

A black and white scanning electron micrograph (SEM) showing a close-up view of what appears to be a colony of microorganisms, possibly bacteria or fungi, growing on a surface. The organisms are small, circular, and have a textured, somewhat cratered appearance. They are densely packed in several distinct clusters across the frame.

Should we be screening MSM for gonorrhoea?

CHRIS KENYON
ITM

Current NG/CT screening guidelines for MSM

| | Frequency | Sites |
|---|---|---|
| Centers for Disease Control and Prevention (CDC) | At least annually (every 3-6 months if at increased risk) | urethra, rectum, pharynx regardless of condom use |
| European Centre for Disease Prevention and Control (ECDC) | No recommendation | rectum, penis, urethra, pharynx |

The USPSTF concludes that the **current evidence is insufficient** to assess the balance of benefits and harms of screening for chlamydia and gonorrhea in men.



| | | |
|--------------------------------|-------------------|----------------------------------|
| Belgian PrEP Guidelines | 3 monthly | rectum, urethra, pharynx |
| Public Health Agency of Canada | At least annually | all potential sites of infection |

Key criterion: benefits must outweigh risks & costs

Wilson's criteria for screening

- the condition should be an important health problem
- the natural history of the condition should be understood
- there should be a recognisable latent or early symptomatic stage
- there should be a test that is easy to perform and interpret, acceptable, accurate, reliable, sensitive and specific
- there should be an accepted treatment recognised for the disease
- treatment should be more effective if started early
- there should be a policy on who should be treated
- diagnosis and treatment should be cost-effective
- case-finding should be a continuous process

Wilson Principles and practice of screening for disease; 1968



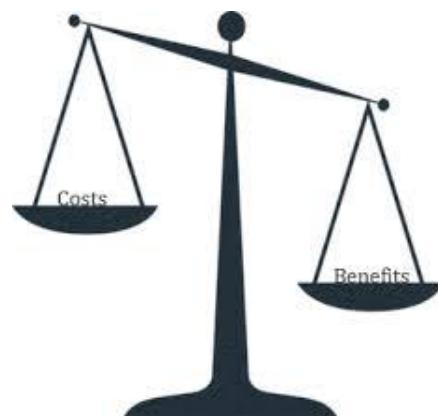
Cost vs. benefits of screening MSM for *N. gonorrhoea*

■ Benefits

- ↓ prevalence
- ↓ resistance
- ↓ HIV transmission
- ↓ morbidity

■ Costs/Risks

- Cost of PCRs
- ↑ resistance
- Certificate of health effect
- Prevent natural immunity



Unemo BMC ID 2015; Steward Brown BMJ 1997;
Future Microbiol. 2014;9(2):189-201

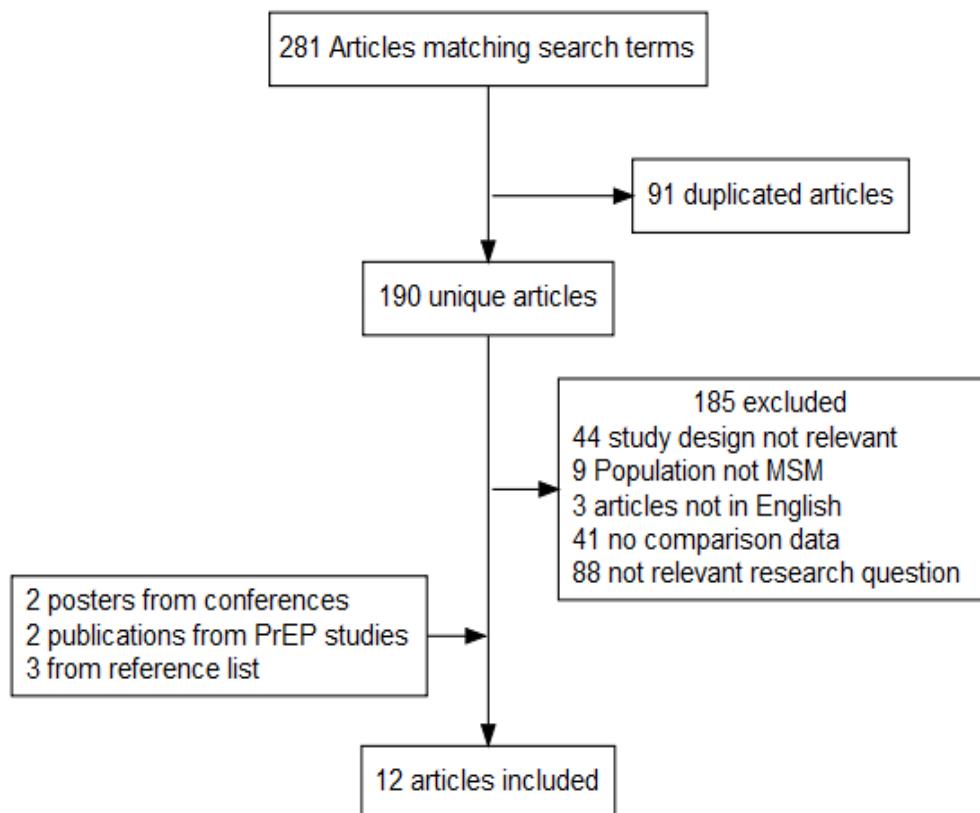
Do screening programmes for chlamydia and gonorrhea in MSM reduce the prevalence of these infections?

A systematic review of observational studies

A Tsoumanis, N Hens, C Kenyon

- Inclusion:

- Randomized clinical trial or a cohort study
- Screening for CT and/or NG
- Data from at least 2 time points within a period of 12 months
- MSM study population



Incr. prevalence

Decr. prevalence

C. trachomatis

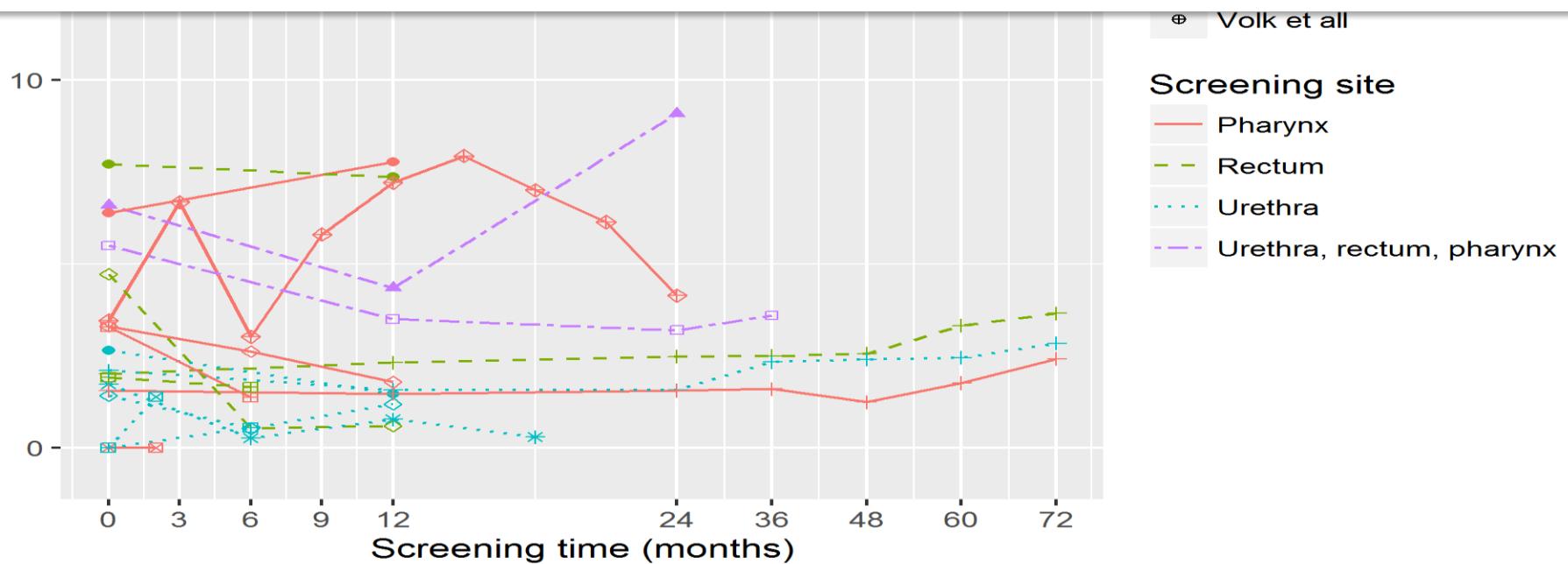
2

0

N. gonorrhoeae

2

2

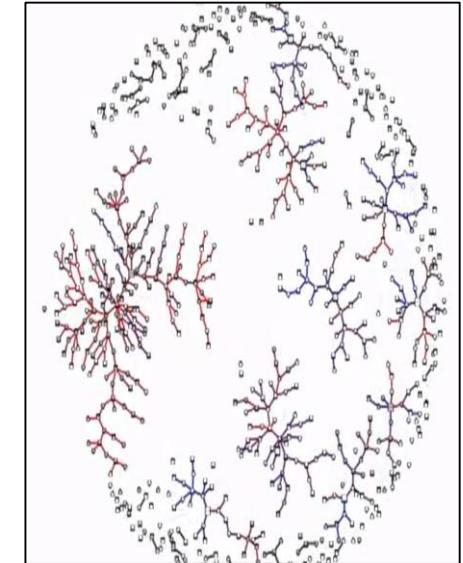


Do screening programmes for gonorrhea MSM reduce the prevalence of gonorrhoea?

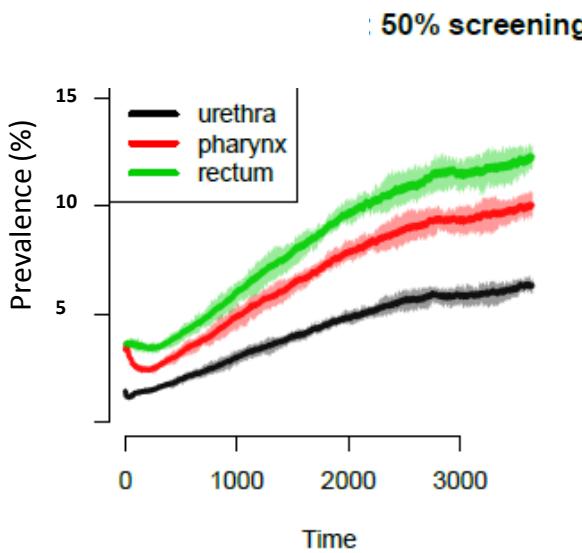
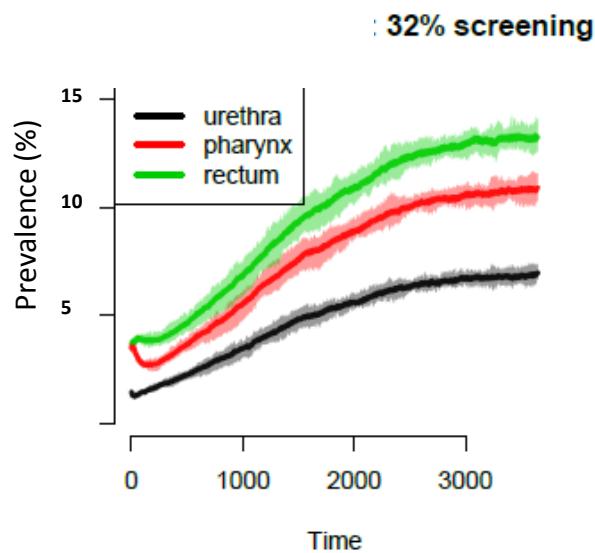
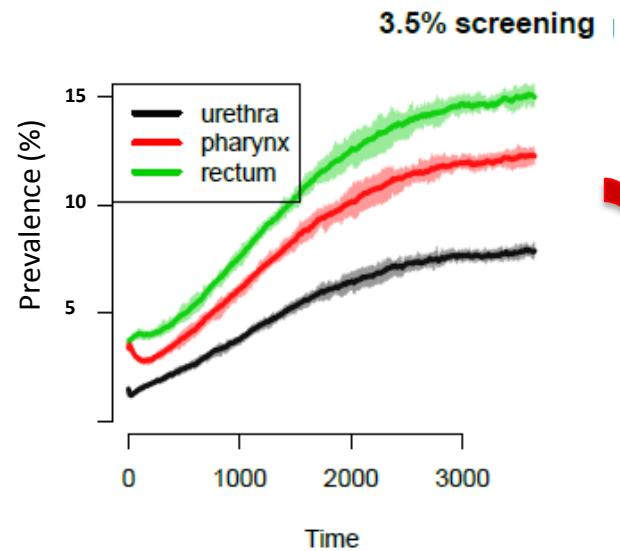
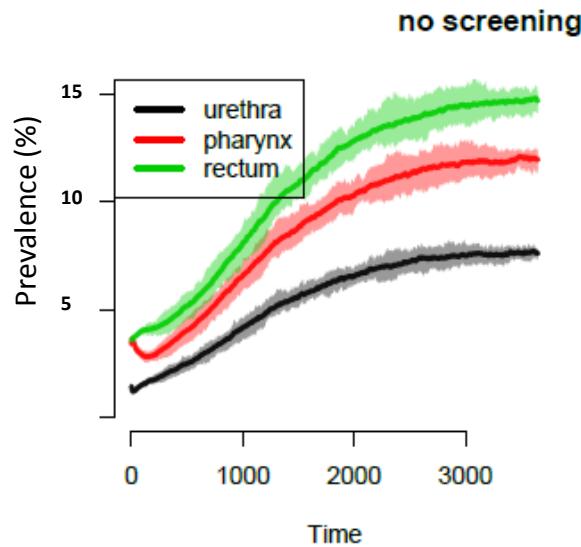
A modeling study

J Buyze, N Hens, W Vanden Berghe, C Kenyon

- Separable temporal exponential random graph models to model the sexual relationships network
- Behavioural parameters from Belgians in European MSM Internet Survey (n=3982)
- Simulate transmission of NG on this dynamic network
- Implemented in R package ‘EpiModel’

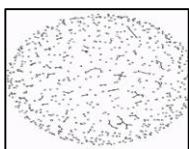


Screening has a small impact on prevalence



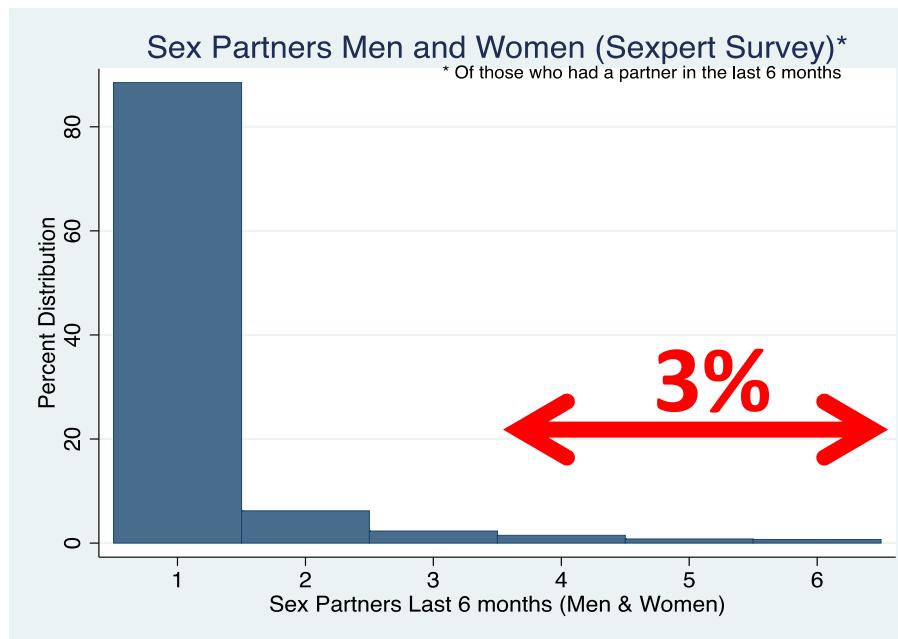
**11x incr.
in
antibiotics**

A dense network underpins high STI prevalences



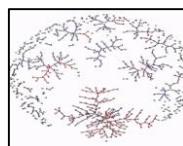
Heterosexuals (Sexpert)

No. of partners ≥ 4

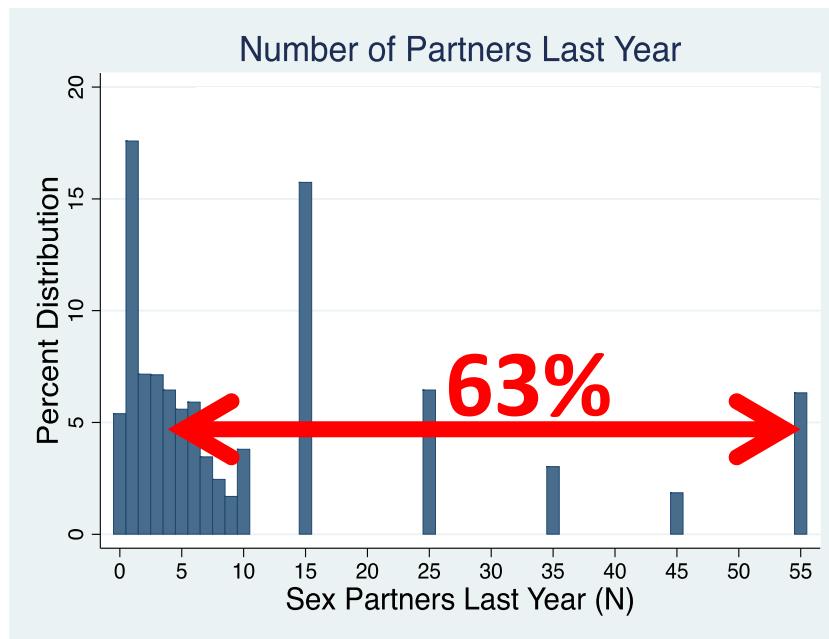


Concurrency*

9%



MSM (EMIS)



52%

* In past 12 months; EMIS; Leridon et al 1998



A dense network underpins high STI prevalences

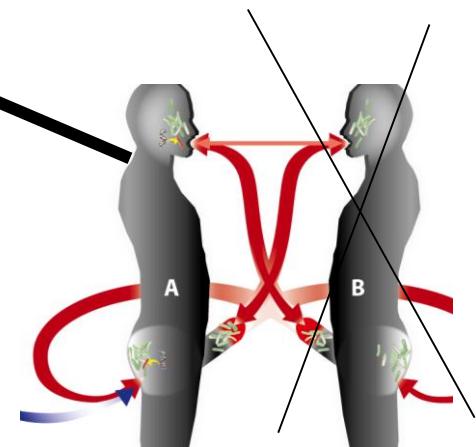
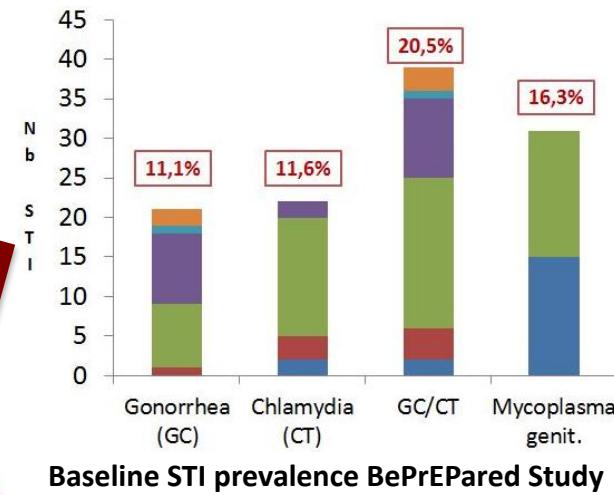
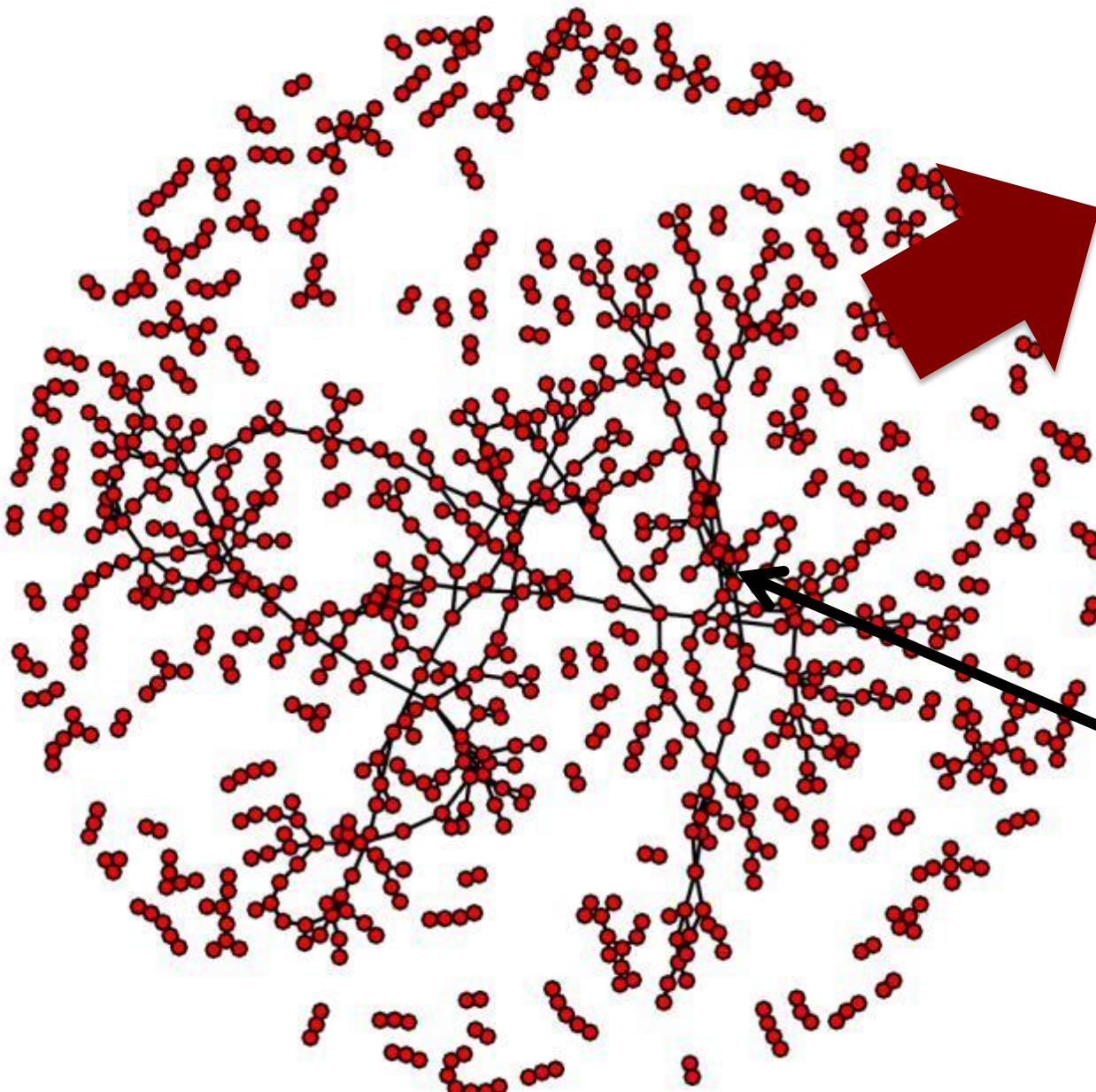


Image: M Laga

Effect of azithromycin on resistome

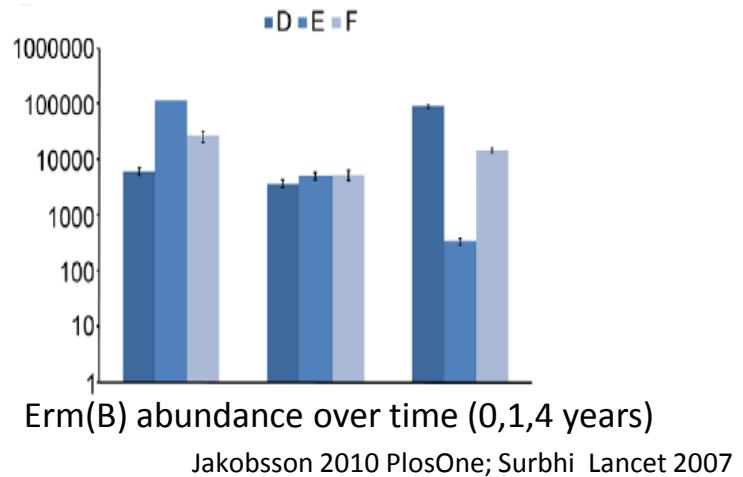
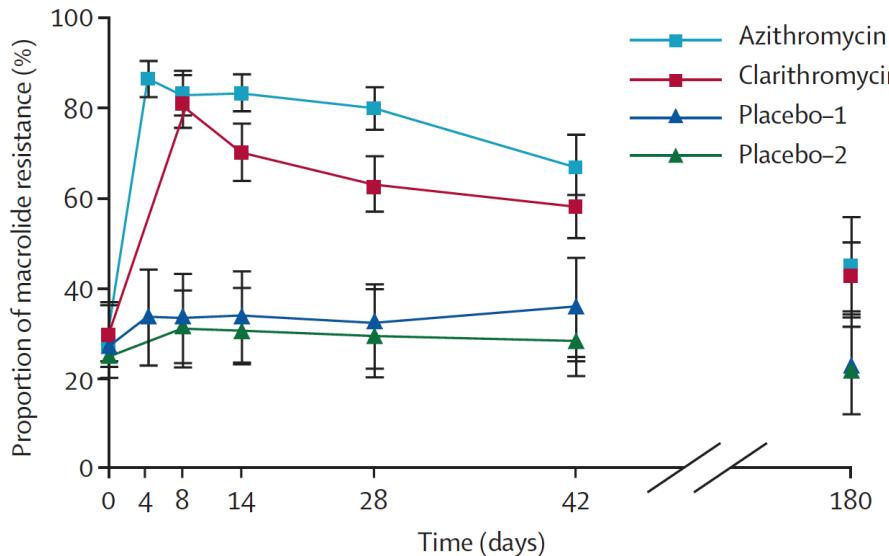
■ Erm's elevated x 4 years

■ Adamsson JAC 1999; Jakobsson Plos1 2010

■ After 1 year incr:

■ Staph, strep, enterococci & bacteroides

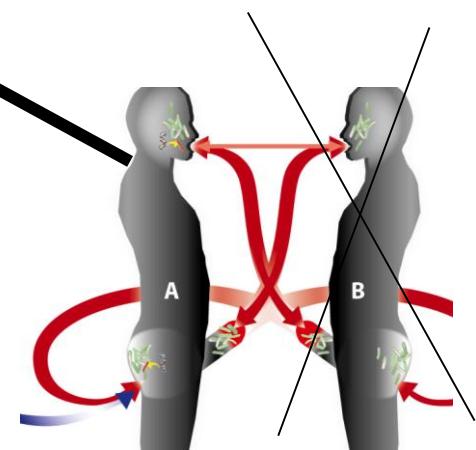
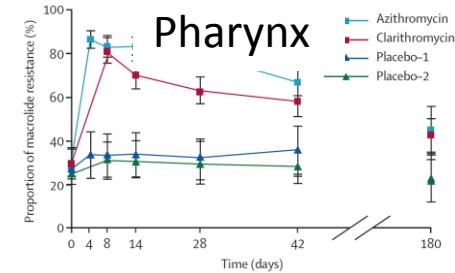
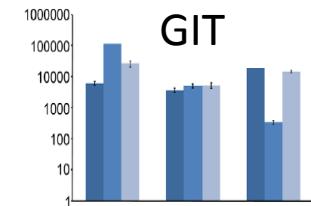
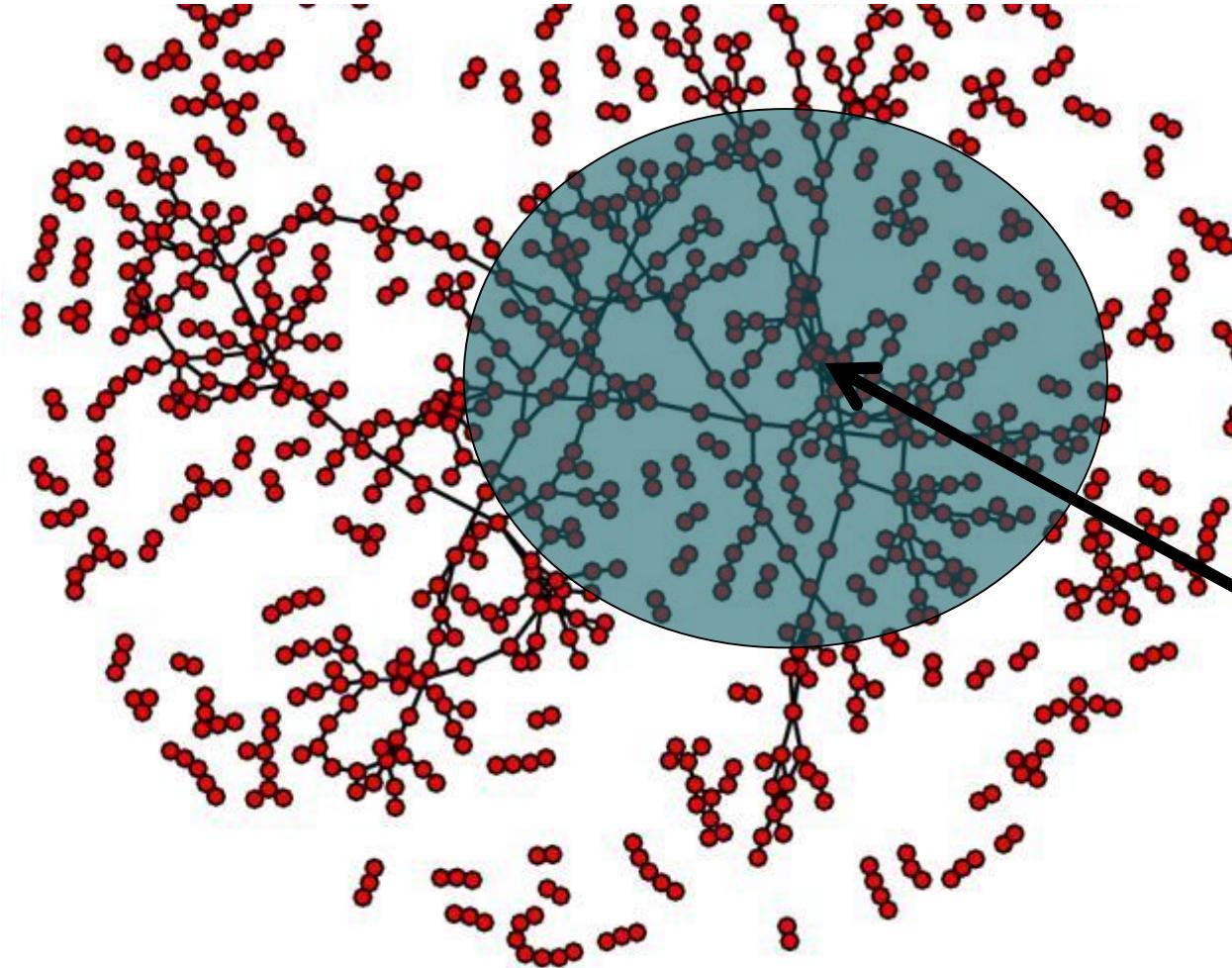
■ Jakobsson 2007 Scand J ID



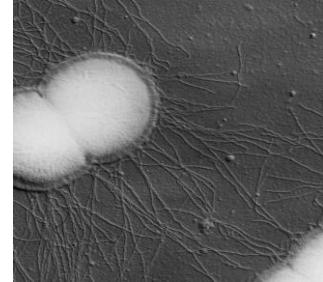
Jakobsson 2010 PlosOne; Surbhi Lancet 2007



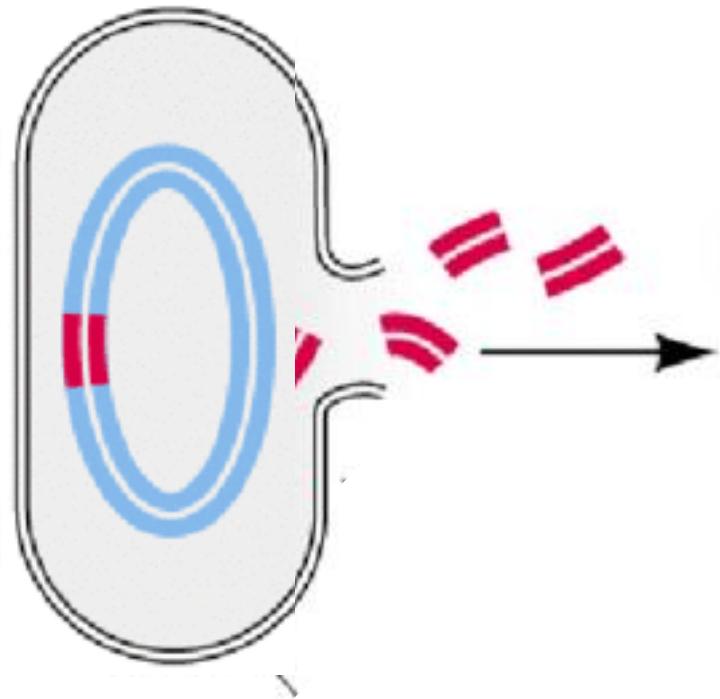
Net effect of screening in a densely connected network?



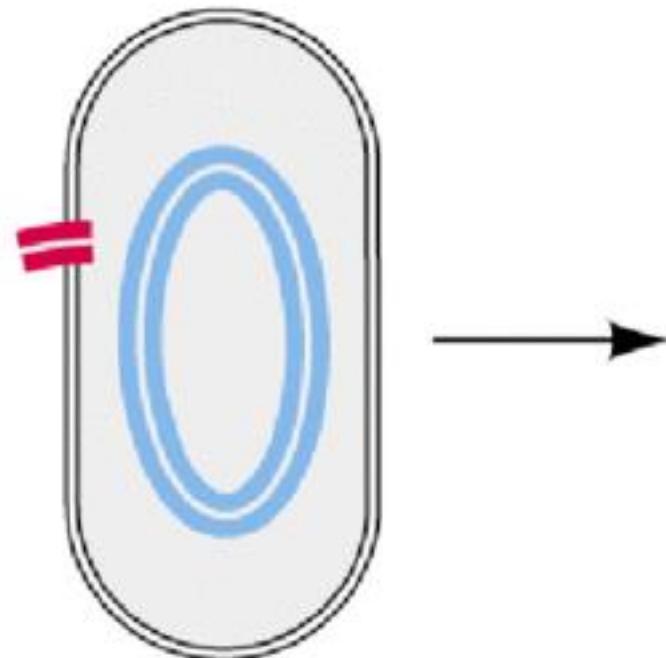
Gonococcus is a DNA sponge



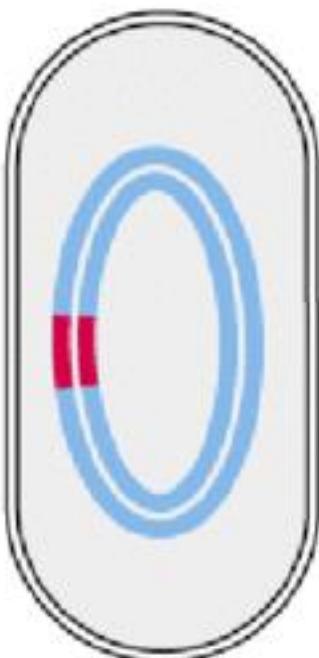
Cefixime Resis
oral *Neisseria* spp.



Cefixime Sens
N. gonorrhoea

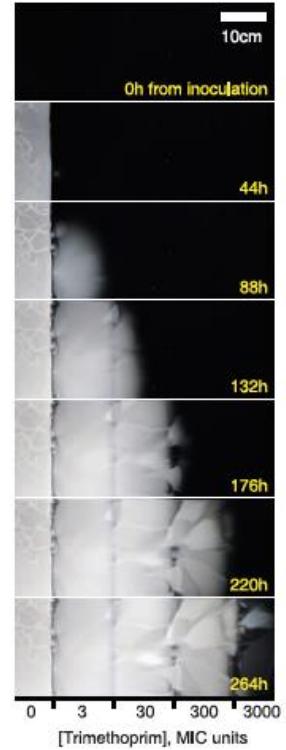
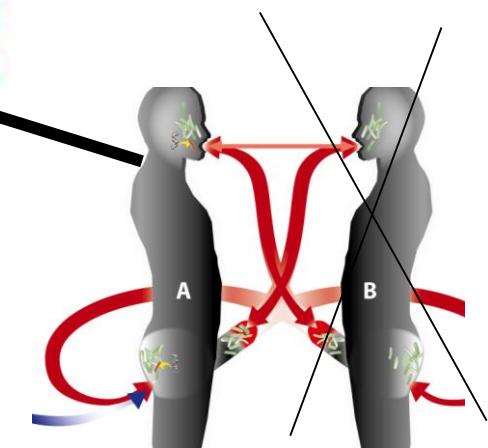
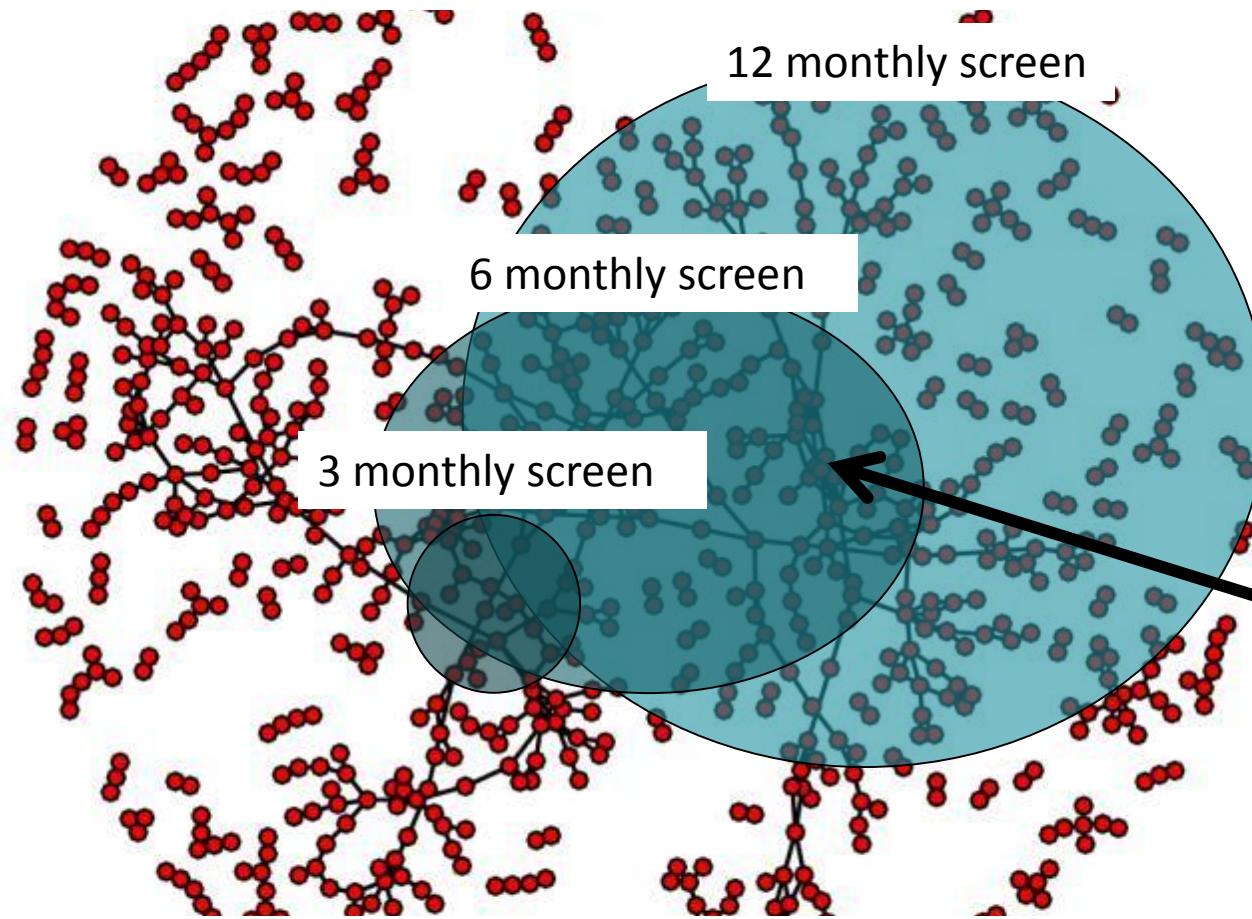


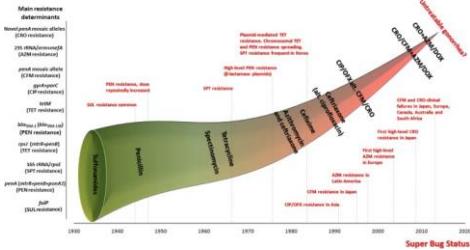
Cefixime Resis
N. gonorrhoea



Unemo Clin Micro Rev 2014

Dense network -> ↑STI prev
Using ABs to ↓prev -> resistance

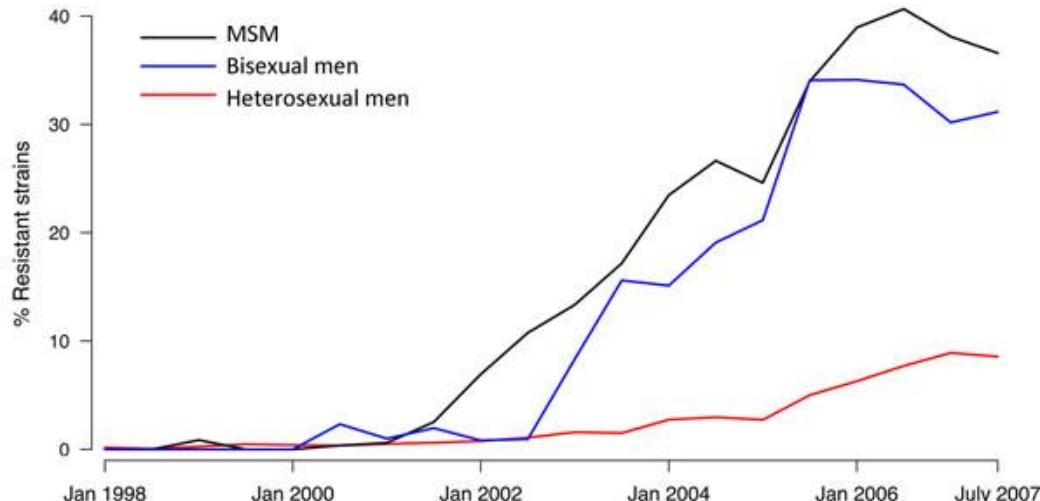




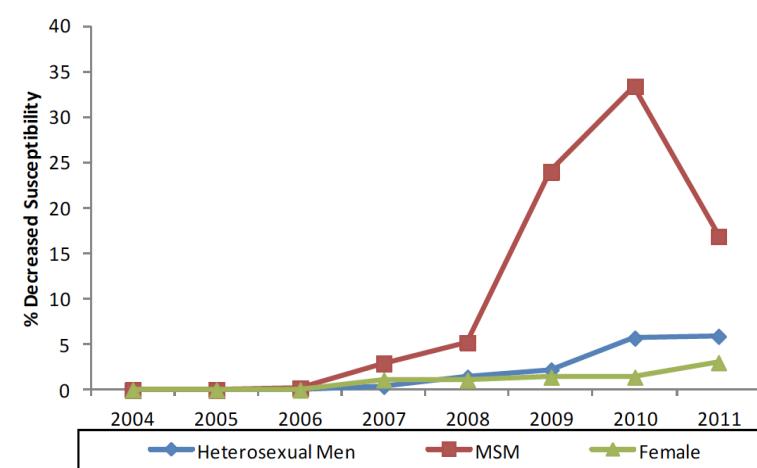
The role of core groups in the emergence and dissemination of antimicrobial-resistant *N gonorrhoeae*

D A Lewis^{1,2,3}

USA - Ciprofloxacin



UK - Cefixime



Resistance to tetracycline/ciprofloxacin/cefixime in gonorrhoea occur first in MSM (USA and UK)

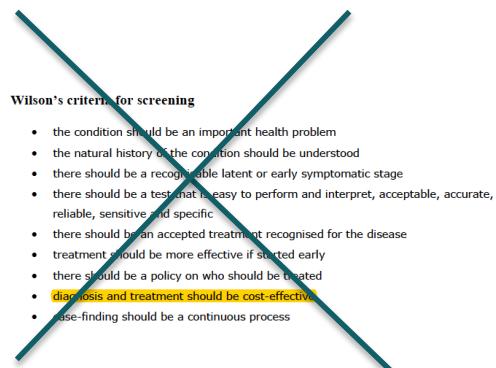
Conclusion – net benefit of NG screening?

■ Benefits

- ↓ prevalence **+/-**
- ↓ resistance -
- ↓ HIV transmission -
- ↓ morbidity -

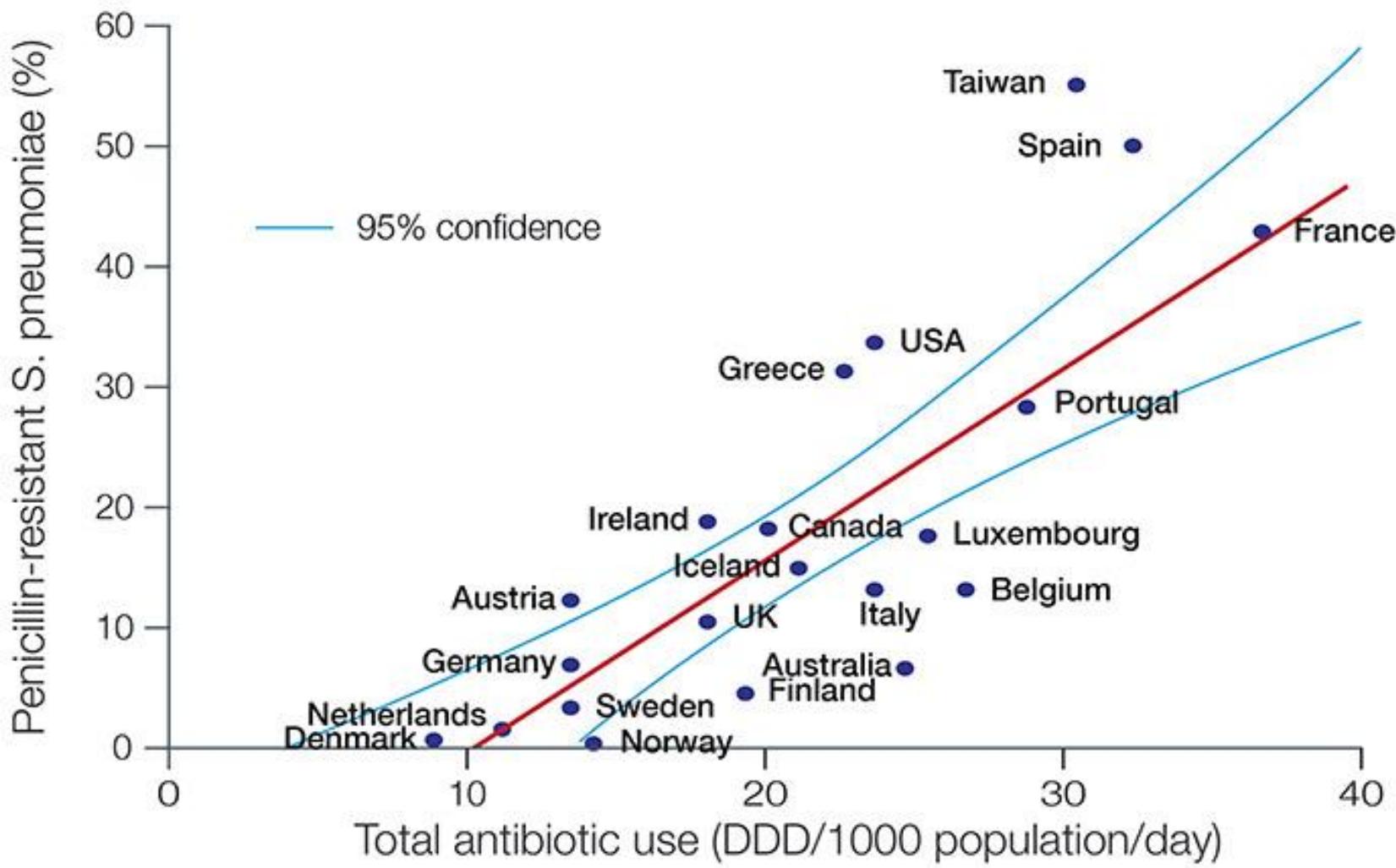
■ Costs/Risks

- Cost of screening +
- ↑ Resistance ++
- Certificate of health effect ?
- Prevent natural immunity ?



Study teams

- Jozefien Buyze
- Achilleas Tsoumanis
- Niel Hens
- Wim Vanden Berghe



Source: WHO data 2000-2003

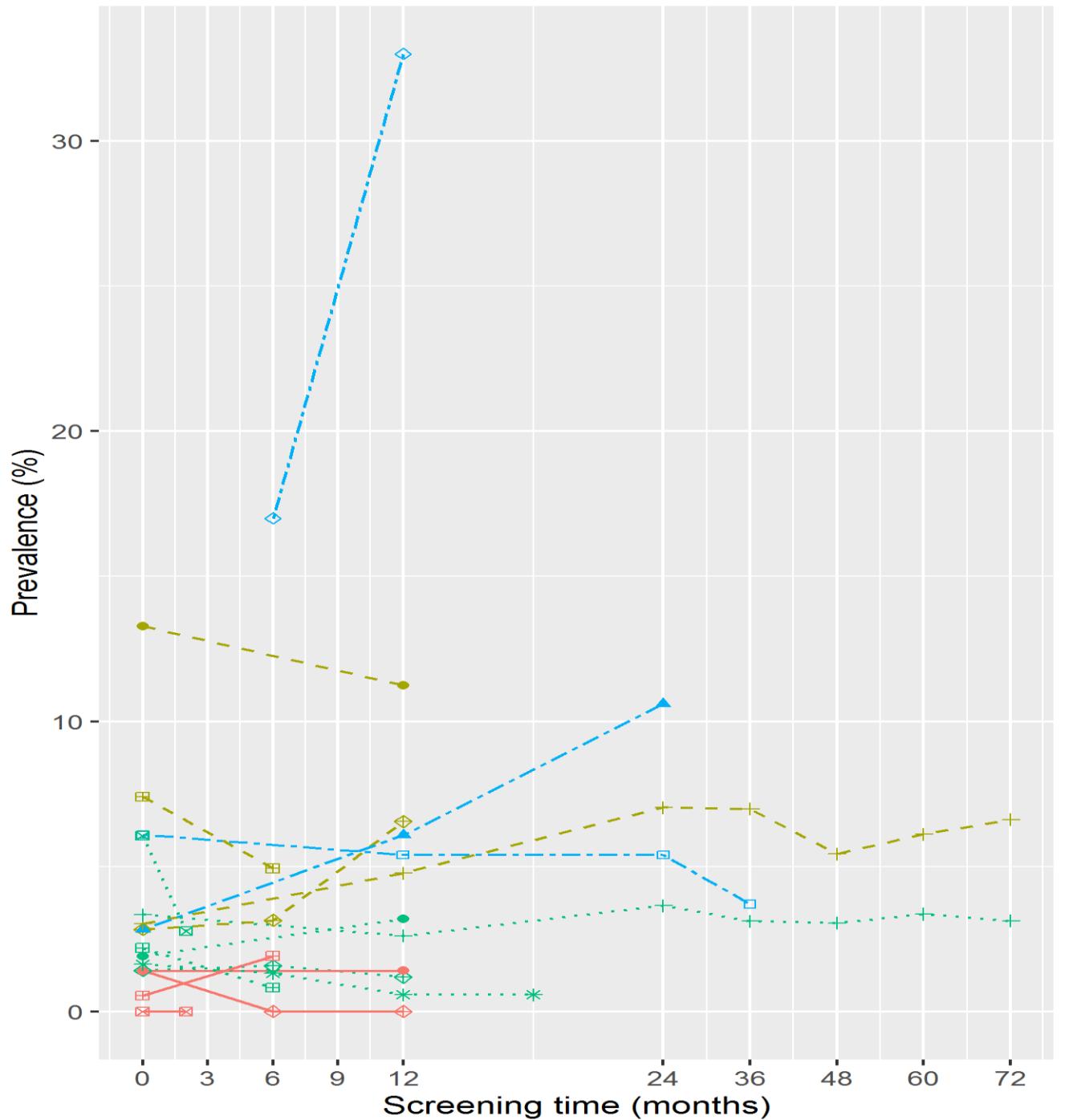
Risks 1

Screening could seriously damage your health

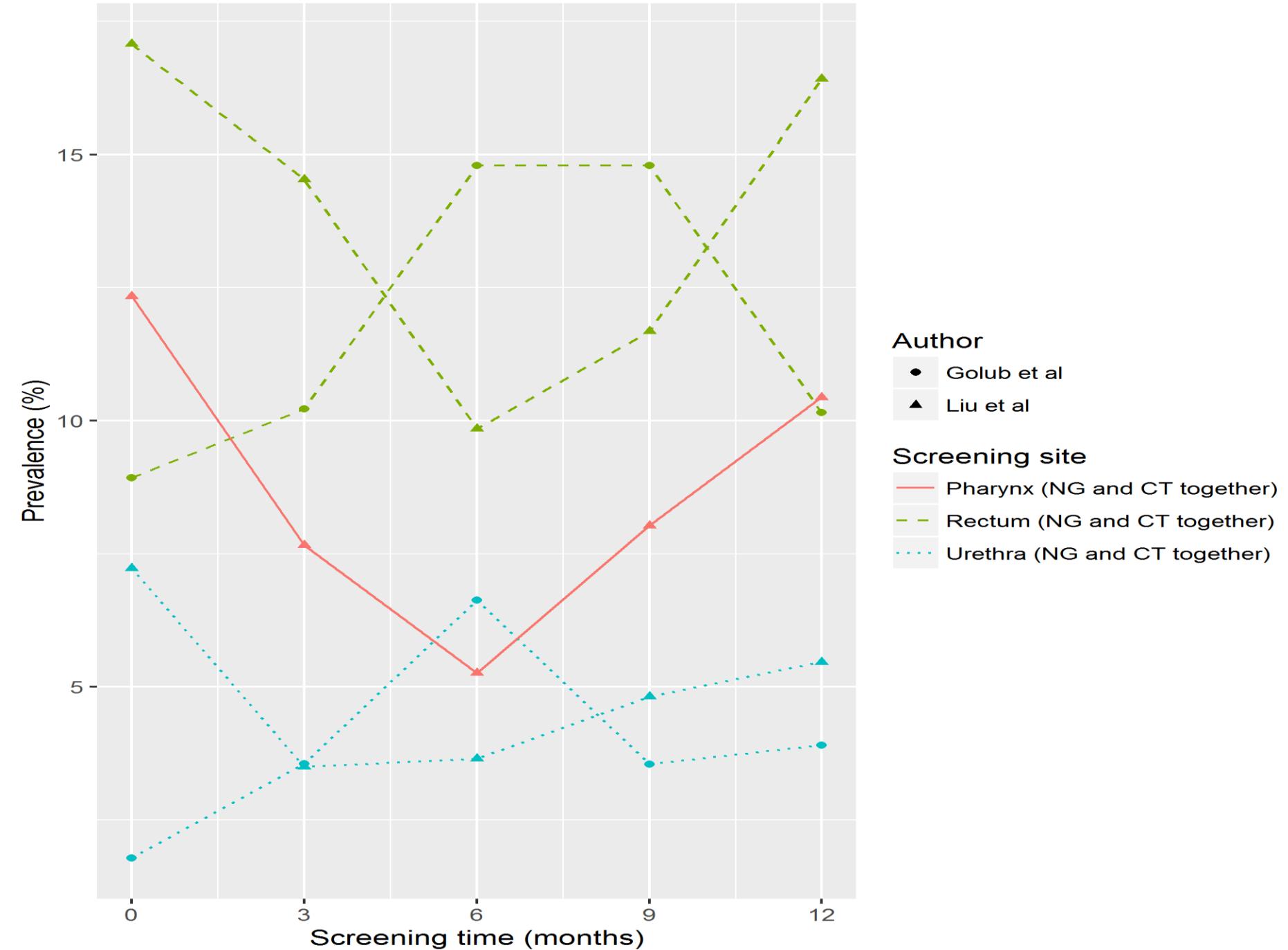
Decisions to screen must take account of the social and psychological costs

- ‘certificate of health effect’
 - eg people who screen negative for cancer may feel safe continuing smoking
 - Screening programmes may also imply that good health can be maintained by regular visits to the doctor for check ups and that individual behaviour is less important.

Reported prevalence for CI per site



CT and NG reported together



Results – Study characteristics

- All studies between 2001 and 2016, almost all in high income countries
- Six were cohort studies, one a screening evaluation study, one RCT of a behavioral intervention and four PrEP studies
- All studies reported screening data for CT and NG, either separately for the two infections and the different screening sites or combinations of them
- Three focused only on HIV-positive MSM, 5 only on HIV-negative ones and 4 included MSM regardless of HIV-status.

Results – Study characteristics

- Four performed screening at least annually, 4 offered screening every 6 months and 3 studies screened quarterly. Only one screened at two time points, 2 months apart.
- In almost all studies (11 out of 12), screening included urethral testing, whereas 10 studies screened for pharyngeal infections and 9 for rectal infections. Only 8 studies screened at all three sites.

Discussion

- Significant change in prevalence only in 3 out of 14 possible analyses.
- All of them debated by the respective authors or possibly explained by small number of cases.

Discussion

- Our review provides little evidence that screening for NG and CT in MSM has an effect on the prevalence of these organisms.
- No evidence was found to supports a dose-response effect. Frequent screening does not seem to reduce prevalence more effectively than annual screening.

Limitations

- No control group available → Real effect of screening ?
- Limited generalizability (studies from high-income countries)
- Variant population (e.g. open cohort studies)
- Unavailable denominator data (stat. tests not possible).
- Focus only on effect of screening on prevalence. No consideration of confounding characteristics in each study (e.g. condom use, contact tracing and partner therapy).

Other considerations

- Paradox that NG control may result in the generation of antibiotic resistance in core groups.
- Antibiotic stewardship, a key component of which is restricting the use of antibiotics to cases where benefits clearly outweigh risks.
- Possible benefits in preventing the acquisition and lowering the transmission of HIV by treating asymptomatic NG and CT?

Need for update/validation of current guidelines?

WHO criteria for introducing screening programmes include:

- scientific evidence of screening effectiveness
- overall benefits of screening should outweigh the harms

Our study was not able to provide evidence showing that screening for CT and NG consistently lowers the prevalence of these infections in MSM.

Suggestions for evidence generation

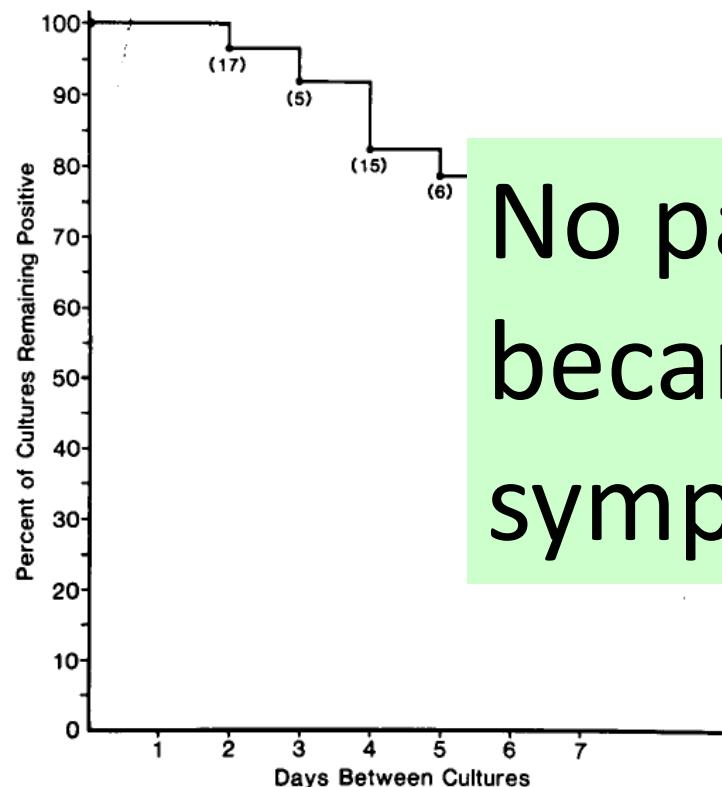
- Conducting cluster randomized controlled trials in high and low risk MSM groups.
- Including CT, NG and HIV testing in later phases of multi-country studies, e.g. EMIS

What happens if one doesn't screen?

Natural history of pharyngeal gonorrhoea

■ 1 week fu:

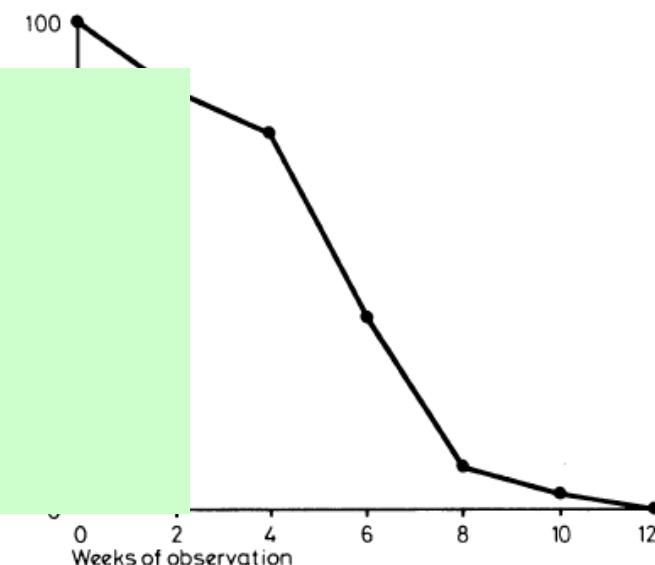
60 pts had culture repeated without treatment



• 12 week fu:

17 pts had culture repeated without treatment

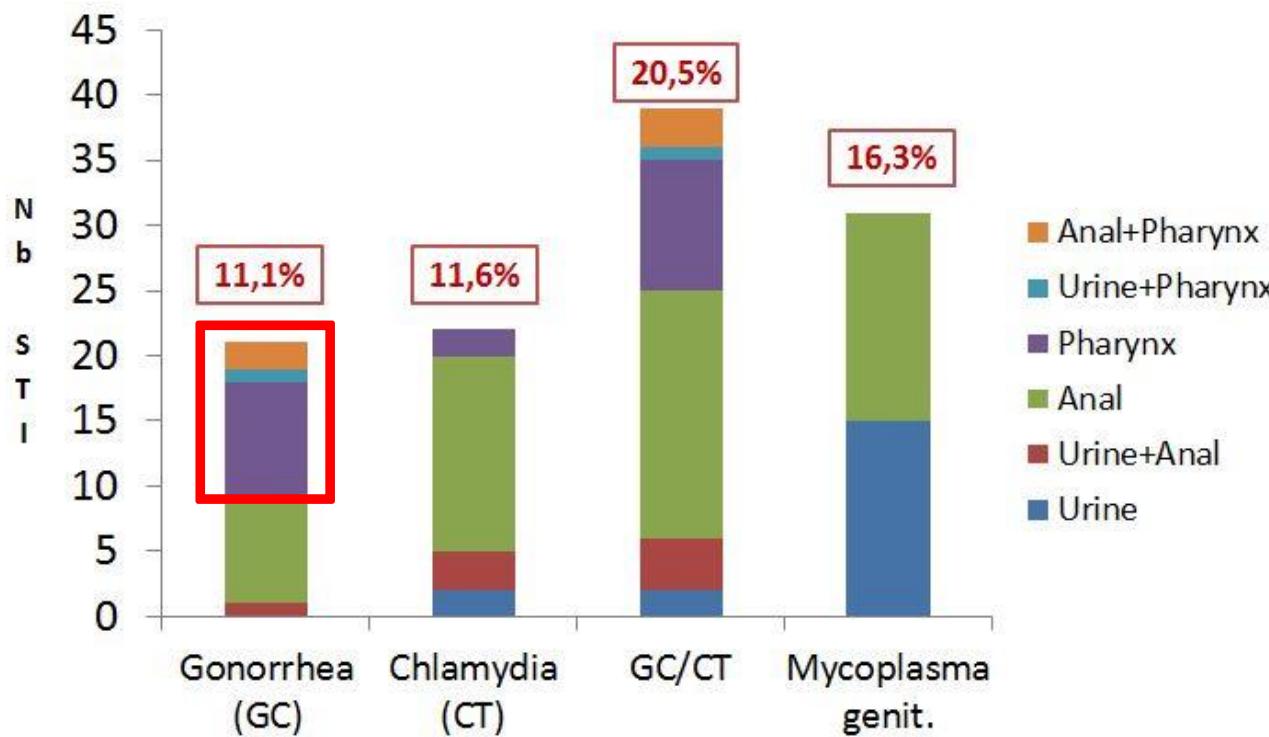
No patient became symptomatic



Proportion of 17 untreated patients with throat cultures positive for *N gonorrhoeae* during period of observation after initial positive culture.

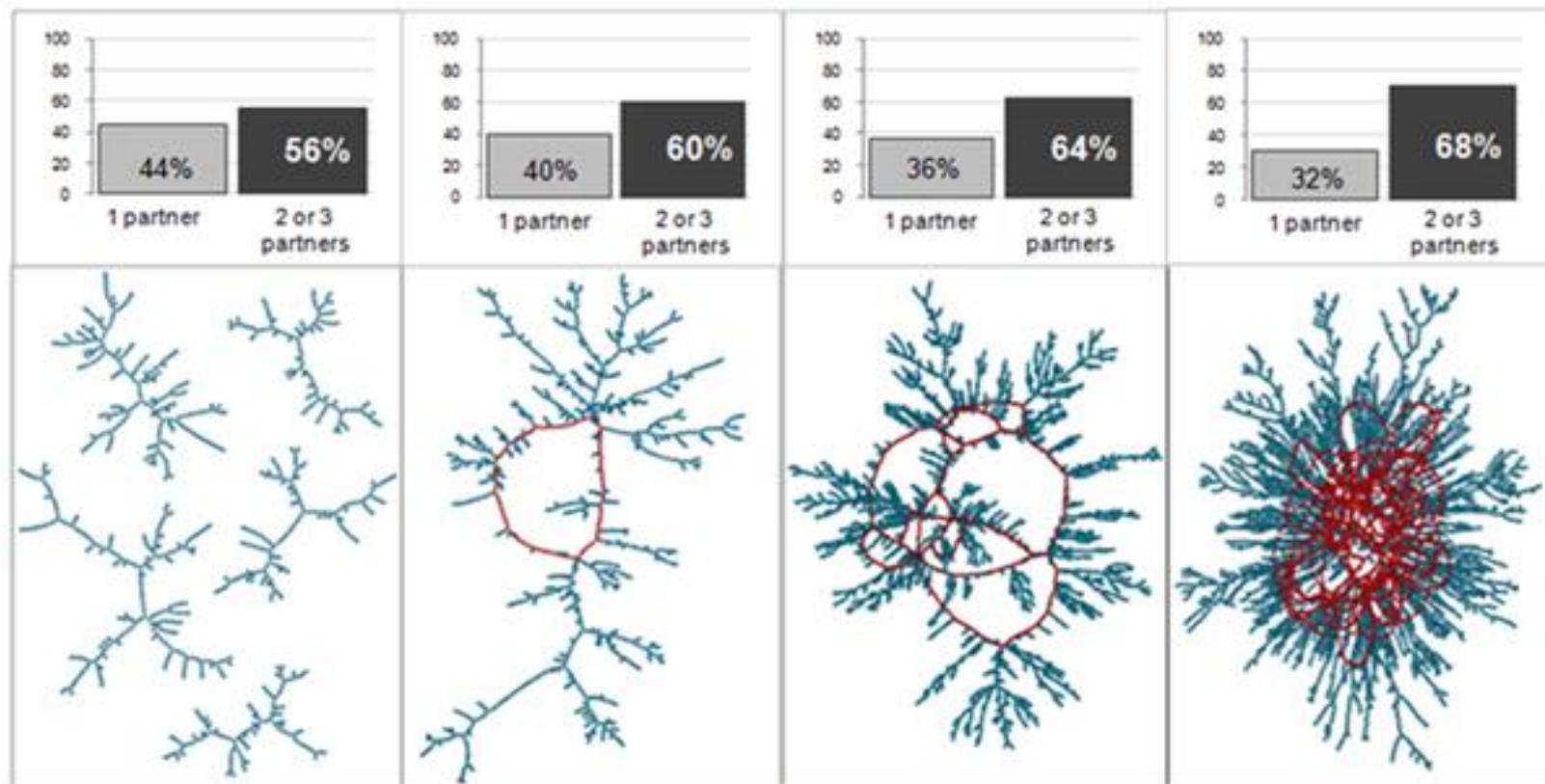


Be PrEP ared Study: Prevalence of STIs at baseline visit



Slide: Irith De Baesler

Small increases in concurrency lead to massive increases in the connected component



2%

10%

41%

64%

Percent of people that are connected in the network through their sexual partnerships

Carnegie NB, Morris M (2012) Size Matters: Concurrency and the Epidemic Potential of HIV in Small Networks. PLoS ONE 7(8): e43048. doi:10.1371/journal.pone.0043048

<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0043048>

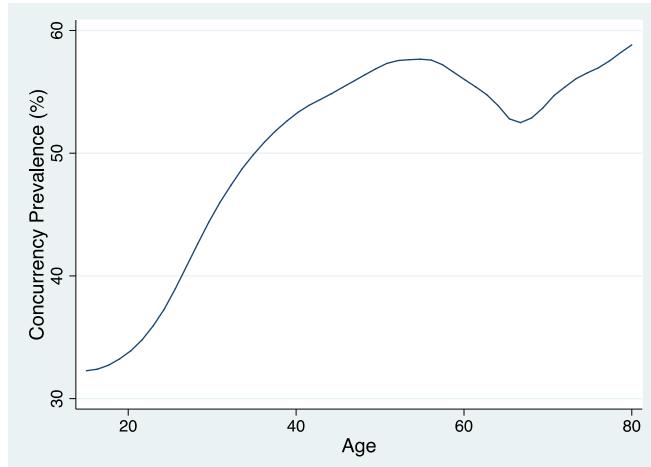
Sexual Partner Concurrency

Concurrency in last year in Belgium:

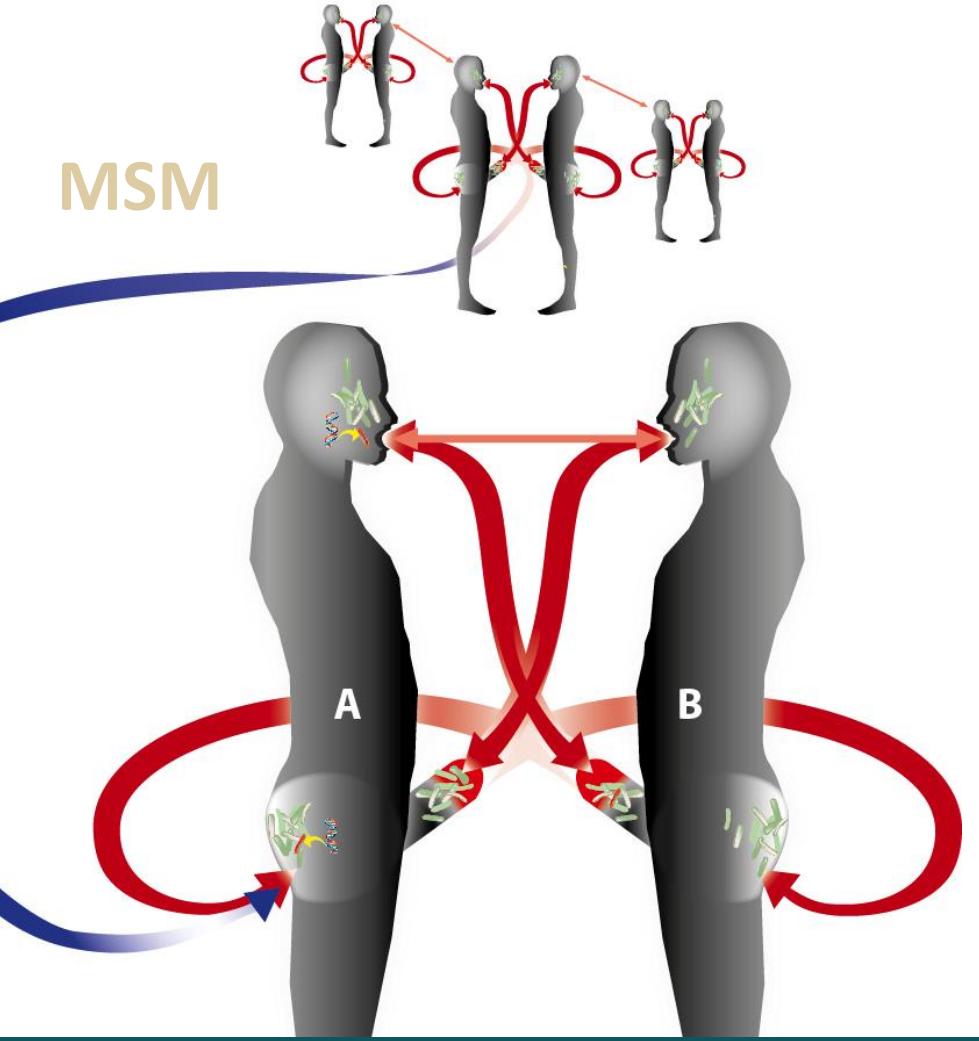
MSM 52.3%

Heterosexuals 9.2%

Leridon et al 1998

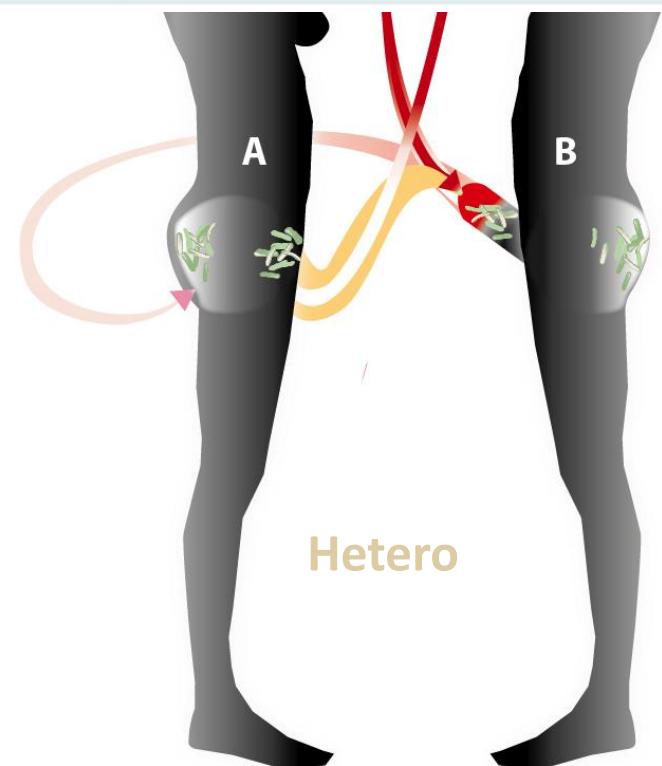


MSM

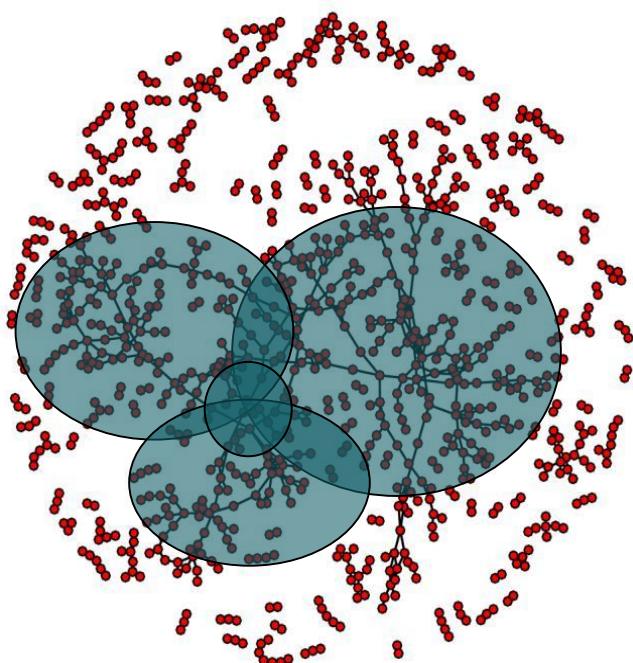


A sexual ecosystem at high risk for resistance

1. Dense network
2. High NG prevalence & frequent ABs
3. Incr. shuttling between GIT/Mouth/Urethra



Spatiotemporal microbial evolution on antibiotic landscapes



Bayn Science 2016

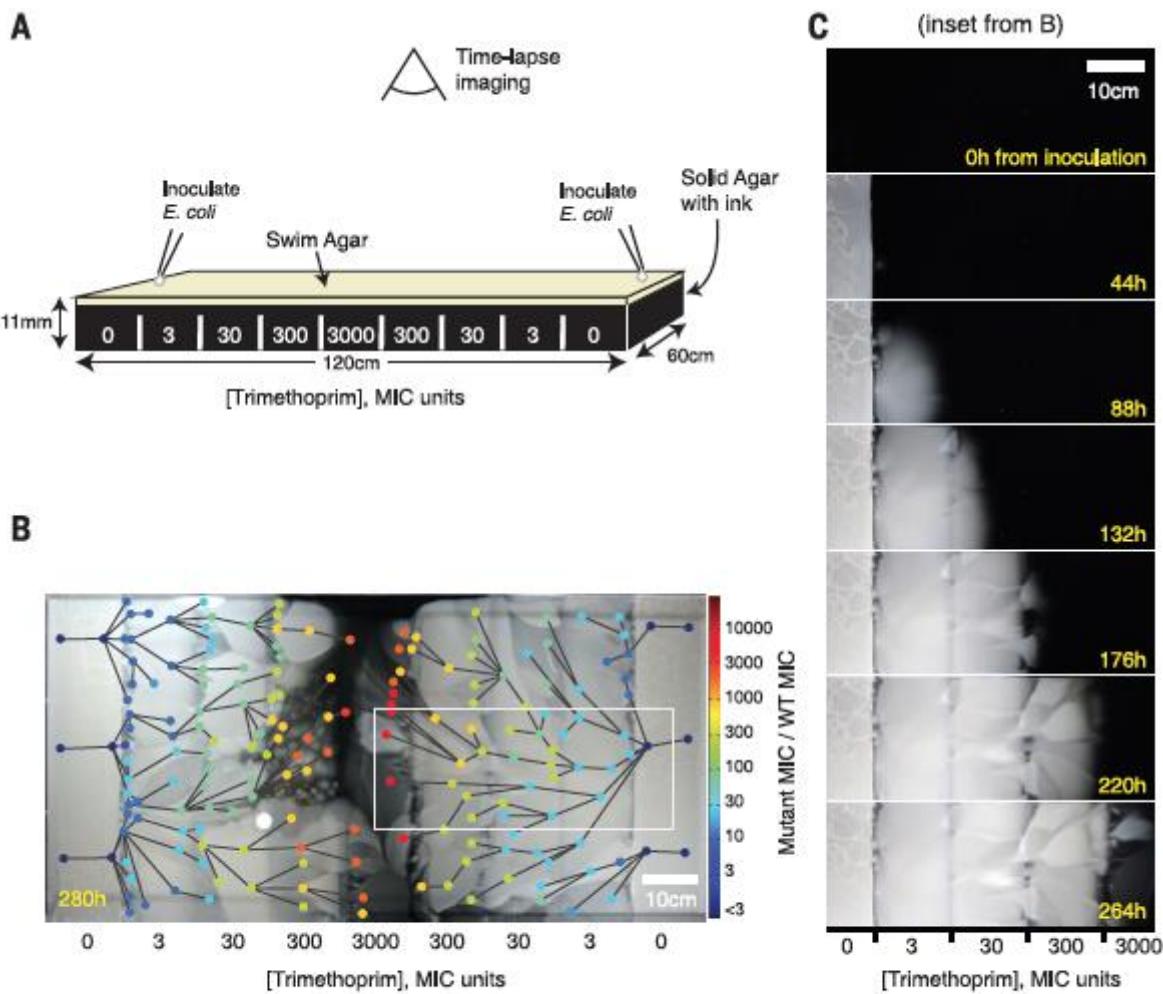


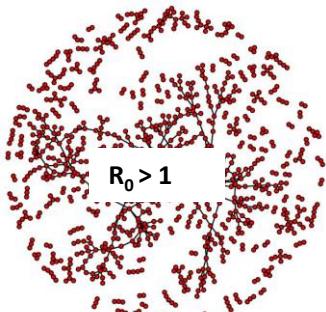
Fig. 1. An experimental device for studying microbial evolution in a spatially structured environment. (A) Setup of the four-step gradient of trimethoprim (TMP). Antibiotic is added in sections to

NG Prevention paradox

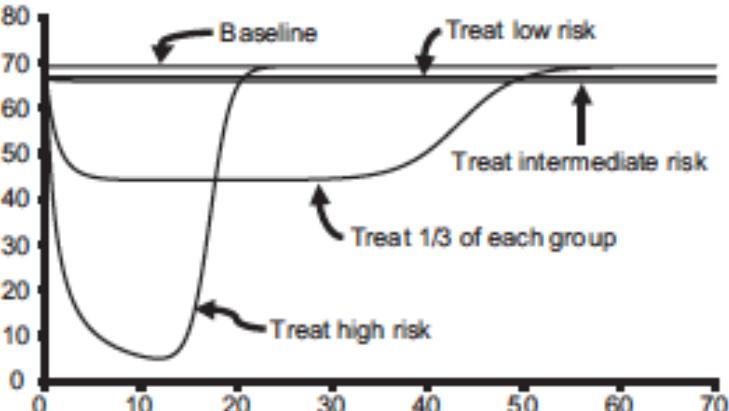
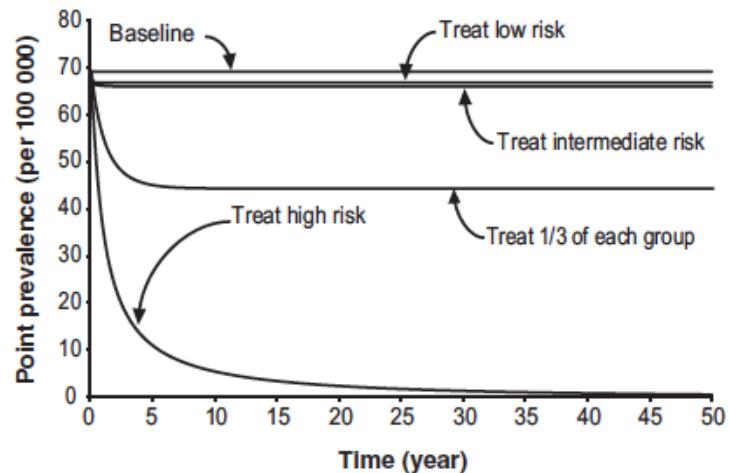
Core groups, antimicrobial resistance and rebound in gonorrhoea in North America

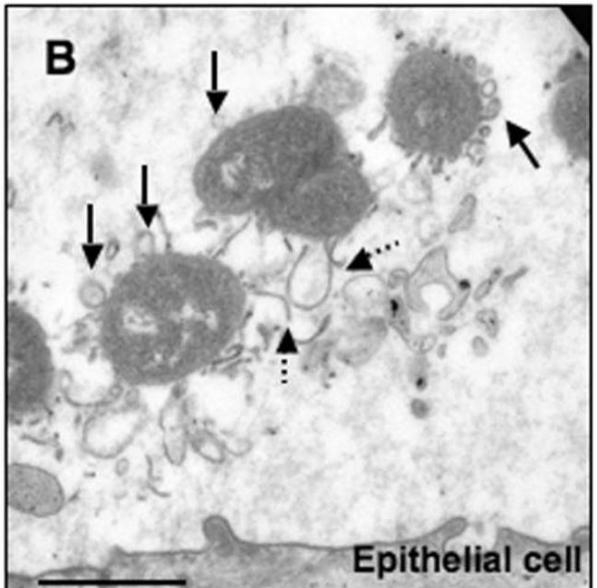
Christina H Chan,^{1,2} Caitlin J McCabe,^{1,2} David N Fisman^{1,2}

NG control only possible if core groups targeted

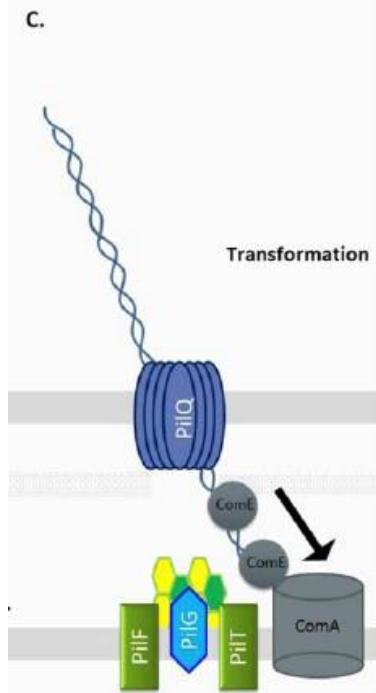
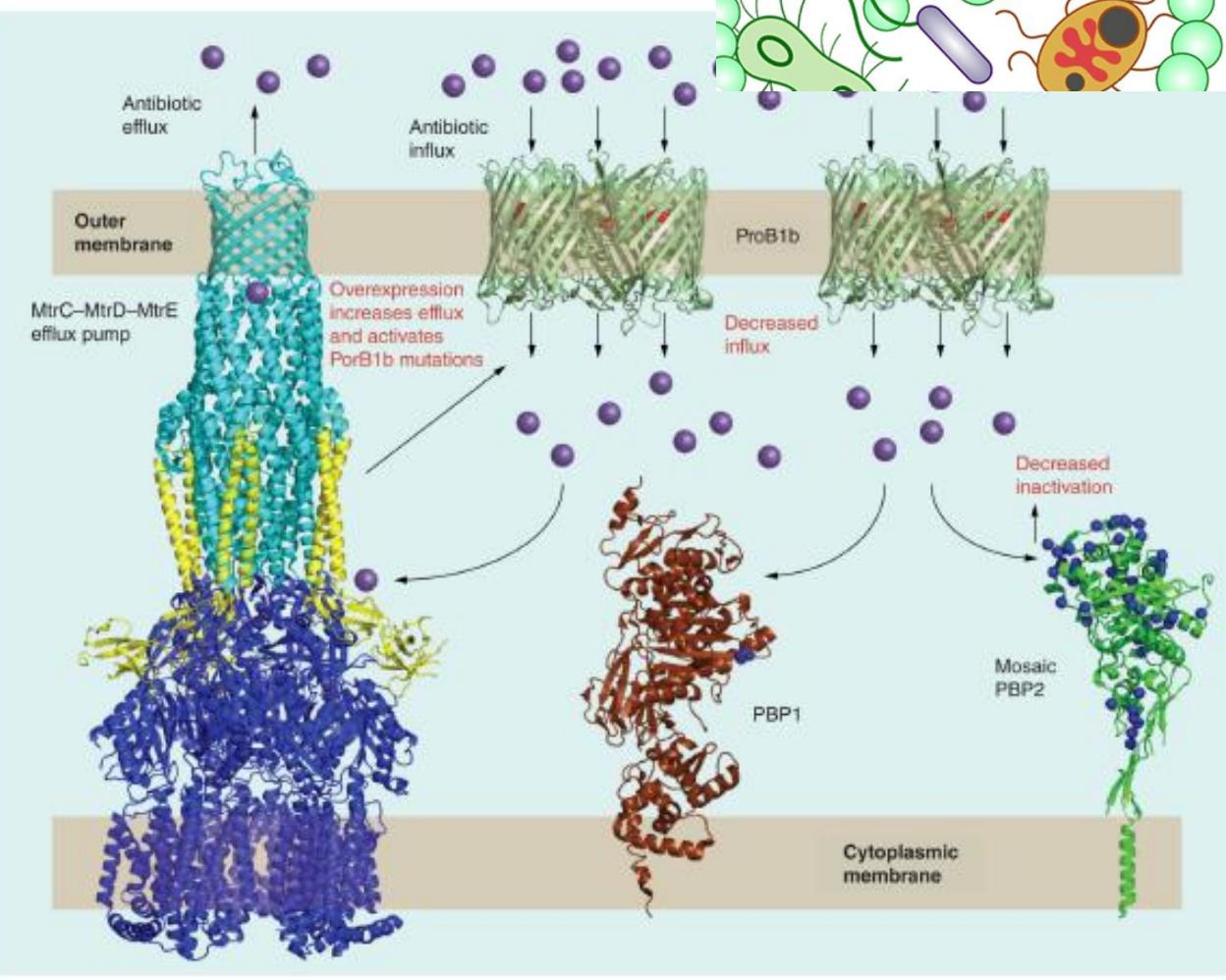
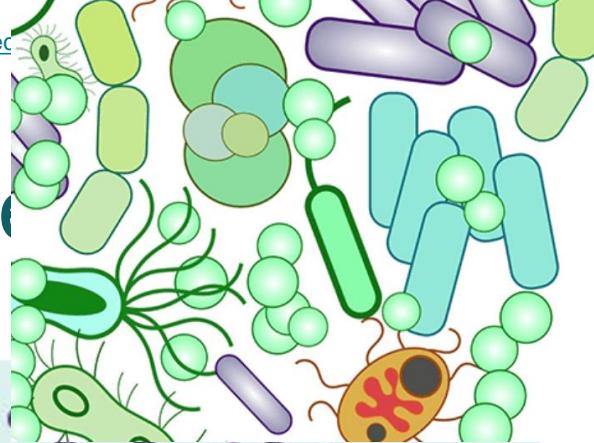


When antimicrobial resistance exists, a focus on the core group causes rebound in incidence, with maximal dissemination of antibiotic resistance.





NG = DNA sponge



Resistance in hospitals vs. core groups

Hospital resistance

- large no. patients in close proximity
- Immunosuppression
- HCWs as vectors
- Frequent and prolonged ABs

Sexual core groups

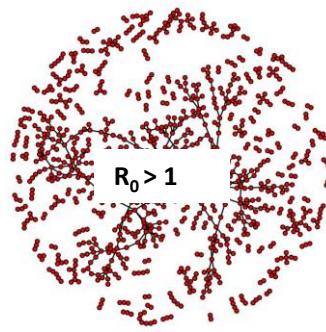
- Dense sex networks
- Immunosuppression?
- Sex as vector
- ABs?

Response

- Reduce AB use
- IC programmes
 - Hand washing
 - Isolation
 - Surveillance
 - Sterilization of equipment

Response

- Screen (and increase AB use)
IC programmes
 - Throat washing
 - Condoms
 - Isolation
 - Surveillance



Risks 2: Is gonorrhoea becoming untreatable?

Future Microbiol. 2014;9(2):189-201



Azithromycin-resistant *Neisseria gonorrhoeae* isolates in Guangzhou, China (2009–2013): coevolution with decreased susceptibilities to ceftriaxone and genetic characteristics

Jing-Yao Liang^{1,2†}, Wen-Ling Cao^{1,2†}, Xiao-Dong Li^{1,2}, Chao Bi^{1,2}, Ri-Dong Yang^{1,2}, Yan-Hua Liang^{1,2}, Ping Li^{1,2}, Xing-Dong Ye^{1,2}, Xiao-Xiao Chen^{1,2} and Xi-Bao Zhang^{1,2*}

Azithromycin Resistance Is Coevolving with Reduced Susceptibility to Cephalosporins in *Neisseria gonorrhoeae* in Ontario, Canada

Vanessa G. Allen,^{a,b} Christine Seah,^b Irene Martin,^c Roberto G. Melano^{a,b,d}

Public Health Ontario Laboratories, Toronto, Ontario, Canada^a; Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada^b;

2016 STD Prevention Conference Press Release



For immediate release: September 21, 2016

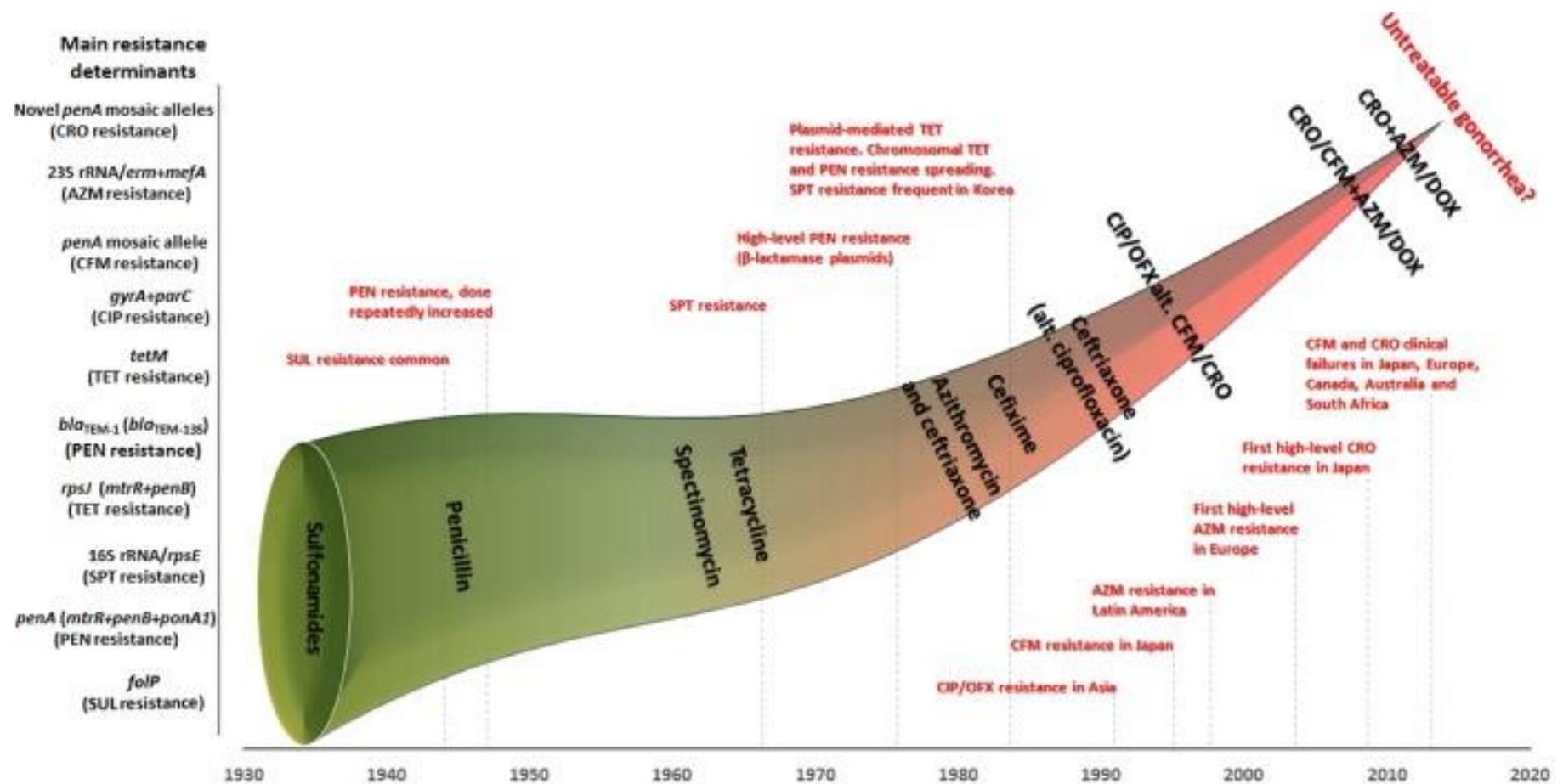
Contact: National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

(404) 639-8895 | NCHHSTPMediaTeam@cdc.gov

New Warning Signs that Gonorrhea Treatment May be Losing Effectiveness

ANTIBIOTIC RESISTANCE THREATS in the United States, 2013 CDC

With Gono resistance is inevitable...



Clin Microbiol Rev. 2014 Jul; 27(3): 587–613.

Super Bug Status!

Resistance within 3 years...

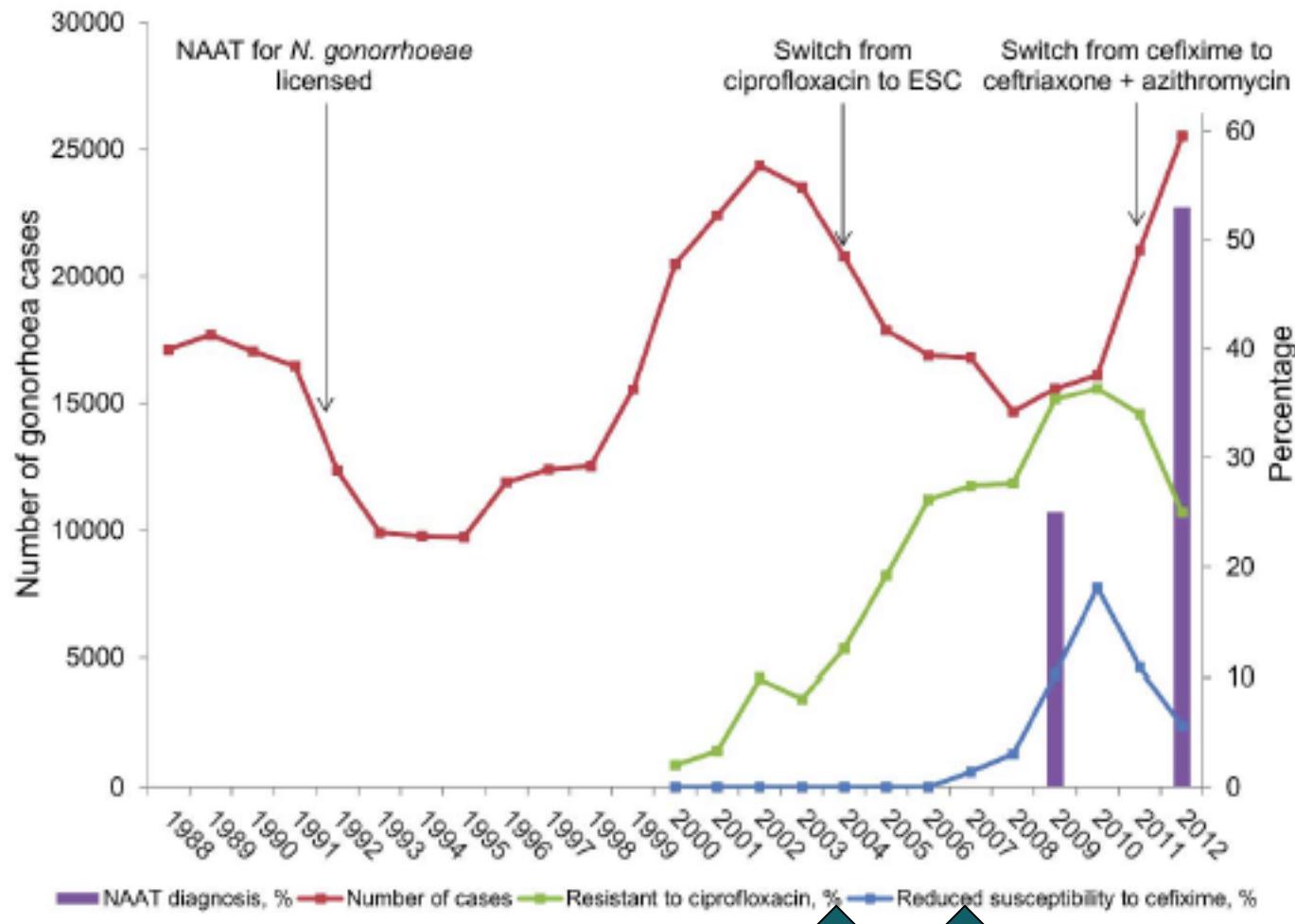
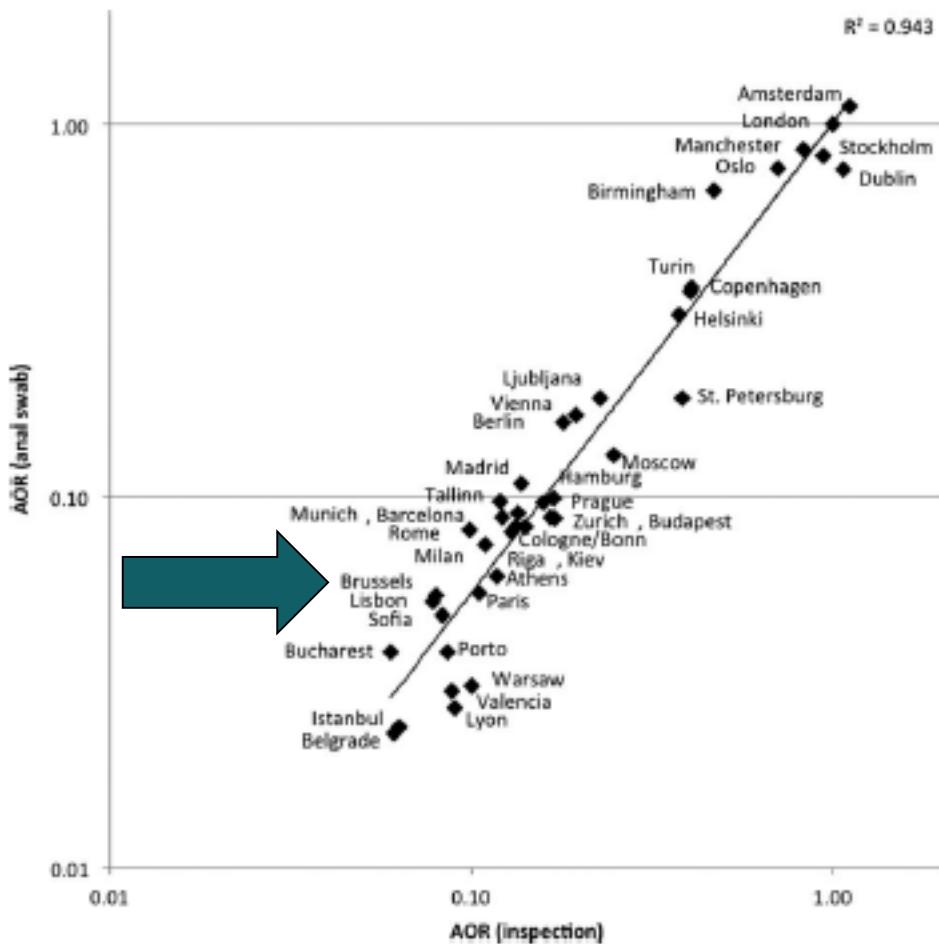


Figure 1. Trend in number of cases of gonorrhoea diagnosed, NAAT testing for gonorrhoea, and selected antimicrobial resistance in genitourinary medicine clinics in England and Wales. Cases of gonorrhoea are from Public Health England; percentages of tests

Half-hearted screening is particularly dangerous

How are we doing in Belgium?



Chance of screening for bacterial STIS acc.
EMIS:

| | Brussels | Amsterdam |
|------------|----------|-----------|
| Inspection | 7% | 58% |
| Anal swab | 3.5% | 72% |

Schmidt AJ, et al. Sex Transm Infect 2013

Figure 1 Scales in antibiotic resistance studies

| Genetic level of bacteria | Mutations, gene transfers Bacterial fitness | Emergence of new resistance mechanisms |
|---|---|---|
| Bacterial population | Colonization of ecosystems Competition Under antibiotic exposure: elimination of susceptible germs; persistence of resistant bacteria | Intra-host emergence and selection of resistant bacteria |
| Host level and Interactions with | | |
| Human population level | Cross transmission between humans via contact or environment Epidemic fitness | Selection of resistant bacteria in population and their spread |

At the bacterium genetics level, new resistance mechanisms emerge through modifications of the microbe's genome. These changes may arise through two different evolutionary processes: vertical evolution, via a mutation or combination of mutations; and horizontal evolution, resulting from the exchange of genetic material between two different strains or species. One microorganism within the bacterial population colonizing or infecting a host may undergo genome modification leading to the evolution of a resistant phenotype. At the individual level, when a colonized individual is exposed to an antibiotic, the sensitive strains present in the host's ecosystems are eliminated, whereas the resistant strains persist. The latter are, thus, able to multiply in the niche partially liberated by the elimination of the susceptible bacteria, resulting in intra-host selection of drug-resistant bacteria. At the population level, bacterial strains are transmitted among individuals in the human population. Hence, because of the individual level events described above, the probability of transmitting a resistant strain is higher for an individual exposed to antibiotics. High numbers of individuals exposed to a particular molecule within the population will be likely to induce high frequencies of resistant strain selections within the individual and, therefore, high transmission levels. Therefore, exposing the population to antibiotics confers a selective advantage to resistant strains, which are more likely to be selected than susceptible strains, leading to the selection of resistance within the population.

Will targeting oropharyngeal gonorrhoea delay the further emergence of drug-resistant *Neisseria gonorrhoeae* strains?

DA Lewis^{1,2}

tests (NAAT) are the assay of choice. Screening for oropharyngeal gonorrhoea should be performed in high-risk populations, such as men-who-have-sex-with-men (MSM). NAATs have a poor positive predictive value when used in low-prevalence populations. Gonococci antibiotics may help reduce ESC use. Future trials of antimicrobial agents for gonorrhoea should be powered to test their efficacy at the oropharynx as this is the anatomical site where treatment failure is most likely to occur. It remains to be determined whether a combination of frequent screening of high-risk individuals and/or laboratory-directed fluoroquinolone therapy of oropharyngeal gonorrhoea will delay the further emergence of drug-resistant *N. gonorrhoeae* strains.

The role of core groups in the emergence and dissemination of antimicrobial-resistant *N gonorrhoeae*

D A Lewis^{1,2,3}

- The early detection and treatment of gonorrhoea among core members should be a crucial component of gonorrhoea control programmes.

Current and future antimicrobial treatment of gonorrhoea – the rapidly evolving *Neisseria* *gonorrhoeae* continues to challenge

Magnus Unemo

Pharyngeal gonorrhoea is mostly asymptomatic, and gonococci and commensal *Neisseria* spp. can coexist for long time periods in the pharynx and share AMR genes and other genetic material. Accordingly, an enhanced

focus on early detection (screening of high-risk populations, such as MSM, with nucleic acid amplification tests (NAATs) should be considered) and appropriate treatment of pharyngeal gonorrhoea is imperative [2,3,8,13,56,].

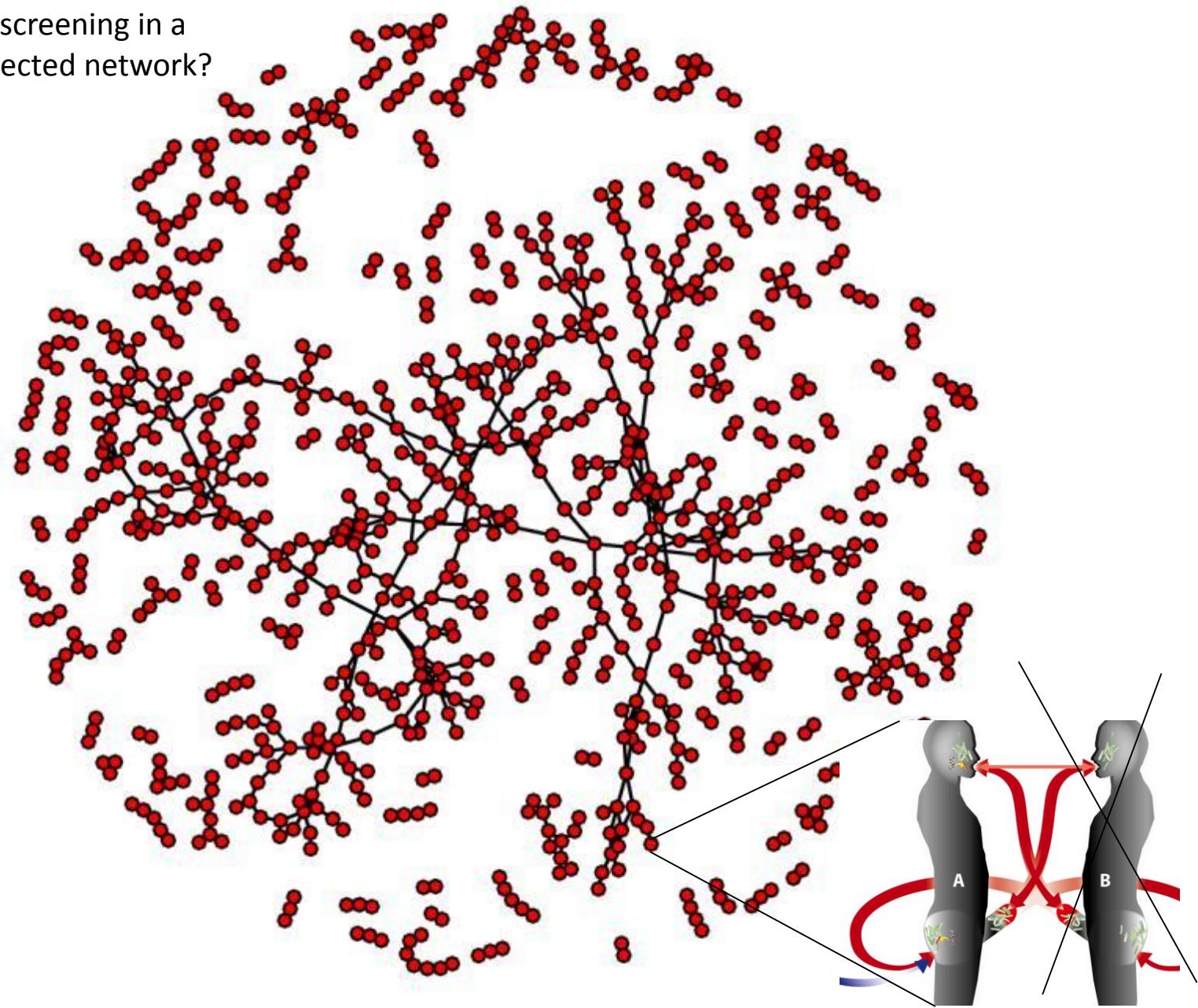
CORE GROUPS AND RESISTANT *N. gonorrhoeae*

Even though it is now widely admitted that prevention and treatment of gonococcal infections within core groups is essential for gonorrhoea control, a paradox emerges. Indeed, according to a modelling study by Chan *et al.*²⁷ the treatment of core

groups in the presence of antimicrobial resistance (AMR) maximises dissemination of antimicrobial-resistant gonorrhoea by selection pressure, which, in turn, translates to a rebound in gonorrhoea prevalence within the overall population, undermining control efforts. When represented in terms of fraction of cases caused by resistant strains, a core group-focused strategy resulted in >90% of infections, being caused by resistant strains within 16 years; this threshold was crossed 32 years more slowly when treatment was distributed across groups and was not crossed within a 500-year time span when treatment was focused on low-risk groups or on the intermediate-risk group.

Furthermore, several worldwide pieces of evidence recently reviewed by Lewis²⁸ show that, most of the time, gonorrhoea-resistant strains emerged from or were amplified by core groups. That is, since the mid-1970s, decreased susceptibilities and gonorrhoea resistance to penicillin, quinolones, tetracyclines, spectinomycin, azithromycin and cephalosporins have developed worldwide and were mostly linked to FSWs and MSMs, and also to foreign labourers, street gangs, gonorrhoea repeaters or military personnel. Moreover, extensively drug-resistant gonorrhoea isolates were recently reported and were found to be emerging also within classical core groups, with the first identified case being an FSW in Japan in 2011, followed by MSMs in France and Spain. Penicillin, tetracyclines and quinolones are no longer recommended to treat gonorrhoea

Net effect of screening in a
densely connected network?



Screening aims to reduce Duration of infectivity

$$R_0 = C \times B \times D$$

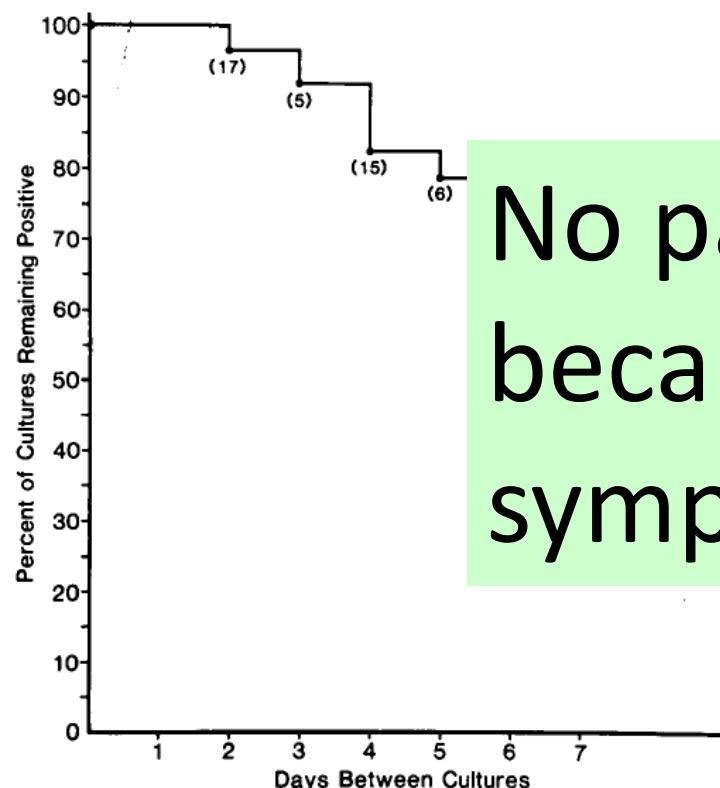
| Agent | Duration of Infectious Period (D) in years | Transmission Probability per Partnerships (β) | Effective Mean Rate of Partner Change (c) per year |
|------------------------------|--|---|--|
| <i>Neisseria gonorrhoeae</i> | | | |
| No control | 0.5 | 0.5 | 4 |
| Control | 0.15 | 0.5 | 13 |

What happens if one doesn't screen?

Natural history of pharyngeal gonorrhoea

■ 1 week fu:

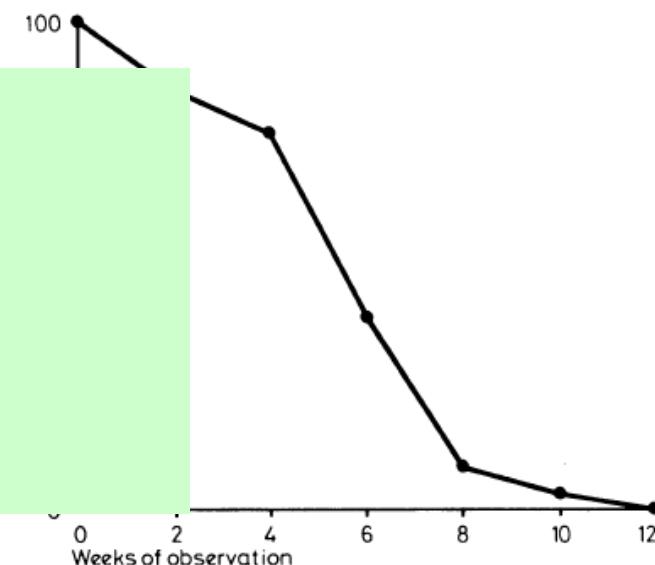
60 pts had culture repeated without treatment



No patient became symptomatic

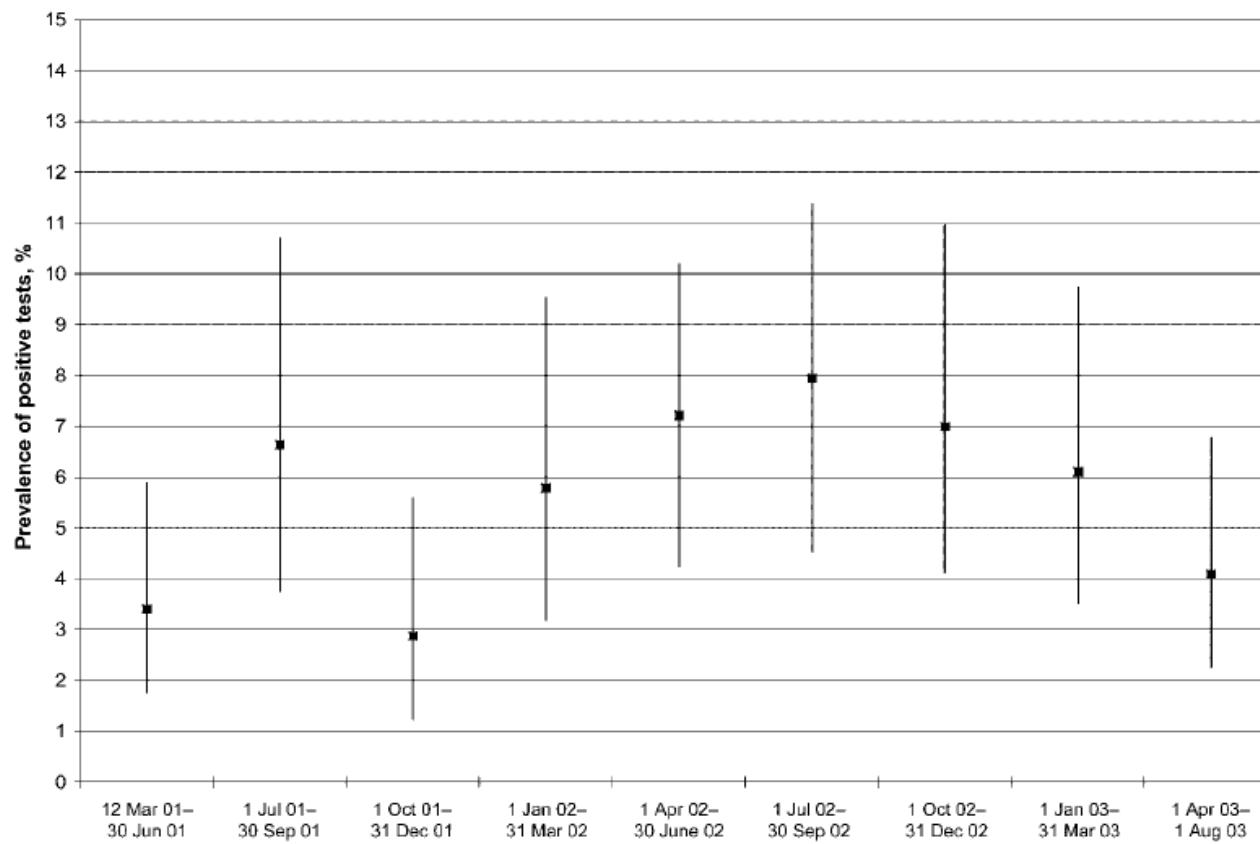
• 12 week fu:

17 pts had culture repeated without treatment



Proportion of 17 untreated patients with throat cultures positive for *N gonorrhoeae* during period of observation after initial positive culture.

No effect of screening/Rx 6 monthly on pharyngeal gonorrhoea prevalence



Prevalence and Incidence of Pharyngeal Gonorrhea in a Longitudinal Sample of Men Who Have Sex with Men: The EXPLORE Study

Morris Clin Infect Dis. 2006 Nov 15;43(10):1284-9.

In a nutshell

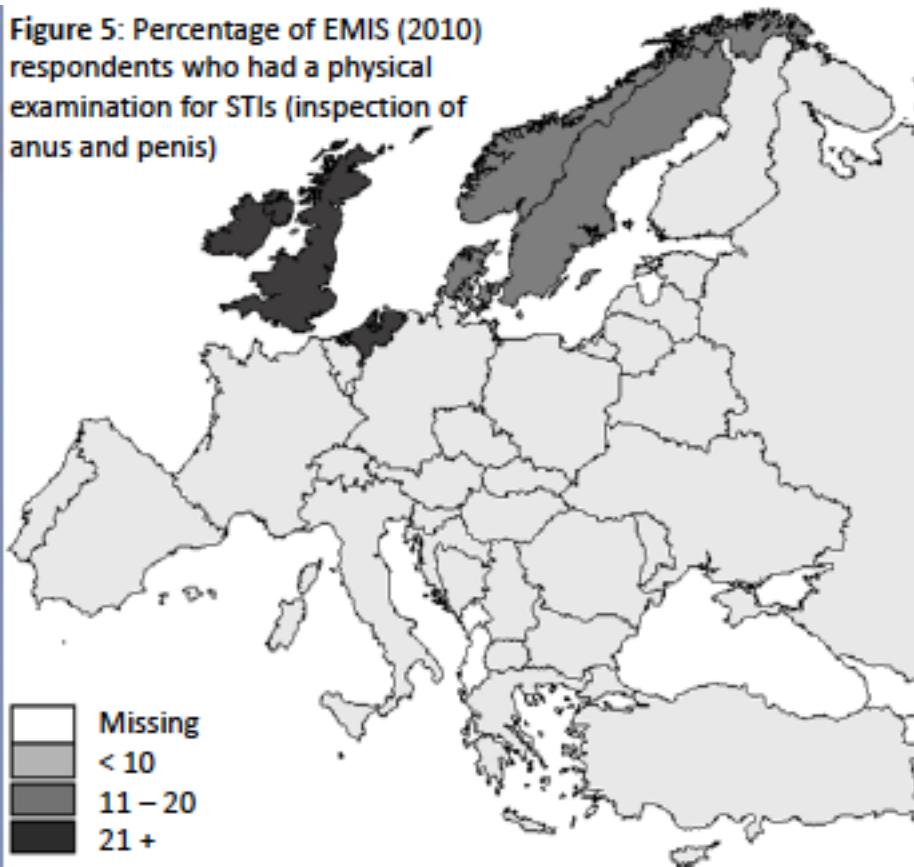
1. High prevalence of gonorrhoea in MSM
2. NG is fast evolving to being untreatable & frequently antibiotic resistance has started in MSM
3. CDC and other guidelines recommend 3-12 monthly screening of MSM
 - Proper screening would be screening pharynx, rectum and urethra separately by PCR (€80 per screen – PCR cost only)
4. Would screening reduce the prevalence of NG?
 - Observational data suggests not
5. Modelling may help illustrate efficacy of various strategies
6. HR MSM networks densely connected

Are there other non-biomedical options ?

| Survey description | Type of sex | MSM | Heterosexual Men | Heterosexual Women |
|--|--|------|------------------|--------------------|
| ASHR. A representative sample of 10,173 men and 9,134 women aged 16-59 years from Australia in 2001-2 [11,12] | Oral sex Insertive (MRS*) | 75.9 | 30.3 | |
| | Oral sex Receptive (MRS) | 75.1 | | 23.7 |
| | Anal sex Insertive (MRS) | 37.5 | 0.9 | |
| | Anal sex Receptive (MRS) | 29.8 | | 0.7 |
| | Vaginal sex (MRS) | | 95.9 | 93.9 |
| | No. sex partners lifetime (mean) | 79.1 | 16.7 | 6.5 |
| | No. sex partners lifetime (median) | 32 | 8 | 3 |
| | No. sex partners in last year (mean) | 10.7 | 1.5 | 1.0 |
| | No. sex partners in last year (median) | 2 | 1 | 1 |
| NHSLS. A nationally representative probability sample of 1,511 men and 1,921 women aged 18 to 59 years from the USA conducted in 1992 [14] | Oral sex Insertive | 89.5 | | |
| | Oral sex Receptive | 89.5 | | |
| | Anal sex Insertive | 75.7 | 10 | |
| | Anal sex Receptive | 81.6 | | 9 |
| NATSAL II. A national probability sample of 11 161 persons aged 16-44 living in the Britain in 2000 [72,73] | Any oral sex in last year | 73.6 | | |
| | Any anal sex in last year | 62.6 | | |
| | Any oral sex in last 28 days | 57.8 | | |
| | Any anal sex in last 28 days | 40.2 | | |
| | No sex partners last 5 years (Mean) | 24.1 | 3.8 | 2.4 |
| | No sex partners last 5 years (Median) | 4 | 1 | 1 |
| ACHA–NCHA 2009. Survey of 25,553 students from 57 universities in the USA in 2009 [22] | Anal sex in last 30 days | 53.9 | 6.1 | 4.4 |
| | Vaginal sex in last 30 days | 2.2 | 66.9 | 72.3 |
| | Oral sex in last 30 days | 74.5 | 59.3 | 59.7 |
| Survey of every second person entering one of two gay bars in Adelaide, Australia, in 1988, n=172 [71] | Analingus Insertive | 23.6 | | |
| | Analingus Receptive | 47.2 | | |
| | Digitoanal Insertive | 64.5 | | |
| | Digitoanal Receptive | 54.0 | | |
| | Oral sex Insertive | 87.7 | | |
| | Oral sex Receptive | 89.1 | | |
| | Anal sex Insertive | 61.9 | | |
| | Anal sex Receptive | 48.5 | | |

- The guidelines recommend at least annual screening of all men who report one or more male sexual partners in the preceding year.⁶ Screening should include HIV, syphilis, hepatitis A and B serology (with vaccination where appropriate), pharyngeal gonococcal culture, first-catch urine chlamydia nucleic acid amplification test (NAAT), rectal gonococcal culture or NAAT and rectal chlamydia NAAT. Rectal swabs are recommended for all men having unprotected anal intercourse, and also for those having any anal intercourse, protected or unprotected, with casual partners.

Figure 5: Percentage of EMIS (2010) respondents who had a physical examination for STIs (inspection of anus and penis)

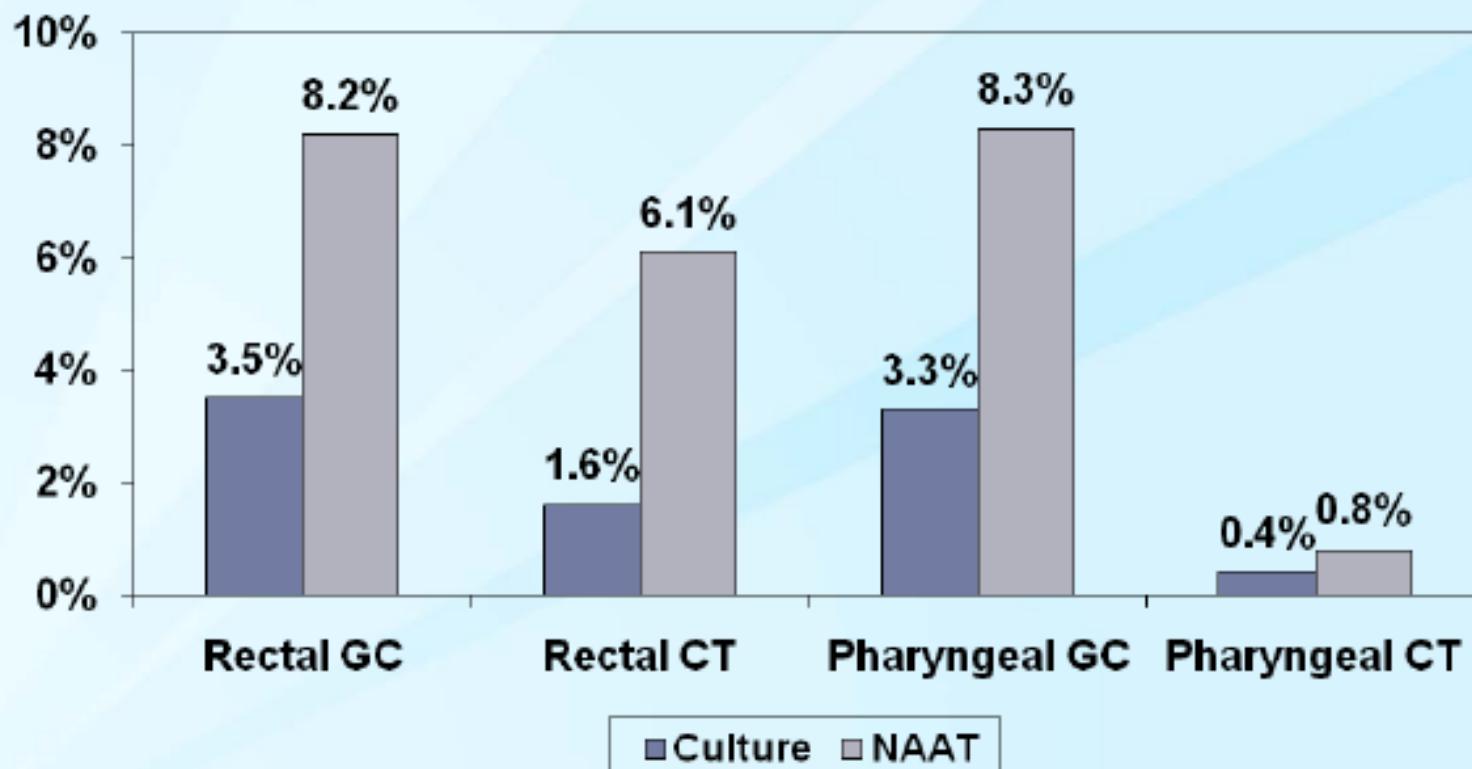


STD Screening: 2009 HIVMA Primary Care Guidelines

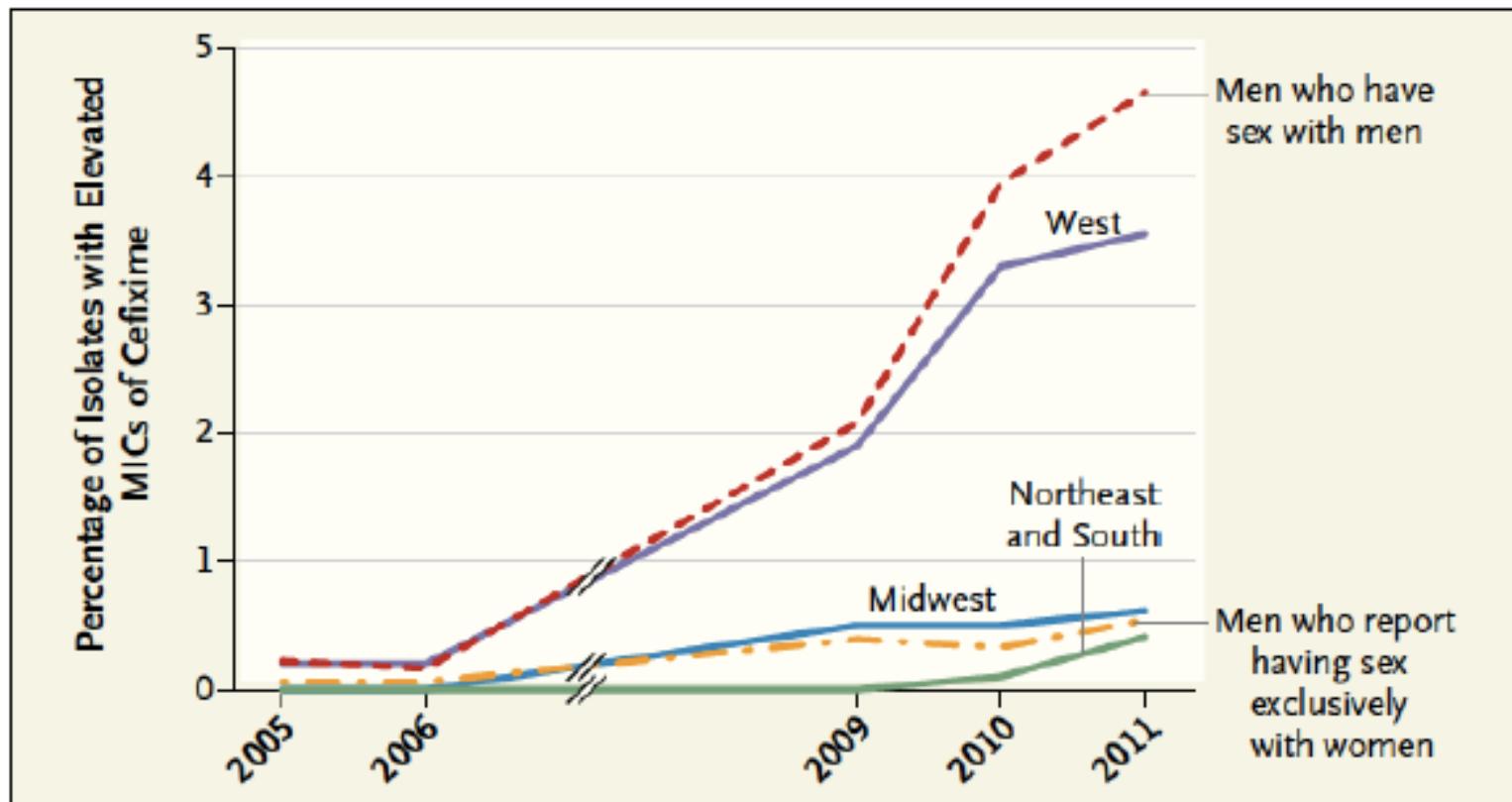
- **Syphilis: At entry to care and periodically thereafter, depending on risk**
- **Gonorrhea: At entry to care and periodically thereafter, depending on risk**
 - Rectal testing if receptive anal sex
 - Oral testing if receptive oral sex
- **Chlamydia: At entry to care and periodically thereafter, depending on risk**
 - Rectal testing if receptive anal sex

NAAT Testing, Extragenital Sites

- Not FDA-cleared for rectal or pharyngeal specimens, but preferred over culture



Percentage of Isolates with Elevated MICs to Cefixime ($\geq 0.25 \mu\text{g}/\text{ml}$), 2005–2011*



Percentage of Isolates in Which Minimal Inhibitory Concentrations (MICs) of Cefixime Were $0.25 \mu\text{g}$ per Milliliter or Higher, 2005–2011.

Susceptibility to cefixime was not tested in 2007 or 2008. From the Gonococcal Isolate Surveillance Project.



Sexually Transmitted Diseases Treatment Guidelines, 2010

- Routine laboratory screening tests should be performed at least annually for sexually active MSM:
 - HIV serology, if HIV negative or not tested within the previous year;
 - syphilis serology, with a confirmatory testing to establish whether persons with reactive serologies have incident untreated syphilis, have partially treated syphilis, or are manifesting a slow serologic response to appropriate prior therapy;
 - a test for urethral infection with *N. gonorrhoeae* and *C. trachomatis* in men who have had insertive intercourse^t during the preceding year; testing of the urine using nucleic acid amplification testing (NAAT) is the preferred approach;
 - a test for rectal infection^s with *N. gonorrhoeae* and *C. trachomatis* in men who have had receptive anal intercourse^t during the preceding year (NAAT of a rectal swab is the preferred approach); and
 - a test for pharyngeal infection^s with *N. gonorrhoeae* in men who have had receptive oral intercourse^t during the preceding year (NAAT is the preferred approach). Testing for *C. trachomatis* pharyngeal infection is not recommended.
- More frequent STD screening (i.e., at 3–6-month intervals) is indicated for MSM who have multiple or anonymous partners. In addition, MSM who have sex in conjunction with illicit drug use (particularly methamphetamine use) or whose sex partners participate in these activities should be screened more frequently

2009 European (IUSTI/WHO) Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults

C Bignell MBBS FRCP

Indications for testing (level of evidence IV; grade C recommendation)

- Symptoms or signs of urethral discharge in men;
- Vaginal discharge with risk factor for STI (age <30 years, new sexual partner);
- Mucopurulent cervicitis;
- Sexually partner of a person with sexually transmitted infection (STI) or PID;
- Acute epididymo-orchitis in male aged <40 years;
- Acute PID;
- Screening of young adults for STI;
- Screening individuals with new or multiple recent sexual partners;
- Purulent conjunctivitis in a neonate.

Asymptomatic Sexually Transmitted Infections in HIV-Infected Men Who Have Sex with Men: Prevalence, Incidence, Predictors, and Screening Strategies

were identified from extragenital mucosal sites such as pharynx and rectum that are often not tested in clinical practice

A recent study of HIV-uninfected MSM from San Francisco tested for pharyngeal NG at 6 month intervals revealed an incidence of NG at the pharyngeal site of 11.2 to 11.7 cases per 100 person-years follow-up.¹² Subsequent screening for rectal and urethral NG in the same cohort showed an incidence of 3.5 cases and 1.5 cases per 100 person-years, respectively.

In fact, Morris and colleagues¹² found that NG was almost 10 times more frequently present in pharyngeal and rectal sites than the urethral site. The relative scarcity of asymptomatic urethral STIs in MSM was also recently shown in a study from the greater Boston area reporting a prevalence rate of asymptomatic urethral STIs of less than 1% among MSM.¹³

TABLE 2. NUMBER OF BASELINE AND INCIDENT SEXUALLY TRANSMITTED INFECTIONS (STIs) AT EACH SITE FOR EACH INFECTION AT EACH VISIT^a

| <i>STI/screened, n/N (%)</i> | <i>Visit 1 (%) (baseline)</i> | <i>Visit 2 (%)</i> | <i>Visit 3 (%)</i> |
|------------------------------|-----------------------------------|--------------------|--------------------|
| Total | 29/212 (13.7) | 18/191 (9.4) | 21/168 (12.5) |
| Newly reactive RPR | 6/206 (2.9) | 5/155 (3.2) | 5/156 (3.2) |
| Gonorrhea | | | |
| Pharynx | | | |
| Culture | 0/207 (0) | 0/172 (0) | 0/141 (0) |
| NAAT | 7/212 (3.3) | 5/191 (2.6) | 3/164 (1.8) |
| Rectal | | | |
| Culture | 1/202 (0.5) | 0/170 (0) | 0/140 (0) |
| NAAT | 9/209 (4.3) | 1/188 (0.5) | 1/162 (0.6) |
| Urine | | | |
| NAAT | 3/204 (1.5) | 1/175 (0.6) | 2/155 (1.3) |
| Chlamydia (NAAT) | | | |
| Pharyngeal | 3/212 (1.4) | 0/191 (0) | 0/164 (0) |
| Rectal | 6/209 (2.9) | 6/188 (3.2) | 11/163 (6.8) |
| Urine | 3/204 (1.5) | 3/175 (1.7) | 2/155 (1.3) |

Limiting screening
to only those MSM who reported being sexually
active in
the preceding 6 months would have missed up to
24% of
asymptomatic STIs, compared to screening all
subjects, as
was done in this study.

However, compared to testing every 6 months, annual screening
would have delayed diagnosing an STI in up to 46% of
cases

STD Screening in MSM: 2010 CDC STD Treatment Guidelines

- **HIV: HIV serology, if negative or not tested in past year**
- **Syphilis: Syphilis serology**
- **Gonorrhea and Chlamydia:**
 - Urethral GC/CT if insertive intercourse in past year (urine NAAT preferred)*
 - Rectal GC/CT if receptive intercourse in past year (NAAT on rectal swab preferred)*
 - Pharyngeal GC if receptive oral sex in past year (NAAT on pharyngeal swab preferred)
- **Hepatitis B: HBsAg to detect current infection**
- **Hepatitis C: HCV testing if HIV+ or IDU**

consider HSV-2 type-specific serologic testing and anal Pap for HPV

**regardless of reported condom use*

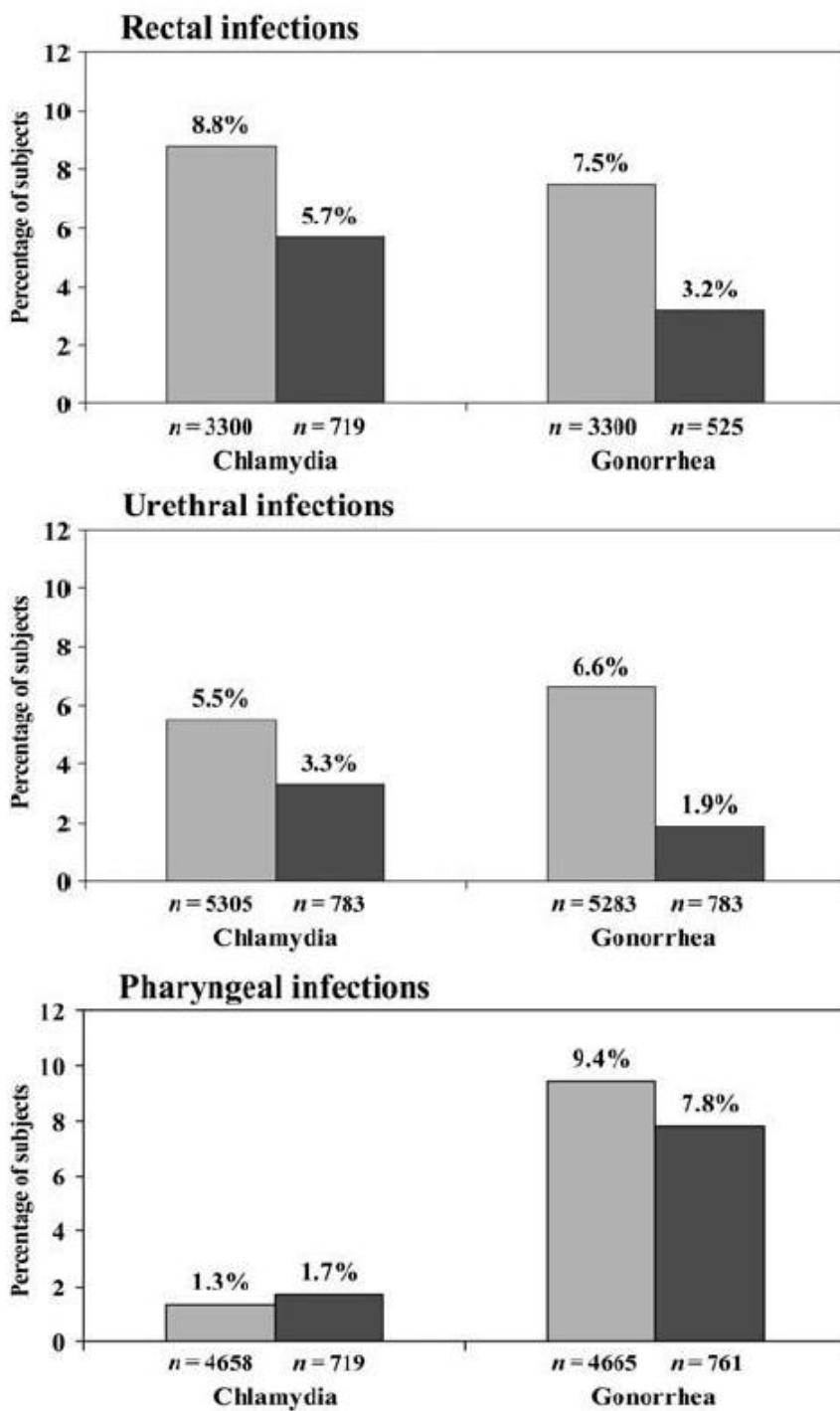
| Infection (N = 626) | NG (Prevalence 15%, N = 94) | CT (Prevalence 31%, N = 191) | |
|--|--|---|------------------------------------|
| Overall Sensitivity % (95% CI) | PS: 92 (87–93) SOC:99 (97–100) | Overall Sensitivity % (95% CI) | PS: 96 (90–98) SOC:98 (93–99) |
| Method A% (95% CI%) N = 460 | PS: 90(82–93) SOC:99(96–100) | Method A % (95% CI%) N = 460 | PS: 94 (86–98) SOC:97 (90–99) |
| Method B % (95% CI%) N = 166 | PS: 96(87–99) SOC:100(93–100) | Method B % (95% CI%) N = 166 | PS: 100(87–100) SOC:100(87–100) |

Unpooled missed 4 infections

Pooled missed 22 infections
(20 of these used method A)

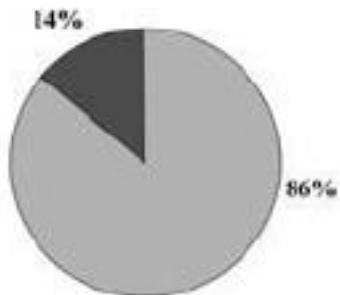
Prevalence of Rectal, Urethral, and Pharyngeal Chlamydia and Gonorrhea Detected in 2 Clinical Settings among Men Who Have Sex with Men: San Francisco, California, 2003

Clinical Infectious Diseases 2005;41:67–74

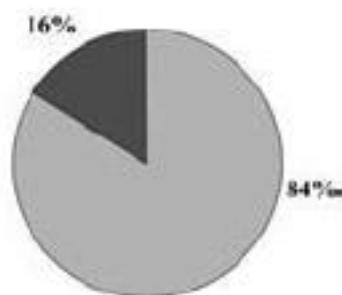


■ STD
■ Gay men's health center

Rectal chlamydial and gonococcal infections

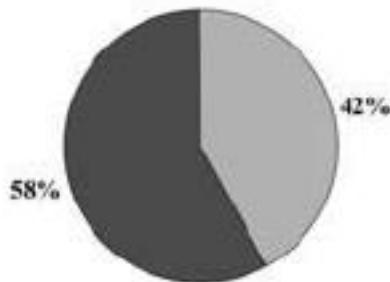


Chlamydia
n = 316

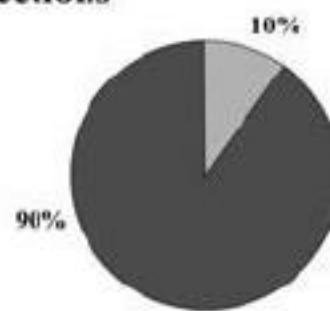


Gonorrhea
n = 264

Urethral chlamydial and gonococcal infections



Chlamydia
n = 315



Gonorrhea
n = 364

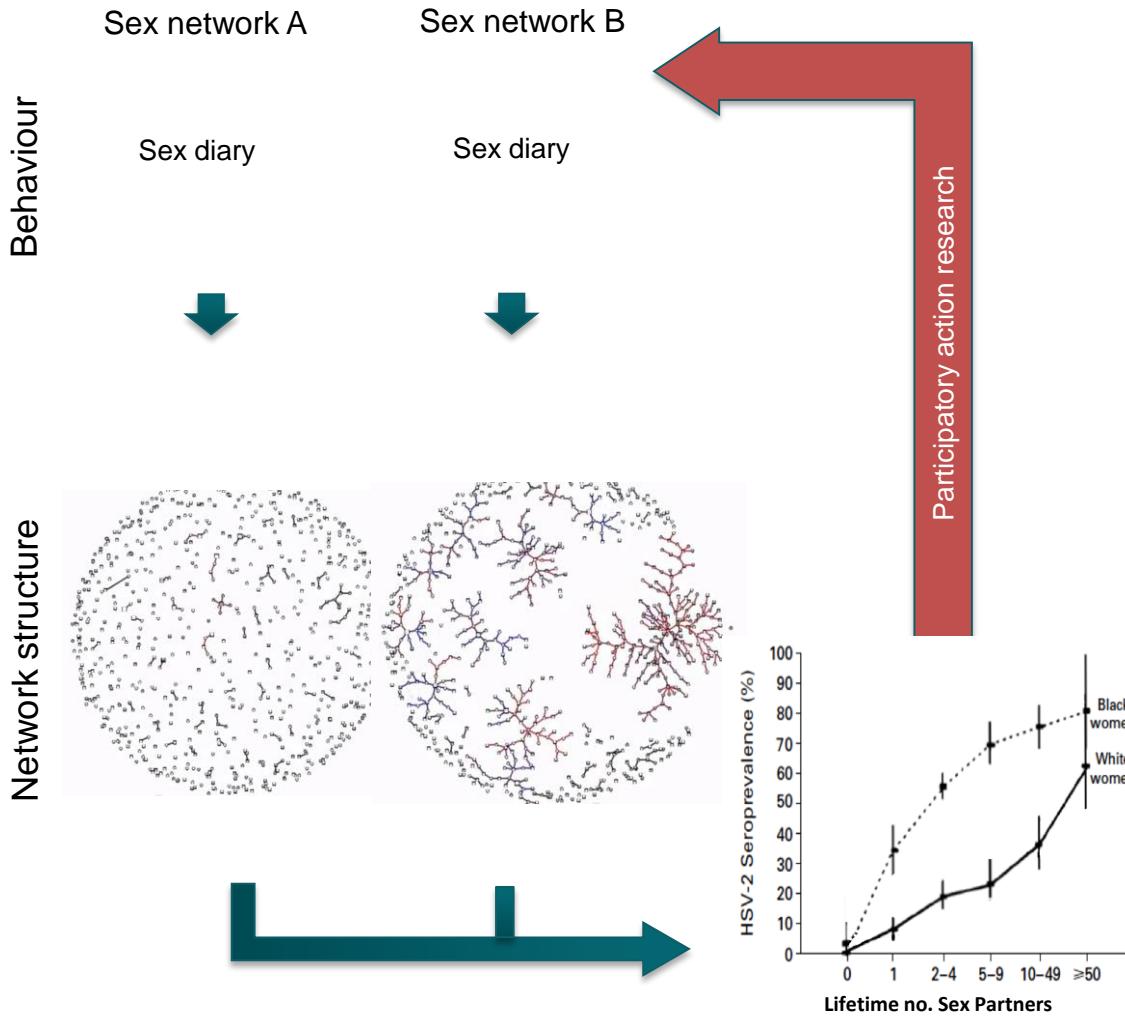
■ Asymptomatic ■ Symptomatic

Demographic and clinical characteristics of 1,596 patients with at least one *Neisseria gonorrhoeae* isolate; STI outpatient clinic, Amsterdam, the Netherlands, 2006-2008

| Patient characteristics | cefotaxime MIC ≤ 0.125 µg/ml (n= 1,494) | cefotaxime MIC > 0.125 µg/ml, (n=102) | OR (95%CI) | Overall p value ¹ |
|---|---|---------------------------------------|---------------|------------------------------|
| Age | | | | |
| ≤35 years | 847 (56.7%) | 43 (42.2%) | 1 (ref) | 0.004 |
| >35 years | 647 (43.3%) | 59 (57.8%) | 1.8 (1.2-2.7) | |
| Sexual preference | | | | |
| Men who have sex with women (exclusively) | 317 (21.2%) | 9 (8.8%) | 1 (ref) | <0.001 |
| Women who have sex with men | 192 (12.9%) | 3 (2.9%) | 0.6 (0.1-2.1) | |
| Men who have sex with men (and/or women) | 985 (65.9%) | 90 (88.2%) | 3.2 (1.6-6.5) | |

Reducing contact numbers/concurrency

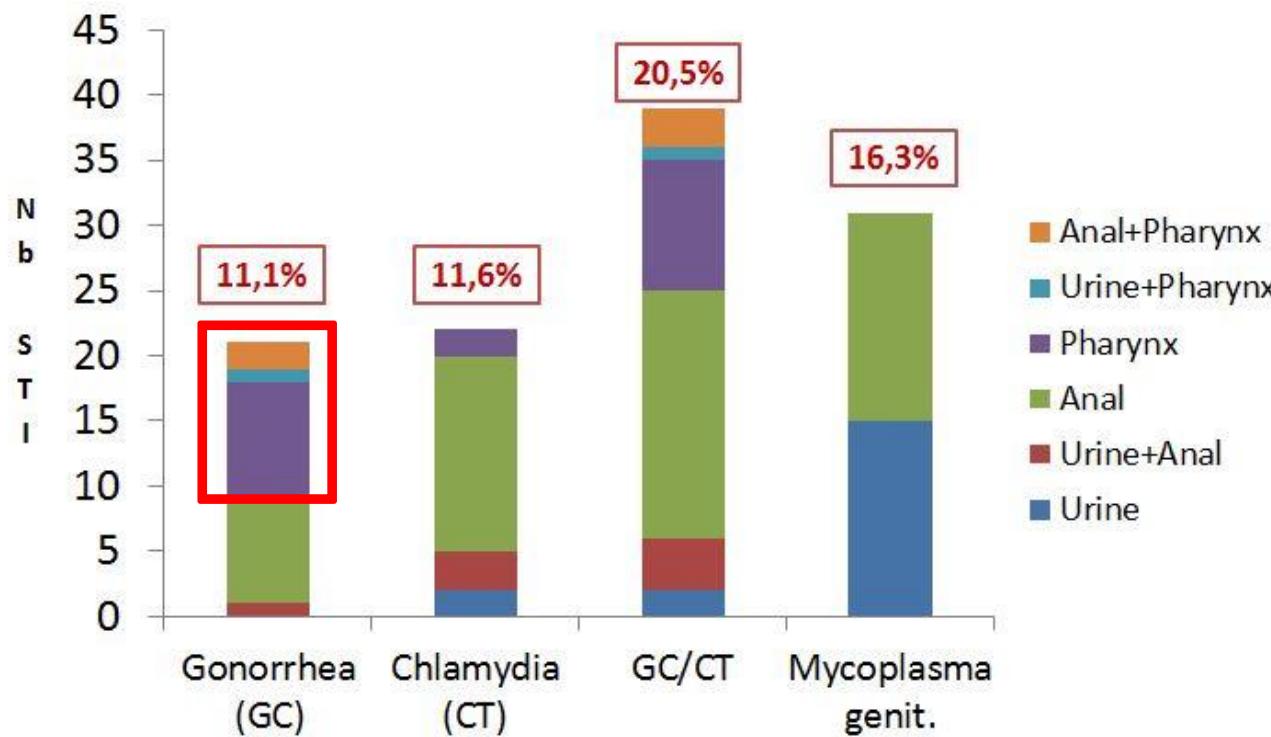
Know your network



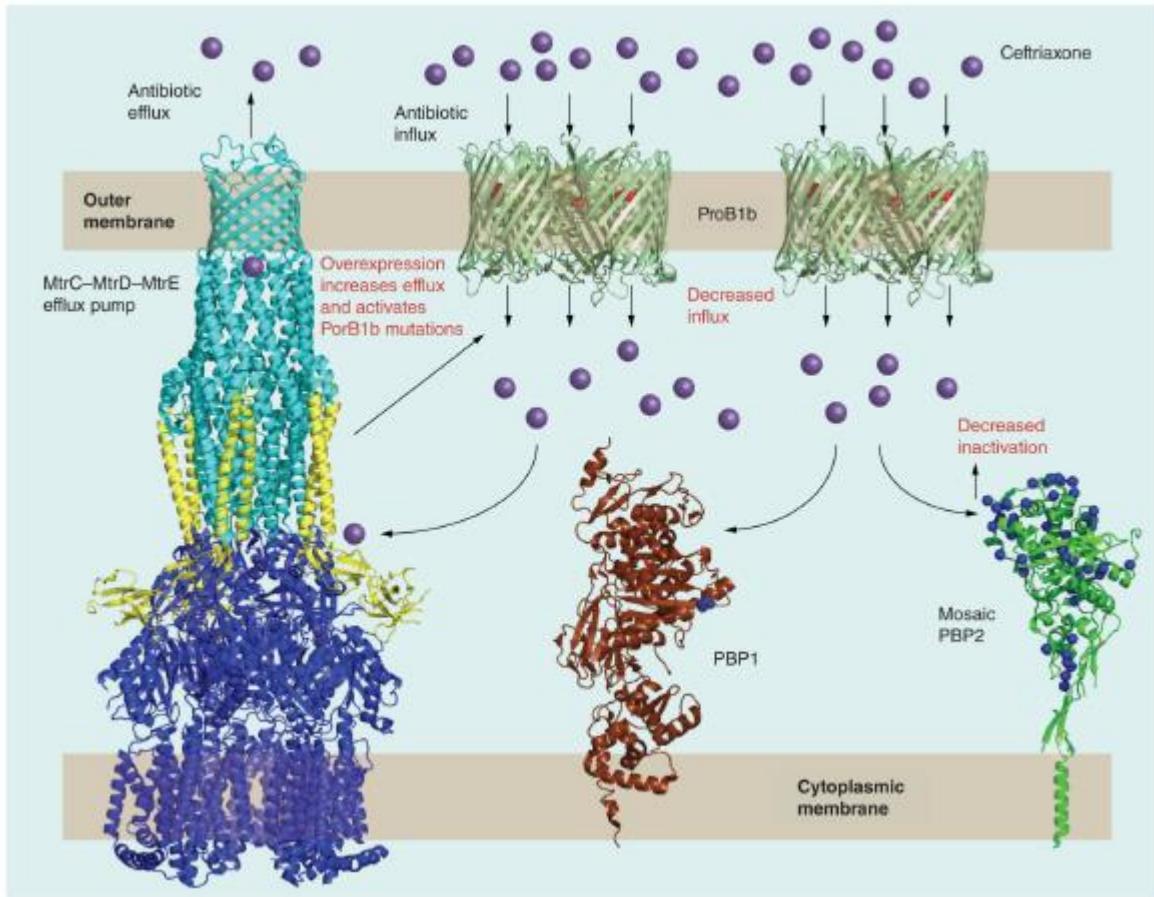
Morris SSM 2015, AJPH 2009
Fleming NEJM 1997



Be PrEP ared Study: Prevalence of STIs at baseline visit



Slide: Irith De Baesler



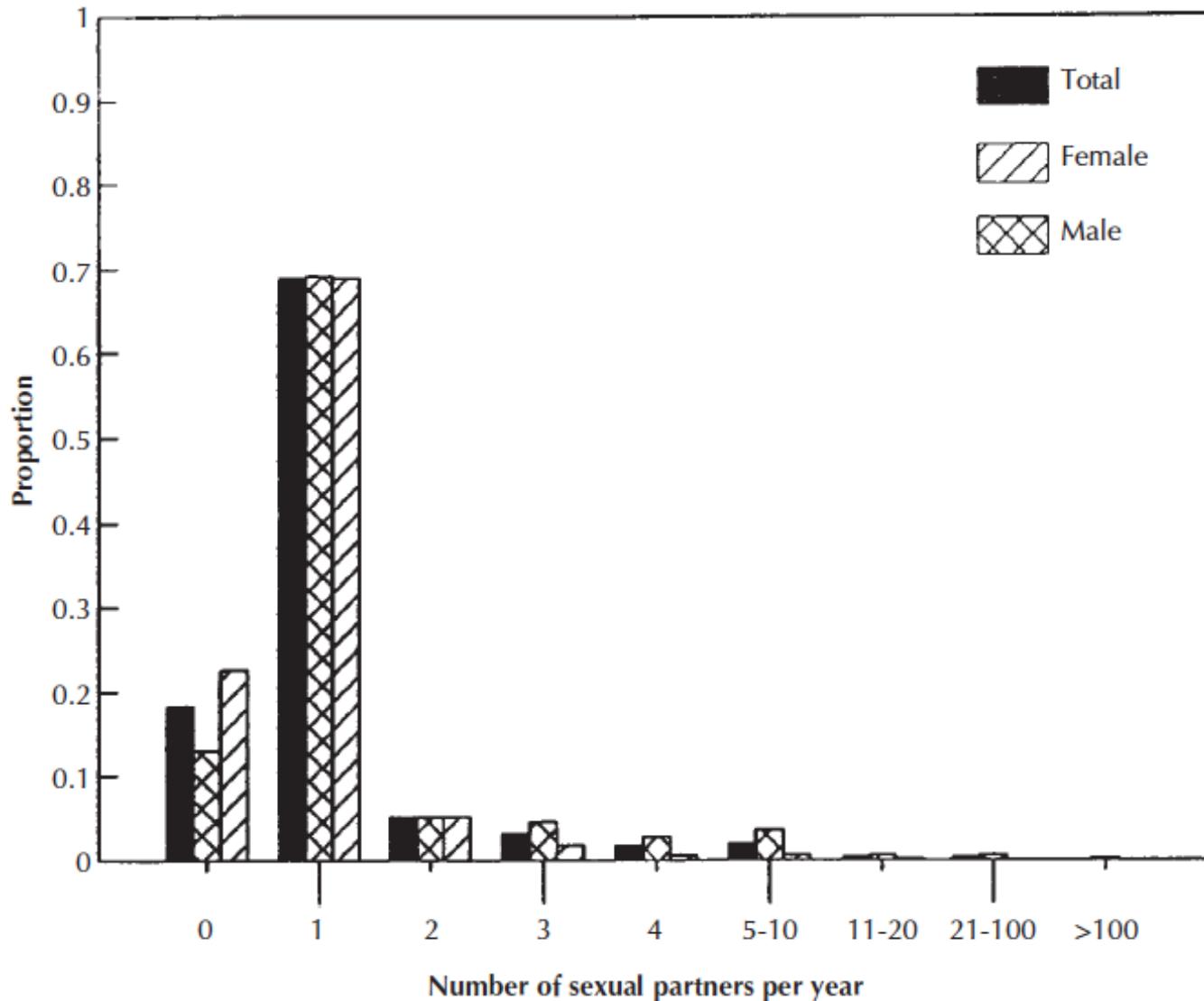


Figure 2. Distribution of sexual activity in a random sample of the general population of the U.S.³⁹

Boily 1997

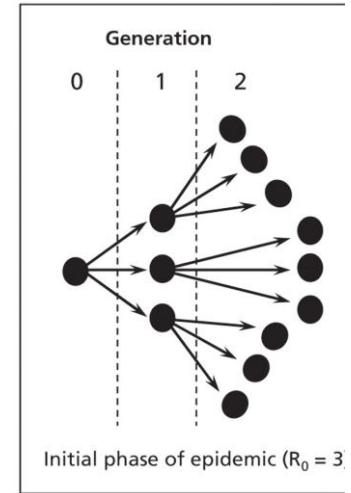
R_0 = is the number of cases one case generates on average over the course of its infectious period, in an otherwise uninfected population

$$R_0 = \beta \square \times c \times D$$

β - mean probability of transmission per exposure

C - mean rate of sexual partner change within the population

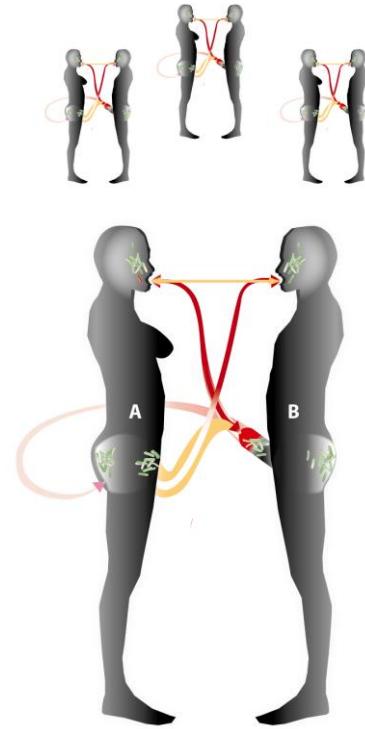
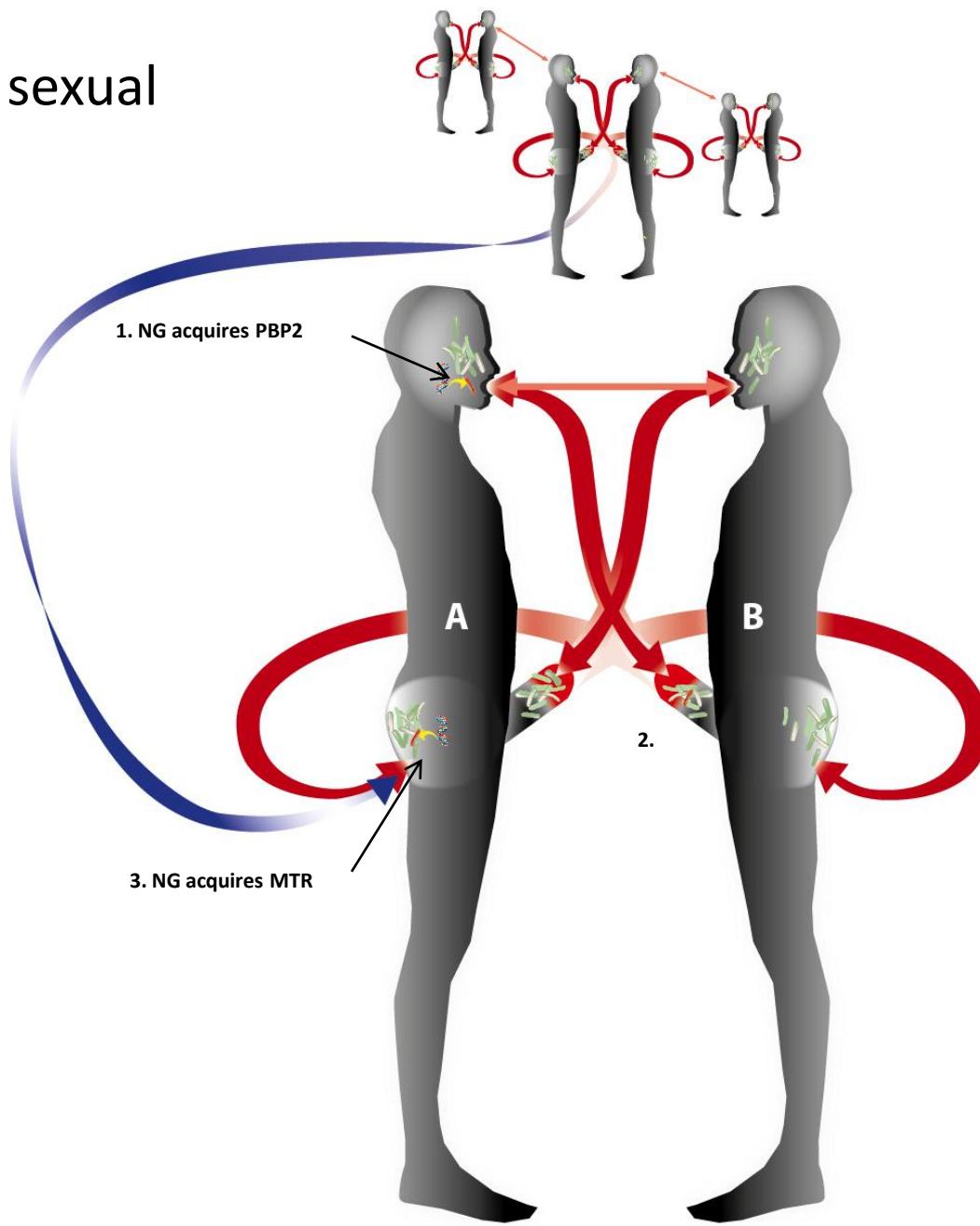
D - mean duration of infectiousness of the newly infected persons



| Agent | Duration of Infectious Period (D) in years | Transmission Probability per Partnerships (β) | Effective Mean Rate of Partner Change (c) per year |
|------------------------------|--|---|--|
| <i>Neisseria gonorrhoeae</i> | | | |
| No control | 0.5 | 0.5 | 4 |

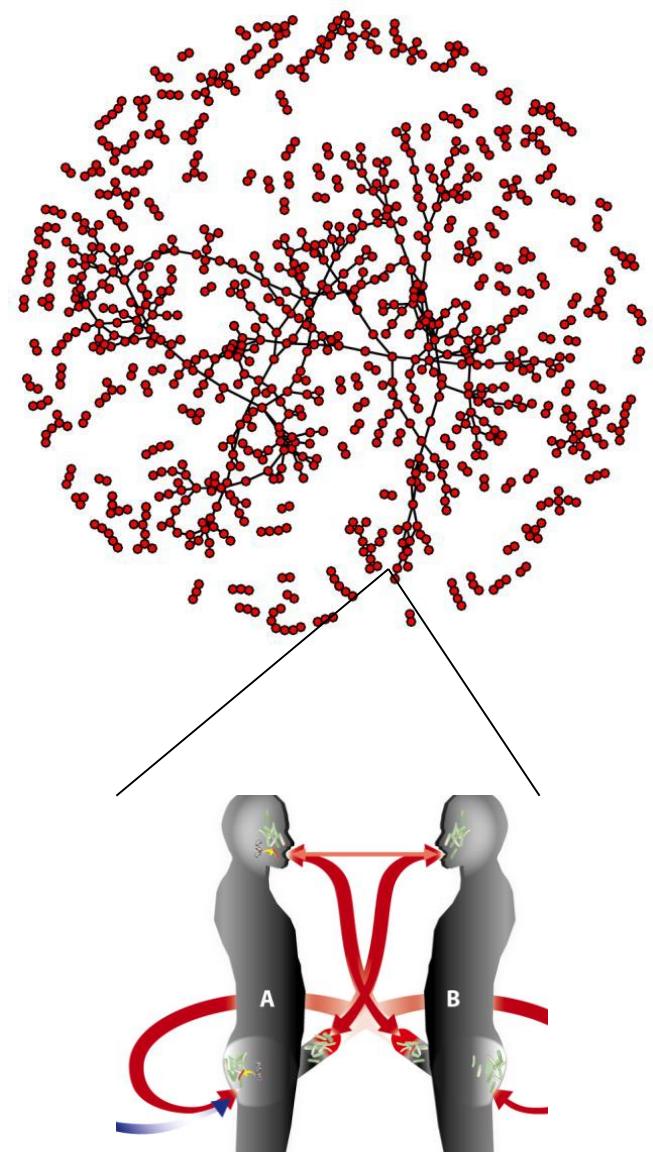
→ $0.5 \times 0.5 \times 4 = 1$

Know your sexual ecology



Methods

- STERGMs* to model network
- Basic model available in R-EpiModel
- Extensions:
 - Network of main and casual partners
 - Three sites of infection
 - Six possible acts/transmission routes
 - Symptomatic/asymptomatic infection
- Outcome
 - Effect of different screening programmes on prevalence of gonorrhoea



*Separable temporal exponential-family random graph models

Behavioral data

- **European MSM Internet Survey:** 174 209 MSM from 36 European countries completed online behavioural survey (in 2010)
- ? biased to higher risk MSM
- 3843 from Belgium
 - Single 49.9%
 - In steady relationship with one man 46.9%
 - In steady relationship with more than one man 3.2%

TABLE 1 Resistance determinants and mechanisms in *Neisseria gonorrhoeae* for antimicrobials previously or currently recommended for treatment of gonorrhea

| Antimicrobial class | Resistance determinants/mechanisms |
|---|--|
| Sulfonamides | Oversynthesis of <i>p</i> -aminobenzoic acid, which dilutes the sulfonamide. Mutations in <i>folP</i> (encoding the sulfonamide target DHPS) reduce target affinity. The <i>folP</i> mutations comprise SNPs or a mosaic <i>folP</i> gene containing sequences from commensal <i>Neisseria</i> spp. |
| Penicillins (e.g., penicillin G and ampicillin) | Mutations in <i>penA</i> (encoding the main lethal target PBP2). Traditionally, the mutations were the single amino acid insertion D345 in PBP2 and 4 to 8 concomitant mutations in the PBP2 carboxyl-terminal region, decreasing the PBP2 acylation rate and reducing susceptibility ~6- to 8-fold. In the last decade, many mosaic <i>penA</i> alleles with up to 70 amino acid alterations, also reducing PBP2 acylation, were described. Mutations in <i>mtrR</i> , in the promoter (mainly a single nucleotide [A] deletion in the 13-bp inverted repeat sequence) or coding sequence (commonly a G45D substitution), result in overexpression of and increased efflux from the MtrCDE efflux pump. See the text for rarer mutations resulting in increased MtrCDE efflux. <i>porB1b</i> SNPs, e.g., encoding G120K and G120D/A121D mutations in loop 3 of PorB1b, reduce influx (<i>penB</i> resistance determinants). Interestingly, the <i>penB</i> phenotype is apparent only in strains with the <i>mtrR</i> resistance determinant. A SNP in <i>pilQ</i> (encoding the pore-forming secretin PilQ of the type IV pili), i.e., E666K, reduces influx. Note that this SNP has been found only in the laboratory and is unlikely to be present in clinical isolates, because it disrupts type IV pilus formation, which is essential for pathogenesis. A SNP in <i>ponA</i> (encoding the second penicillin target, PBP1), i.e., “ <i>ponA1</i> determinant” (L421P), reduces penicillin acylation of PBP1 ~2- to 4-fold. “Factor X,” an unknown, nontransformable determinant, increases penicillin MICs ~3- to 6-fold. |
| Tetracyclines (e.g., tetracycline and doxycycline) | Penicillinase (TEM-1 or TEM-135)-encoding plasmids, i.e., Asian, African, Toronto, Rio, Nimes, New Zealand, and Johannesburg plasmids, hydrolyze the cyclic amide bond of the β -lactam ring and render the penicillin inactive. A SNP in <i>rpsJ</i> (encoding ribosomal protein S10), i.e., V57M, reduces the affinity of tetracycline for the 30S ribosomal target. <i>mtrR</i> mutations (see above). <i>penB</i> mutations (see above). A SNP in <i>pilQ</i> (see above). TetM-encoding plasmids, i.e., American and Dutch plasmids. Evolved derivatives have been described in Uruguay and South Africa. TetM, resembling elongation factor G, binds to the 30S ribosomal subunit and blocks tetracycline target binding. A 16S rRNA SNP, i.e., C1192U, in the spectinomycin-binding region of helix 34, reduces the affinity of the drug for the ribosomal target. |
| Spectinomycin | A 16S rRNA SNP, i.e., C1192U, in the spectinomycin-binding region of helix 34, reduces the affinity of the drug for the ribosomal target. Mutations in <i>rpsE</i> (encoding the 30S ribosomal protein S5), i.e., the T24P mutation and deletions of V25 and K26E, disrupt the binding of spectinomycin to the ribosomal target. |
| Quinolones (e.g., ciprofloxacin and ofloxacin) | <i>gyrA</i> SNPs, e.g., S91F, D95N, and D95G, in the QRDR, reduce quinolone binding to DNA gyrase. <i>parC</i> SNPs, e.g., D86N, S88P, and E91K, in the QRDR, reduce quinolone binding to topoisomerase IV. Many additional mutations in the QRDR of <i>gyrA</i> and <i>parC</i> have been described. An overexpressed NorM efflux pump also slightly enhances quinolone MICs. |
| Macrolides (e.g., erythromycin and azithromycin) | 23S rRNA SNPs, i.e., C2611T and A2059G (in 1 to 4 alleles), result in a 23S rRNA target (peptidyltransferase loop of domain V) with a reduced affinity for the 50S ribosomal macrolide target. <i>mtrR</i> mutations (see above). <i>erm</i> genes (<i>ermB</i> , <i>ermC</i> , and <i>ermF</i>), encoding rRNA methylases that methylate nucleotides in the 23S rRNA target, block the binding of macrolides. MacAB efflux pump; its overexpression increases the MICs of macrolides. |
| Cephalosporins (e.g., ceftibuten, cefpodoxime, cefixime, cefotaxime, and ceftriaxone) | <i>mef</i> -encoded efflux pump exports macrolides out of the bacterial cell and increases the MICs of macrolides. Mosaic <i>penA</i> alleles encoding mosaic PBP2s with a decreased PBP2 acylation rate. These proteins have up to 70 amino acid alterations and are derived from horizontal transfer of partial <i>penA</i> genes from mainly commensal <i>Neisseria</i> spp. Mutations in mosaic PBP2s verified to contribute to resistance are A311V, I312M, V316T, V316P, T483S, A501P, A501V, N512Y, and G545S. The resistance mutations need other epistatic mutations in the mosaic <i>penA</i> allele. <i>penA</i> SNPs, i.e., A501V and A501T, in nonmosaic alleles can also enhance cephalosporin MICs. Some additional SNPs (G542S, P551S, and P551L) were statistically associated with enhanced cephalosporin MICs, but their effects remain to be proven with, e.g., site-directed <i>penA</i> mutants in isogenic backgrounds. <i>mtrR</i> mutations (see above). <i>penB</i> mutations (see above). “Factor X,” an unknown, nontransformable determinant (see above). |

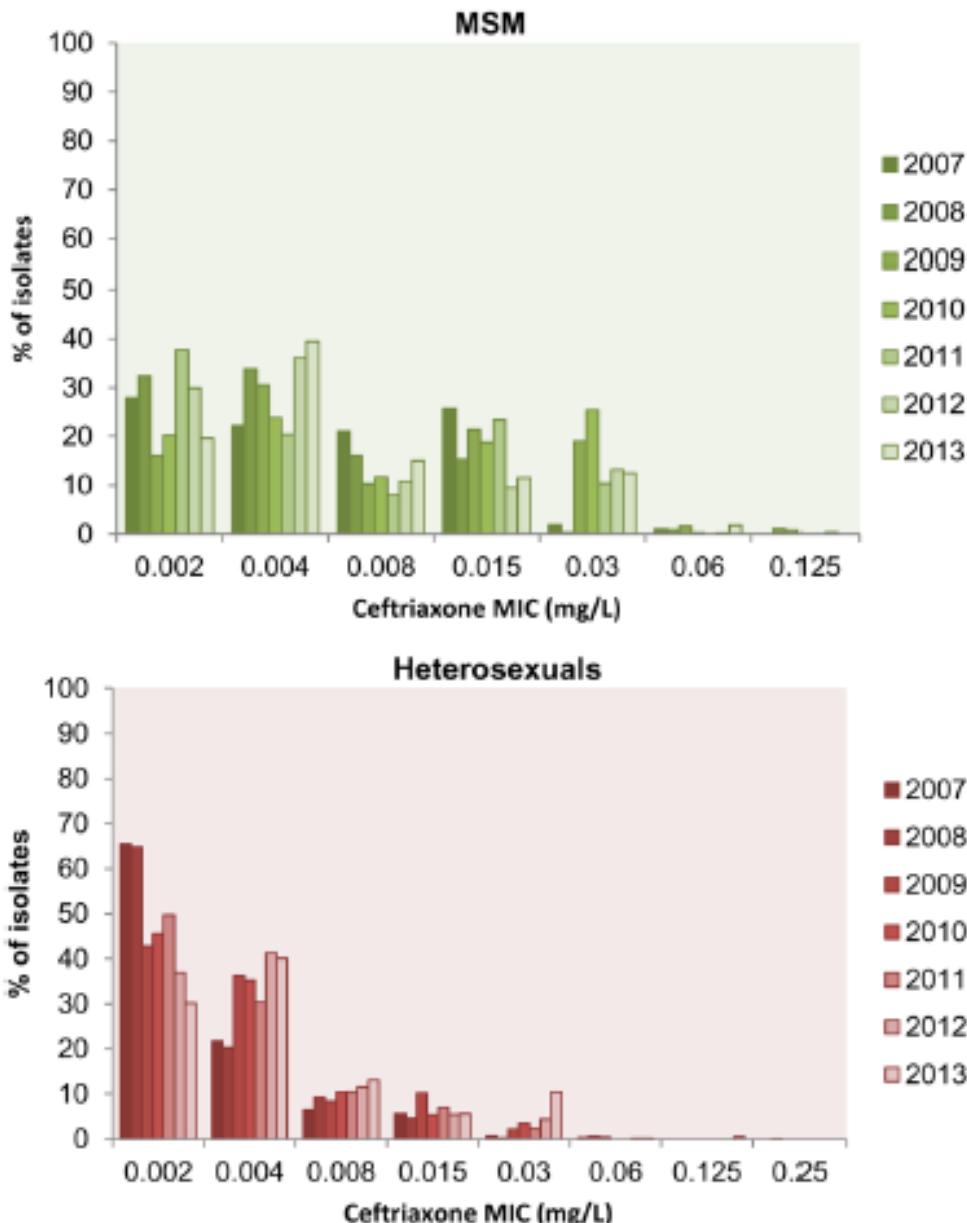


Figure 1 Change in susceptibility to ceftriaxone between 2007 and 2013 for men who have sex with men (MSM) and heterosexuals (men and women grouped). MIC, minimum inhibitory concentration.

Targeting core groups for gonorrhoea control: feasibility and impact

Katia Giguère,^{1,2} Michel Alary^{1,2,3}

- 2014, and an estimated 31% of all
- gonorrhea cases in 2013 occurred in the
- 2% of the US population who are MSM

When to Perform a Test of Cure for Gonorrhea: Controversies and Evolving Data

Lindley A. Barbee^{1,2} and Matthew R. Golden^{1,2}

AMR gonorrhea remains a threat and requires Action. **Part of that action needs to be more screening.** Case finding and treatment are mainstays of public health gonorrhea control. The United States instituted widespread gonorrhea screening in women in the 1970s, and that effort was temporally associated with a decline in gonorrhea rates

However, the risk of HIV associated with rectal infections appears to be independent of sexual behavior [14, 16–18], suggesting that these sexually transmitted infections (STIs) facilitate HIV transmission, a hypothesis that is supported by biological plausibility [19, 20]. Last, infection with gonorrhea in the pharynx is thought to contribute to the evolution of antimicrobial resistance.

First nationwide study regarding ceftriaxone resistance and molecular epidemiology of *Neisseria gonorrhoeae* in China

Shao-Chun Chen¹, Yue-Ping Yin^{1*}, Xiu-Qin Dai¹, Magnus Unemo² and Xiang-Sheng Chen¹

Table 1. Antimicrobial resistance of *N. gonorrhoeae* isolates (*n*=1257) in China, 2012–13

| GASP sentinel surveillance sites | Isolates per site | Antimicrobial resistance of <i>N. gonorrhoeae</i> isolates (<i>n</i> =1257) | | | | |
|----------------------------------|-------------------|--|---|---|--|---------------------------|
| | | ceftriaxone ^a (<i>n</i> =1242) | spectinomycin ^a (<i>n</i> =1247) | ciprofloxacin ^a (<i>n</i> =1246) | TRNG ^a (<i>n</i> =1247) | PPNG (<i>n</i> =1247) |
| Tianjin | 105 | 0 | 0 | 105 (100%) | 17 (16.2%) | 24 (22.9%) |
| Shanghai | 79 | 0 | 0 | 79 (100%) | 36 (45.6%) | 36 (45.6%) |
| Jiangsu | 80 | 0 | 0 | 80 (100%) | 31 (38.8%) | 24 (30.0%) |
| Zhejiang | 100 | 0 | 0 | 100 (100%) | 45 (45%) | 51 (51%) |
| Guangdong | 221 | 9 (4.1%) | 0 | 221 (100%) | 104 (47.1%) | 86 (38.9%) |
| Guangxi | 156 | 1 (0.6%) | 1 (0.6%) | 154 (98.7%) | 65 (41.7%) | 43 (27.6%) |
| Hainan | 258 | 32 (13.0%) | 0 | 248 (100%) | 109 (43.8%) | 73 (29.3%) |
| Chongqing | 76 | 1 (1.3%) | 0 | 75 (98.7%) | 41 (53.9%) | 45 (59.2%) |
| Sichuan | 159 | 11 (6.9%) | 2 (1.3%) | 159 (100%) | 85 (53.5%) | 96 (60.4%) |
| Xinjiang | 23 | 1 (4.5%) | 0 | 22 (100%) | 2 (9.1%) | 8 (36.4%) |
| Total | 1257 | 55 (4.4%) | 3 (0.2%) | 1243 (99.8%) | 535 (42.9%) | 486 (39.0%) |

AZM resistance >5% all regions

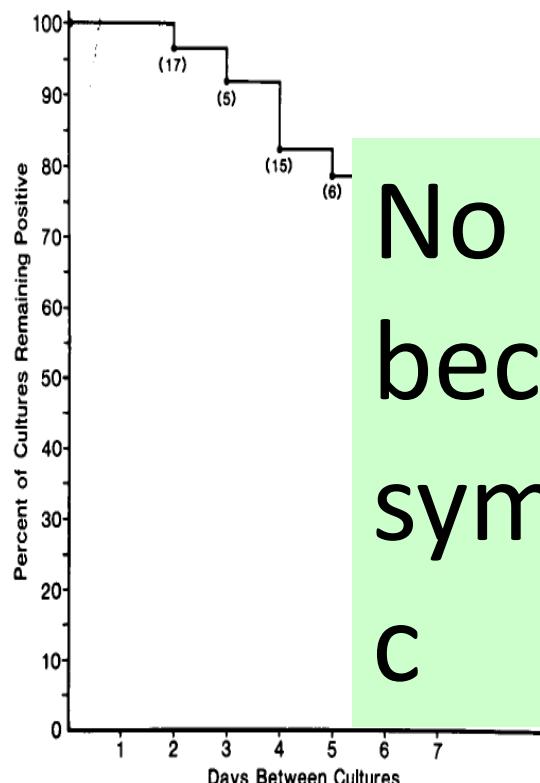
Jac 2016

What happens if one doesn't screen?

Natural history of pharyngeal gonorrhoea

■ 1 week fu:

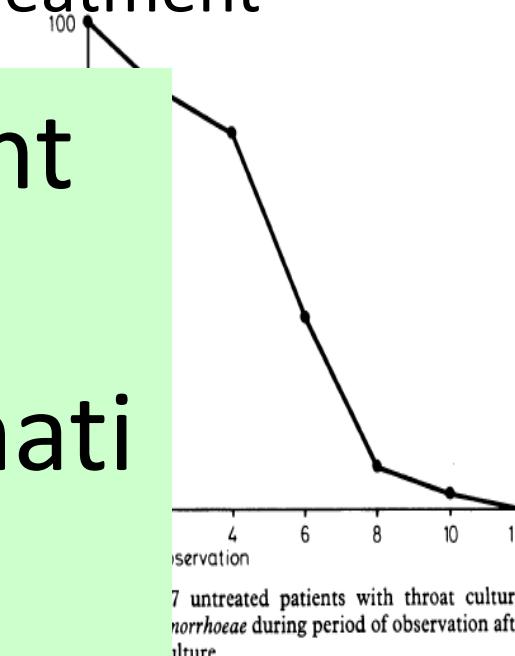
60 pts had culture repeated
without treatment



Hepatology. 1984;4:408-12.

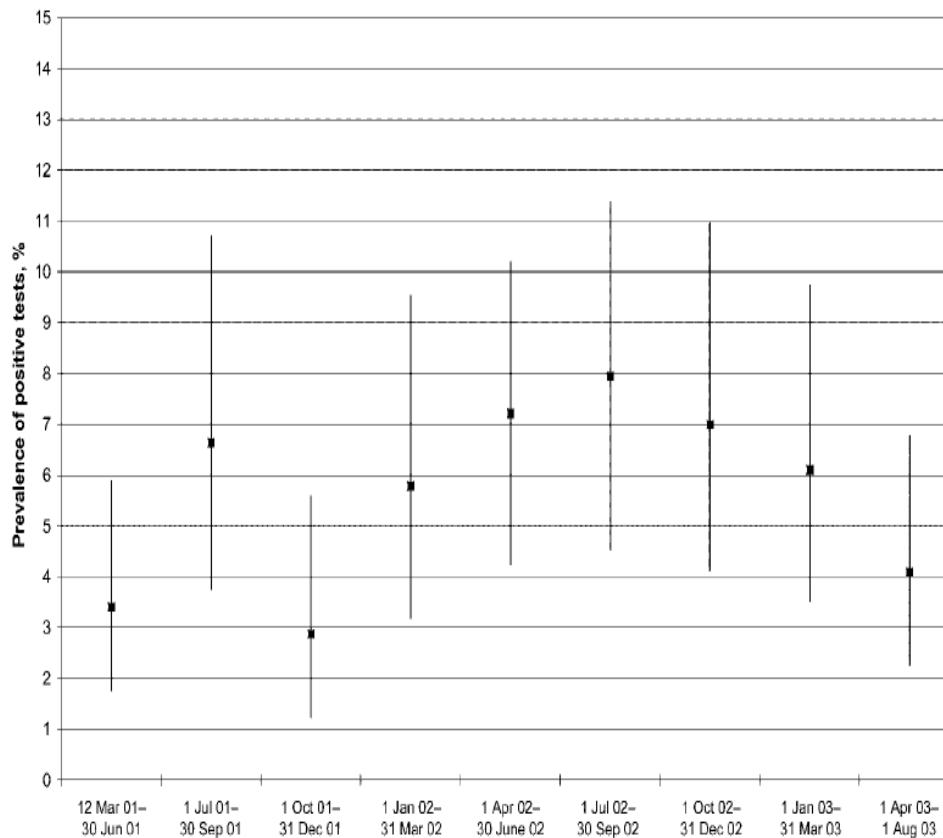
• 12 week fu:

17 pts had culture
repeated without
treatment



No patient
became
symptomati
c

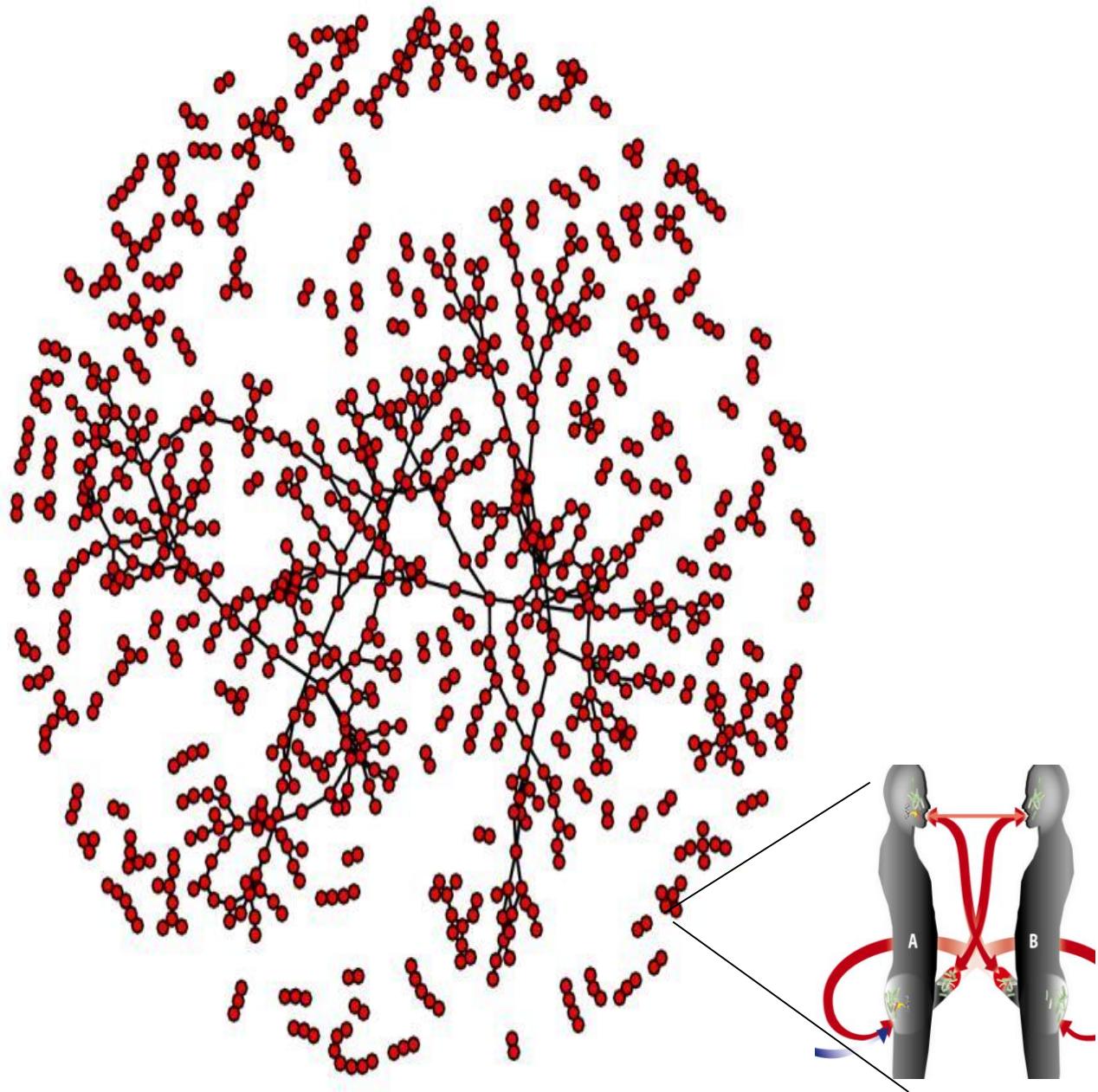
No effect of screening/Rx 6 monthly on pharyngeal gonorrhoea prevalence



Prevalence and Incidence of Pharyngeal Gonorrhea in a Longitudinal Sample of Men Who Have Sex with Men: The EXPLORE Study
Morris Clin Infect Dis. 2006 Nov 15;43(10):1284-9.

Net effect of screening in a densely connected network?

1. Incr. AB exposure
2. Adverse resistome
3. Poor



Male Urethritis Syndrome (MUS)

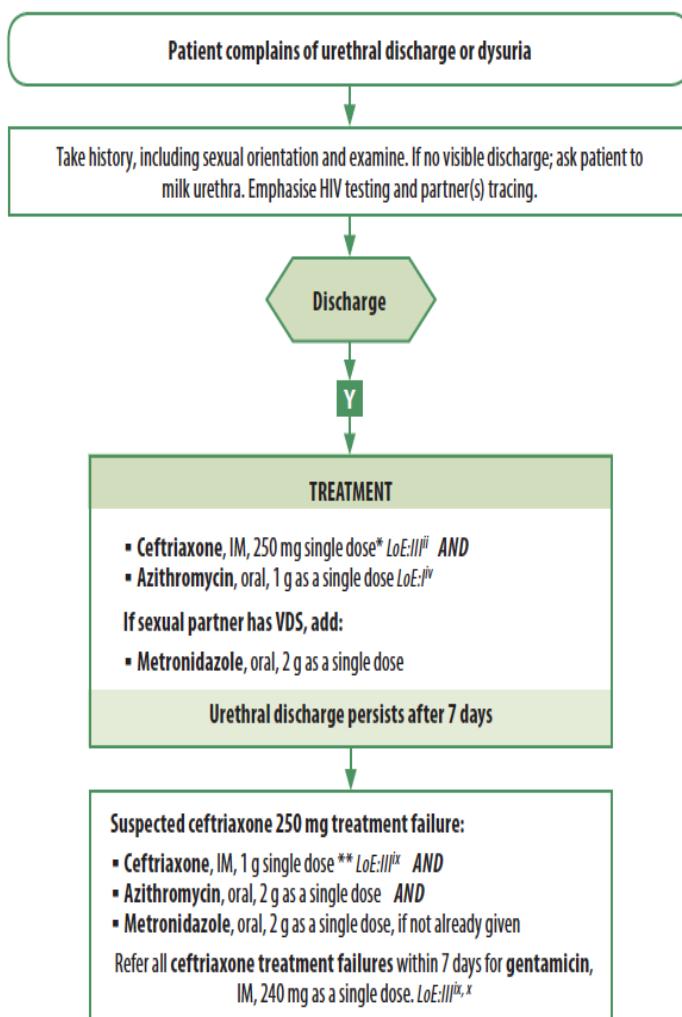


TABLE 4. Relationship between *M. genitalium* and disease compared with *M. hominis* and *Ureaplasma* spp.^a

| Condition | <i>M. genitalium</i> | | <i>M. hominis</i> | | <i>Ureaplasma</i> spp. | |
|---------------------------------|----------------------|------|-------------------|-----|---------------------------|-----|
| | A | C | A | C | A | C |
| NGU | | | | | | |
| Acute | ++++ | ++++ | — | | +++ | +++ |
| Chronic | +++ | +++ | — | | — | |
| Balanoposthitis | +++ | ++ | — | | — | |
| Chronic prostatitis | + | + | — | | — | |
| Epididymitis | ++ | ++ | + | — | ++ | ++ |
| Reiter's disease/ SARA | ++ | + | — | | ++ | ++ |
| BV | ++ | — | ++++ | + | +++ | ± |
| Cervicitis | +++ | +++ | — | | — | |
| Infertility | ++ | ++ | — | | ++ | — |
| Ectopic pregnancy | + | ? | + | — | + | — |
| PID | +++ | +++ | +++ | ++ | + | — |
| Postpartum fever | NE | | +++ | +++ | ++ | — |
| PTB | ++ | + | ++ | — | +++ | ++ |
| Neonatal conjunctivitis | NE | | — | | — | |
| Neonatal respiratory disease | NE | | + | ? | +++ | ++ |

^a Shown are the chances of the indicated mycoplasma being associated with (A) or causing (C) the conditions shown in the left-hand column. +++, overwhelming; ++, good; +, moderate; +, small; —, nil; NE, not examined; ?, not certain.

Aanvragen Chlamydia trachomatis 2015

- Totaal : 3957 PCR CT aanvragen : 302 CT positief (241 A-K, 61 L) , 2 inhibitie, 1 niet bevestigd, 48 geen staal ontvangen
- ProDeo: 164 PCR CT aanvragen, waarvan 125 van Beprepared studie en 39 externe aanvragen: 38 CT positief (19 A-K, 19 L) (7 van BePrep: 6 A-K, 1L), 121 negatief
- BePrep: 187 PCR CT aanvragen: 9 CT positief (8 A-K, 1 L)
-
- Dus in totaal 3731 CT analyses (zonder Prodeo en BePrep): 262 CT positief (220 A-K, 42 L)

- Een totaal van 1298 CT (34,8%) analyses werden aangevraagd door helpcenter waarvan 75 CT positief (allen A-K), 2355 CT (63,1%) analyses werden aangevraagd door ITG artsen, waarvan 145 CT positief (124 A-K, 21 L)
- Buiten het aantal dat opgenomen is in de pro deo; zijn er 78 aanvragen van artsen buiten ITG en helpcenter waarvan 42 CT positief (21 A-K, 21 L)

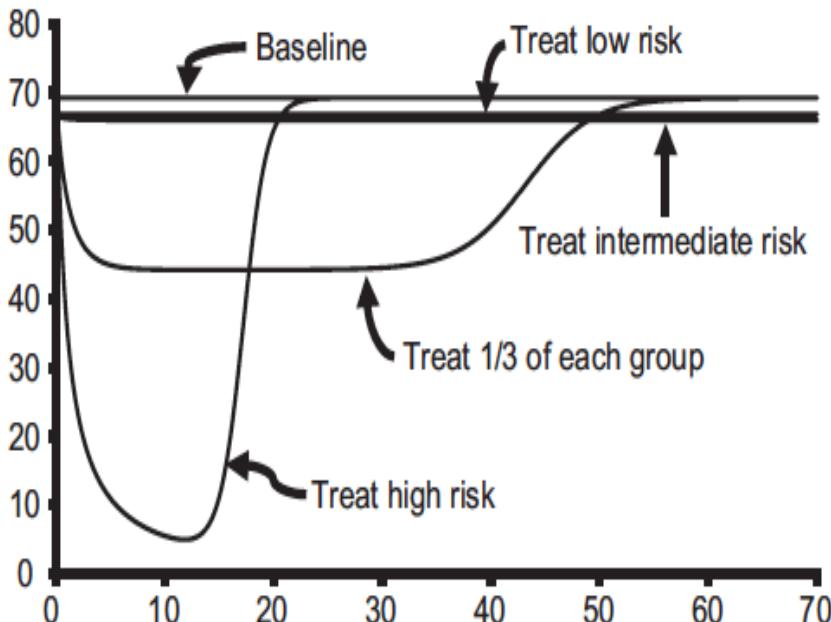
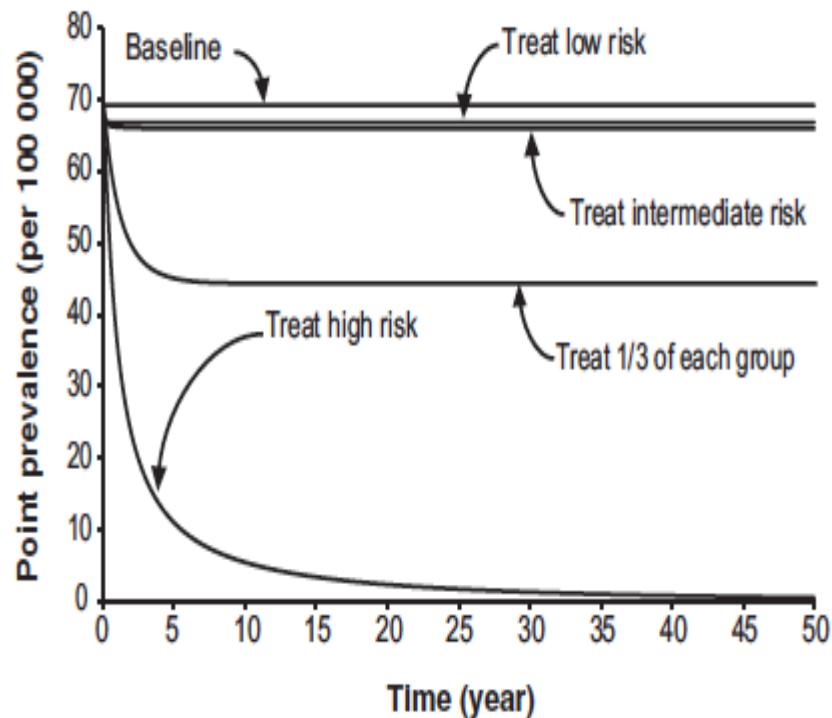
Table 1 Model parameters and baseline values

| Parameter | Symbol | Baseline value | | Source | |
|---|-----------------------------|----------------|-------------------|----------------|--------------|
| Probability of developing de novo resistance on therapy | r_A r_B | 0.000001 | | Assumption | |
| Natural recovery rate (1/year) | v | 8.67 | | Best estimate* | |
| | | High risk | Intermediate risk | Low risk | |
| Population size | N_i | 2308 | 23 077 | 974 615 | |
| Proportion of population | | 0.0023 | 0.023 | 0.97 | |
| Total annual partnerships | c_i | 9.27 | 1.62 | 0.056 | Equation (6) |
| Proportion of sexual partnerships | | | | | |
| High risk | p_{3i} | 0.931 | 0.0669 | 0.002 | |
| Intermediate risk | p_{2i} | 0.4926 | 0.4926 | 0.0148 | |
| Low risk | p_{1i} | 0.33 | 0.33 | 0.33 | |
| Baseline daily rate of treatment using drug A and/or B | t_{Ai} t_{Bi} t_{ABi} | | | | |
| Single-drug treatment | t_{Ai} | 0.003 | 0.003 | 0.003 | |

*Based on descriptions in available medical literature on duration of NG infections lasting from weeks to months when untreated.¹¹⁻³⁰

Core groups, antimicrobial resistance and rebound in gonorrhoea in North America

Christina H Chan,^{1,2} Caitlin J McCabe,^{1,2} David N Fisman^{1,2}



| | | High risk | Intermediate risk | Low risk |
|---------------------------|-------|-----------|-------------------|----------|
| Population size | N_i | 2308 | 23 077 | 974 615 |
| Proportion of population | | 0.0023 | 0.023 | 0.97 |
| Total annual partnerships | c_i | 9.27 | 1.62 | 0.056 |