Top 2020 STI Updates To Watch For

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National Network of STD Clinical Prevention Training Centers

Thank you!

*No commercial disclosures or conflicts of interest

Disclosures

- In the past 12 months, Dr. Hsu has had no relevant financial interests or other relationships with manufacturer(s) of product(s) or provider(s) of service(s) that will be discussed in this presentation

- This presentation will include discussion of pharmaceuticals or devices that have not been approved by the FDA

NEWS FLASH: May 23, 2019
Cepheid and Hologic have now received FDA approval
for extragenital (oropharyngeal and rectal swab) gonorrhea and chlamydia NAAT

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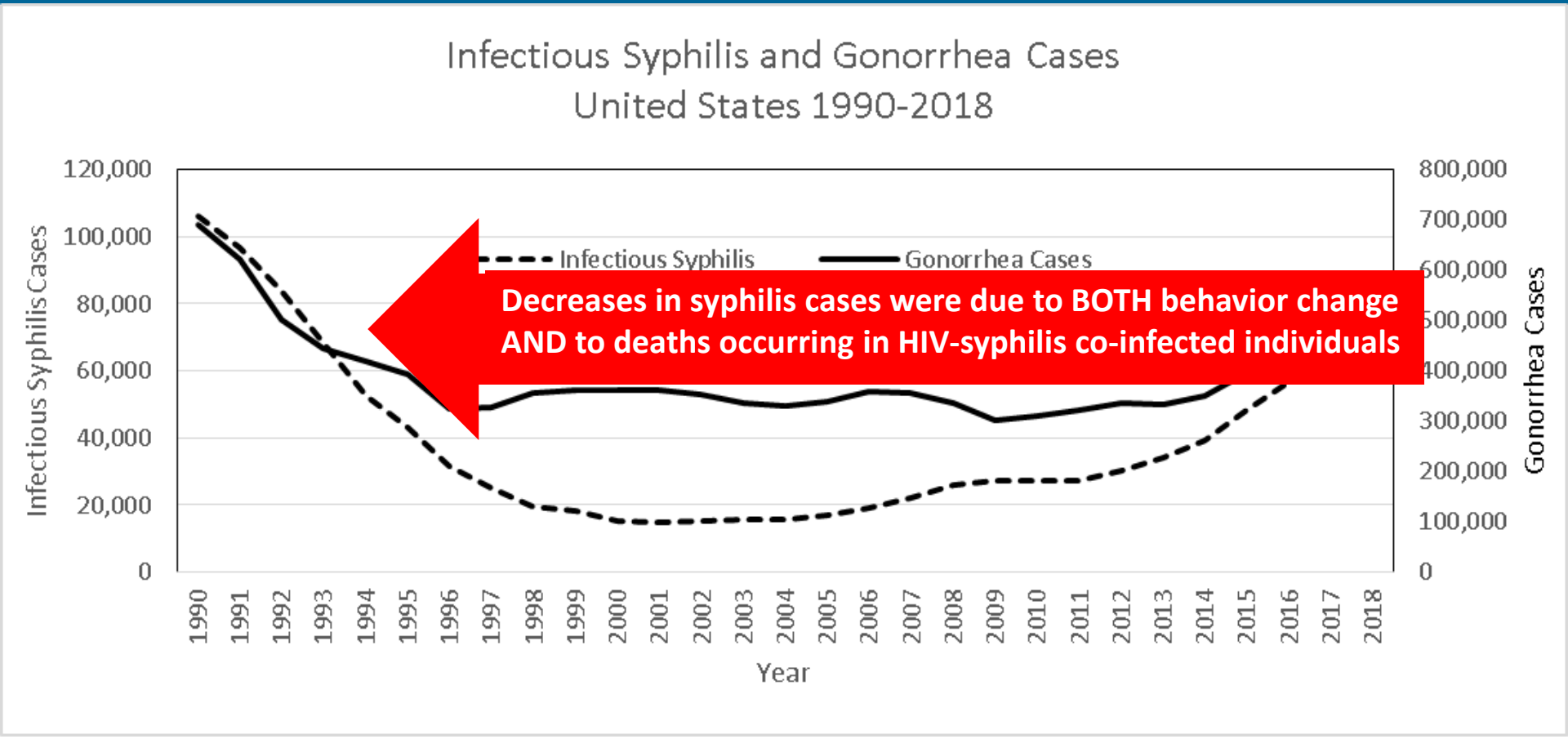
Objectives

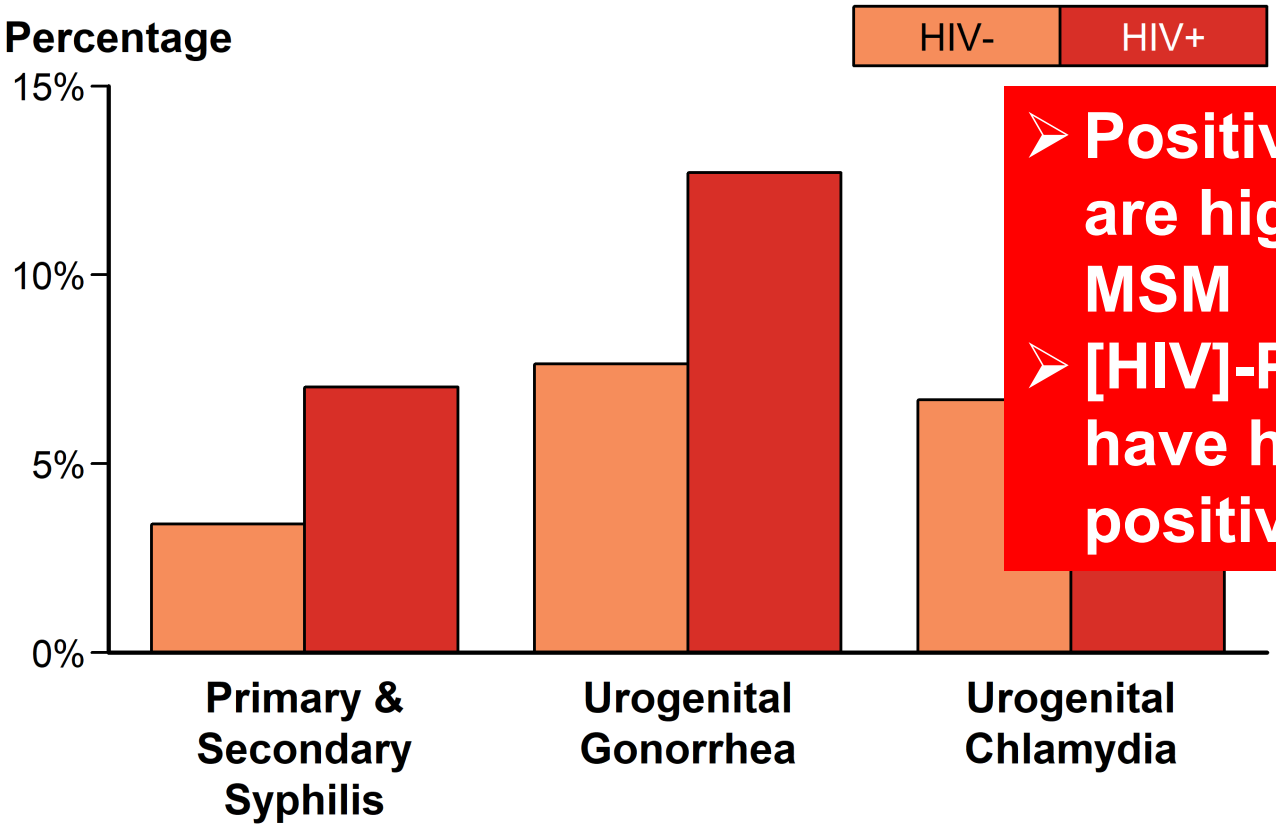
- Discuss shifts in STI/HIV epidemiology
- Provide updates on newer STI diagnostics
- Highlight controversies in management of
  - *N. gonorrhoeae*
  - *C. trachomatis*
  - *M. genitalium*
- Review STI clinical resources

Syphilis and Gonorrhea Over Time



*Infectious syphilis is defined as primary, secondary and early latent stages of syphilis within one year of infection.
Data Source: CDC. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019.

Figure GG. Proportion of MSM Attending STD Clinics with Primary and Secondary Syphilis*, Urogenital Gonorrhea, or Urogenital Chlamydia by Known HIV Status, STD Surveillance Network (SSuN), 2018



- Positivity rates are high in MSM
- [HIV]-Positives have higher positivity

* Includes SSuN jurisdictions that reported data on at least 20 patients with a diagnosis of primary and secondary syphilis in 2018.
NOTE: See section A2.2 in the Appendix for SSuN methods.
ACRONYMS: MSM = Gay, bisexual, and other men who have sex with men.

Chlamydia, Gonorrhea, and Syphilis: Massachusetts HIV-Coinfection Rates

- Chlamydia
  - 2% of cases were HIV co-infected in 2017 and 2018
- Gonorrhea
  - In 2017 and 2018, HIV co-infection is ~9 - 10%
  - Among MSM, HIV co-infection is ~20%
- Early Syphilis
  - HIV co-infection is 32-39% between 2015-18

Data are current as of 4/5/2019 and are subject to change
* HIV status is based on a full of year match with eHARS

Population-level Control of STIs

Basic Reproductive Rate

Transmissibility

No. of Sexual Contacts

Duration of infectiousness

$$R_o = T \cdot C \cdot D$$

Screening and *RAPID APPROPRIATE* treatment decrease D (duration) of carriage and therefore transmission

But if sexual contacts are not treated, index cases may become re-infected!

Treatment of STI in HIV-infected Persons

- CDC STD Treatment Guidelines highlight specific regimens for HIV-infected persons when appropriate

- In general, treatment guidelines are similar between HIV-infected and non-infected patients
  - Bacterial STIs: no treatment differences
  - Viral/protozoan STIs: treat with higher doses and/or longer

www.cdc.gov/std/treatment

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5. STI DIAGNOSTIC TESTING: APPROVAL FOR NEW ORGANISMS AND MORE SAMPLE SITES; FASTER!

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Mycoplasma genitalium: Diagnostics

- Very slow-growing organism
  - Culture can take up to 6 months
  - Only a few laboratories in the world are able to recover clinical isolates
- Nucleic acid amplification testing (NAAT) is the preferred method to detect *M. genitalium*
  - Research settings
  - In-house PCR assays (?)
  - NOW - several commercially available NAATs (FDA approved, 2019)
    - https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629746.htm

Self-collected STI Testing

Let's Take A "Selfie": Self-Collected Samples for Sexually Transmitted Infections

Charlotte A. Gaydos, MS, MPH, DrPH

The use of self-collected samples for the diagnosis of sexually transmitted infections (STIs) has been around for a long time and predates by many years the popular use of the word "selfie" to describe the practice of taking a picture of oneself.[1–6] Both examples might be called a "selfie" because the person is in charge of producing a product, but the potential benefits are different. The picture is often intended for posting on social media. Benefits from self-collecting one's own specimen are more practical. The privacy associated with self-collection, compared with provider-collected specimens, may be highly valued. Additionally, convenience may be important. Self-collection can be time-saving, because a provider appointment is not always necessary, and in some cases it may be done at home and the specimen mailed to a laboratory. Five commercial companies have Federal Drug Administration clearance for self-collected vaginal swabs for women and urine for men when nucleic acid amplification tests are performed. The Centers for Disease Control and Prevention recommend vaginal swabs, either self- or clinician-collected, for screening women and urine for screening men for chlamydia (CT) and gonorrhea (NG).[6] Many investigators have reported that self-collected urogenital specimens were acceptable to men and women and provided accurate results.[7–11]

Although urine has been well accepted for screening men, the adaption of vaginal swabs has been slower. In this journal, Habel et al[12] report the acceptability and uptake of self-collected urogenital samples among university students who were offered the option of participating in an innovative "selfie" program. They used the term "self-testing," but "self-collection" is more appropriate. Self-testing suggests the patients performed the tests themselves, which may be possible in the future. Semantics aside, allowing university students to self-collect samples for testing for CT and NG was acceptable, efficient, and effective.[12] The authors did not report which assay was used, but it probably was a nucleic acid amplification test, as recommended by the Centers for Disease Control and Prevention.

The reported overall increase in uptake of any testing in 2015, compared with a 2013 baseline, was 28.5% for men and 13.7% for women.[12] For women opting for the "selfie," the specimen changed from a clinician-collected cervical swab to the self-collected vaginal swab. The urine specimen offered to men opting for the "selfie" did not change. What did change for these students was the dispensing of the requirement for an appointment with a clinician. They found 31.0% of men and 13.6% of women opted for the "selfie." Less than one fourth of those opting for the "selfie" completed a survey, and 96.3% of these were "very" or "somewhat satisfied" with the "selfie" program. Interestingly, women were more likely to test positive for CT/NG when they selected the self-collected specimen (12.4%, compared to 4.8% for those with clinician collected specimens, $p < .01$). No significant difference in positivity by testing option was observed for men (12.9% vs 12.4%). Clinician testing for 2015, compared with 2013, declined 11.3% for men and 1.8% for women.

It is interesting to note that a higher percentage of men were in favor of the "selfie" than women. The reasons are not apparent. Perhaps, women were more used to seeing clinicians for reproductive health issues. Convenience may have contributed to the male choices. Although the student response to the "selfie" program was modest, the results presented are encouraging in that more people got tested. Continual assessment of the option program may show greater selection of the "selfie" as more students learn of the benefits.

Increasing the options for getting tested for STIs is expected to increase testing of those at risk. Innovative programs are being developed, implemented and evaluated. Although home collection of urogenital samples with mail transport to a testing site has not yet been cleared by the Federal Drug Administration,[13] many such programs have been implemented and evaluated and found acceptable to participants.[14–19] Self-collected vaginal swabs appear to be cost-effective.[20,21] Pharmacy

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ceived for publication December 28, 2017; and accepted January 2, 2018.
I: 10.1097/OLQ.0000000000000785

- Acceptable to many patient populations
- FDA-approved for certain GC/CT/trich NAAT testing platforms and sample types
- Equivalent or greater sensitivity than clinician-collected samples
- Improved uptake of STI screening

Training Centers

Gaydos. *Sex Trans Dis*, 2018

Hsu, Katherine (DPH) - Outlook Web | Resources | STD TCG | UW STD Prevention Training Center

Not secure | uwptc.org

Apps | Outlook Web App | Oracle HR-CMS Peopl... | Virtual Gateway | BMC Intranet | Alumni Medical Library... | Imported From IE | Pregnancy Calculator | Sign In - UpToDate | Other bookmarks

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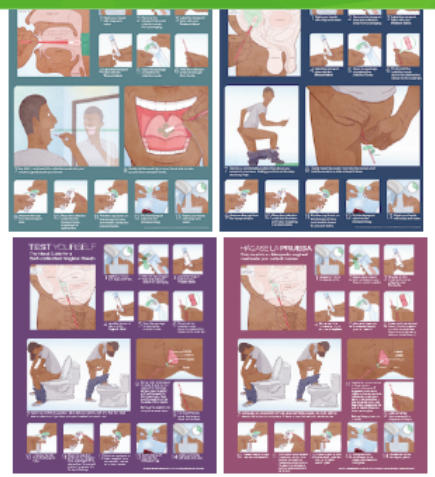
staff, students, and health care organizations.

TEST YOURSELF

The Visual Guide for a Self-collected Swab



The UW PTC is happy to provide free, high-quality prints of our pharyngeal, rectal, and vaginal self-testing visual aids for your clinic.

Wall Posters (16" x 20")

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- Rectal Swab — Spanish
- Pharyngeal Swab — English
- Pharyngeal Swab — Spanish
- Vaginal Swab — English
- Vaginal Swab — Spanish

Small Guides (8.5" x 11"; 2-sided)

- Rectal and Pharyngeal Swabs — English
- Rectal and Pharyngeal Swabs — Spanish
- Vaginal Swab — English/Spanish

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Start | 12:23 PM 5/3/2019

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http://uwptc.org/

Chlamydia and Gonorrhea Nucleic Acid Amplification Testing

NEWS FLASH: May 23, 2019
Cepheid and Hologic have now received FDA approval for extragenital (oropharyngeal and rectal swab) gonorrhea and chlamydia NAAT

preferred testing method over culture

Truly rapid STI testing now approved in U.S.

- binx io® received 510(k) marketing clearance August 2019 (“substantially equivalent”) from U.S. FDA
- Vaginal swab CT/NG NAAT assay using a proprietary electrochemical detection technology
- Results in 30 minutes

- Settings in which rapid tests should be used will be dependent on whether tests can be used by non-laboratorians, cost, and availability

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1. *Neisseria gonorrhoeae*: ongoing (resisting resistance futile) and new (extragenital PK/PD) concerns; new drugs

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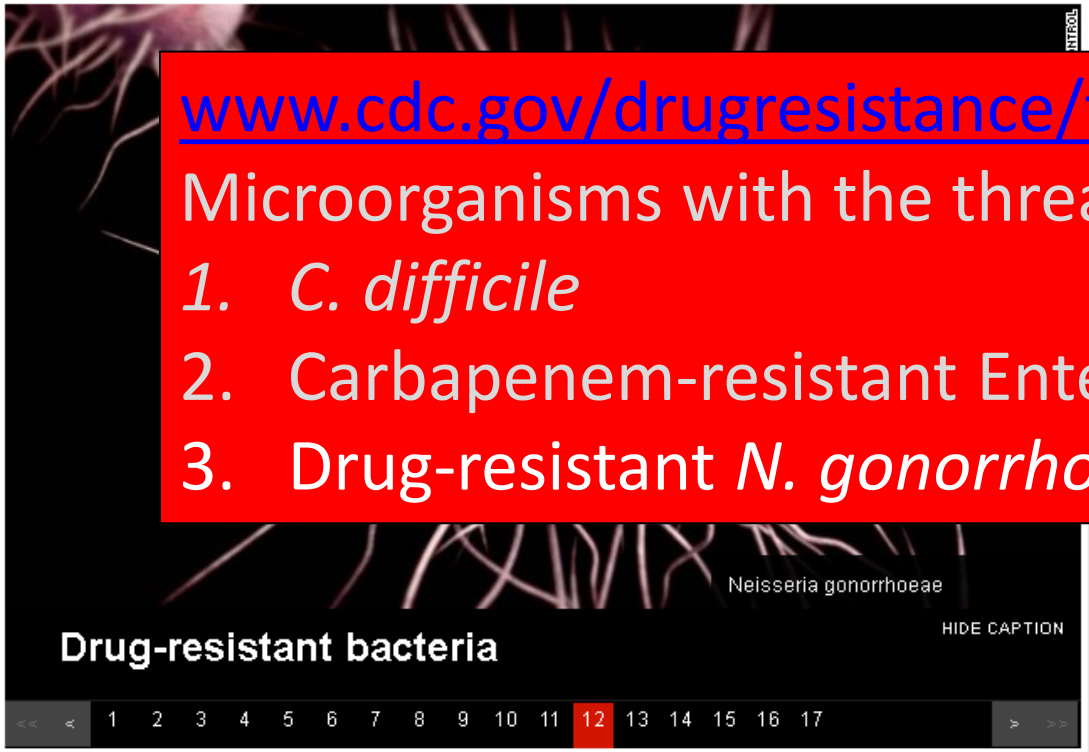
CDC sets threat levels for drug-resistant 'superbugs'

By **Miriam Falco**, CNN
updated 5:48 PM EDT, Tue September 17, 2013



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

www.cdc.gov/drugresistance/threat-report-2013/

Microorganisms with the threat level of URGENT:

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

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
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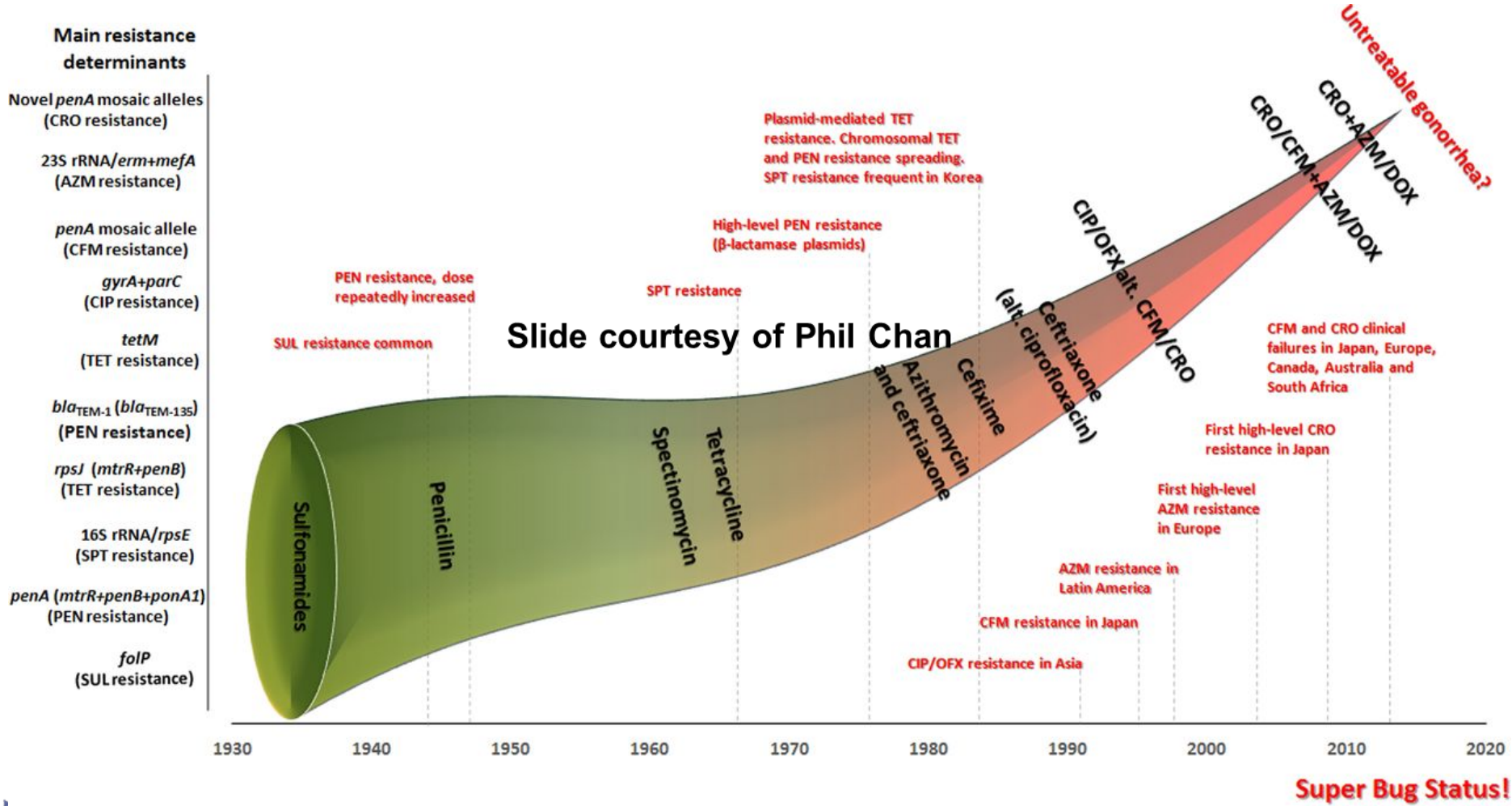
rooms if they have washed their hands.

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

Evolution of Antimicrobial Resistance in *N. gonorrhoeae*



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Unemo & Shafer, *Clin Microbiol Rev* 27:587-613, 2014

Slide courtesy of Sanjay Ram

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*

Unemo & Shafer, Ann NY Academy of Sciences, 2011

First Description of High-Level Cephalosporin Resistance

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3538–3545 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.00325-11

Is *Neisseria gonorrhoeae* Initiating a Future Era of Untreatable Gonorrhea?: Detailed Characterization of the First Strain with High-Level Resistance to Ceftriaxone[▽]†

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

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

- Isolate came from pharynx of female CSW in Kyoto
- **Cftx MIC 2 mcg/ml**
  - (R) to cefixime (MIC 8 mcg/ml), β-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

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

Health Protection Report Volume 12 Number 14

Update on investigation of UK case of *Neisseria gonorrhoeae* with high-level resistance to azithromycin and resistance to ceftriaxone acquired abroad

Details of a case of multi-drug-resistant *Neisseria gonorrhoeae* (MDRGC) were published in an HPR Advanced Access Report on 29 March 2018 [1,2]. The isolate was confirmed by the PHE Reference Laboratory as resistant to the current recommended dual first-line therapy [3]. The isolate had a ceftriaxone MIC of 0.5 mg/L and an azithromycin MIC of >256 mg/L (high-level azithromycin resistant, HLAziR). On wider antimicrobial susceptibility testing, the strain was susceptible only to spectinomycin. Two cases of gonorrhoea with resistance to ceftriaxone, azithromycin, ciprofloxacin, penicillin and tetracycline have subsequently been reported in Australia: one had had sex recently in south east Asia; the other case had no recent overseas travel [4].

The strain seen in the UK was isolated from a heterosexual man who had

- Cftx MIC 0.5 mcg/ml
- Azithromycin MIC >256 mcg/ml
- Pharyngeal carriage finally eradicated by ertapenem IV x 3 days

health services in England in early 2018. The case reported

sexual contact in south eas

the urine NAAT was

reinfection was excluded indicating treatment failure. The

low (0.032 mg/L) suggesting that this may be an effective therapy, although there are no defined breakpoints, and the patient was successfully treated with three days of IV ertapenem. The investigation co-ordinated by PHE concluded that there had been no spread of the isolate within the UK. Efforts to contact

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Gonorrhea: When/How To Do Test-of-Cure?

- Pharyngeal gonorrhea treated with an alternative regimen (anything other than combined ceftriaxone + azithromycin)
  - Use either culture or NAAT 14 days post-treatment

- Symptoms that persist after treatment
  - Evaluate using culture and susceptibility testing

CDC 2015 STD Treatment Guidelines

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

Back-Pocket GC Treatment Regimens:
U.S. 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

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Kirkcaldy RD et al. *CID* 2014

2019 BASHH Gonorrhea Guidelines

- RECOMMENDED treatment of uncomplicated anogenital & pharyngeal infection in adults
  - When antimicrobial susceptibility is not known prior to treatment:
    - Ceftriaxone 1g intramuscularly as a single dose (Grade 1C)
  - When antimicrobial susceptibility is known prior to treatment:
    - Ciprofloxacin 500mg orally as a single dose (Grade 1A) (if phenotypic or genotypic data indicate susceptibility)

https://www.bashhguidelines.org/current-guidelines/all-guidelines/

2019 BASHH Gonorrhea Guidelines

- ALTERNATIVE treatment of uncomplicated anogenital & pharyngeal infection in adults - use dual therapy with azithromycin 2g where possible (Grade 2C)
  - Cefixime 400mg orally as a single dose + azithromycin 2g orally (Grade 1B)
    - Only advisable if an intramuscular injection is contraindicated or refused by the patient. Resistance to cefixime is currently low in the UK.
  - Gentamicin 240mg intramuscularly as a single dose + azithromycin 2g orally (Grade 1A)
  - Spectinomycin 2g intramuscularly as a single dose + azithromycin 2g orally (Grade 1B)
    - Spectinomycin is not recommended for pharyngeal infection because of poor efficacy.
  - Azithromycin 2g as a single oral dose (Grade 1B)
    - Clinical efficacy of azithromycin does not always correlate with in vitro susceptibility testing and azithromycin resistance is high.

https://www.bashhguidelines.org/current-guidelines/all-guidelines/

New Treatments

Solithromycin (Cempra Inc.) – oral fluoroketolide with activity against *N. gonorrhoeae*, *M. genitalium*, and *C. trachomatis*. Good efficacy in a Phase II study, with a 100% efficacy for genital, oral, and rectal sites of infection in men and women. A Phase III trial is ongoing.

Zoliflodacin (Entasis Therapeutics) – spiropyrimidinetrione topoisomerase II inhibitor with activity *N. gonorrhoeae*, and *C. trachomatis*. Phase II trial – high efficacy against urogenital infections (98%–100% microbiological cure rate); >90% of participants were male.

Gepotidacin (GSK) – another bacterial topoisomerase II inhibitor; phase II trial - ~95% cure rates. >90% of the participants were male.

Slide courtesy of Sanjay Ram

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

Stephanie N. Taylor, M.D., Jeanne Marrazzo, M.D., M.P.H., Byron E. Batteiger, M.D., Edward W. Hook, III, M.D., Arlene C. Seña, M.D., M.P.H., Jill Long, M.D., M.P.H., Michael R. Wierzbicki, Ph.D., Hannah Kwak, M.H.S., Shacondra M. Johnson, B.S.P.H., Kenneth Lawrence, Pharm.D., and John Mueller, Ph.D.

Also active vs chlamydia, ureaplasma, *M. genitalium*

- 179 participants (167 men, and 12 women); 141 participants in the micro-ITT population could be evaluated,
- Microbiologic cure at urogenital sites in in 55 of 57 (96%) who received 2 g of zoliflodacin, 54 of 56 (96%) who received 3 g of zoliflodacin, and 28 of 28 (100%) who received ceftriaxone.
- Rectal infections cured in all 5 participants who received 2 g of zoliflodacin and all 7 who received 3 g, and in all 3 participants who received ceftriaxone.
- Pharyngeal infections were cured in 4 of 8 participants (50%), 9 of 11 participants (82%), and 4 of 4 participants (100%) in the groups that received 2 g of zoliflodacin, 3 g of zoliflodacin, and ceftriaxone, respectively.
- 21 adverse events related to zoliflodacin, mostly GI.

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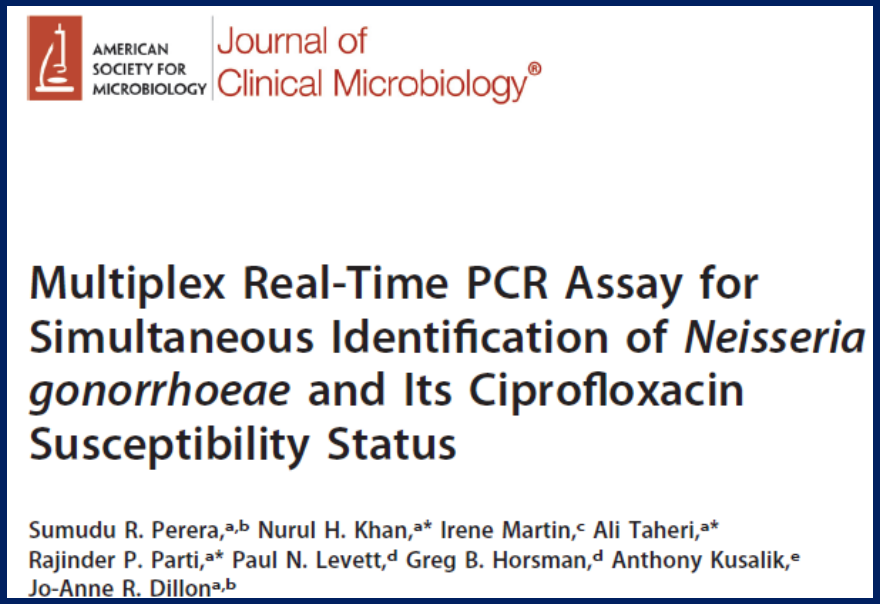
Slide courtesy of Sanjay Ram

Can molecular diagnostics help 'repurpose' drugs?



Mutations in amino acid 95 in GyrA highly predictive of Cipro resistance

Utility will depend on cost of testing (in turn depends on number of tests run), and prevalence of Cipro-resistant isolates.
Allan-Blitz et al, Sex Transm Dis, 2018

Slide courtesy of Sanjay Ram

The Journal of Infectious Diseases

MAJOR ARTICLE

Impact of Rapid Susceptibility Testing and Antibiotic Selection Strategy on the Emergence and Spread of Antibiotic Resistance in Gonorrhea

Ashleigh R. Tuite,[1] Thomas L. Gift,[2] Harrell W. Chesson,[2] Katherine Hsu,[3] Joshua A. Salomon,[1] and Yonatan H. Grad[1]

[1]Harvard T. H. Chan School of Public Health, Boston, Massachusetts; [2]Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Massachusetts Department of Public Health, Boston

Background. Increasing antibiotic resistance limits treatment options for gonorrhea. We examined the impact of a hypothetical point-of-care (POC) test reporting antibiotic susceptibility profiles on slowing resistance spread.

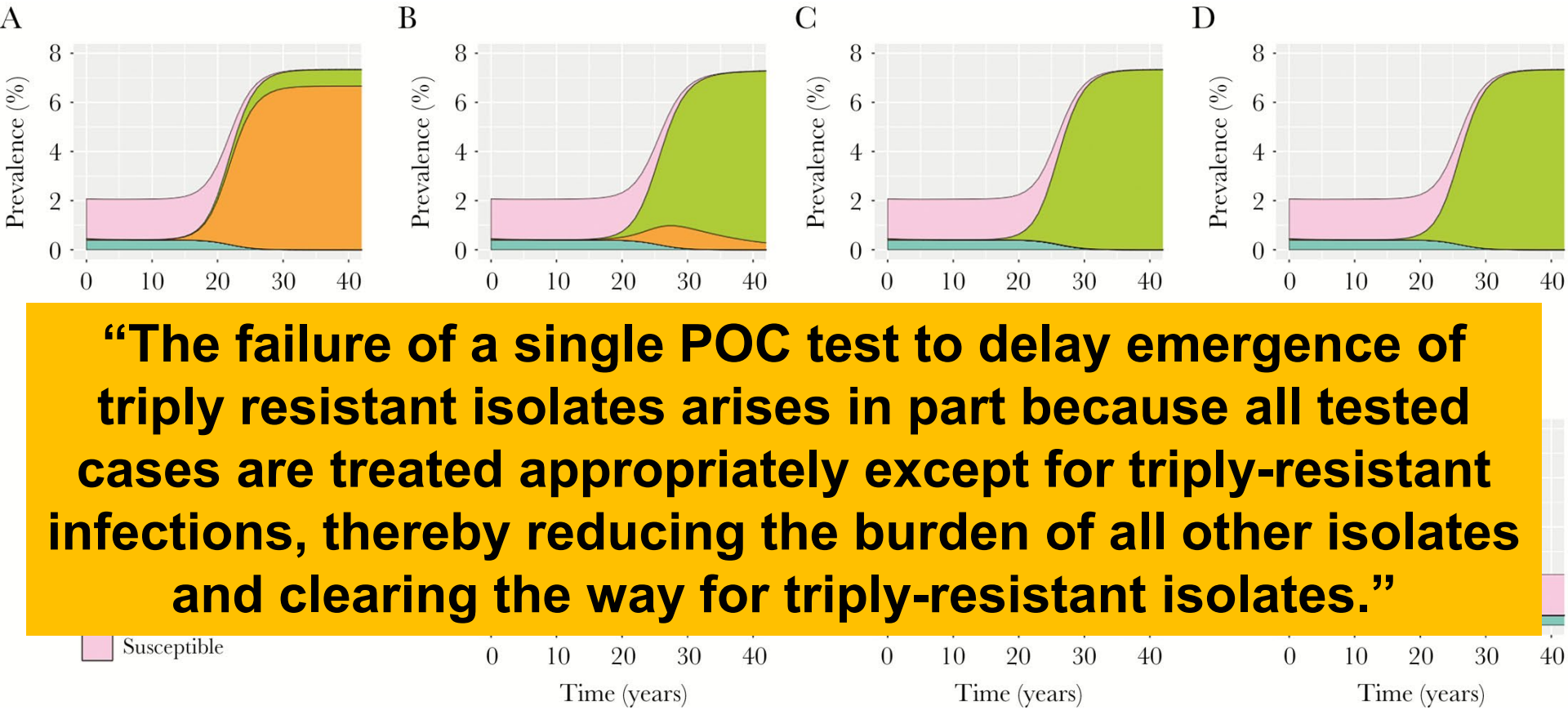
Methods. A mathematical model describing gonorrhea transmission incorporated resistance emergence probabilities and fitness costs associated with resistance based on characteristics of ciprofloxacin (A), azithromycin (B), and ceftriaxone (C). We evaluated time to 1% and 5% prevalence of resistant strains among all isolates with the following: (1) empiric treatment (B and C), and treatment guided by POC tests determining susceptibility to (2) A only and (3) all 3 antibiotics.

Results. Continued empiric treatment without POC testing was projected to result in >5% of isolates being resistant to both B and C within 15 years. Use of either POC test in 10% of identified cases delayed this by 5 years. The 3 antibiotic POC test delayed the time to reach 1% prevalence of triply-resistant strains by 6 years, whereas the A-only test resulted in no delay. Results were less sensitive to assumptions about fitness costs and test characteristics with increasing test uptake.

Conclusions. Rapid diagnostics reporting antibiotic susceptibility may extend the usefulness of existing antibiotics for gonorrhea treatment, but ongoing monitoring of resistance patterns will be critical.

Keywords. antibiotic resistance; gonorrhea; mathematical model; point-of-care test.

Fig. 2 Projected impact of point-of-care (POC) tests on gonorrhea prevalence and resistance



"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."

Population prevalence and prevalence of different strains are shown in the face of (A) no POC testing, (B and E) 10%, (C and F) 25%, and (D and G) 50% of cases tested.

- B–D show the results for a POC test for resistance to antibiotic A only.
- E–G show results for a POC test for resistance to all 3 antibiotics.

For the 3-resistance POC test, cases undergoing testing and displaying susceptibility to >1 antibiotic were treated with the antibiotic with the highest fitness cost associated with resistance acquisition. For both scenarios, all untested cases were treated in combination with antibiotics B and C. Results are shown for tests with perfect sensitivity and specificity.

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Tuite et al., JID 2017

3. *Chlamydia trachomatis*: new concerns about treating rectal infection

Azithromycin vs. Doxycycline

- CDC recommendation based on meta-analysis of 12 urogenital RCTs (Lau et al., 2002)
  - Efficacy azithro 97%, doxy 98%
  - Less sensitive tests (vs NAATs) may underestimate treatment failure
  - Doxy adherence not assured
- Question therefore raised about efficacy of azithro
  - 3 studies, efficacy <90%

The Answer:

RCT: Urogenital Chlamydia Treatment
Azithromycin vs. Doxycycline

Antibiotic group	Treatment failures	Efficacy
Doxycycline	0	100%
Azithromycin	5 (3.2%; 95%CI 0.4-7.4%)	97%

- Captive audience: juvenile detention facilities
- Difference in failure rates was 3.2%
- The non-inferiority of azithromycin was not established
- Both medications are effective
- **Azithro had some treatment failures, but adherence is likely to be much greater with single-dose azithromycin**

National Network of STD Clinical Prevention Training Centers

Geisler et al. NEJM 2015;373:2512-2521

Centers for Disease Control and Prevention
MMWR
Recommendations and Reports / Vol. 64 / No. 3

Sexually Transmitted Diseases Treatment Guidelines, 2015

Morbidity and Mortality Weekly Report
June 5, 2015

Recommended Regimens

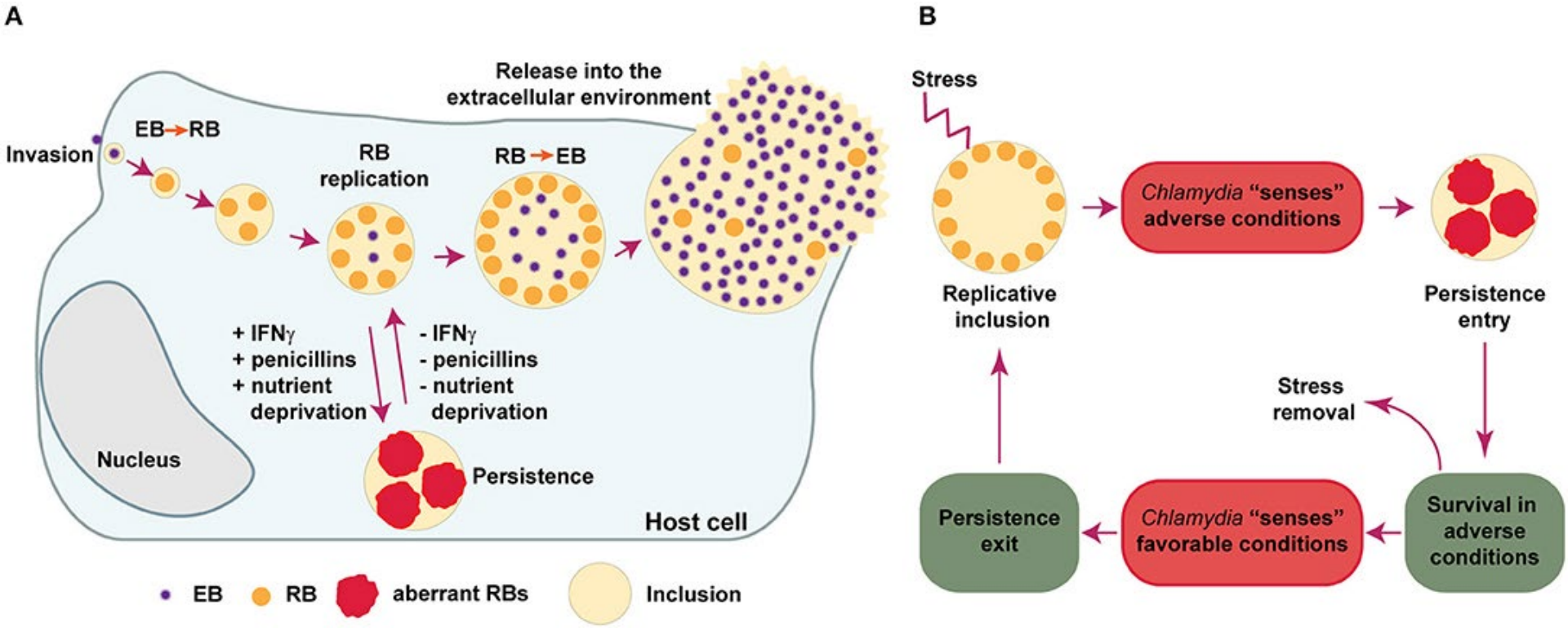
Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

Will these switch in 2020?

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days
OR
Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
OR
Levofloxacin 500 mg orally once daily for 7 days
OR
Ofloxacin 300 mg orally twice a day for 7 days

Slide courtesy of Brad Stoner



Panzetta *et al. Front Microbiol* 2018

Chlamydia Resistance: Myth or Fact?

In vitro

- Chlamydia culture not standardized AND difficult to obtain
  - Meaning of *in vitro* MIC data varies from lab to lab
- Heterotypic resistance exists
  - Replication of heterogenous population of unequally resistant bacteria occurs from subculture of one organism
  - Seen best with large inocula (Wang, 2005)
- Chlamydia persistence has been identified (Wyrick, 2010)
  - Reticulate bodies (RBs) can be metabolically active OR aberrant and nondividing (reversible states)

In vivo

- Meaning of above unclear
- Azithromycin tolerance may *occur at tissue level*

Azithro vs doxy for rectal chlamydia

		N (%) positive at follow-up	
		Azithro	Doxy
White 2009	UK	8/18 (44%)	0/119 (0%)
Steedman 2009	UK	7/68 (10%)	----
Elgalib 2010	UK	5/26 (19%)	1/186 (1%)
Drummond 2011	Australia	5/85 (6%)	----
Hathorn 2012	UK	9/42 (21%)	0/40 (0%)
Ding 2013	UK	2/11 (18%)	----
Khosropour 2013	US	8/49 (16%)	2/21 (10%)
Khosropour 2014	US	50/230 (22%)	2/56 (4%)

Slide courtesy of Brad Stoner

Study limitations

- Mostly retrospective, observational
- Treatment assignment not random
- High loss to follow up
- Tx failure vs reinfection difficult to discern
- Inconsistent study designs
  - comparative vs. noncomparative
  - pooled men & women
  - pooled symptomatic & asymptomatic

Slide courtesy of Brad Stoner

Baetteiger BE. *Sex Transm Dis* 2017; 44:403.

J Antimicrob Chemother 2015; **70**: 1290–1297
doi:10.1093/jac/dku574 Advance Access publication 29 January 2015

Journal of Antimicrobial Chemotherapy

The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis

Fabian Yuh Shiong Kong[1]*, Sepehr N. Tabrizi[2,3], Christopher Kincaid Fairley[4,5], Lenka A. Vodstrcil[1,2,5], Wilhelmina M. Huston[6], Marcus Chen[5], Catriona Bradshaw[5] and Jane S. Hocking[1]

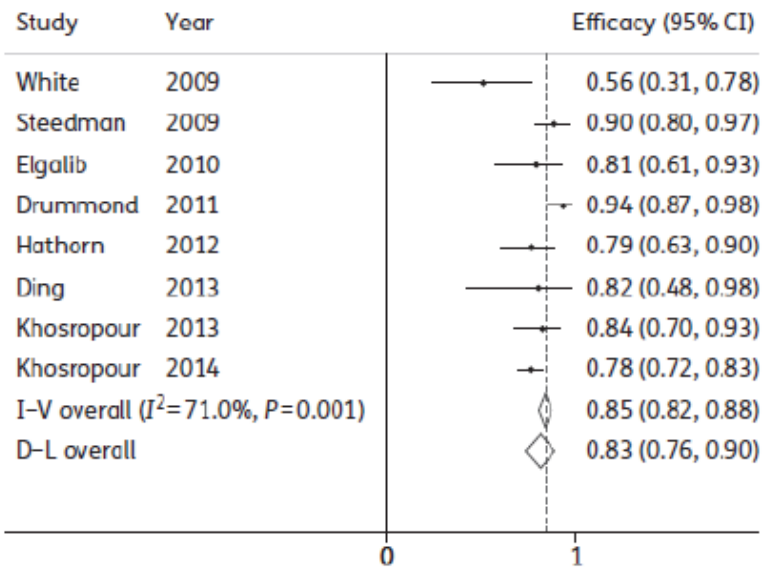


Figure 2. Efficacy of 1 g of azithromycin as a single dose for the treatment of rectal chlamydia infections. I–V, inverse-variance (fixed) method; D–L, DerSimonian and Laird (random-effects) method; I^2, test for heterogeneity.

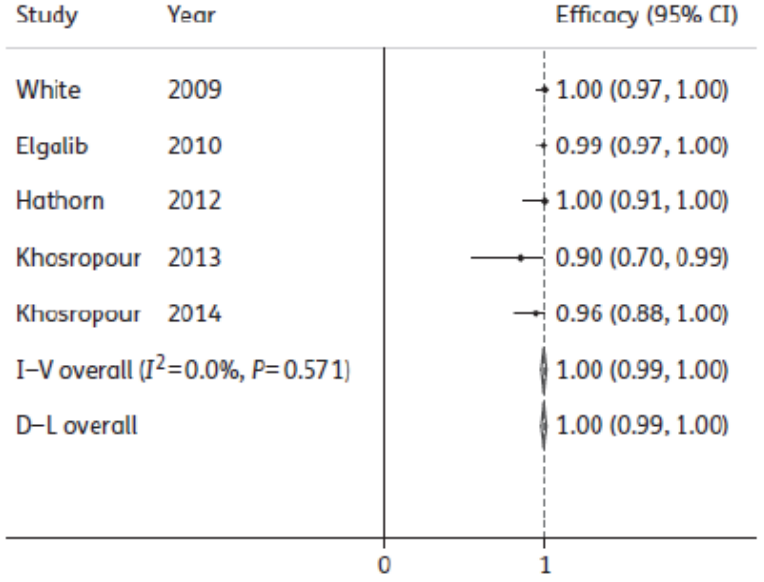


Figure 3. Efficacy of doxycycline (100 mg twice daily) for 7 days for the treatment of rectal chlamydia infections.

Slide courtesy of Brad Stoner

Kong FYS et al. *J Antimicrob Chemother* 2015; 70:1290.

UNIVERSITY OF WASHINGTON STD Prevention Training Center

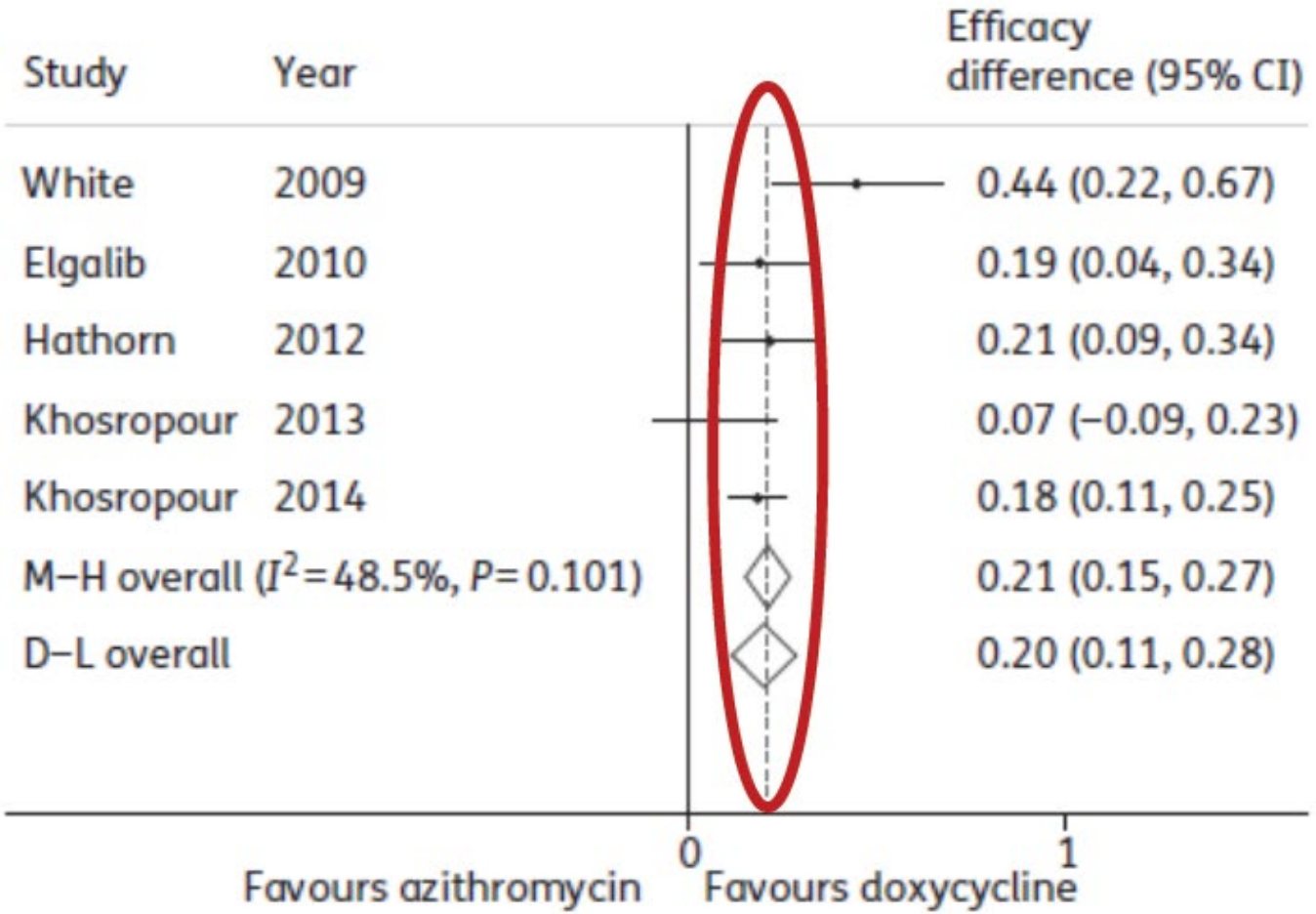


Figure 4. Efficacy difference between 7 days of doxycycline versus single-dose azithromycin for the treatment of rectal chlamydia infections. M–H, Mantel–Haenszel (fixed) methods.

Slide courtesy of Brad Stoner

Kong et al 2015

Theories of Treatment Failure in *C. trachomatis* Anorectal Infection

- Pharmacokinetics/ pharmacodynamics?
  - Efficacy differences between azithromycin vs. doxycycline further accentuated at rectal site
    - Doxy highly lipid soluble: facilitates rapid distribution into tissue and site of infection
    - Azithro delivered via phagocytic cells produced during immune response (which is inconsistent)
- Heterotypic resistance?
  - Higher organism load in rectal infections means higher odds of small proportion of resistant organisms
- Persistent infection?
  - *C. trachomatis* develops non-infectious aberrant bodies (under selective pressure of beta-lactams or deprivation of nutrients), which are semi-refractory to azithro or doxy treatment, but can revert to infectious
- Auto-inoculation of chlamydia from rectal to cervical sites in women?
- Missed LGV diagnosis?

Kong & Hocking, *BMC Infect Dis* 2015

Asymptomatic Lymphogranuloma Venereum in Men who Have Sex with Men, United Kingdom

Cara Saxon, Gwenda Hughes, Catherine Ison, for the UK LGV Case-Finding Group[1]

We investigated prevalence of lymphogranuloma venereum (LGV) among men who have sex with men who were tested for chlamydia at 12 clinics in the United Kingdom during 10 weeks in 2012. Of 713 men positive for *Chlamydia trachomatis*, 66 (9%) had LGV serovars; 15 (27%) of 55 for whom data were available were asymptomatic.

Of 713 men po
66 (9%) had LG
15 (27%) of 55 f
were available wer

outbreak of LGV among MSM worldwide (*3*,*4*). Infection control in England has relied on CT DNA typing and treatment of symptomatic MSM who have CT-positive rectal infections and their contacts, as well as health promotion. These measures were supported by a large prospective study in the United Kingdom during 2006–2007 that reported <6% of LGV CT infections were asymptomatic (*5*). However, studies in the Netherlands and Germany, and a smaller UK study, have reported higher proportions (17%–53%) of asymptomatic infection (*6*–*8*). We reinvestigated the prevalence of asymptomatic LGV CT infection among MSM in the United Kingdom to assess whether it may be sustaining the current epidemic.

The Study

In the UK, STI clinics are open access and provide free testing and treatment. Regular STI and HIV screening is encouraged for sexually active MSM with or without symptoms (*9*). A full medical and sexual history are recorded for all patients, and a physical examination is done for those with symptoms.

Twelve UK STI clinics participated; all serve cities with large MSM populations and routinely screen MSM for CT by examining urine or swab samples of the pharynx,

Author affiliation: Public Health England, London, UK

DOI: http://dx.doi.org/10.3201/eid2201.141867

SURVEILLANCE

Lymphogranuloma venereum in Quebec: Re-emergence among men who have sex with men

CA Boutin[1], S Venne[2], M Fiset[2], C Fortin[1,3], D Murphy[3], A Severini[4], C Martineau[1,3], J Longtin[3], AC Labbé[1,3]*

Abstract

Background: Lymphogranuloma venereum (LGV) is a sexu
by *Chlamydia trachomatis* genotypes L_1, L_2 and L_3. This LG
morbidity and increased risk of HIV transmission. While fe
reported in Qu
period of low i

Objectives: To
population, inc
treatments and

Methods: Des
Institut nationa
obtained throu
Quebec Minist

Results: There were 338 cases of LGV over the four-year p
excluding one transsexual. Mean age was 41 years. Most
men who have sex with men (MSM; 99%). The majority (83
more in the last year, met mostly through the Internet (77
sexual intercourse with out-of-province residents decrease
2005–2012 (38%). History of STIs was frequent: 83% were
syphilis and 78% previous gonorrhea. Recreational drug u
71% in 2016. Most cases were symptomatic, a proportion
compared with 2013–2015 (82%; p=0.006). Clinical preser
lymphadenopathy (13%) and ulcer/papule (12%). Reinfecti
infection, occurred in 35 individuals (10%).

Conclusion: The re-emergence of LGV in Quebec involves
almost exclusively of MSM with STIs, who have a high num

Most cases
a proportion
2016 (68%
2013-15 (8

Suggested citation: Boutin CA, Venne S, Fiset M, Fortin C, Murphy
Labbé AC. Lymphogranuloma venereum in Quebec: Re-emergence
Commun Dis Rep. 2018;44(2):55-61. https://doi.org/10.14745/ccdr.

Introduction

Lymphogranuloma venereum (LGV) is a sexually transmitted
infection (STI) caused by *Chlamydia trachomatis* genotypes
L_2 and L_3 (L_{1-3}). It is associated with anogenital fistula, stenos
formation and lymphatic obstruction, among others (1) and
increased risk of HIV transmission (1-3). This information was
rarely reported in industrialized countries until the early 200
but it has since been described in urban settings, mainly am
men who have sex with men (MSM). Recent outbreaks occur
in Belgium, France, the Netherlands, the United Kingdom ar
the United States of America (2). Over the last decade, LGV
emerged in Canada, with sporadic outbreaks mainly in majo
urban centres (3-5).

Baetselier *et al. BMC Infectious Diseases* (2018) 18:589
https://doi.org/10.1186/s12879-018-3600-0

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Lymphogranuloma venereum is on the rise in Belgium among HIV negative men who have sex with men: surveillance data from 2011 until the end of June 2017

Irith De Baetselier[1*], Achilleas Tsoumanis[1], Ruth Verbrugge[2], Bénédicte De Deken[1], Hilde Smet[1], Saïd Abdellati[1], Vicky Cuylaerts[1], Ludwig Apers[1] and Tania Crucitti[1]

A rise in the number of asy
LGV cases (6.7%) was ob
(OR 1.39, p = 0.047

Results: The number of LGV cases rose by a factor four, from 21 in 2011 to 88 in 2
showed a positive trend estimate of 14% increase per half year ($p < 0.001$). LGV dec
(odds ratio (OR): 0.79, $p < 0.001$) and increased among HIV negative cases (OR: 1.27
the number of asymptomatic LGV cases (6.7%) was observed (OR:1.39, $p = 0.047$). A
likely to be HIV ($p = 0.046$) or Hepatitis C positive ($p = 0.027$).

Conclusions: The rise of LGV in HIV negative MSM has now been documented. If
HIV negative MSM, future public health strategies should include LGV testing of all
samples from MSM.

Keywords: Lymphogranuloma venereum, LGV, Chlamydia trachomatis, Pre-exposu
sex with men, MSM

Background

Lymphogranuloma venereum (LGV) is a bacterial sexually transmitted infection (STI) caused by the L serovars of *Chlamydia trachomatis* (CT). Although initially a tropical infection characterized by inguinal buboes, LGV under the form of proctocolitis has become endemic among men who have sex with men in Europe. The CT L serovar is more invasive compared to the other serovar types leading to more sever
to be associated with i
tion [1]. The number
Western and Central E
LGV surveillance has b
ber of European cases
compared to 2013 [2].
an underestimate as n
identify CT serovar/ge
addition, only suspecte
reports have shown th
higher than initially the

* Correspondence: idebaetselier@itg.be
[1]Department of Clinical Sciences, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium
Full list of author information is available at the end of the article

BMC

Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

Observational study of anorectal *Chlamydia trachomatis* infections in France through the lymphogranuloma venereum surveillance network, 2010–2015

International Journal of STD & AIDS
2018, Vol. 29(12) 1215–1224
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B de Barbeyrac[1,2,3], C Laurier-Nadalié[1,2,3], A Touati[1,2,3], C Le Roy[1,2,3], L Imounga[1,2,3], N Hénin[1,2,3], O Peuchant[1,2,3], C Bébéar[1,2,3], G La Ruche[4] and N Ndeikoundam Ngangro[4], on behalf of the French surveillance of *C. trachomatis* proctitis network

Most LGV patients in France were symptomatic (54%) as they were in the UK. However, 42.7% missing data on symptoms, hampering accurate estimation.

Keywords
Lymphogranuloma venereum, *Chlamydia trachomatis*, anorectal infection, surveillance, epidemiology

Date received: 2 March 2018; accepted: 1 June 2018

[1]Mycoplasmal and Chlamydial Infections in Humans, University of

What's needed?

- RCT: doxy vs azithro for asymptomatic rectal infection
  - Australia protocol published 2017
    - 700 MSM
    - f/u CT test at 4 wks
    - WGS, mRNA
      - (tx failure vs. reinfection vs. false +)
- US STI CTG also under way

Lau *et al. BMC Infectious Diseases* (2017) 17:35
DOI 10.1186/s12879-016-2125-7

BMC Infectious Diseases

STUDY PROTOCOL Open Access

Treatment efficacy of azithromycin 1 g single dose versus doxycycline 100 mg twice daily for 7 days for the treatment of rectal chlamydia among men who have sex with men – a double-blind randomised controlled trial protocol

Andrew Lau[1], Fabian Kong[1], Christopher K. Fairley[2,3], Basil Donovan[4], Marcus Chen[2,3], Catriona Bradshaw[1,2,3], Mark Boyd[4], Janaki Amin[4], Peter Timms[5], Sepehr Tabrizi[6], David G. Regan[4], David A. Lewis[7,9], Anna McNulty[8] and Jane S. Hocking[1,2*]

Slide courtesy of Brad Stoner

Lau A et al, *BMC Infectious Diseases* 2017; 17:35.

australian STI MANAGEMENT GUIDELINES
FOR USE IN PRIMARY CARE

Principal Treatment Options		
Situation	Recommended	Alternative
Uncomplicated genital or pharyngeal infection	Azithromycin 1g PO, stat	Doxycycline 100mg PO, BD 7 days
Ano-rectal infection	Doxycycline 100mg PO, BD 7 days if asymptomatic, but 21 days if symptomatic (see ano-rectal syndromes)	Azithromycin 1g PO, stat, and repeat in 1 week

2015 European guideline on the management of *Chlamydia trachomatis* infections

Recommended treatment for uncomplicated C. trachomatis non-LGV rectal and pharyngeal infections

- Doxycycline 100 mg twice a day for seven days (oral) [I; A] (preferred if rectal infection)
  or alternatively:
- Azithromycin 1 g stat (oral) [IIa; A] (if rectal infection, a TOC should be subsequently performed)

Slide courtesy of Brad Stoner

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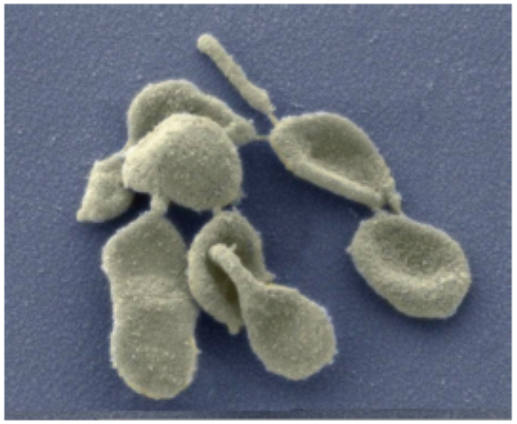
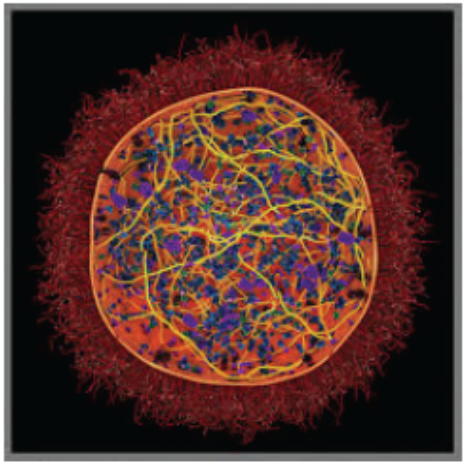
2. *Mycoplasma genitalium*: cause of persistent urethritis, cervicitis, other; do we need to treat it and if so, with what?

What is *Mycoplasma genitalium*?

- Mollicute
  - Lacks a cell wall
- Smallest known genome[1,2]
  - 580 kb translating to <500 genes
- First identified in 1981 from 2 of 13 men with NGU[3]
- Extremely fastidious
  - Culture only achieved by ~3-4 laboratories worldwide
  - Takes ~6 months[4]



Scanning electron micrograph



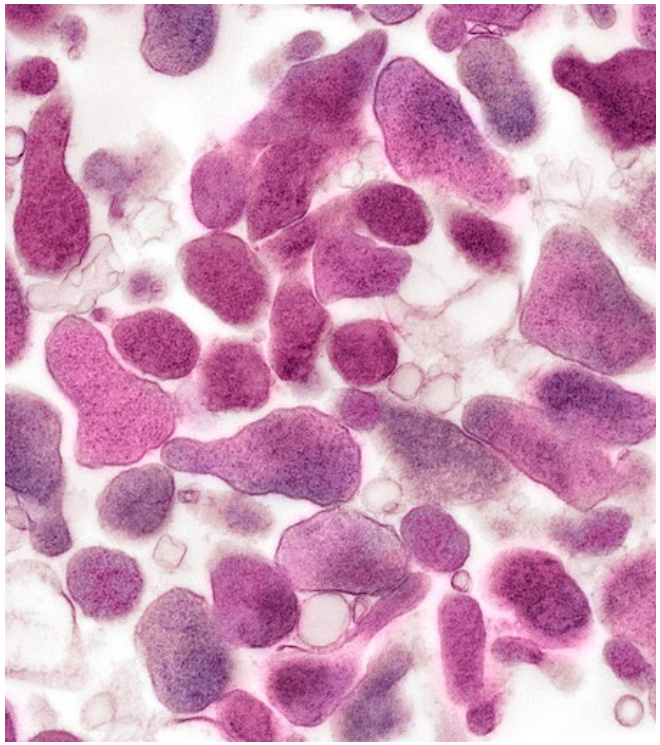
Computer assembled & generated 3D model

Slide courtesy of LE Manhart

[1]Glass et al, PNAS 2006; [2]Gibson et al, Science 2008; [3] Tully et al, Lancet 1981, [4]Jensen et al, J Clin Micro 1996

Mycoplasma genitalium: Epidemiology

- First identified in the early 1980's
- Cause of male urethritis
  - 15-20% of non-gonococcal urethritis (NGU) cases
  - 20-25% of non-chlamydial NGU
  - 30% of persistent or recurrent urethritis
  - More common than *N. gonorrhoeae* but less common than *C. trachomatis*
  - Co-infection with other STIs is common

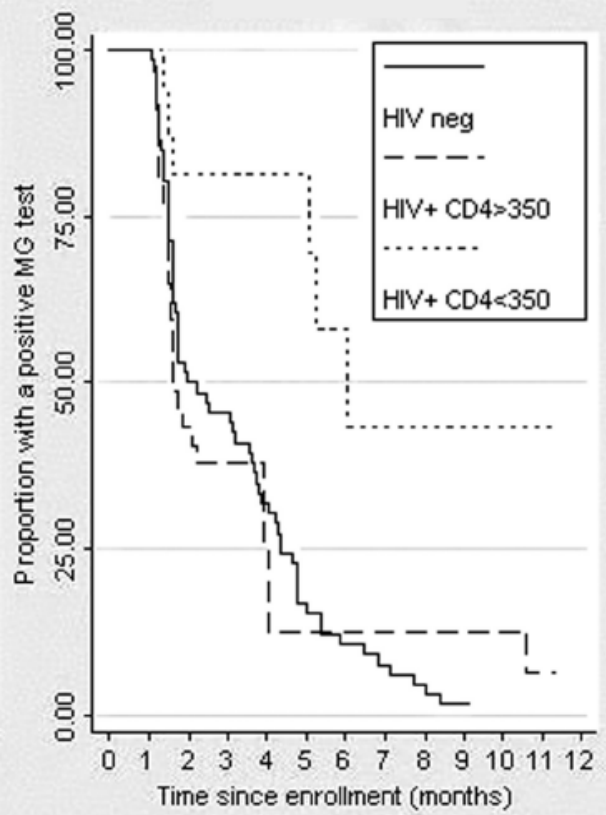


Mycoplasma genitalium

Disease Associations

1. Asymptomatic*
2. Urethritis/cervicitis (discharge, dysuria, discomfort, etc.)
3. Pelvic inflammatory disease (PID)
4. Infertility (weak association)
5. Pregnancy outcomes (preterm birth and spontaneous abortions)

*A significant number (30-50%) of men and women may be asymptomatic (Falk et al., 2004, 2005, Gesink et al., 2016)



Time to First Negative Test

Mycoplasma genitalium

Natural History (Women)

In a cohort of women in Uganda (N=119) who had *M. genitalium* infection at baseline, the following was observed:

- **55% cleared the infection by 3 months**
- **83% cleared the infection by 6 months**
- **93% cleared the infection by 12 months**
- **HIV+ women cleared infections slower**
- **Lower CD4 counts were even slower**
- **(Re-infection rates of 39%)**

***No studies on the natural history of *M. genitalium* in men.**

Slide courtesy of Phil Chan

Vandepitte et al., 2013

Mycoplasma genitalium

What about extragenital sites?

An initial study showed *no* extragenital infections, suggesting *M. genitalium* infections may be limited to the urogenital tract. Among 99 male patients presenting for STD testing, 17% had urethral infection and none had pharyngeal or rectal infection (Jensen et al., 1993)

Among 398 women presenting to an STD Clinic in new Orleans, 4.3% had a rectal infection (Lillis et al., 2011)

Subsequent studies among MSM have demonstrated rectal infections:

1. Among 438 MSM in the UK, 2.7% of urethral and 4.4% of rectal specimens were positive (Soni et al., 2010).
2. Among 409 MSM in China, 3.4% of urethral and 5.4% of rectal specimens were positive (Zheng et al., 2014).
3. Among 500 MSM in SFO, 5.4% had a positive rectal specimen (Francis et al., 2014)

Slide courtesy of Phil Chan

Jensen et al., 1993

Treatment of MG:
RCTs Comparing Doxycycline vs. Azithromycin

Study	Year	N	Drugs & Dosages	Micro Cure
Mena	2009	36 42	DOXY 100mg PO bid X 7d AZM 1g PO X1	45% 87%
Schwebke	2011	39 45	DOXY 100mg PO bid X 7d AZM 1g PO X 1 +/- Tinidazole	31% 67%
Manhart	2013	35 35	DOXY 100mg PO bid X 7d AZM 1g PO X 1	30% 40%

Mena 2009 *Clin Inf Dis*; 48:1649; Schwebke 2011 *Clin Inf Dis*; 52:163; Manhart 2013 *Clin Inf Dis*;56:934

- Doxycycline largely ineffective against *M. genitalium:* median cure rate of ~31%
- Resistance to azithromycin appears to be emerging: median cure rate for men and women ~85%, but only 40% in most recent trial
- Longer courses of AZM (e.g. 500 mg PO X1 followed by 250 mg QD X 4d) yield higher cure rates and may lead to decreased emergence of resistance

National Network of STD Clinical Prevention Training Centers

Reviewed by Manhart, 2013 Infect Dis Clin N Am 27;:779

CDC 2015 STD Treatment Guidelines

"The **1-g single dose of azithromycin** was significantly more effective against *M. genitalium* than doxycycline in two randomized urethritis treatment trials and is **preferred over doxycycline.** However, **resistance** to azithromycin appears to be **rapidly emerging**….

Moxifloxacin (400mg daily x 7, 10, or 14 days) has been successfully used to treat *M. genitalium* in men and women with previous treatment failures….

Although generally considered effective, studies in Japan, Australia, and the United States have reported **moxifloxacin treatment failures after the 7 day regimen**."

Slide courtesy of LE Manhart

2018 BASHH *M. genitalium* Guidelines

- RECOMMENDED treatment of uncomplicated urogenital infection (urethritis, cervicitis)
  - Doxycycline 100mg bid for 7 days followed by azithromycin 1g orally as a single dose then 500mg orally once daily for 2 days where organism is known to be macrolide-sensitive or where resistance status is unknown (1D)
  - Moxifloxacin 400mg orally once daily for 10 days if organism known to be macrolide-resistant or where treatment with azithromycin has failed (1B)
- RECOMMENDED treatment of complicated urogenital infection (PID, epididymo-orchitis)
  - Moxifloxacin 400mg orally once daily for 14 days (1D)

https://www.bashhguidelines.org/current-guidelines/all-guidelines/

Mycoplasma genitalium
2016 European Guidelines

- Recommend macrolide resistance testing
- First-line treatment for uncomplicated *M. genitalium* with **azithromycin** 500mg on day one, then 250mg on days 2-5 (extended course).
  - Or **josamycin*** 500mg TID for 10 days
- Second-line treatment with **moxifloxacin** 400mg QD for 7-10 days
- Third-line treatment (or persistent) with **doxycycline** 100mg BID for 14 days (may cure 30%)
  - **Pristinamycin*** 1g 4XD for 10 days (90% cure)

Test of cure is recommended! (3 weeks or later)

***Not available in U.S.**

Slide courtesy of Phil Chan

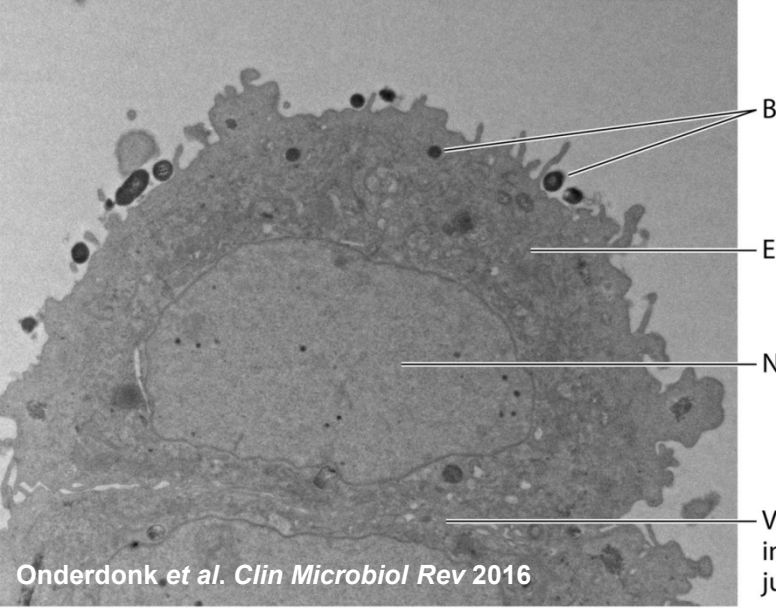
Partner Management

Considerations

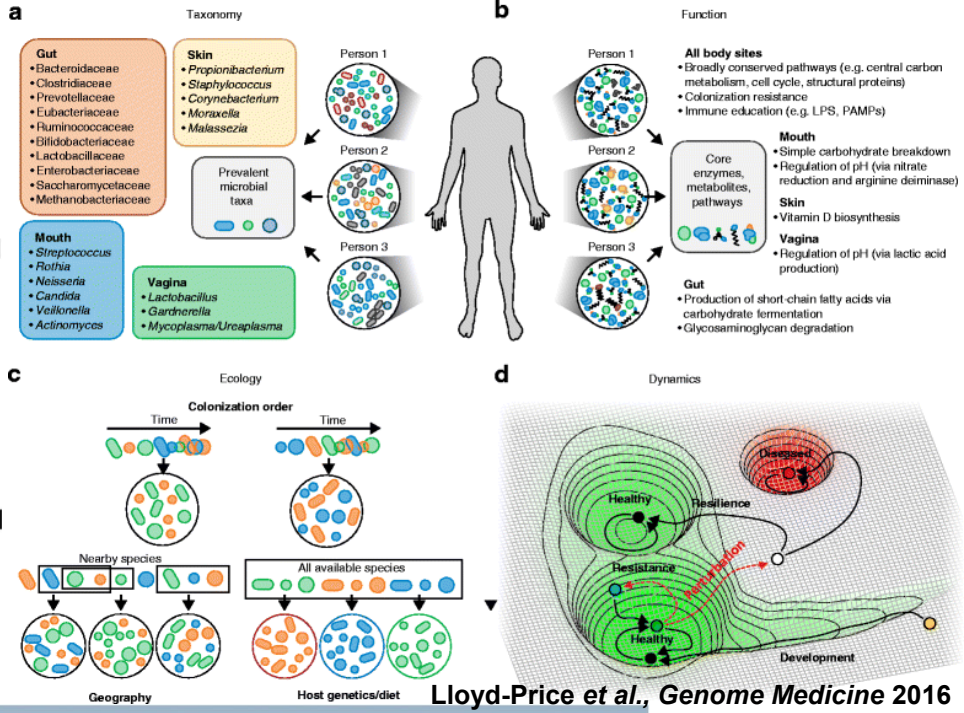
1. Treatment guidelines are inconsistent about the need for presumptive treatment for sex partners.
2. United States and UK guidelines do not recommend presumptive treatment.
3. Australian guidelines do.
4. Recent sex partners (within 60 days of symptoms) should be referred for evaluation (or last sex partner).

Slide courtesy of Phil Chan

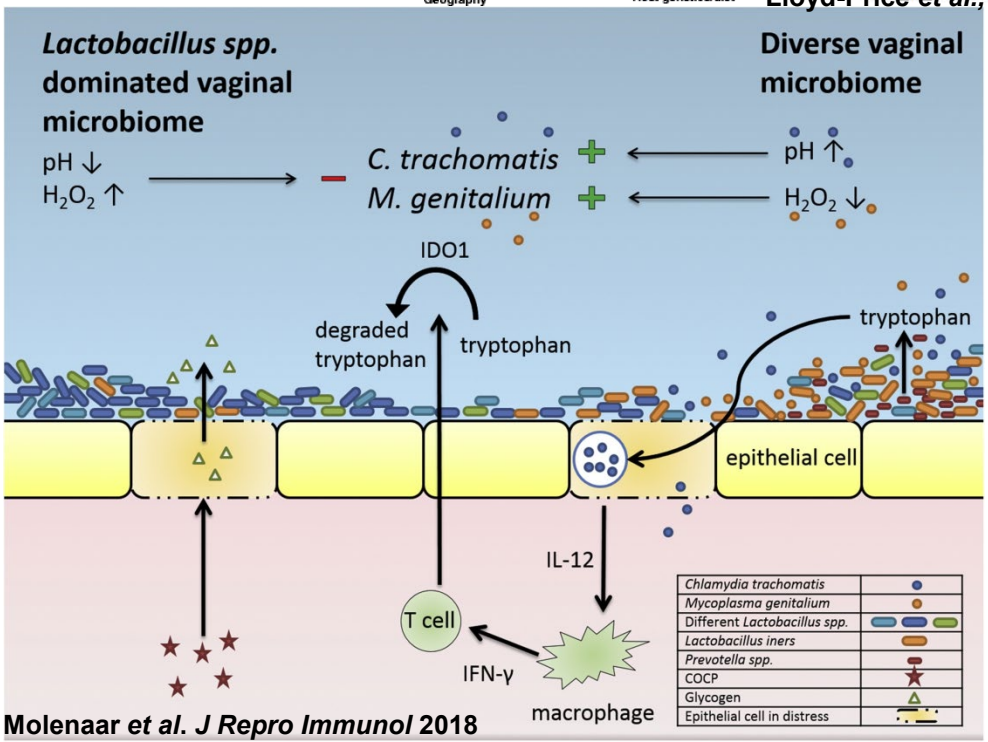
Is our lack of understanding about the genital microbiome contributing to controversies in STI treatment?



Onderdonk *et al. Clin Microbiol Rev* 2016



Lloyd-Price *et al., Genome Medicine* 2016



Molenaar *et al. J Repro Immunol* 2018

National Network of STD Clinical Prevention Training Centers

5. STI DIAGNOSTIC TESTING: APPROVAL FOR NEW ORGANISMS AND MORE SAMPLE SITES; FASTER!

4. *NEISSERIA GONORRHOEAE*: ONGOING (RESISTING RESISTANCE FUTILE) AND NEW (EXTRAGENITAL PK/PD) CONCERNS; NEW DRUGS?

3. *CHLAMYDIA TRACHOMATIS*: NEW CONCERNS ABOUT TREATING RECTAL INFECTION

2. *MYCOPLASMA GENITALIUM*: CAUSE OF PERSISTENT URETHRITIS, CERVICITIS, OTHER; DO WE NEED TO TREAT IT AND IF SO, WITH WHAT?

IS OUR LACK OF UNDERSTANDING ABOUT THE GENITAL MICROBIOME CONTRIBUTING TO CONTROVERSIES IN STI TREATMENT?

National Network of STD Clinical Prevention Training Centers

Drum roll please …

1. CDC STD Treatment Guidelines:

A rose by any other name …

National Network of
STD Clinical Prevention
Training Centers

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 64 / No. 3
June 5, 2015

- Harmony with USPSTF screening guidelines on gonorrhea/chlamydia in adolescents
- New hepatitis C screening recommendations for HIV+ MSM
- New information on clinical management of transgender men and women

Sexually Transmitted Diseases Treatment Guidelines, 2015

Misnomer!

•Prevention
•Screening
•Counseling
•Management

AND

•Treatment Guidelines

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CONTENTS

CONTENTS (*Continued*)

CDC STD Treatment Guidelines Development

- Evidence-based on principal outcomes of STD therapy
  1. Microbiologic eradication
  2. Alleviation of signs & sx
  3. Prevention of sequelae
  4. Prevention of transmission
- Recommended regimens preferred over alternative regimens
- Alphabetized unless there is a priority of choice
- ~~Reviewed April 2013; published 2015~~ Reviewed June 2019; Published 2020?
- www.cdc.gov/std/treatment
  - Pocket guides, teaching slides, charts, app

Language in yellow highlighted boxes reflects changes between 2010 and 2015 guidelines

Want to know more about STDs?

There's an app for that.

CDC STD Treatment Guidelines App for Apple and Android

Available now, **FREE!** (accept no competitors)

Search "STD Treatment" in App store

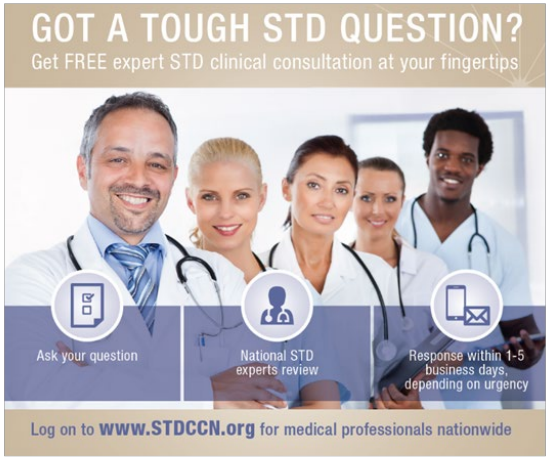
STD Clinical Consultation Network
STDCCN – NEW!!!

- Provides STD clinical consultation services within 1-5 business days, depending on urgency, to healthcare providers nationally
- Your consultation request is linked to your regional PTC's STD expert faculty
- Just a click away!
- www.STDCCN.org

For U.S. clinicians only?
(advice based on U.S. CDC Guidelines)

National Network of
STD Clinical Prevention
Training Centers

STD Clinical Consultation Network



National STD Curriculum

www.std.uw.edu

The *National STD Curriculum* integrates the most recent CDC STD Treatment Guidelines into a free, up-to-date, educational website. The site addresses the epidemiology, pathogenesis, clinical manifestations, diagnosis, management, and prevention of STDs.

- **Seven Self-Study Modules**
- **Twelve Question Bank topics with 100+ interactive board-review style questions**
- **Modular learning in any order with progress tracker**
- **Group registration and tracking for staff, students, and health care organizations**
- **FREE CME and CNE credits**

National Network of STD Clinical Prevention Training Centers

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