amplification Testing for C. trachomatis and *N. gonorrhoeae* at non-genital Sites (N=1110)



- Sensitivity based on 2 positive tests
- **Specificity AC2 for NG and CT >99%**
- PCR - insensitive and nonspecific for NG in the pharynx
- SDA - somewhat less sensitive than AC2. May be less specific for pharyngeal GC

STD 2008;35:637

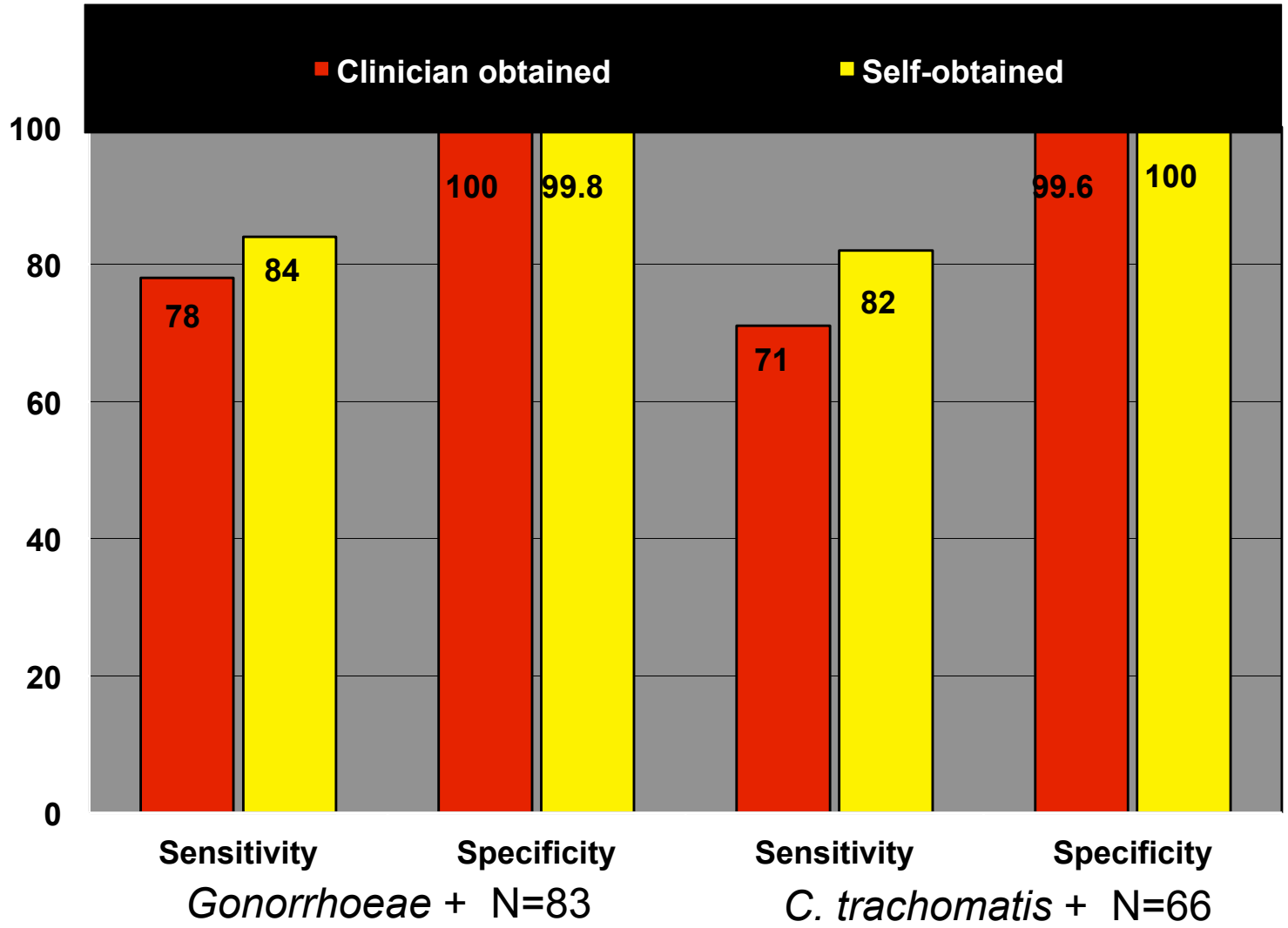
Sensitivity of Self-Obtained Nucleic Acid Amplification Testing for *C. trachomatis* and *N. gonorrhoeae* at non-genital Sites (N=272)



- Aptima Combo 2 NAAT used for self-testing
- Specificity of self-obtained specimens 88-100% - based on culture as a gold standard

JCM 2009;47:1657

Self-Obtained Nucleic Acid Amplification Testing for Rectal *C. trachomatis* and *N. gonorrhoeae* (N=907)



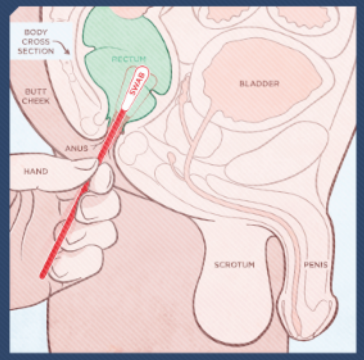
- Self-obtained rectal specimens appear to be as good or better than clinician obtained specimens

JCM 2009;47:1657

Seattle STD/HIV Prevention Training Center

TEST YOURSELF

The Visual Guide for a **Self-collected Rectal Swab**



1 Wash your hands with soap and water.

2 Remove the transport tube and collection swab from packaging.

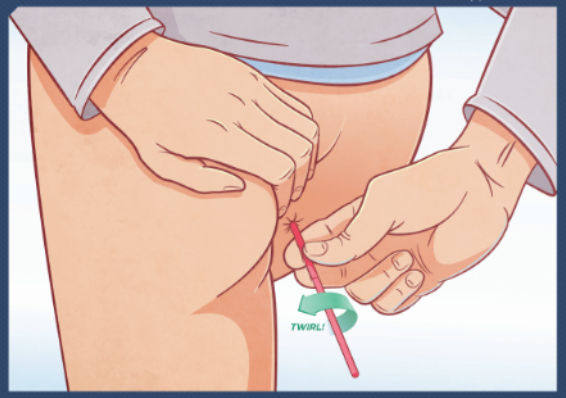
3 Label the transport tube with your **Patient label**.

4 Label the transport tube with the **Rectal label**.

5 Open the package containing the collection swab.

6 Firmly hold the collection swab above the dashed line (closer to the swab tip).

7 Get into a comfortable position that allows you access to your anus. Putting your foot on the step stool may help.



8 Gently insert the swab 1 inch into the rectum and twirl the swab in a circle at least 5 times.

9 Unscrew the cap from the transport tube.

10 Place the collection swab into the transport tube, snapping it at dashed line.

11 Put the cap back on the transport tube and twist it closed to prevent leaks.

12 Put the transport tube into the biohazard bag.

13 Wash your hands with soap and water.

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Challenges & Opportunities: New Treatments

- **Dual therapy**
  - CDC recommends ceftriaxone 250mg IM + azithro 1g OR Doxy 100mg x 7d
  - **Evidence favors the use of Azithro, not doxy**

Recurrent Pharyngeal Gonorrhea at 7-180 day Follow-up

Treatment Regimens	Positivity 7 – 180 days	Adjusted Relative Risk* (95% Confidence Interval)
Oral Combination Therapy with Azithro	**7.0%** (8/115)	Referent Group
Oral Combination Therapy with Doxy	**33.3%** (14/42)	4.18 (1.64 – 10.7)
Oral Cephalosporin Monotherapy	**29.8%** (17/57)	3.98 (1.70 – 9.36)
Ceftriaxone Combination therapy	**11.3%** (7/62)	1.20 (0.43 – 3.33)
Ceftriaxone Monotherapy	**9.1%** (4/44)	0.81 (0.18 – 3.60)

*** Adjusted for time from treatment to TOC, year, sexual behavior, sexual orientation, age**

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Challenges & Opportunities: New Treatments

- Higher doses of existing drugs
  - ? Ceftriaxone 500mg, 1g or 2g
  - Cefixime 600-800mg q8 or q12
    - PK modeling suggests achievable levels would be adequate to treat pharyngeal GC with MICs of .5-1
- New uses of old drugs
  - Gentamicin 240-280mg IM x 1 – 91% effective alone (Dowel D. Postgrad Med J 2013:89:142)
  - Gentamicin + Azithro 2g OR Gemifloxicin 320mg – 100% cure (Kircaldy R, ISSTDR 2013)
    - Uncertain what efficacy would be if isolates were resistant

Challenges & Opportunities: New Treatments

- New Drugs
  - Solithromycin (CEM-101) - Macrolide
    - 4-32-fold higher activity than Azithro
      - Likely active against gonococci with Azitho MICs 1-2
    - 3 bacterial ribosomal binding sites (vs. 2 with azithro)
    - Shorter T1/2
    - Phase 2 trial – cured all treated persons

Conclusions

- Decrease susceptibility *N. gonorrhoeae* is a problem
  - How imminent a problem is less certain
  - Gay men are likely to be the leading edge of antimicrobial resistance
- Increased STI screening of extra-genital sites is likely to be a key to control
  - Screening should rely on NAATs
  - Self-obtained specimens are acceptable to patients and perform well
- Dual therapy with ceftriaxone and azithromycin is the preferred regimen for gonorrhea