

**“Super Gonorrhea”, Emerging Antimicrobial Resistance in *Neisseria Gonorrhoeae* and Implications for Management**

Satellite Conference and Live Webcast  
 Tuesday, December 4, 2018  
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Consultant: Hologic

Speakers Bureau: None

***Neisseria Gonorrhoeae***

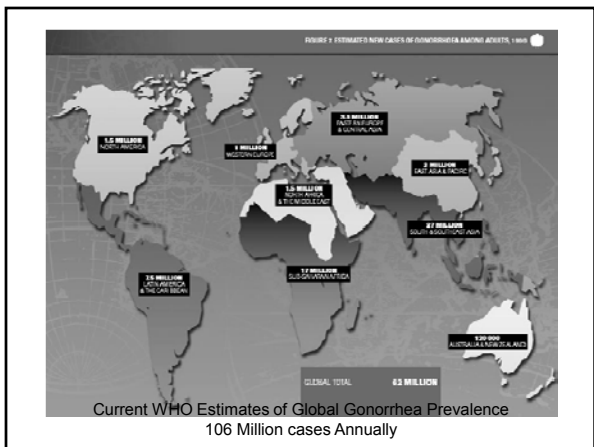
**Presentation Overview**

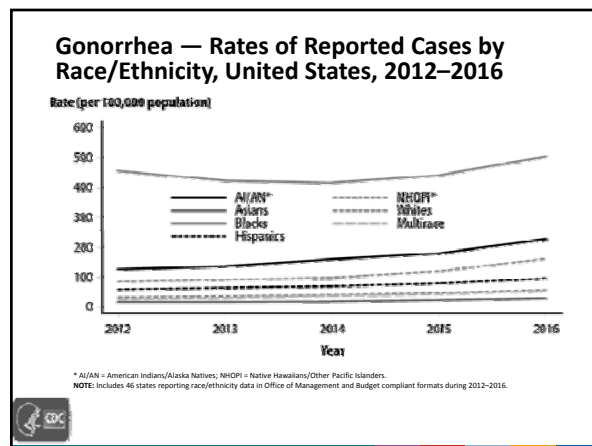
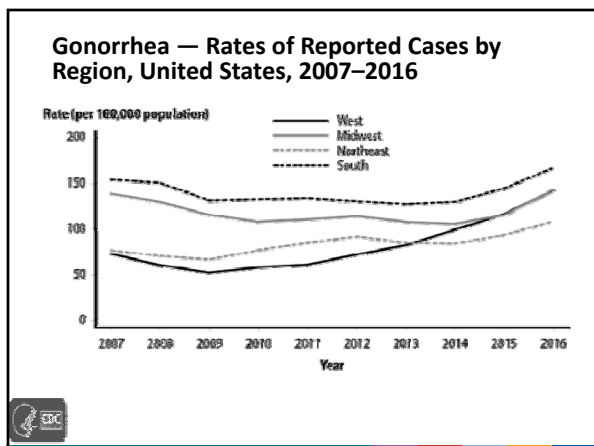
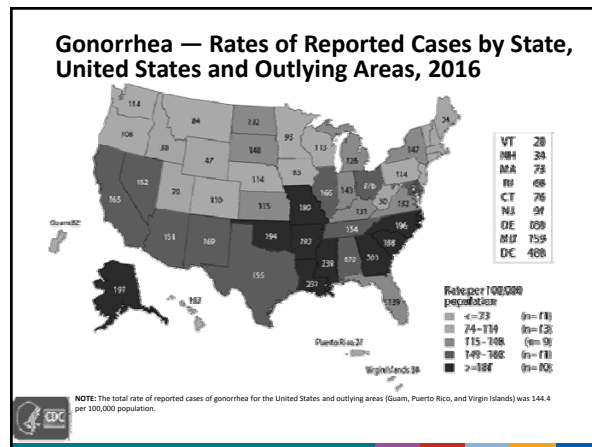
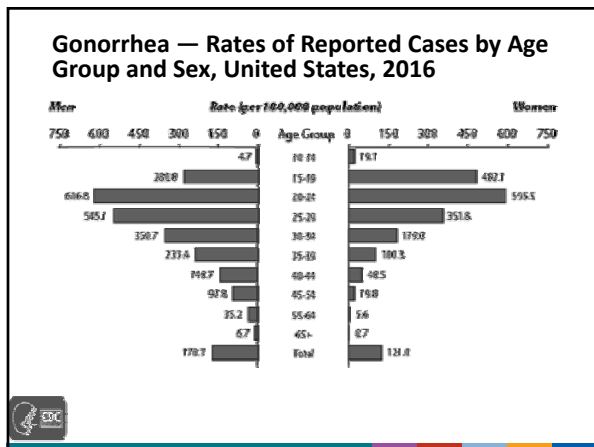
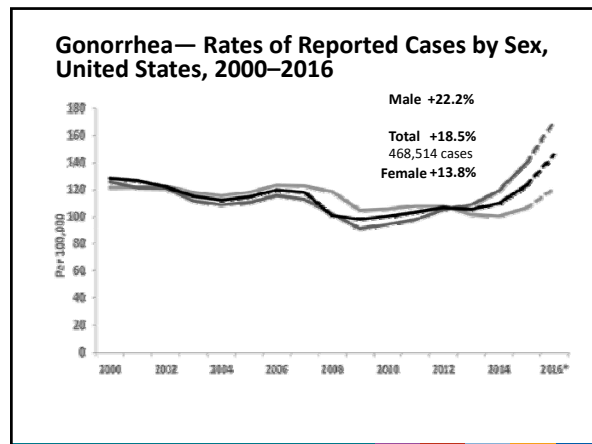
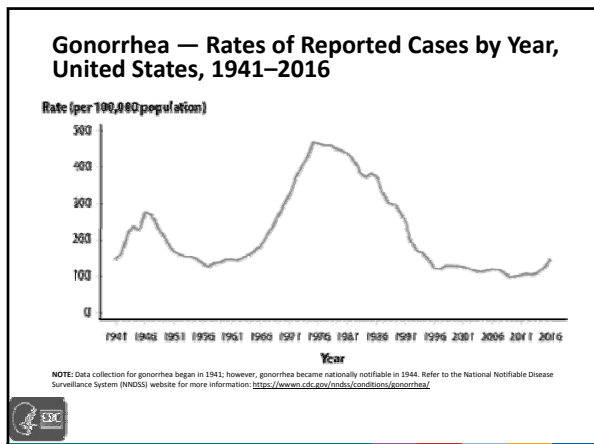
Epidemiology

Diagnosis

Treatment/Antimicrobial Resistance

Control Measures

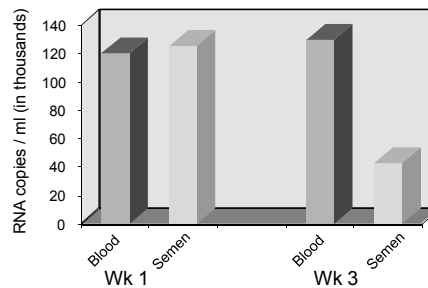




### Features of US Gonorrhea Epidemiology

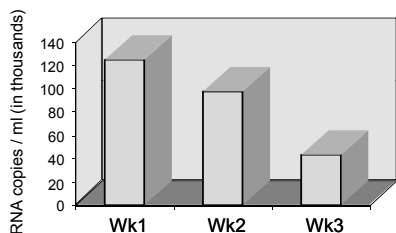
- Incidence in non-whites 10 times greater than in whites
- Urban residence
- Lower socioeconomic status
- Early coital debut
- Single People
- Past history of gonorrhea
- Increasing focus on extra-genital infections and antimicrobial resistance

### HIV-1 RNA in Blood and Semen of Urethritis Patients (median values)



### Effect of STD Treatment on HIV-1 RNA in Semen of Urethritis Patients

(Cohen et al. Lancet 349: 1868-1873, 1997)



### Neisseria Gonorrhoeae Presentation Overview

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### Gonorrhea Detection

Gram's Stain

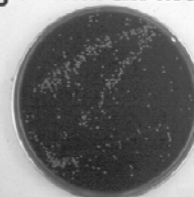
Culture

Antigen Detection

Nucleic Acid Detection

Nucleic Acid Amplification

Cervical Specimen  
Thayer-Martin Medium



Positive Colonial Morphology

### Changing Paradigms For Urogenital Specimen Collection

**Pre-NAAT's: Specimen Quality Critical**  
 - Endocervical Or Urethral Swabs  
 - Swab Order Impacts Test Results

**: Culture > Non-Amplified Nucleic Acid Detection > Antigen Detection**

**NAAT's: More Forgiving Specimen Collection**  
 - Vaginal Swab ≥ Endocervical Swab  
 ≥ Initial Void Urine

### Impact of NAATs Testing for STDs – Alabama\*

Cumulative Reported Infections as of:

	Oct 1, 2005 (Pre-NAATs)	Sept 30, 2006 (NAATs Testing)	
<i>N. gonorrhoeae</i>	6,698	7,110	(6% ↑)
<i>C. trachomatis</i>	11,638	15,314	(32% ↑)

\*MMWR, Oct 6, 2006. pp:571-572.

### Performance of NAATs for Diagnosis of Pharyngeal *N. Gonorrhoeae* and Infections

Pharyngeal Gonococcal Infection By Site	
Site	No (%) Individuals
Genital and Oral	23 (28%)
Genital Only	28 (34.1%)
Oral Only	31 (37.8%)
<b>Total Genital or Oral</b>	<b>82 (100%)</b>

### *Neisseria Gonorrhoeae* Presentation Overview

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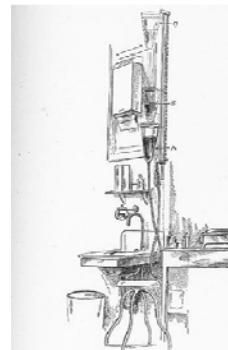
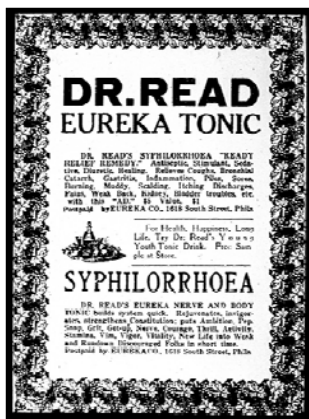
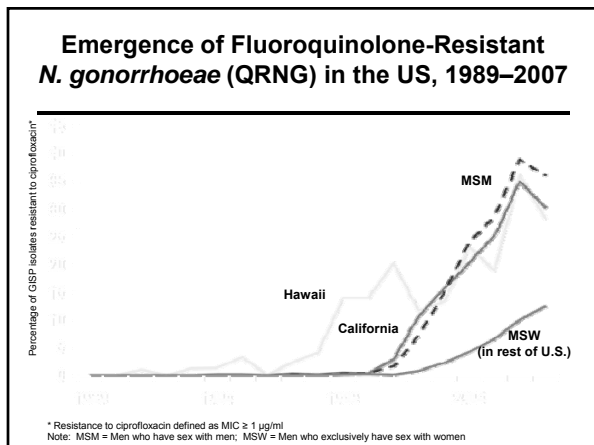
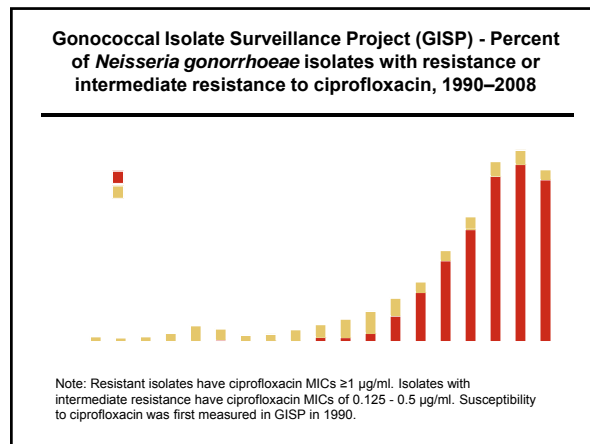
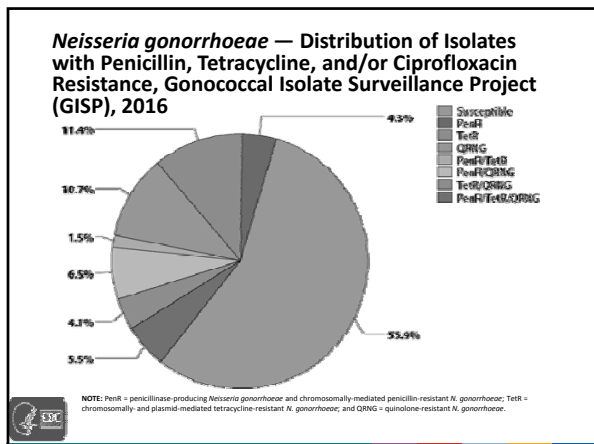


Fig. 37.—Archard's instrument used. Patient stands in front of the table, which is placed lower than the average knee height. A. Position of jar for anterior irrigation; B, position of jar for posterior irrigation; C, dangerous pressure for gonococcal infection.





### 2006 CDC STD TREATMENT GUIDELINES Uncomplicated Gonorrhea

Ceftriaxone 125 mg IM  
 or  
 Cefixime 400 mg PO  
 or  
~~Ciprofloxacin 500 mg PO~~  
 or  
 Ofloxacin 400 mg PO  
 or  
 Levofloxacin 250 mg PO

Plus, IF CHLAMYDIAL INFECTION IS NOT RULED OUT  
 Azithromycin 1.0 g Single Dose Or  
 Doxycycline 100 BID x 7d

### 2010 CDC STD TREATMENT GUIDELINES Uncomplicated Gonorrhea

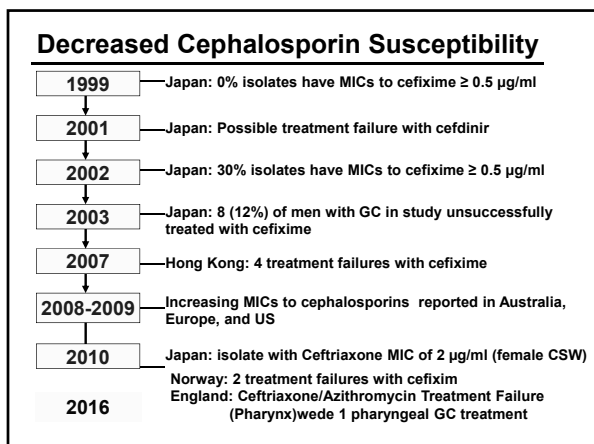
Ceftriaxone 250 mg IM  
 or  
 Cefixime 400 mg PO

PLUS

Azithromycin 1.0 g Single Dose or  
 Doxycycline 100 BID x 7d

**"Those who cannot remember the past are condemned to repeat it."**

George Santayana



PRELIMINARY COMMUNICATION

JAMA 2013;309(2);163-170

### *Neisseria gonorrhoeae* Treatment Failure and Susceptibility to Cefixime in Toronto, Canada

## Cephalosporin-Resistant Gonorrhea in North America

### *N. Gonorrhoeae* Treatment Failures to Cefixime, Toronto, Canada

**Rx failure overall – 6.8% (95% CI – 3.1-12.5%)**

If cefixime MIC  $\geq$  0.12 – 25% (95% CI 10.7-44.9%)

If cefixime MIC  $<$  0.12 – 1.9% (95% CI 0.23-6.7%)

RR 13.13 (95% CI 2.9-59.72)

**Treatment failures:**

- 4 of 76 urethral (5.3%)
- 2 of 7 pharyngeal (28.6%)
- 3 of 39 rectal (7.7%)

Neisseria gonorrhoeae Treatment Failure and Susceptibility to Cefixime in Toronto, Canada, JAMA, 2013;309(2):163-170.

### 2015 CDC STD TREATMENT GUIDELINES

#### Uncomplicated Gonorrhea

**Ceftriaxone 250 mg IM**

**PLUS**

**Azithromycin 1.0 g Single Dose ~~or~~**  
**Doxycycline 100 BiD x 7d**  
**Even if chlamydia negative**

### Alternative GC Treatment

#### 2015 CDC STD Treatment Guidelines

<p><b>Cefixime 400mg po x 1</b> <b>Plus</b> <b>Azithromycin 1gm po x 1</b></p> <p><b>TOC in 1 week 14d</b></p>	<p><del>If cephalosporin allergy:</del></p> <p><del><b>Azithromycin 2gm po x 1</b></del></p> <p><del><b>TOC in 1 week 14d</b></del></p>
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### Gonorrhea Treatment- What's Next

Salvage Therapy:

- Gentamicin 240 IM/ Azithromycin 2.0g PO (IM Administration/Toxicity)
- Gemifloxacin 340 mg/Azithromycin 2.0g PO (GI Toxicity)

On The Horizon:

- ~~Solithromycin (??)~~
- ~~Delafloxacin~~
- AZ D0914 (Zoliflodacin)
- BTZ116576 (Gepotidacin)
- Others

**ETX0914 Urogenital Microbiological Per Protocol Cure Rates**

Therapy	Confirmed Infections	Cures	Micro. Cure Rate %	Micro. Cure % 95% CI
ETX0914 2g	49	48	<b>97.96</b>	89.15, 99.95
ETX0914 3g	47	47	<b>100.00</b>	92.45, 100.00
Ceftriaxone 500 mg	21	21	<b>100.00</b>	83.89, 100.00

S Taylor et al. IDSA 2016

**ETX0914 Pharyngeal Microbiological Per Protocol Cure Rates**

Therapy	Confirmed Infections	Cures	Micro. Cure Rate %	Micro. Cure % 95% CI
ETX0914 2g	6	4	<b>66.67</b>	22.28, 95.67
ETX0914 3g	9	7	<b>77.78</b>	39.99, 97.19
Ceftriaxone 500 mg	4	4	<b>100.00</b>	39.76, 100.00

S Taylor et al. IDSA 2016

## A New Model for STD Treatment Trials

**Collaborative, multinational trial of Zoliflodacin, a candidate antibiotic for treatment of uncomplicated gonorrhoea.**

Led by GARDP (Global Antibiotic Research and Development Partnership)

Collaborators: Entasis Pharmaceuticals, NIAID, WHO

Study sites in : U.S. Thailand, South Africa, E.U.

Goal: Approval of a non-beta-lactam antibiotic effective vs. resistant gonorrhoea

## Gonorrhoea Treatment- What's Next (Hook's Guess)

Resistance will continue to progress

Reconsideration of the role of TOC

Pressing need to better understand pharyngeal and rectal GC epidemiology

Timeline to new antibiotics: three years minimum

Dual therapy, possibly fixed drug combinations

Multiple dose therapies

## Gonorrhoea Treatment Research Key Questions

- Origins of resistance
  - Selection resulting from antimicrobial use
  - Acquisition of resistance from other organisms
- Optimal strategies to slow further development of resistance
  - New drugs
  - Combination therapy
  - Multi-dose therapy
- How important is pharyngeal gonorrhoea as a source of development of resistance &/or a public health problem
- How can whole genome sequencing help answer continuing questions

## Neisseria Gonorrhoeae Presentation Overview

**Epidemiology**

**Diagnosis**

**Treatment/Antimicrobial Resistance**

**Control Measures**



**Reasons for STD Treatment Failure**

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Reinfection

Wrong Therapy

    Wrong diagnosis

    Wrong dosage/duration

    Self medication

Resistant Organisms

Other

**STD Incidence Modifiers- GC**

$$R = BcD$$


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R= Reproductive Rate

B= Infectivity: GC biologic characteristics, Condoms, (Vaccine)

C= Sexual Partner Selection (rate and variability) and Notification Parameters

D= Duration of Infectivity: Expeditious Detection and Effective Treatment (AMR)

After Anderson, RM and May RM; Nature 1988;333:323-320

**Gonorrhea Prevention**

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Current:

    Expeditious Diagnosis and Therapy

    Behavior Change

    Condoms

    Antimicrobial Prophylaxis

Future:

    Vaccines (New Hope, New Energy)

    Microbicides