

# The Specter of MDR GC: *Resisting* Resistance is Futile?

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October 2017



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A Project of the Division of STD Prevention  
Massachusetts Department of Public Health  
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# Disclosures

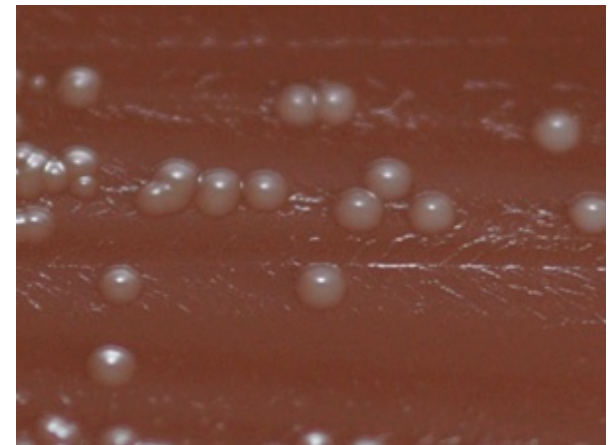
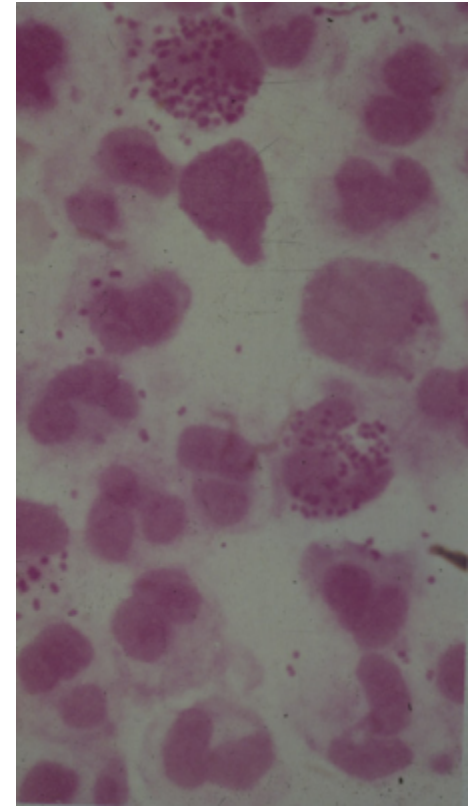
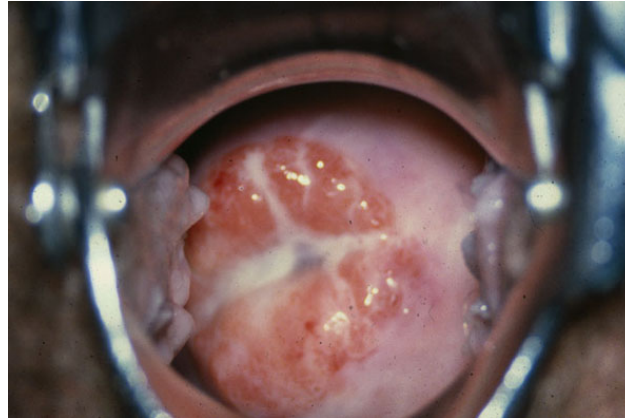
- In the past 12 months, Dr. Hsu has had the following significant financial interests or other relationships with manufacturer(s) of product(s) or provider(s) of service(s) that will be discussed in this presentation:
  - Participated in consultations on PrEP sponsored by Gilead Sexual Health and on Neisseria vaccines sponsored by GSK
- This presentation will include discussion of pharmaceuticals or devices that have not been approved by the FDA
  - “Off-label” use of extra-genital (rectal and pharyngeal) nucleic acid amplification tests (NAATs) for gonorrhea and chlamydia
  - Tenofovir/emtricitabine for HIV PrEP not currently licensed for use in those <18 years

# Goals

- Review clinical presentation of gonorrhea including complications
- Review gonococcal biology and reasons for resistance development
- Review epidemiology of drug-resistant gonorrhea
- Preview potential ways to slow development of drug-resistant gonorrhea



# Gonorrhoea: Mucosal and Systemic Disease



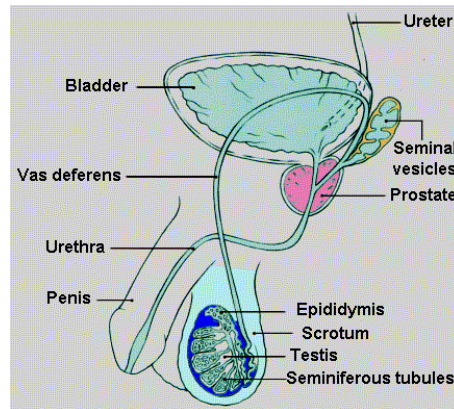
# Gonorrhea

**Local infection** – urethritis (males), cervicitis, proctitis, pharyngitis, ocular infection

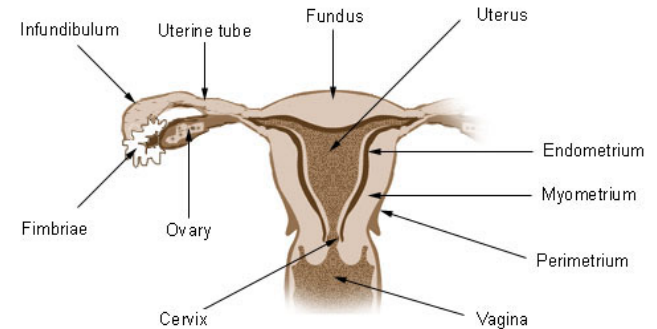
## Contiguous spread

**Women** – endometritis, salpingitis, tubo-ovarian abscess, peritonitis, perihepatitis

**Men** – prostatitis, epididymo-orchitis



**Uterus and Uterine tubes**



## Dissemination via blood stream



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Slide courtesy of Dr. Sanjay Ram

# Additional local complications of gonorrhea

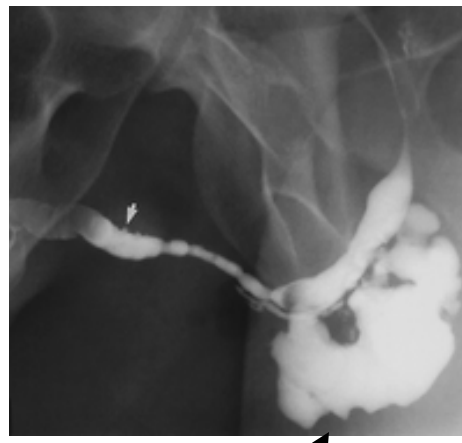
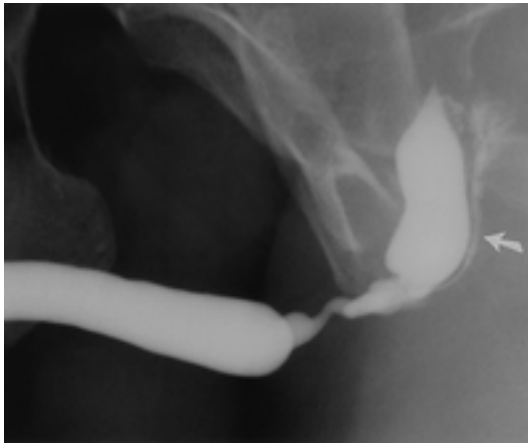
Relatively uncommon in antibiotic era...

Urethral stricture

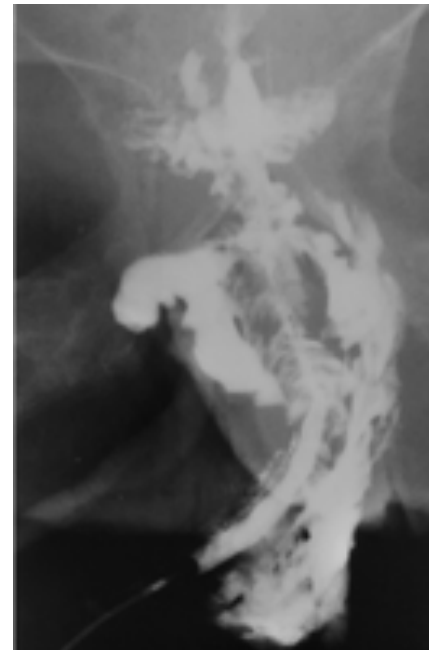
Prostatitis

Fistulae communicating with perineum – “watering can perineum”

## Urethral stricture



Periurethral abscess



Kawashima et al,  
Radiographics, 2004

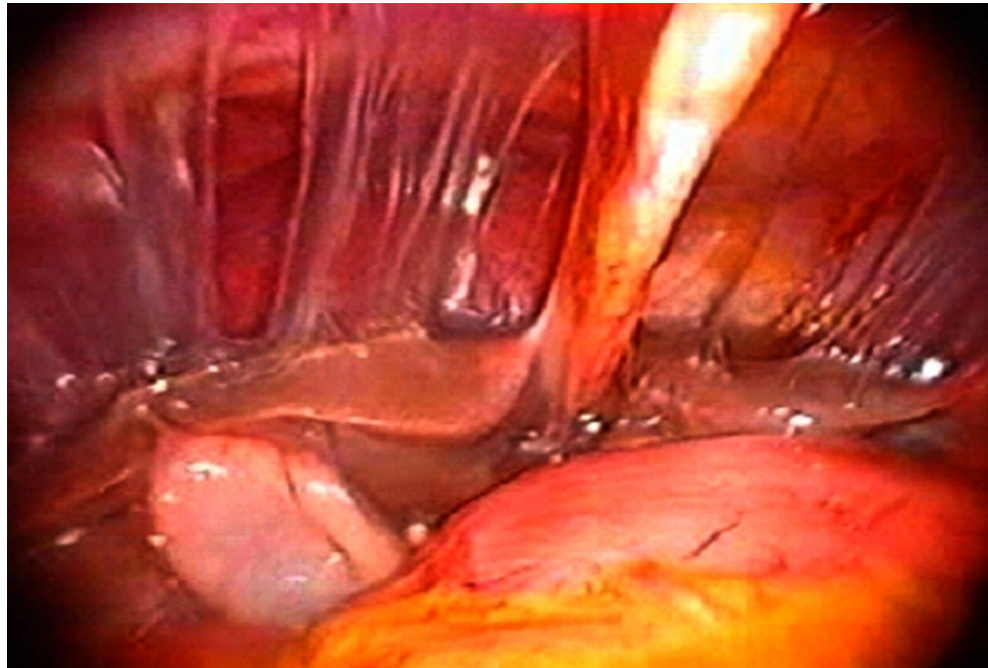
Slide courtesy of Dr. Sanjay Ram

# Complications of gonorrhea - epididymoorchitis



# Spread of gonorrhea / chlamydia into peritoneum

**Acute perihepatitis (Fitz-Hugh and Curtis syndrome) - direct extension of *N. gonorrhoeae* or more commonly, *Chlamydia trachomatis* from the fallopian tube to the liver capsule and overlying peritoneum**



From website - Geneva Foundation for Medical Research



# Biology of *Neisseria gonorrhoeae*

- Oxidase-positive, gram-negative diplococcus
  - Ferments glucose, not maltose, sucrose, fructose, or lactose
- Atmospheric conditions crucial
  - Does not tolerate drying
  - Transport within 15 minutes to 2% to 10% CO<sub>2</sub>
  - Within 30 minutes to 35-36°C incubation
  - Preferential to pre-incubate 12-16 hrs before transporting
- **Identification now rests on molecular AND phenotypic testing**



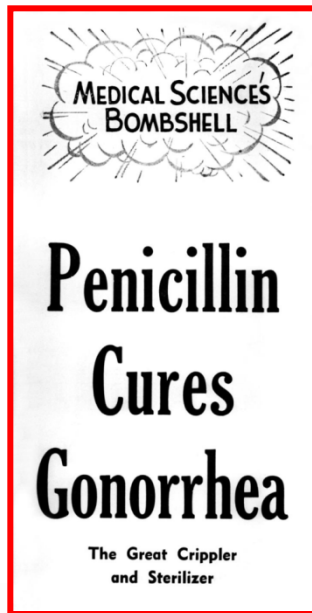
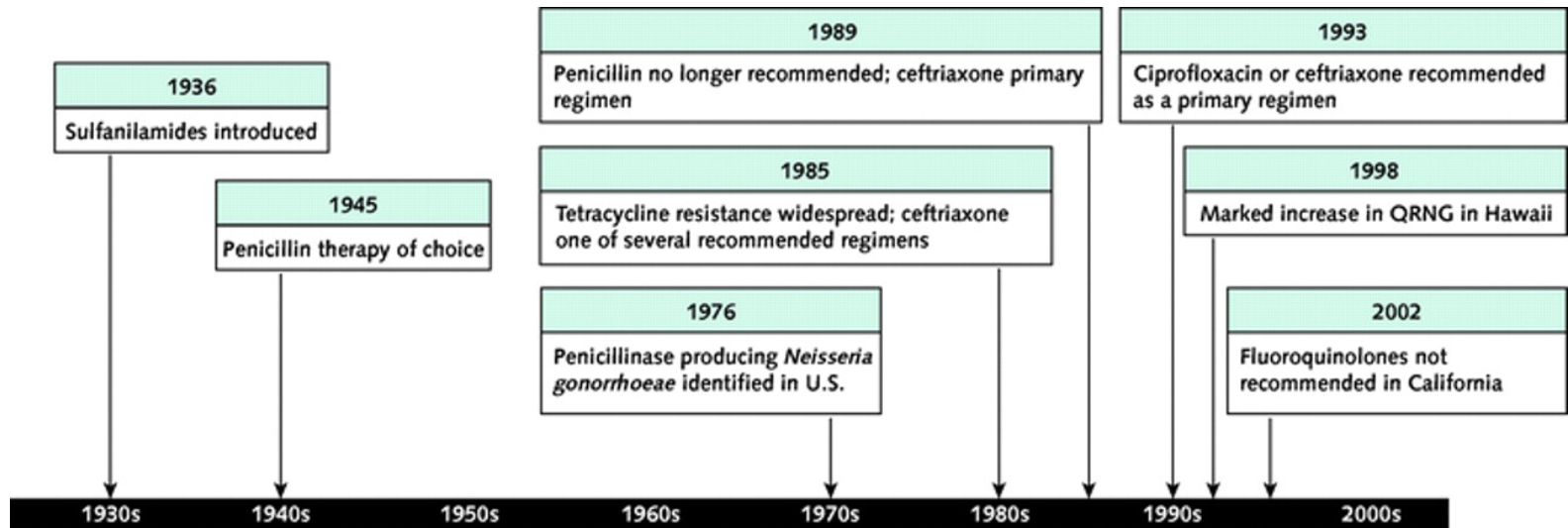
 Mosby  
*STD Atlas, 1997*



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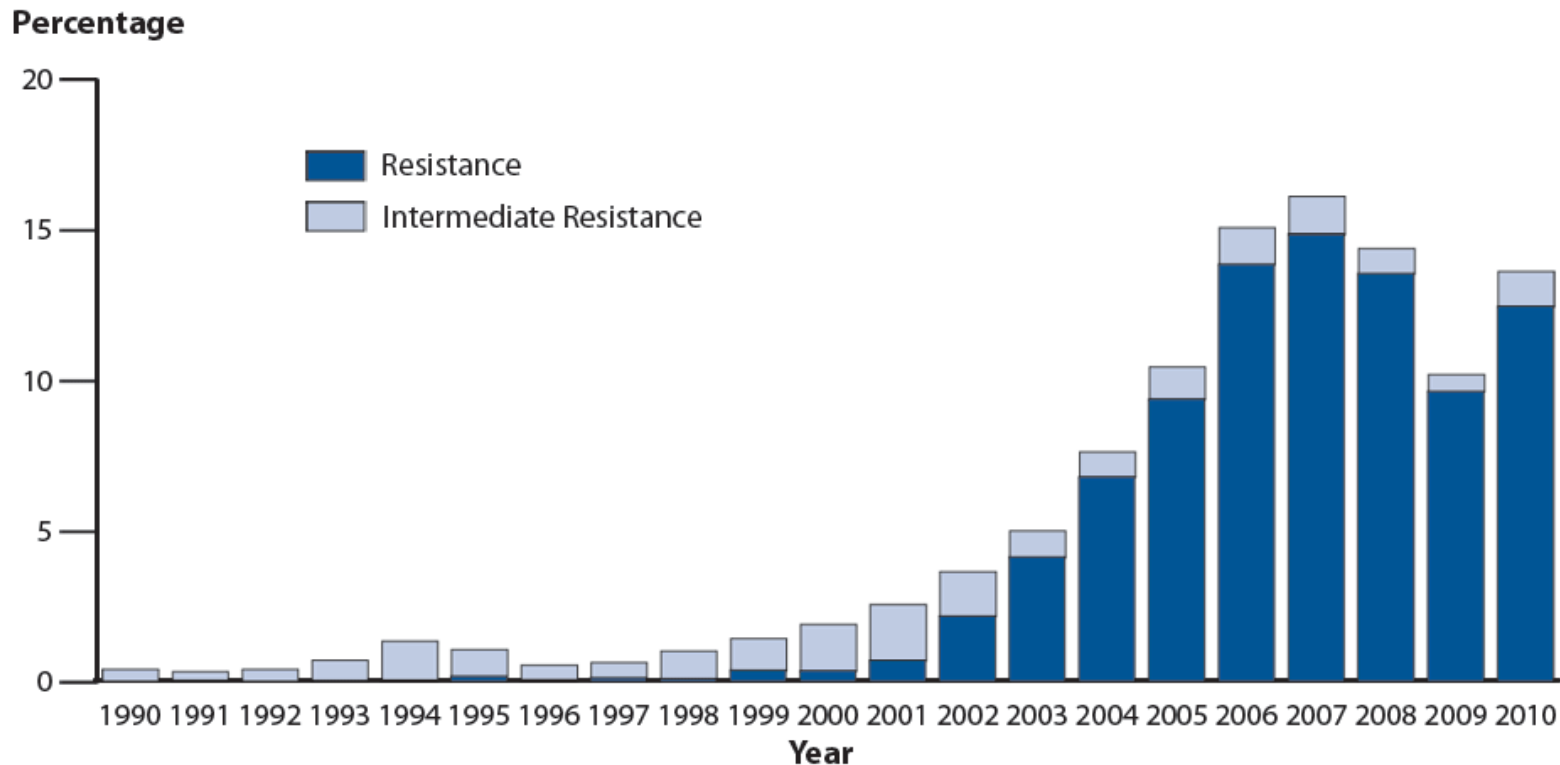
Figure 126-2. Historical Perspective, Gonococcal Antimicrobial Resistance in United States



(till the 1970s...)

Annals of Internal Medicine

# Gonococcal Isolate Surveillance Project (GISP): Percentage of *Neisseria gonorrhoeae* Isolates with Resistance or Intermediate Resistance to Ciprofloxacin, 1990–2010



**NOTE:** Resistant isolates have ciprofloxacin minimum inhibitory concentrations (MICs)  $\geq 1$   $\mu\text{g/ml}$ . Isolates with intermediate resistance have ciprofloxacin MICs of 0.125–0.5  $\mu\text{g/ml}$ . Susceptibility to ciprofloxacin was first measured in GISP in 1990.

## *Neisseria gonorrhoeae* with Reduced Susceptibility to Azithromycin — San Diego County, California, 2009

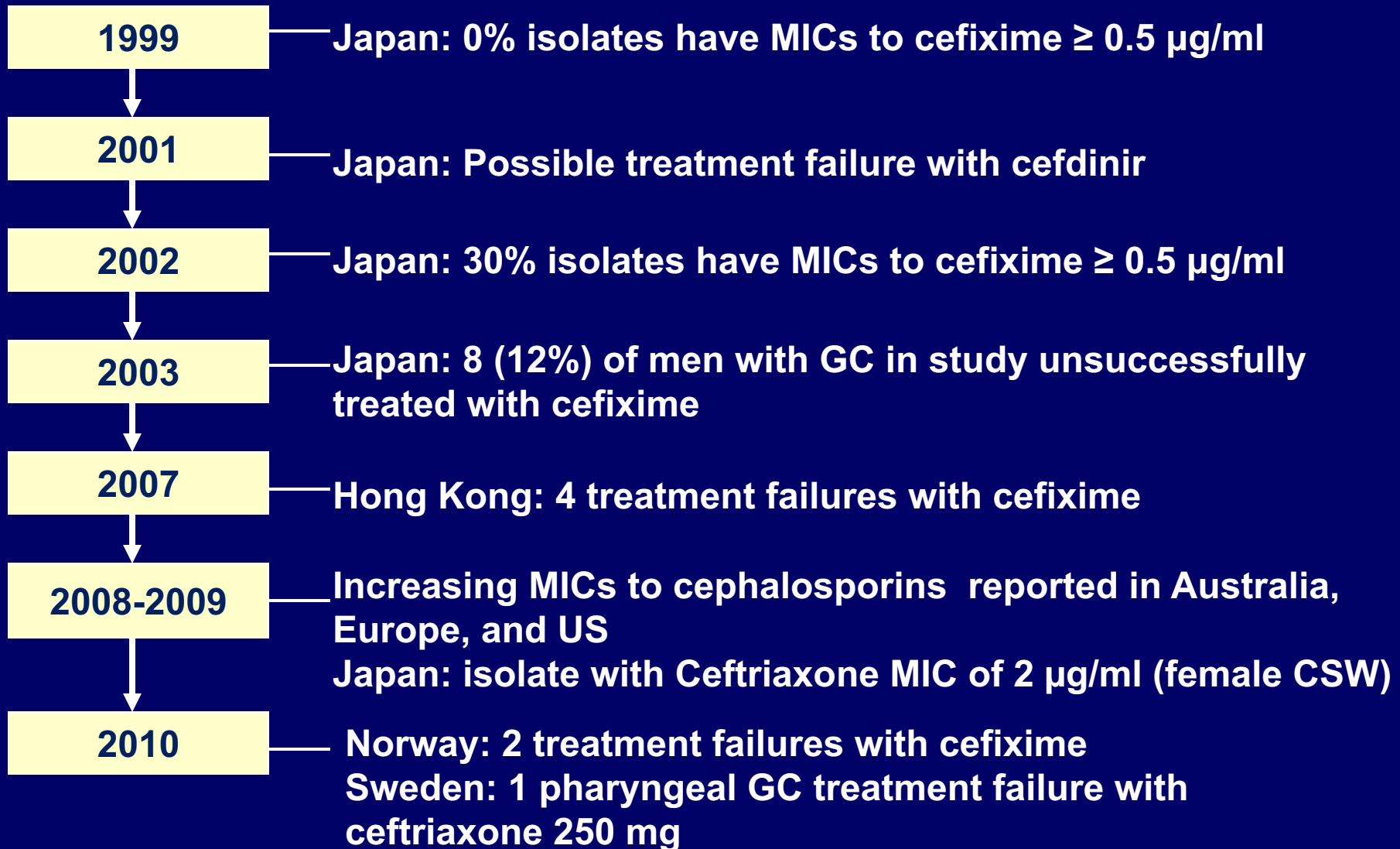
A single 2 g dose of azithromycin effectively treats genitourinary infections caused by susceptible *Neisseria gonorrhoeae* and has been used to treat uncomplicated gonorrhea in persons with cephalosporin allergy. However, azithromycin is not recommended as monotherapy because of concern over the emergence of resistance. Instead, a 1 g dose of azithromycin is recommended as a component of dual therapy for gonorrhea, in conjunction with a cephalosporin (i.e., 250 mg of ceftriaxone or 400 mg of cefixime, if ceftriaxone is not an option). During January 1992–July 2009, of 87,566 *N. gonorrhoeae* isolates tested for azithromycin susceptibility by CDC's national Gonococcal Isolate Surveillance Project (GISP), only 39 (0.04%) had minimum inhibitory concentrations (MICs)  $\geq 8$   $\mu\text{g}/\text{mL}$  (including 25 with 8  $\mu\text{g}/\text{mL}$  and 14 with 16  $\mu\text{g}/\text{mL}$ ).

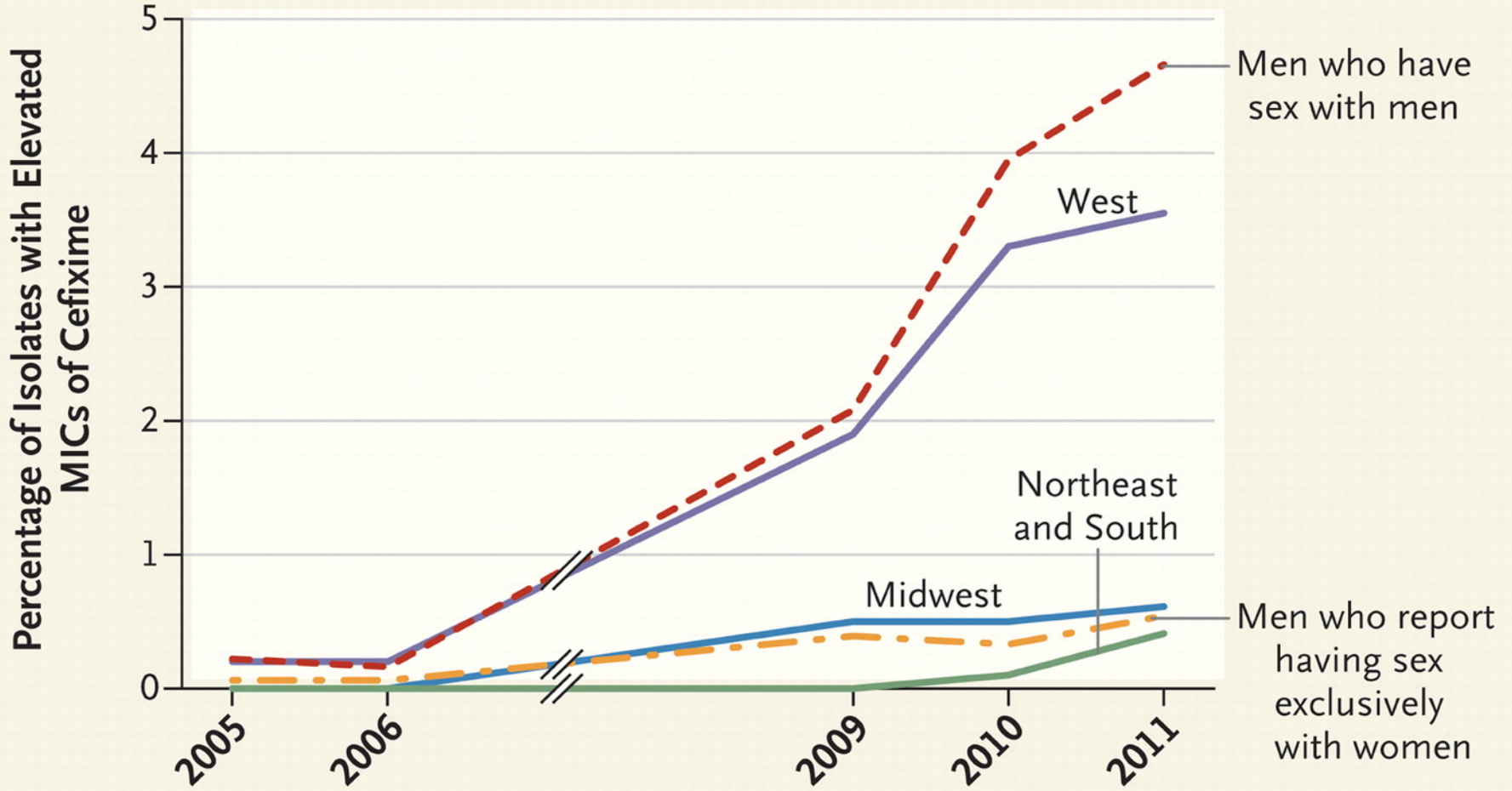
and two with 16  $\mu\text{g}/\text{mL}$ ) were diagnosed by Gram stain and confirmed by NAAT at San Diego County's main municipal STD clinic. The five *N. gonorrhoeae* isolates with high MICs (9.1%) obtained from the five patients were among 55 *N. gonorrhoeae* isolates obtained from men with symptomatic urethritis tested during the 3-month period. All five patients were men who have sex with men (MSM). Four were human immunodeficiency virus (HIV)-negative by self-report and one had an HIV-negative test result.

Three of the five patients were non-Hispanic white men, one was non-Hispanic black, and one was Hispanic. Four were San Diego County residents, and one was a resident of a Midwestern state. Median age was 29 years (range: 19–31 years). None had traveled internationally within 3 months of receiving their con-

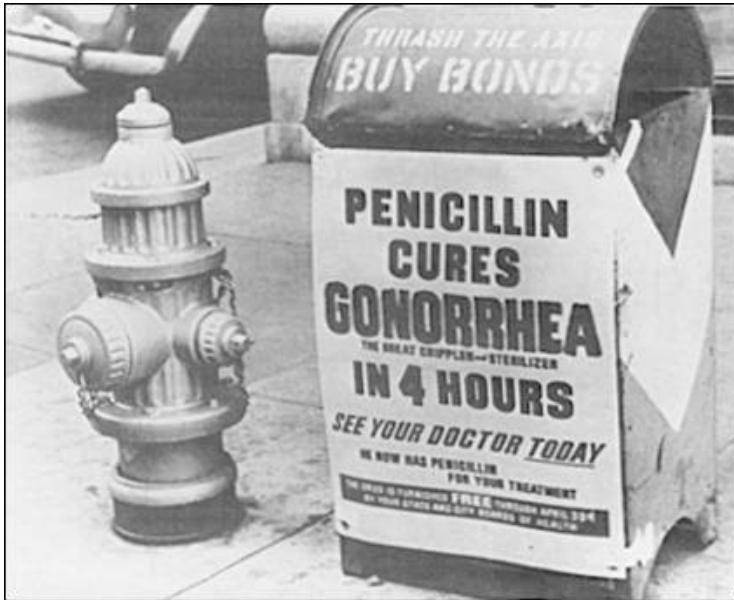
# Decreased Cephalosporin Susceptibility

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# *N. gonorrhoeae* – evolution into a ‘superbug’



**TIME** Partners with **ON.**

## Scientists Discover Drug-Resistant Gonorrhea 'Superbug'

By [Laura Blue](#) Monday, July 11, 2011

A new, untreatable strain of the sexually transmitted disease gonorrhea has been discovered in Japan, according to an international team of infectious disease experts. The strain, named H041, is resistant to all known forms of antibiotics.



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# CDC sets threat levels for drug-resistant 'superbugs'

By Miriam Falco, CNN

updated 5:48 PM EDT, Tue September 17, 2013

[www.cdc.gov/drugresistance/threat-report-2013/](http://www.cdc.gov/drugresistance/threat-report-2013/)

Microorganisms with the threat level of URGENT:

1. *C. difficile*
2. Carbapenem-resistant Enterobacteriaceae
3. Drug-resistant *N. gonorrhoeae*

Neisseria gonorrhoeae

## Drug-resistant bacteria

HIDE CAPTION

### STORY HIGHLIGHTS

- More than 2 million people get antibiotic-resistant infections

**(CNN)** -- Health officials have been warning us about antibiotic overuse and drug-resistant "superbugs" for a long time. But today the Centers for Disease Control and Prevention is [sounding the](#)

**Neisseria gonorrhoeae** -- the drug-resistant form of this bacteria causes gonorrhea, the second most commonly reported infection in the United States. Gonorrhea can cause a variety of illnesses in men and women, including infertility. The CDC estimates there are 820,000 infections each year. In nearly a third of the cases, treatment of the sexually-transmitted disease, is hampered by growing antibiotic resistance.

[Sexually-transmitted superbug could be major crisis](#)

Frieden said if the current trends continue, "the medicine cabinet may be empty for patients who need them in the coming months and years."

To avoid what Frieden calls a "post-antibiotic" era, where none of

rooms if they have washed their hands.

Patients should also only take antibiotics when they are really necessary. Changing the way antibiotics are used is perhaps "the single most important action needed to greatly slow the development and spread of antibiotic-resistant infections," Frieden said.

Patients need to demand fewer antibiotics and doctors have to resist patients requests for them when they know they won't work. Also, lowering the use of antibiotics in animals to only when it's



# How does gonococcal resistance develop?

- Transformation plays the key role
  - *N. gonorrhoeae* highly competent for transformation throughout life cycle by its own DNA or via closely related bacteria such as other *Neisseria* commensals and *N. meningitidis*
    - **Pharyngeal gonorrhea** may act as a reservoir where asymptomatic co-colonization with other *Neisseria* species of this obligate human pathogen can occur
      - Example: Asp345A insertion in PBP2 resulting in decreased penicillin binding affinity, likely originates from commensal *Neisseria* species
  - Cross-species conjugal plasmid transfer also possible
    - *TetM* and B-lactamase-encoding plasmids relatively efficiently transferred intercellularly between *N. gonorrhoeae* strains, as well as *N. meningitidis*, *H. influenzae*, and *E. coli*

# First Description of High-Level Cephalosporin Resistance

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3538–3545  
0066-4804/11/\$12.00 doi:10.1128/AAC.00325-11  
Copyright © 2011, American Society for Microbiology. All Rights Reserved.

Vol. 55, No. 7

## Is *Neisseria gonorrhoeae* Initiating a Future Era of Untreatable Gonorrhea?: Detailed Characterization of the First Strain with High-Level Resistance to Ceftriaxone<sup>∇†</sup>

Makoto Ohnishi,<sup>1</sup> Daniel Golparian,<sup>2</sup> Ken Shimuta,<sup>1</sup> Takeshi Saika,<sup>3</sup> Shinji Hoshina,<sup>4</sup>  
Kazuhiro Iwasaku,<sup>5</sup> Shu-ichi Nakayama,<sup>1</sup> Jo Kitawaki,<sup>5</sup> and Magnus Unemo<sup>2\*</sup>

National Institute of Infectious Diseases, Tokyo, Japan<sup>1</sup>; Swedish Reference Laboratory for Pathogenic *Neisseria*, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden<sup>2</sup>; Mitsubishi Chemical Medience Corporation, Tokyo, Japan<sup>3</sup>; Hoshina Clinic, Kyoto, Japan<sup>4</sup>; and the Kyoto Prefectural University of Medicine, Kyoto, Japan<sup>5</sup>

- Isolate came from pharynx of female CSW in Kyoto
- Cftx MIC 2 mcg/ml
  - (R) to cefixime (MIC 8 mcg/ml),  $\beta$ -lactams, fluoroquinolones, macrolides, tetracycline, TMP-SMX, chloramphenicol, nitrofurantoin
  - (S) to spectinomycin, rifampin, possibly aminoglycosides and tigecycline, possibly carbapenems
- Unique *penA* mosaic allele similar to that found in *N. meningitidis* and *N. flavescens* – encodes variant of PBP2

*mtrB*, *penB*, *ponA1* mutations also present



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# Subsequent Cephalosporin Treatment Failures Mostly Described in Pharynx

- Unemo et al. Ceftriaxone treatment failure of **pharyngeal gonorrhoea** verified by international recommendations, Sweden, July 2010. Euro Surv, 2011
  - Cftx MIC 0.125-0.25 mcg/ml
  - Mosaic *penA*, *mtrB* and *penB* alterations identified
  - 250 mg cftx: median times of free cftx in serum above MIC only 24 and 15 hours for these MICs; pharyngeal accessible cftx is of shorter duration
- Unemo et al. Treatment failure of **pharyngeal gonorrhoea** with internationally recommended first-line ceftriaxone verified in Slovenia, September 2011. Euro Surv, 2012
  - Cftx MIC 0.125 mcg/ml
  - Mosaic *penA*, *mtrB* and *penB* alterations identified
- Unemo et al. High-level cefixime- and ceftriaxone-resistant *Neisseria gonorrhoeae* in France: novel pen A mosaic allele in a successful international clone causes treatment failure. Antimicrob Agents Chemo, 2012
  - **Urethral isolate in MSM, unknown if orally acquired**
  - Cftx MIC 1-2 mcg/ml, cefixime MIC 4 mcg/ml
  - Mosaic *penA* alteration identified

# The NEW ENGLAND JOURNAL of MEDICINE

June 23, 2016

## Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea

Letter to the Editor:

- GC treatment failure at pharyngeal site in heterosexual man in United Kingdom (Ceftriaxone 500mg IM x 1 plus azithromycin 1gm PO x 1)
- Individual had traveled to Japan and had female partner from Japan
- Isolates from d 15, 79 and 98 identical with 4 major mutations in each.
- Ultimately successfully treated with Ceftriaxone 1gm + 2g

Azithromycin PO x 1



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# Cluster of Hawaii Gonorrhea Isolates with Diminished Susceptibility to Multiple Antibiotics, Including Very High Azithromycin MIC and Alert-Value Ceftriaxone MIC

## April-May, 2016

Minimum Inhibitory Concentrations, $\mu\text{g/mL}$			
	azithro*	ceftriax*	cefix*
1	> 256	0.125	0.094
2	> 256	0.125	0.094
3	> 256	0.190	0.190
4	> 256	0.125	0.125
5	> 256	0.094	0.094
6	> 256	0.125	0.125
7	> 256	0.125	0.094

\*Hawaii State Laboratories Division

\*\*Seattle GISP Reference Lab

# Gonorrhea Treatment

## Uncomplicated Genital, Rectal, or Pharyngeal Infections

Ceftriaxone 250 mg IM  
in a single dose

**PLUS\***

Azithromycin  
1 g orally

**\* Regardless of CT test result**

*Doxycycline demoted from recommended to alternative,  
because of tetracycline resistance in U.S. GISP isolates*



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**CDC 2015 STD Treatment Guidelines**  
[www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment)

# Gonorrhea Treatment Alternatives Just for *Anogenital* Infections

## *IF CEFTRIAZONE UNAVAILABLE*

❖ Cefixime 400 mg orally once

**PLUS**

❖ Dual treatment with azithromycin 1 g

## *IN CASE OF ALLERGY TO AZITHROMYCIN:*

❖ Cefixime 400 mg orally once

**PLUS**

❖ Dual treatment with doxycycline 100 mg BID x 7 days

***Azithromycin 2 g orally removed as an alternative regimen***

Prior TOC recommendation: Test of cure in 1 week for anyone treated w/ alternative regimens

**New TOC recommendations: Limit TOC only to pharyngeal GC not treated with recommended regimen, perform TOC at 14 days with either NAAT\* or culture**

\*Not FDA-approved for extragenital testing, but has been validated

# Back-Pocket GC Treatment Regimens: Alternatives for cephalosporin-allergic patients

- Trial conducted in Baltimore, Birmingham, Pittsburgh, San Francisco
- 401 men and women 15 - 60 yrs
- 202 received gent 240 mg IM + azithro 2 g PO: 100% effective
- 199 received gemiflox 320 mg PO + azithro 2 g PO: 99.5% effective

Probably fine for urogenital gonorrhea  
Trial not powered for extragenital gonorrhea,  
though it worked in the few cases enrolled

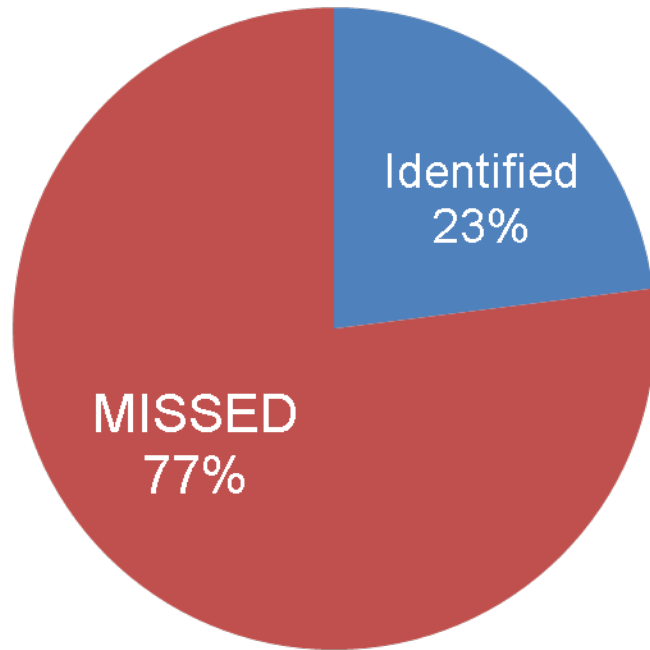
Efficacy limited by tolerance  
8% vomited in the gemiflox + azithro group and  
needed re-treatment with standard cftx + azithro



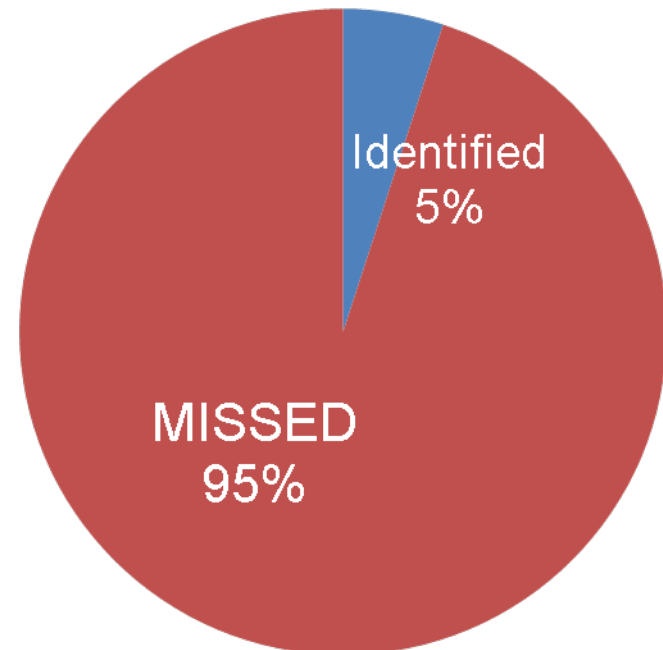
# Q: Which of the following is true...

1. Oral and rectal gonorrhoea are almost always symptomatic
2. Tests of choice for extra-genital gonococcal and chlamydial testing are culture-based
3. In asymptomatic MSM, extra-genital testing uncovers more GC and CT infection than genital testing alone

# Proportion of CT and GC infections **MISSED** among 3398 asymptomatic MSM if screening only urine/urethral sites, San Francisco, 2008-2009



**Chlamydia**



**Gonorrhea**

# Who needs a test of cure?

- **Patients with pharyngeal GC treated with an alternative regimen, 14 days after tx, using either culture or NAAT**
- **Cases of suspected treatment failure (with culture and simultaneous NAAT)**



# Who needs test of reinfection?

- *Women with CT, GC or trich should be rescreened at 3 months after treatment.*
- *Men with CT or GC should be rescreened at 3 months after treatment.*
- *Patients diagnosed with syphilis should undergo follow up serologic serology per current recommendations.*
- *HIV testing should also be considered in all patients with a prior STD history*



# Suspected GC Treatment Failure\*

## After Recommended Dual Therapy

### What do I do?

**CULTURE:** If GC culture not available, call your local health department STD controller

**RETREATMENT:** Gemifloxacin\* 320 mg PO + Azithromycin 2 g PO OR Gentamicin\* 240 mg IM + Azithromycin\* 2 g PO

**REPORT:** Report failure to your local or state health department within 24 hours; consult an ID specialist or call CDC (404-639-8659) for advice

**TREAT PARTNERS:** ID sex partners from preceding 60 days and treat with same regimen that patient receives

**TEST OF CURE (TOC):** Patient returns 7-14 days after retreatment for TOC culture and NAAT

**If reinfection suspected instead of tx failure, OK to repeat tx with ceftriaxone 250 mg IM + azithromycin 1 g PO**

\*If pregnant, check with ID specialist AND consider pregnancy category classifications (gemifloxacin = pregnancy category C, gentamicin = pregnancy category D, azithromycin = pregnancy category B)

# Other Ways to Stem Tide of MDR GC (1)

- Rapid POC testing – same day diagnosis
  - Almost prime time
  - May include POC testing for resistance too
  - Will eliminate gap time to treatment for asymptomatic patients (therefore less carriage and transmission)
  - May provide information for more targeted antimicrobial treatment



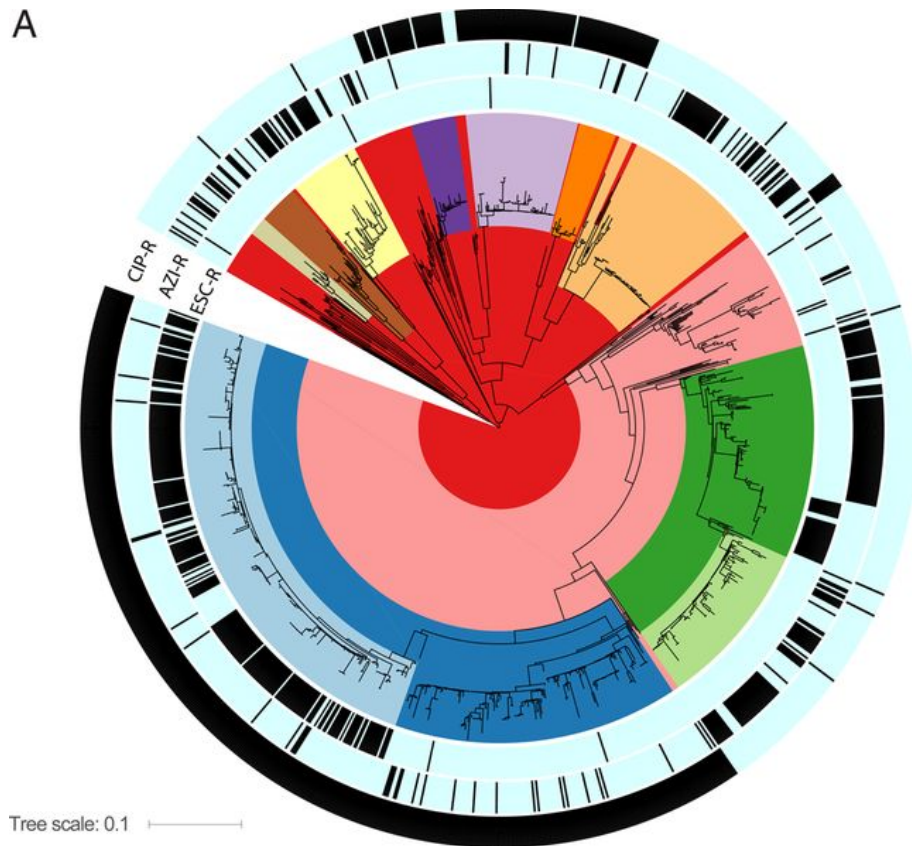
## Impact of rapid susceptibility testing on emergence and spread of antibiotic resistance in gonorrhea

Ashleigh Tuite, Harvard T.H. Chan School of Public Health  
For the PPML STD Work Group

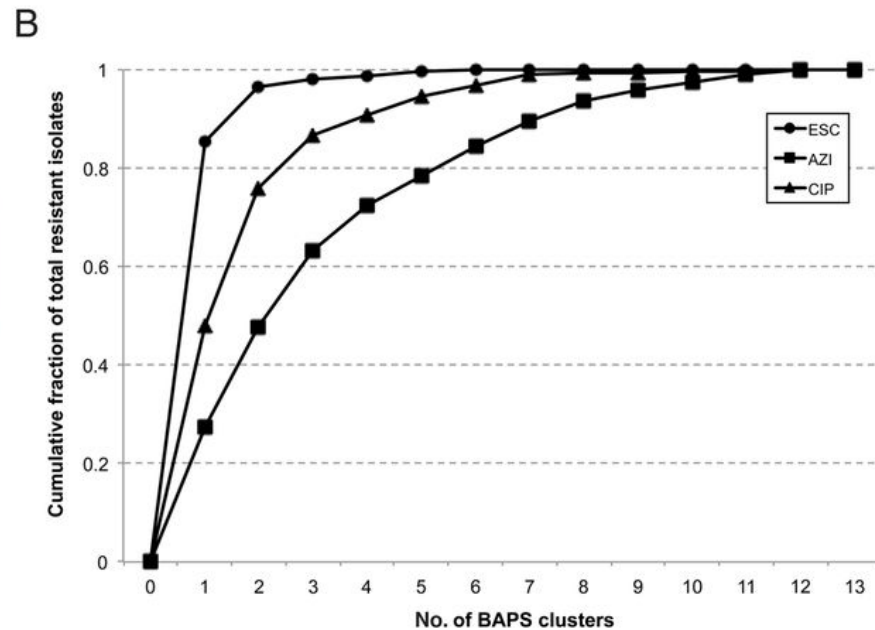
**NEEMA All Grantee Meeting, Atlanta**

May 1<sup>st</sup>-2<sup>nd</sup>, 2017

# Modeling Resistance Emergence and Transmission



Grad et al. J Infect Dis. 2016;214:1579-1587



Antimicrobial class	Example	Resistance acquisition	Fitness cost
(A) Fluoroquinolones	Ciprofloxacin	Likely	None
(B) Macrolides	Azithromycin	Moderately likely	High
(C) Extended spectrum cephalosporins	Ceftriaxone	Less likely	Intermediate



# Model Assumptions

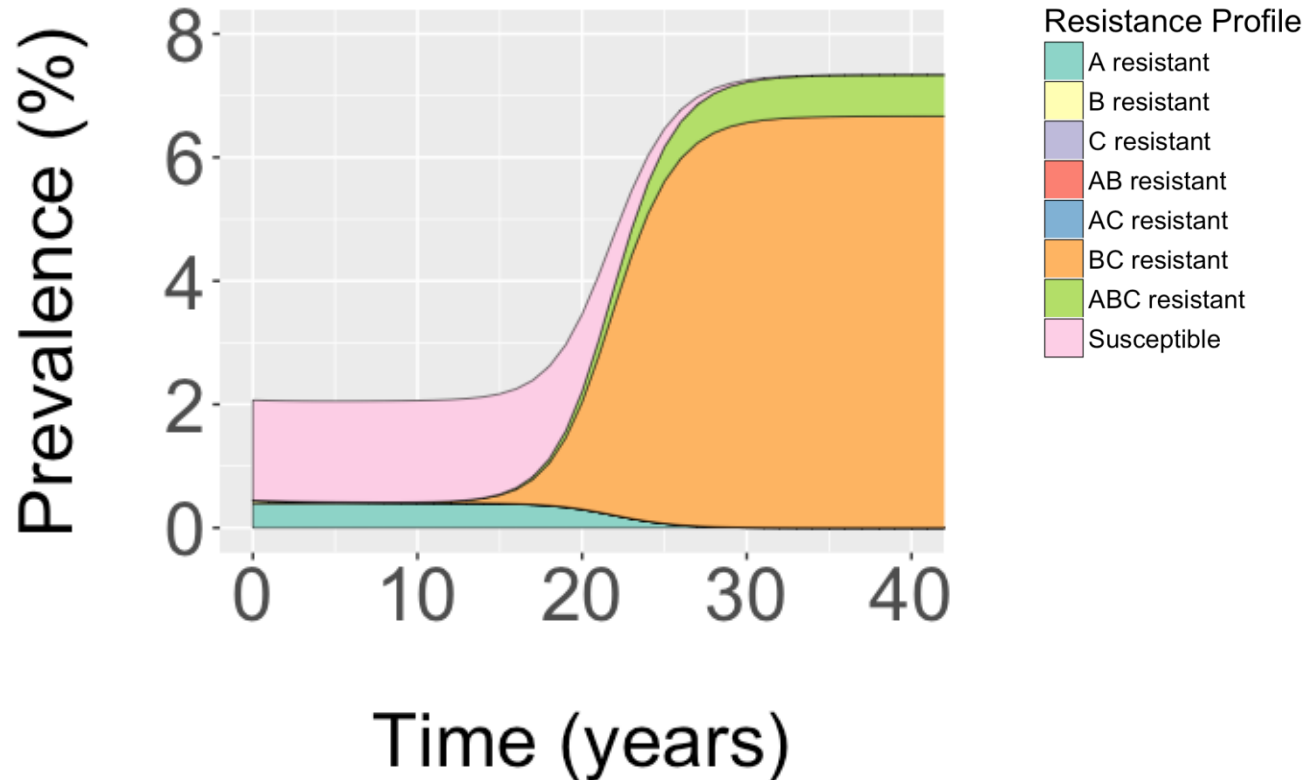
In the absence of a point-of-care test, treat identified cases according to guidelines (combo therapy with azithromycin + ceftriaxone (B+C))

## Possible outcomes:

1. Receive effective treatment and return to susceptible state
2. Receive inappropriate treatment (due to pre-existing resistance) and not cured
  - i. If symptomatic infection, probability of re-treatment with effective drug, with some delay
  - ii. If asymptomatic, remain infected until natural clearance
3. Receive appropriate treatment but develop *de novo* resistance
  - Move to new infected state and go through same set of possible transitions as in (2)

# Timeline for Resistance Emergence with Combination Therapy and No POC Test

Treat entire population with BC



# Introduction of POC Tests to Guide Treatment

Compare empirical treatment to POC test determining susceptibility to:

A. Single antibiotic (A – fluoroquinolone)

- Treat A susceptible infections with antibiotic A
- Treat A resistant infections with antibiotics BC

B. Three antibiotics

- If susceptible to single antibiotic, treat with that
- If susceptible to multiple antibiotics, treat with antibiotic with highest fitness cost associated with resistance
- If resistant to all three antibiotics, treated with alternate agent or higher antibiotic doses

Possible outcomes: cure, treatment failure, *de novo* acquisition of resistance mutation

# Projected Impact of POC Tests

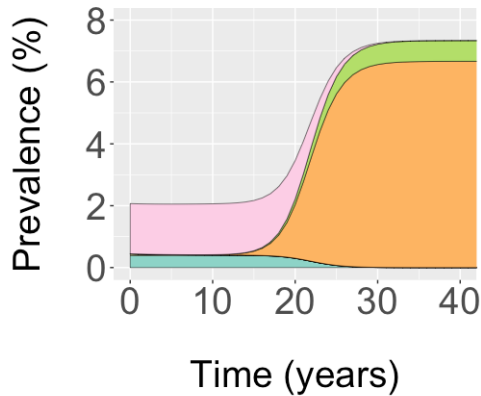
No test

10% POC

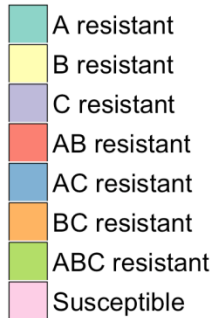
25% POC

50% POC

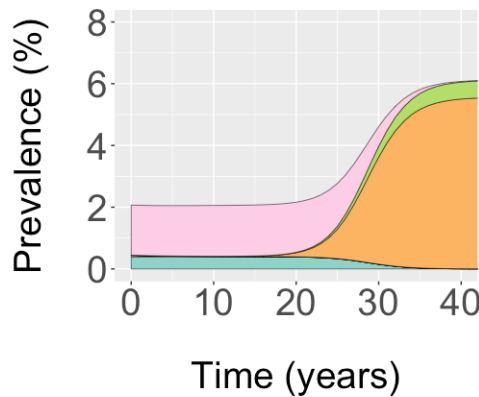
**A**



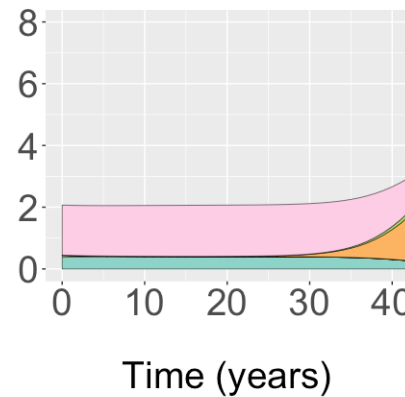
Resistance Profile



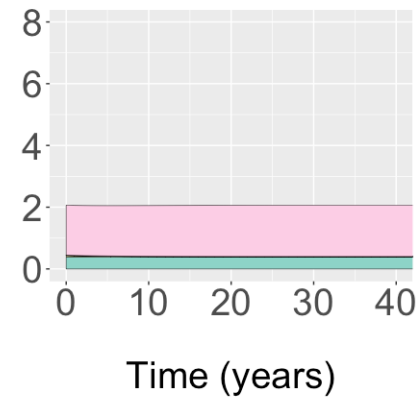
**E**



**F**

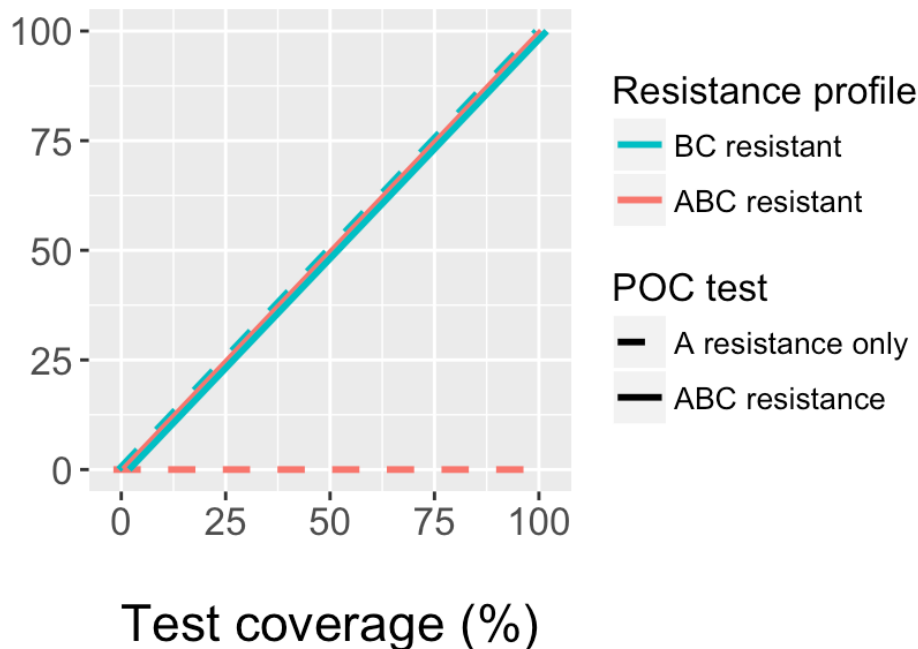


**G**



# Single Antibiotic Test Does Not Improve Diagnosis of Triple-Resistant Infections

Identified infections treated with effective antibiotic (%)



**“The failure of a single POC test to delay emergence of triply resistant isolates arises in part because all tested cases are treated appropriately except for triply-resistant infections, thereby reducing the burden of all other isolates and clearing the way for triply-resistant isolates.”**

# Other Ways to Stem Tide of MDR GC (2)

Articles

## Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study



Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black

### Summary

**Background** Gonorrhoea is a major global public health problem that is exacerbated by drug resistance. Effective vaccine development has been unsuccessful, but surveillance data suggest that outer membrane vesicle meningococcal group B vaccines affect the incidence of gonorrhoea. We assessed vaccine effectiveness of the outer membrane vesicle meningococcal B vaccine (MeNZB) against gonorrhoea in young adults aged 15–30 years in New Zealand.

**Methods** We did a retrospective case-control study of patients at sexual health clinics aged 15–30 years who were born between Jan 1, 1984, and Dec 31, 1998, eligible to receive MeNZB, and diagnosed with gonorrhoea or chlamydia, or both. Demographic data, sexual health clinic data, and National Immunisation Register data were linked via patients' unique personal identifier. For primary analysis, cases were confirmed by laboratory isolation or detection of *Neisseria gonorrhoeae* only from a clinical specimen, and controls were individuals with a positive chlamydia test only. We estimated odds ratios (ORs) comparing disease outcomes in vaccinated versus unvaccinated participants via multivariable logistic regression. Vaccine effectiveness was calculated as  $100 \times (1 - OR)$ .

**Findings** 11 of 24 clinics nationally provided records. There were 14730 cases and controls for analyses: 1241 incidences of gonorrhoea, 12487 incidences of chlamydia, and 1002 incidences of co-infection. Vaccinated individuals were significantly less likely to be cases than controls [511 [41%] vs 6424 [51%]; adjusted OR 0.69 [95% CI 0.61–0.79];  $p < 0.0001$ ]. Estimate vaccine effectiveness of MeNZB against gonorrhoea after adjustment for ethnicity, deprivation, geographical area, and sex was 31% (95% CI 21–39).

**Interpretation** Exposure to MeNZB was associated with reduced rates of gonorrhoea diagnosis, the first time a vaccine has shown any protection against gonorrhoea. These results provide a proof of principle that can inform prospective vaccine development not only for gonorrhoea but also for meningococcal vaccines.

**Funding** GSK Vaccines, Auckland UniServices.

### Introduction

Gonorrhoea is associated with significant morbidity, including pelvic inflammatory disease, infertility, and chronic pain, and is a major global public health concern, with an estimated 78 million incident new cases each

extent, Norway,<sup>2,3</sup> suggesting that OMV vaccines could affect the incidence of gonorrhoea.

OMV vaccines are generally only thought to be useful against epidemics dominated by strains belonging to the

Published Online

July 30, 2017  
[http://dx.doi.org/10.1016/S0140-6736\(17\)31449-6](http://dx.doi.org/10.1016/S0140-6736(17)31449-6)

See Online Comment  
[http://dx.doi.org/10.1016/S0140-6736\(17\)31605-7](http://dx.doi.org/10.1016/S0140-6736(17)31605-7)

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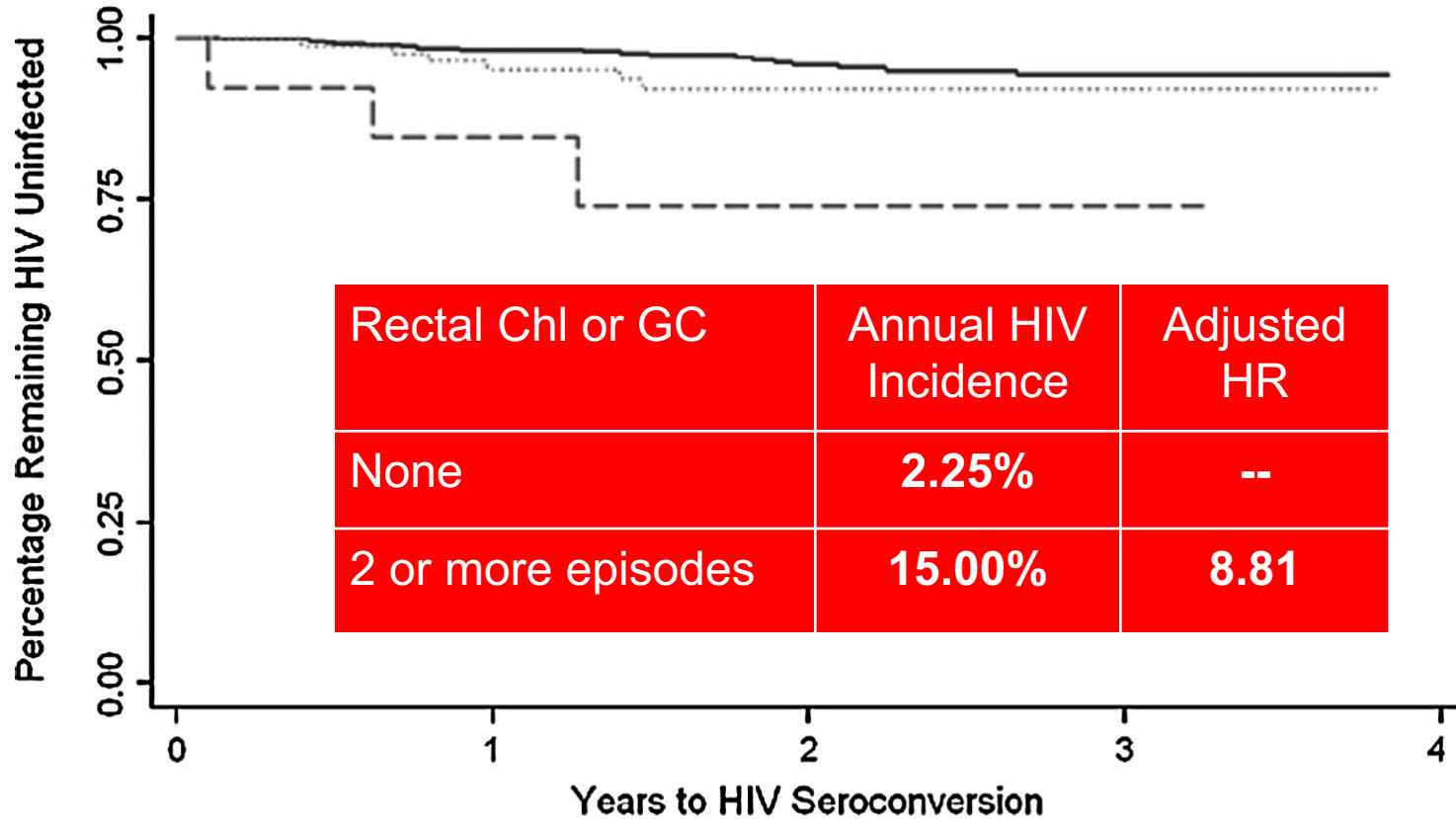
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Petousis-Harris et al.  
Lancet, 2017

# MSM in SF City Clinic Diagnosed with Rectal Chlamydia or Gonorrhea 2003-05

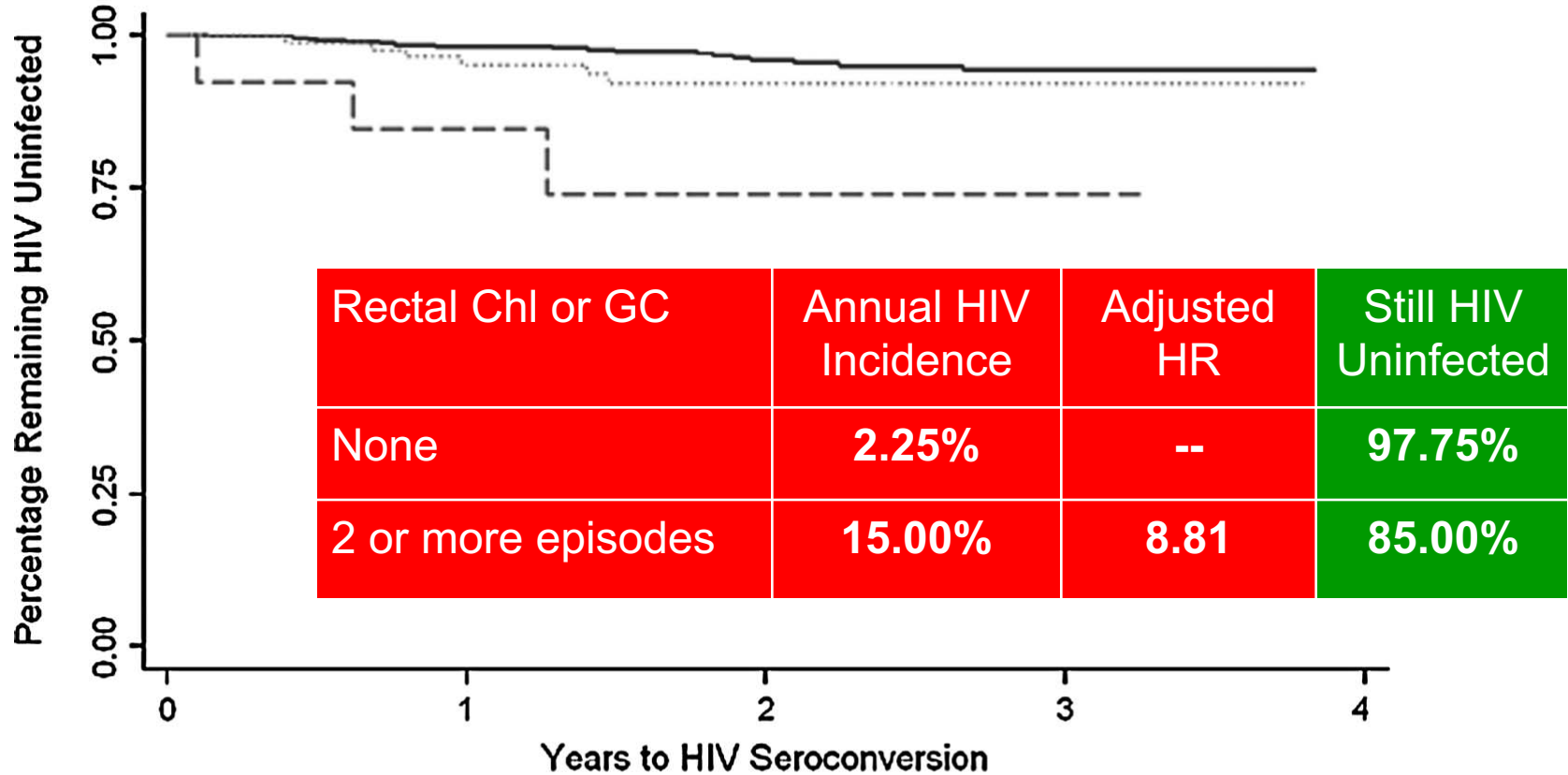
HIV Seroconversion by Number of Prior Rectal Infections



— No Prior Rectal Infections      ..... One Prior Rectal Infection  
 - - - Two Prior Rectal Infections

# MSM in SF City Clinic Diagnosed with Rectal Chlamydia or Gonorrhea 2003-05

HIV Seroconversion by Number of Prior Rectal Infections



————— No Prior Rectal Infections      ..... One Prior Rectal Infection  
 - - - - - Two Prior Rectal Infections



# HIV Treatment as Prevention

*Antiretroviral treatment should be offered to all HIV-infected persons not only to provide benefit to individual health but also to reduce transmission to sex partners.*

*HIV pre-exposure prophylaxis should be available to HIV-negative men and women who are sexually active or injecting illicit drugs who are at substantial risk of HIV infection. All clients requesting PrEP should be counseled that high levels of adherence are needed for the best efficacy.*

**NEW REFERENCE: CDC, USPHS. Pre-exposure prophylaxis for the prevention of HIV infection in the U.S. – 2014. A Clinical Practice Guideline.**

# Take Home Points

- Gonococcal complications are being seen more frequently because there is more gonorrhea
- MDR GC is already here, and MDR including cephalosporin-resistant GC is coming
- We can stem the tide using appropriate treatment, treating quickly (and getting to partners quickly)
  - Continued partnership between public health and clinical settings



# A Quote From Dr. Stanley Falkow: Microbes May Be Smarter Than You Think

- They understand mathematics. They have mastered exponential equations and understand biostatistics.
- They understand physics. They know that a small amount of energy applied to the right point can 'move' a large object.
- They understand military tactics. They strike quickly with overwhelming numbers, cut the lines of communication and wear camouflage.
- They are expert biologists. They have studied biology longer than any other living thing, understood Darwin before he did, and also invented neo-Darwinism. They have mastered genetics, cell biology and immunology.
- **They always have the last laugh. They are generally the first living things we encounter after birth and, when we die, they are the last living cells on our bodies. Then, they devour us.**

Life is a sexually transmitted disease and the mortality rate is one hundred percent.

- R. D. Laing