National Institute for Health Research

BASHH

New paradyms in *Mycoplasma genitalium* testing and treatment

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Disclosures

- None

Outline

- Background
  - Epidemiology
  - Microbiology
  - Treatment and antimicrobial resistance
    - “superbug”
  - BASHH Mgen guidelines
- Pelvic inflammatory disease, NGU and Mgen testing
  - Treatment
  - Partner notification
    - Practical implications of Mgen testing for epidemiological treatment
    - Infection specific partner treatment

To consider

- Does epidemiological treatment of current Mgen -ve & CT -ve partners with doxycycline, of men with Mgen -ve & CT -ve NGU and women with PID (GC-neg) do more good than harm?
  - Yes vs No

Mycoplasma genitalium

- Sexually transmitted

- 1-2% 16-44 yrs olds
  - 7% (4-38%) Sexual Health Clinics

- Risk factors:
  - younger age,
  - non-white ethnicity,
  - higher number of sexual partners,
  - lack of barrier contraception

Epidemiology of *Mycoplasma genitalium* in British men and women aged 16–44 years: evidence from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3)

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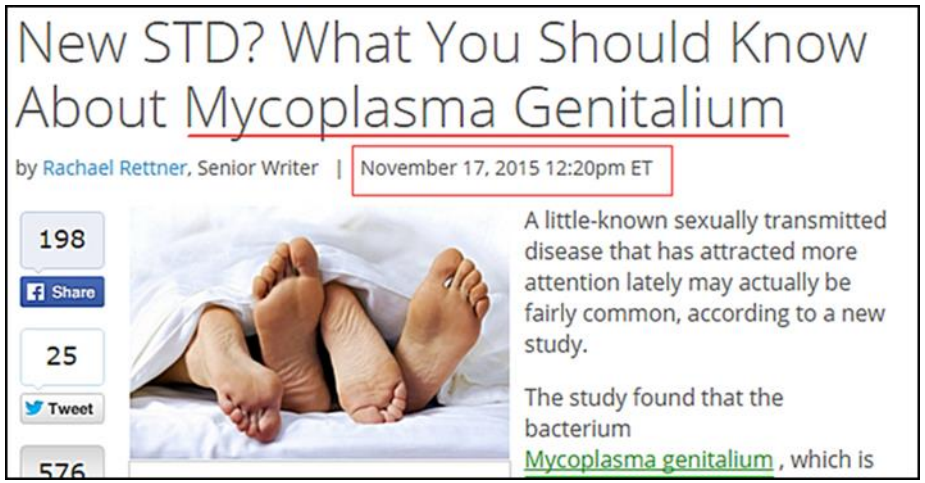

Taylor-Robinson Geniturin Med 1995

M. genitalium – Microbiology and pathogenesis

- Smallest free living micro-organism
- High mutation rate – single copy genome
  - Antimicrobial resistance – single gene mutations
    - Macrolides
    - Quinolones
- Immune evasion: duration infection: < 6mths - >2yrs
  - Antigenic shift
  - Replicates intracellularly and extracellularly
- Very slow growing: routine culture not possible
- Diagnosis and antimicrobial sensitivity testing
  - Nucleic amplification tests (NAATs)

Emerging sex disease MG 'could become next superbug'

By Michelle Roberts
Health editor, BBC News online

11 July 2018 Share

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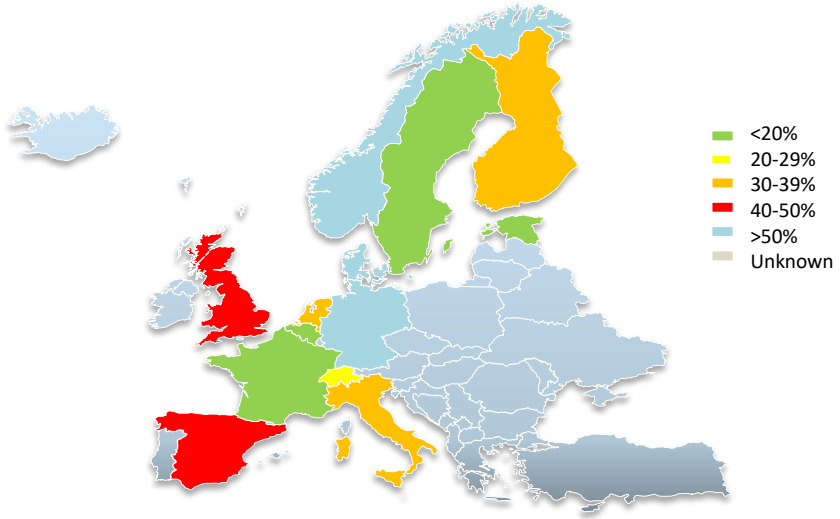
Mycoplasma genitalium

- Ano-genital tract mucosa
  - Majority asymptomatic (>90%)
  - Women
    - Pelvic inflammatory disease (PID) (0.5-1.5% 16-44yrs)
      - <10% will develop PID if left untreated (personal communication – Lewis J, & White P)
    - Cervicitis – post coital bleeding (3% 16-44 yrs) (Bjartling 2012 and Sonnenberg 2015)
      - causal 10-20%
  - Men
    - Non-gonococcal urethritis (0.5% 16-44yrs)
      - 5-10% will develop urethritis (Horner 2017)
    - Proctitis
      - 10% carriage high risk MSM no association symptomatic proctitis (Read 2019)

Mycoplasma genitalium - treatment

- Treatment suboptimal without NAAT and antimicrobial resistance (AMR) testing
- Doxycycline 30-40% effective but v low risk of AMR
- Macrolides
  - 30->50% in some centres
  - Azithromycin 1 g (12% risk AMR)
  - Failure to detect infection and undertake test of cure
- Quinolone AMR increasing
  - 1->5% (50% Japan)
- Prior treatment doxycycline reduces “load” and risk AMR (2-3%)
  - Azithromycin 500mgs then 250mgs od 4 days
  - Azithromycin 1g then 500mgs od 3 days

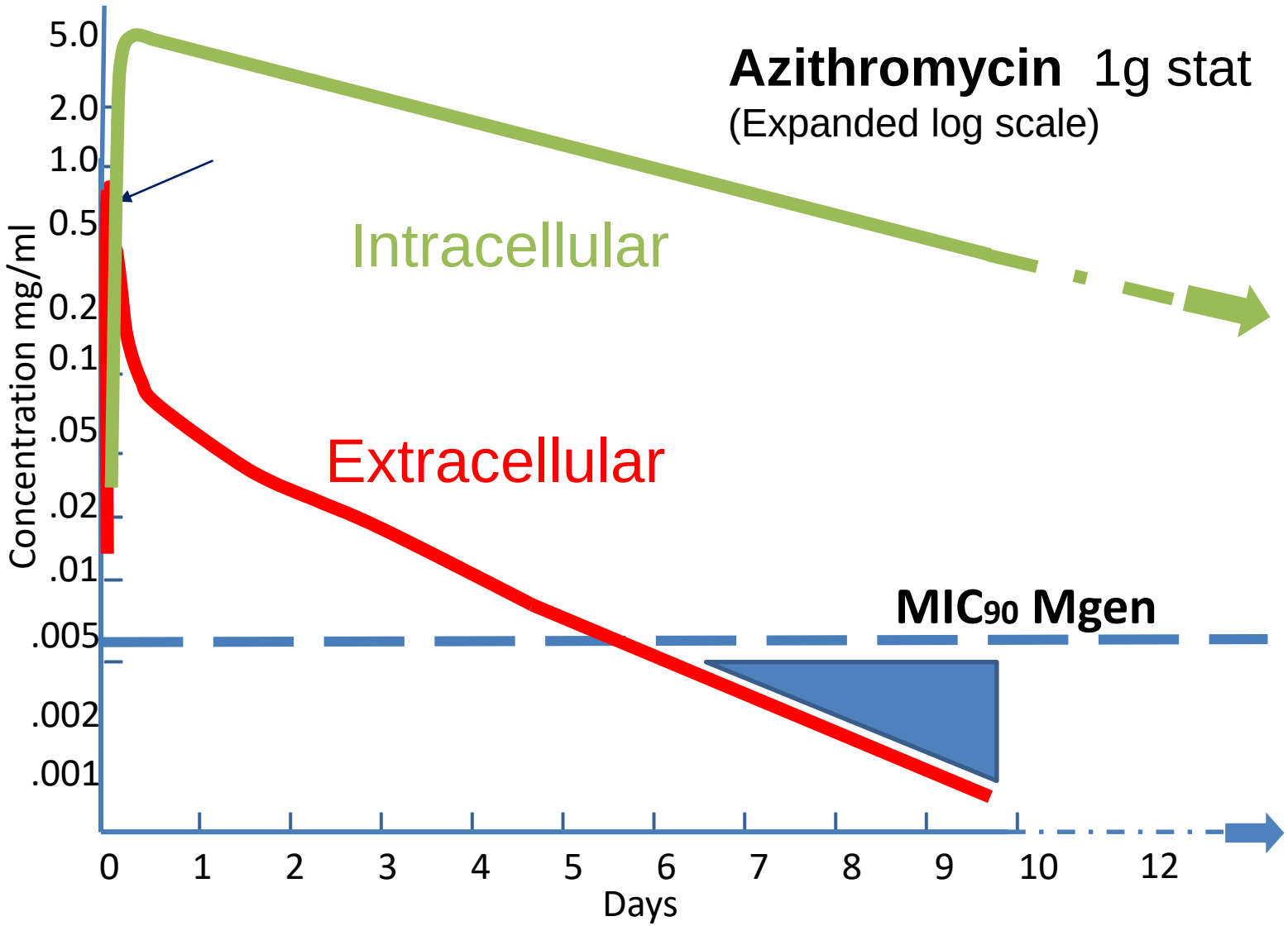
Macrolide AMR Europe (J Jensen)



Taylor-Robinson Genitourin Med 1995

Selection pressure

- Antimicrobial
  - Exposure to sub minimum inhibitory concentrations(MIC) selects for resistance
- High load (symptomatic)
  - Random chance of containing macrolide resistance mutations
- Azithromycin
  - 1 g duration MIC levels too short
  - Prolonged presence sub MIC levels in tissues selects for resistance on re-infection
    - "The greater the dose the longer the duration"



Adapted by P Greenhouse

Horner P STI 2017;93:85; Foulds G JAC 1993 ; Kong F 2019; Horner STD 2019

Selection pressure -quinolones

- Single mutations also associated AMR
- High load (symptomatic)
  - Random chance of containing quinolone resistance mutations
  - Is this happening in vivo?

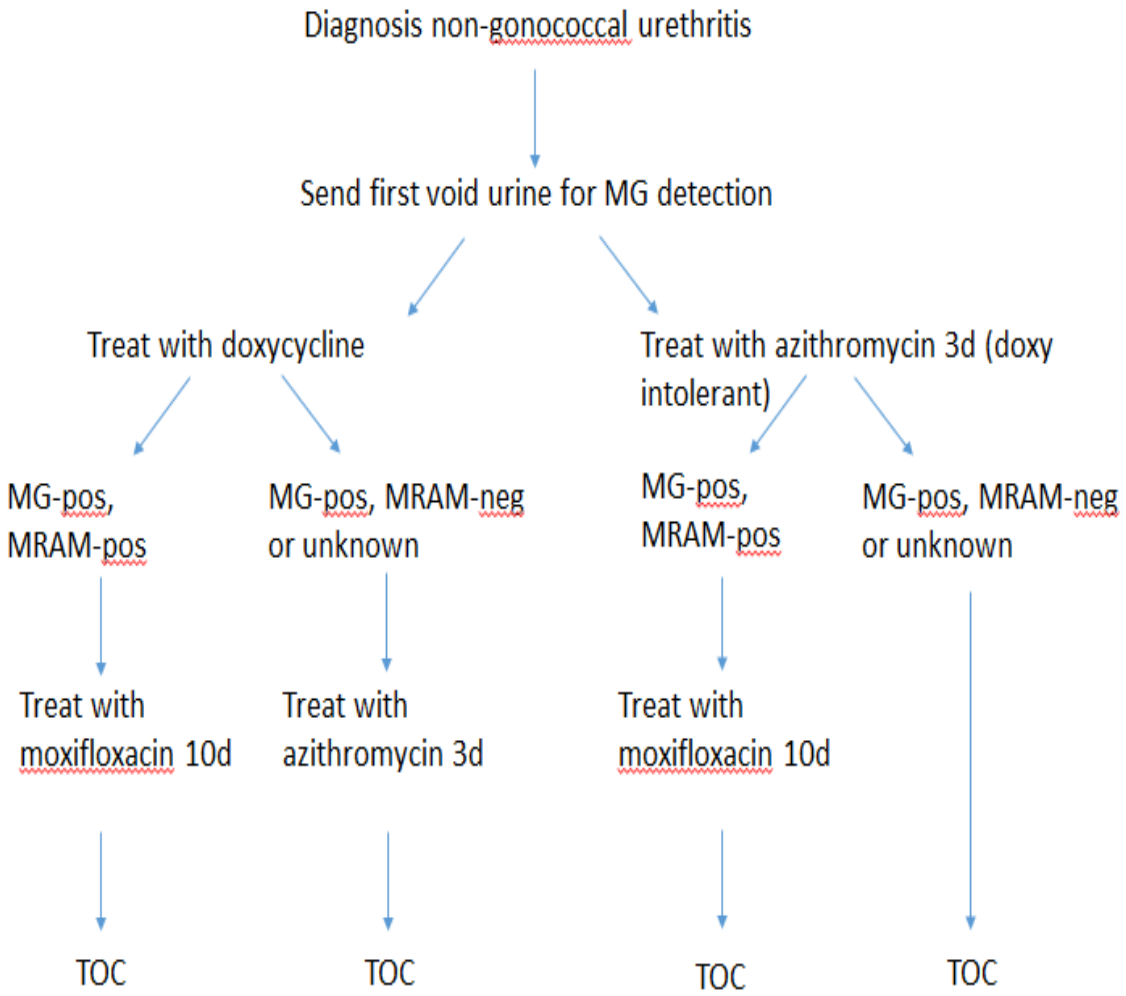
Horner P STI 2017;93:85 & Foulds G JAC 1993;31 supp E;39; Horner STD 2019

BASHH and Mgen AMR

- Developed new evidence based Mgen guidelines - 2018
  - Concern a “superbug” could become common within 10yrs
  - Mgen testing
- Stopped use of azithromycin 1g
  - Extended course
  - 2 weeks no sexual intercourse
- Unified new Mgen guideline with gonorrhoea, NGU & chlamydia

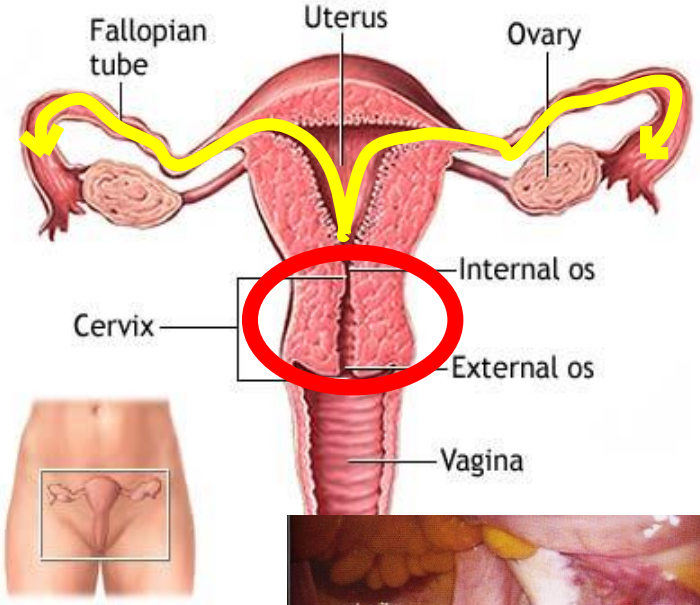
Recommendations for testing

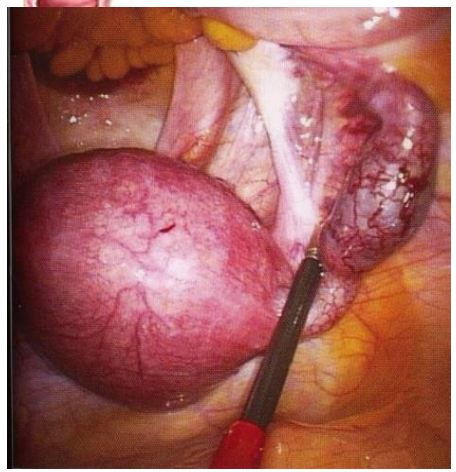
- Who
  - No Asymptomatic screening
  - All women with PID
  - All men with NGU
  - Current partners of Mgen +ves
- Which test
  - Mgen NAAT
  - If +ve reflex NAAT AMR testing
    - Test of cure
    - Improves outcomes
    - Stops development AMR



Pelvic inflammatory disease (PID)

- 30-50000 women 16-44yrs
- Aetiology
  - Chlamydia 20% (35% <24 yrs)
  - *Mycoplasma genitalium* 10% (3-5000)
  - Gonorrhoea (GC) 1-3%
  - Bacterial vaginosis associated bacteria (anaerobes)
  - Respiratory tract and Enteric pathogens
- Complications
  - Tubal factor infertility 2.5% - 4%
  - Ectopic pregnancy risk increased 1-1.5% (normal 1%)
  - Chronic pelvic pain (10-20%)
- Early identification and treatment reduces risk of sequelae





Price M HTA 2016, Bradshaw C STD 2019, Ong K STI 2017, Soni S BASHH 2018, Haggerty C 2008, STI

PID treatment

- Ceftriaxone, doxycycline and metronidazole
  - Reduced efficacy Mgen-positive
    - Probable increased risk of sequelae ?doubled
  - Addition azithromycin 1g increase microbiological cure but not clinical cure (no ceftriaxone)
    - Extended azithromycin if macrolide sensitive more effective (+ceftriaxone)
- Moxifloxacin effective all causes PID
  - Second line because side effects
  - What do we do if quinolone resistant?

Haggerty C 2008, Price M 2016, Ross J 2018, Petrina M 2019, Latimer R 2019

PID costs and Mgen testing

PID	Numbers	Mgen	Cost low	Cost Resistant	Total cost (low)	New cost if 50% resistant	Difference in cost
GUM	12,000	1200	171	600	205,200	462,600	£257,400
Total	50,000	5000	171	600	855,000	1,927,500	£1,072,500

PID	Numbers	Cost sequelae (low)	Additional cost if 50% resistant*	Total increase in cost if 50% resistant
GUM	12,000	59,712	29,856	£287,256
Total	50,000	248,800	124400	£1,196,900

PID	Numbers	Mgen	Cost Mgen testing (£10)	Cost testing plus Mgen +ve (£30) AMR testing
GUM	12,000	1200	120,000	£156,000
Total	50,000	5000	500,000	£650,000

* Assumes risk sequelae doubles: TFI (3%), Ectopic pregnancy (1%), chronic pelvic pain syndrome (15%)

NB if assume high cost sequelae total increase in cost GUM : £701,316

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Haggerty C 2008, Price M 2016, Ong K 2017, Latimer R 2019

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PID - partners

- NAAT testing chlamydia, gonorrhoea current partner (1D)
  - Mgen if index case NAAT-positive
    - Will this miss some partners Mgen positive (46% concordance)
  - Screening partner(s) CT/GC in previous 6 months (2D)
    - Some cases CT PID may not be detectable at lower genital tract
- Epidemiological treatment partners as polymicrobial infection (2D)
  - Doxycycline 100mgs bd 7 days (broad spectrum)
  - Expert opinion weak evidence base
- Are women with CT/GC/Mgen neg partners at increased risk of recurrence if partners are not treated?
  - We do not rescreen for bacterial vaginosis
    - Metronidazole prophylaxis does not prevent PID
  - Treating male partner does prevent recurrence of BV
- What about antimicrobial stewardship?

Non-gonococcal urethritis (NGU)

- 40-80,000 cases annually
- Aetiology
  - Chlamydia 15-30%
  - Mgen 10-25% (20,000)
  - *Ureaplasma urealyticum* 5-10%
  - Unknown 30-40%
    - Bacterial vaginosis associated bacteria
    - Increased pelvic floor tone? Poster 133
- Treatment
  - Doxycycline 100mgs bd 1 week
- Complications
  - Chronic NGU 10-20%
    - 20-40% *M genitalium*
    - Significant morbidity

NGU - partners

- NAAT testing chlamydia current partner (1D)
  - Mgen if index case NAAT positive
  - Screening partner(s) CT/NG in previous 4 weeks (2D)
- Epidemiological treatment all partners previous 4 weeks (2D)
  - Doxycycline 100mgs bd 7 days
  - Expert opinion weak evidence base
- Are men with CT/Mgen -ve partners at increased risk of recurrence?
  - *U. urealyticum* risk of disease decreases with duration infection
  - No evidence treating CT and Mgen -ve partners of benefit
- Are CT/Mgen -ve female partners at increased risk PID
  - Weak evidence Ong J et al 2017 – biased: diagnosis of NGU more likely if contact of PID
- Antimicrobial stewardship?

PID & NGU partners – epidemiological Rx vs Mgen testing

- Time delay in identifying if index case Mgen-positive
  - Partners 40% risk Mgen-positive
  - 1) Epidemiological treatment all
    - Doxycycline 40% effective (NB 25% risk Mgen-positive post Rx)
    - Reduce sensitivity Mgen NAAT if index case Mgen-positive
    - Test of cure 5 weeks vs same treatment as index
      - Risk re-infection and need re-treatment
      - Vs Risk over treatment - quinolone

PID & NGU partners – epidemiological Rx vs Mgen testing

- Time delay in identifying if index case Mgen-positive
  - Partners 40% risk Mgen-positive
  - 2) Mgen test partner
    - Need result of index Mgen test to guide testing
    - Treat partner doxycycline
      - If Mgen-positive add azithromycin or Moxifloxacin
    - ?Save CT/GC specimen for Mgen testing if index Mgen-positive
      - Organisationally complex

PID & NGU partners – epidemiological Rx vs Mgen testing

- Time delay in identifying if index case Mgen-positive
  - Partners 40% risk Mgen-positive
  - 3) Test all partners for CT/GC and Mgen
    - Await results before partner treatment
      - Only treat if NAAT-positive *unless*
      - 2 week window period and index NAAT-positive

Conclusion

- Most persons with Mgen resolve infection without disease
- Treatment effective if sensitive to antimicrobial
  - Treatment of Mgen with macrolide or quinolone has risk of selecting for resistance.
    - Reduced by pre-treatment with doxycycline for azithromycin
    - Abstinence sexual intercourse 2 weeks post
    - Rationale for test of cure
- Mgen NAAT testing likely to be cost effective in PID and NGU
- Weak evidence that treating current partners of NGU of benefit if
  - CT and Mgen NAAT neg
- Weak evidence that treating current partners of PID of benefit if
  - CT , Mgen and GC NAAT neg
- Should we consider NAAT guided infection specific treatment for contacts?
  - Test all current partners for CT/GC and Mgen
  - RANDOMISED CONTROLLED TRIALS

Problems

- Lack of funding to support adoption of BASHH Mgen guidelines
  - Sexual Health clinics
  - Primary care

Acknowledgements

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Question

- Does epidemiological treatment of current Mgen -ve & CT -ve partners with doxycycline, of men with NGU and women with PID (GC-neg) do more good than harm?
  - Yes vs No

Questions

- Does epidemiological treatment of previous CT -ve partners with doxycycline of men with urethritis and women with PID (GC-neg) do more good than harm?
  - Yes vs No