THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Correlates of repeat anorectal infections among men who have sex with men

Kong FYS[1], Tabrizi S[2], Fairley CK[3], Phillips S[2], Fehler G[3],Law M[4], Vodstrcil LA[1,3], Chen M[3], Bradshaw CS[3], Hocking JS[1]

1. School Population and Global Health, University of Melbourne
2. Royal Women's Hospital, Victoria, Australia.
3. Melbourne Sexual Health Centre, University of Melbourne, Victoria, Australia.
4. Kirby Institute, Sydney, Australia.

Background

- Most common bacterial STI among MSM
  - Prevalence twice that of urethral infections
    - Rectal CT prevalence 5.6-11.3% [1-8]
- Increasing reports of treatment failure with repeat infection rates from 13-22% [9-12]
- Lymphogranuloma venereum (LGV) mainly considered symptomatic, but up to 27% can be symptom free and without genotyping could be missed [13]

1. BMC Inf Dis 2012; 12(1):113 . 2. Morb Mortal Wkly Rep 2009; 58(26): 716-9. 3. Sex Transm Infect 2009; 85: 176 - 9. 4. J Clin Microbiol 2013; 51(6): 1855-6 . 5 Clin Infect Dis 2005; 41(1): 67-74 1. 6. Sex Transm Infect 2014; 90(1): 46-51. 7. WHO/RHR/11.37 8. BMC Infect Dis 2011; 11(1): 203 9. Sex Transm Infect 2012; 88: 352–4. 10. Int J STD AIDS 2009; 20: 16–8. 11. J STD AIDS 2011; 22:478–80. 12. Sex Transm Dis 2014; 41: 79–85 13. Sex Transm Infect 2013, **89**(7):548-552.

THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Current treatment

- Recommended treatment for chlamydia[1]
  - Single 1g azithromycin or 7 days (100mg twice daily) doxycycline
  - Varies internationally and nationally
- Sexual health guidelines: Doxycycline preferred for rectal infection in EU and Australia[2,3]
- Meta-analysis rectal chlamydia treatments
  - Azithromycin 82.9% vs doxycycline 99.6% [4]
- Organism load may be associated with treatment failure[5-7]

1. CDC MMWR 2010. 59(No.RR-12):1-116 2. Int J STD AIDS 2010; 21(11):729-737 3. www.sti.guidelines.org.au 4. J Antimicrob Chemother 2015; 70(5): 1290-7. 5. Lancet 2005; 366(9493): 1296-300 6. Plos One 2012; 7(5): e37778. 7. Sex Transm Infect 2015;91(3): 157-64.

THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Aim

To investigate repeat rectal chlamydia infection among MSM and:

1. Estimate the risk of repeat rectal chlamydia among MSM following treatment
2. Describe genovar and organism load profile of rectal chlamydia among MSM
3. Differentiate between re-infection and treatment failure
4. Investigate association of organism load with re-infection and treatment failure
5. Estimate azithromycin treatment efficacy

THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Methods

- **Setting and participants:** MSM attending a large urban sexual health centre (MSHC) who tested positive for rectal chlamydia
- MSHC guidelines: rectal chlamydia treatment is 1g azithromycin
- Chlamydia positive samples are stored for further research
- Eligible: MSM tested positive for rectal chlamydia between July 2008 and Oct 2013 & retested within 100 days of treatment
- MSM with clinical proctitis/symptomatic LGV excluded
- **Laboratory testing:** Chlamydia bacterial load and genovar/MLST
  - Load estimates: quantitative PCR targeting the omp1 gene (qPCR)
  - Genovar: (1) 3 distinct phylogenetic clades based on the *ompA* gene; **B group** (B/Ba, D, E, L1, L2); **C group** (A, C, H, I, J, K, L3); **Intermediate group** (F and G)
  - Multilocus sequence typing (**MLST**): Differentiate between identical genovars from the same individual; analysis over 5 regions of the chlamydia genome *hctB, CT682-pbpB, CT144, CT172, CT058*

THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Methods

- **Electronic patient data**
  - Age, treatment received on initial diagnosis, co-infections with other STIs (including HIV), past STIs, sexual practices, condom use, rectal symptoms, diagnosis of proctitis, time between test results
- **Statistical analysis:**
  - The proportion re-testing positive was calculated with 95%CI using binomial methods
  - Organism load was log 10 transformed
  - Load was calculated as copies per swab
  - Factors associated with treatment success vs treatment failure or reinfection were investigated using logistic regression. Load for index cases was included in the model and variables selected for inclusion on the basis of literature and likelihood ratio test.
- **Ethical approval from Alfred Hospital Ethics Committee**

THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Outcome definition

genovar: index vs follow-up result	Had sex in past 3 months	Any condomless sex, as receptive partner, in past 3 months	Outcome
Different	-	-	Re-infection
Same	-	Yes	
Same	Yes	N/A[2]	
N/A[1]	Yes	N/A[2]	
Same	-	No	Treatment failure
Same	No	N/A[2]	
Same	Yes	No	
N/A[1]	No	N/A[2]	
Same	N/A[2]	N/A[2]	unclassifiable

N/A[1]= genovar data not available; N/A[2] sexual practice data not available

Results - profile of participants

227 index cases included in this analysis

AGE
Median 29 years (range: 18-78 years)

HIV positive
45 (20%)

 # partners / condom use (last 3 months)
26% (>6 partners) and 21% condom all the time

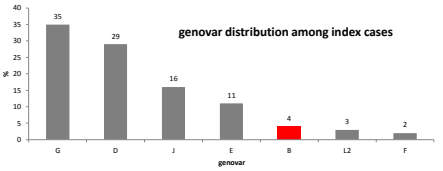
TIME TO RETEST
Median 62 days (50% retested: 6-11 weeks)

Results – repeat positive among index cases (n=227)

Repeat positive	n	%	95%CI
Overall	64	28%	22%-35%
Probable/definite reinfections	35	15%	11%-21%
Definite reinfections	11	5%	2%-9%
Treatment failure	29	13%	9%-18%

THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

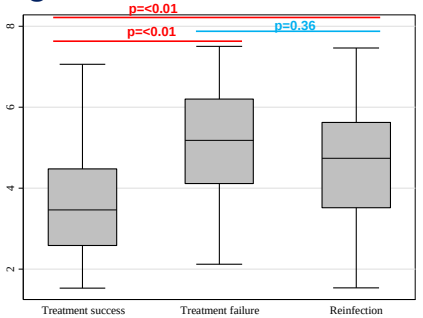
Genovar distribution



- 64 repeat positives
  - 2 (3%) different genovar
  - 46 (71%) same genovar
- 45 positive pairs (same genovar) tested with MLST
  - 9 (20%) different

THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Organism load – index swab



THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Factors associated with treatment failure and re-infection

Variable	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Treatment success vs treatment failure		
Organism load (log10)	1.97 (1.44-2.71)	1.93 (1.40-2.65)[1]
Treatment success vs probable/definitive reinfection		
Organism load (log10)	1.64 (1.26-2.19)	1.59 (1.20-2.12)[1]
Treatment success vs definitive reinfection		
Organism load (log10)	1.51 (0.98-2.31)	1.55 (0.99-2.40)[2]

[1]adjusted for age, HIV status, number of sex partners last 3 months and time between index and repeat test.
[2]adjusted for HIV

Compared to treatment success, load was associated with
- 93% increase in odds of **treatment failure**
- 55%-59% increase in odds of **definitive/probable reinfection**

THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Azithromycin efficacy

- Treatment records for 97% (220/227)
  - Azithromycin 1g only in 203 cases (n=2 doxy)

	Overall	1g Azithro
Treatment success	72% (163/227)	70% ((143/203)
Treatment failure	13% (29/227)	14%* (28/203)
Reinfection	15% (35/227)	16% (32/203)

*1g Azithromycin efficacy of 86% (95%CI: 81-91%)

Discussion

- Repeat positivity rate is common; 28% consistent with previous results[1]
- Genovar distribution was similar among MSM globally [2-4]
  - 3 cases of missed LGV
- Azithromycin efficacy 86% similar to meta-analysis (83%)[5]
- Association between high load and treatment failure is consistent with past findings and raises possibility of:
  - Heterotypic resistance
- Association between high load and re-infection:
  - Impaired rectal immune response to infection?[6]

1. STD 2014; 41(2): 79-85 2. Jap J Infect Dis 2011; **64**: 143-6. 3. STD 2011; **38**: 279-85. 4. J Clin Micro 2012; **50**: 3548-55 5. JAC 2015, **70**(5):1290-1297. 6. *Clin Vaccine Immunol* 2013, **20**(10):1517-1523.

THE UNIVERSITY OF MELBOURNE Faculty of Medicine, Dentistry and Health Sciences Melbourne School of Population and Global Health

Discussion

- Evidence for higher organism loads and azithromycin treatment failure
  - Small study anorectal infections, higher organism load associated with repeat positive[1]
  - Trachoma[2], cohort young Australian women[3]
  - Pharyngeal chlamydia persistence associated with higher load[4]

1. PloS one 2013; 8(11): e81236 2. Lancet 2005; 366(9493): 1296-1300. 3. PloS one 2012; 7(5): e37778 4. Sex Transm Infect 2015, **91**(3):157-164.

THE UNIVERSITY OF MELBOURNE Faculty of Medicine, Dentistry and Health Sciences Melbourne School of Population and Global Health

Strengths and Limitations

- Analysed all positive rectal samples in past 5 years with 95% providing a genovar & load estimate
- Small sample size for analysis of outcome
- MLST cannot definitively discriminate between treatment failure and reinfection[1]
- No MLST data available for 33% of repeat positive samples
- Possible degradation of organism load over time in stored swabs[2]

1. *PloS one* 2013; **8**: e81236. 2. *J Clin Microbiol* 2013, **51**(3):990-992.

THE UNIVERSITY OF MELBOURNE Faculty of Medicine, Dentistry and Health Sciences Melbourne School of Population and Global Health

Implications for practice?

- Better methods for detecting organism load?
  - mRNA (viable organism) vs DNA/rRNA (dead organism)
  - What is the threshold for defining 'high' load?
- Strong recall and test for reinfection to break transmission
- Give everyone 7 day doxycycline? (99% vs 83% efficacy)
  - Issues of compliance?
- Increasing the dose of azithromycin?
  - Total dose over 2-3 days? Need pharmacokinetic studies
  - *See poster on dosing in extended doses of Azithromycin (#100)*
  - *Forthcoming RCT comparing azithromycin vs doxycycline for treating rectal infections (ANZCTR: 12614001125617)*

THE UNIVERSITY OF MELBOURNE Faculty of Medicine, Dentistry and Health Sciences Melbourne School of Population and Global Health

Disclosure of interest and thanks

- FYSK is supported by an Australian Postgraduate Award
- JSH is supported by a National Health and Medical Research Council (NHMRC) Senior Research Fellowship
- Supervisors: Prof Jane Hocking, Prof Christopher Fairley, A/Prof Sepehr Tabrizi, Dr. L Vodstrcil
- World STI & HIV Congress Scholarship

THE UNIVERSITY OF MELBOURNE Faculty of Medicine, Dentistry and Health Sciences Melbourne School of Population and Global Health

Thank you

Fabian Kong
kongf@unimelb.edu.au

Results

227 index cases with second test result

64 with second positive
- genovar + load=56 (87.5%)

163 tested negative
- genovar + load=160 (98.2%)

genovar (64 cases)
- 16 (25.0%) unassessable
- 2 (3.1%) different
- 46 (71.9%) same

45 MLST (of 46 cases)
- 32 (71.1%) same
- 9 (20.0%) different
- 4 (8.9%) unconfirmed

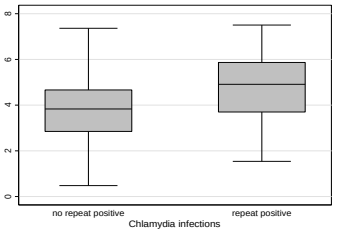
ORGANISM LOAD (n=227)
- 218 (96.0%) load data
  - 87.5% (56/64) repeat positive
  - 99.4% (162/163) no repeat positive

THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Organism load – repeat positive

Organism load (log10) among index cases (n=227)

- Repeat positives vs no repeat positive
  - **Crude**: 4.8 vs 3.7* & **Adjusted**: 1.7 vs 0.8* (*p<0.01)



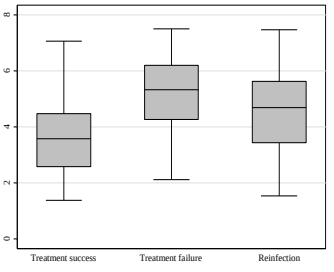
THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Organism load by outcome

Organism load (log10) among index cases (n=227)

	Crude	Adjusted
Treatment success	3.7	0.8
Treatment failure	5.0	1.9
Reinfection	4.6	1.6

Repeat infection vs Tx success (p<0.01)

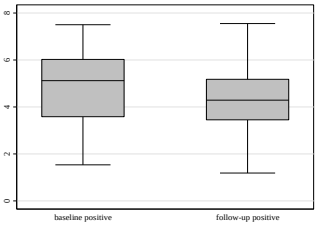


THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Organism load - 1st vs 2nd positive

Organism load (log10) among repeat positive

- Prevalent (baseline) vs incident (follow up) infection
  - Crude: 4.8 vs 4.4 (p=0.14) & Adjusted: 1.7 vs 1.4 (p=0.21)



THE UNIVERSITY OF MELBOURNE
Faculty of Medicine, Dentistry and Health Sciences
Melbourne School of Population and Global Health

Persistent infection

- Persistence of chlamydia in-vitro
  - Exposure to β-lactam antibiotics, interferon-γ or deprived of iron supplements or amino acids can exhibit persistence [1-6]
- Penicillin can induce azithromycin treatment resistance in-vitro (eg. treatment for syphilis) [7,8]
- Co-infection with herpes simplex can contribute to persistence [9-12] although not with HIV[13]
- Re-infections 4x higher with persisted infections at enrolment[14]

1. Infection & Immunity 1995;63:199-205 2. Infection & Immunity 2000;68(3):1457-1464 3. Infection & Immunity 2004;72(4):1843-1855 4. Future Microbiology 2010;5(9):1427-1442. 5. J Infect Dis 2010;201 Suppl2:S88-95. 6. AAC 2013 dec16 7. Circulation 2001;103(3):351-356 8. JAC 2004;54(1):79-85. 9. Cellular Microbiology 2007;9(3):725-737 10. Microbiology 2008;154(3):971-978 11. Microbiology 2010;156(5):1294-1302 12. PloS One 2012;7(10):e47427 13. HIV Med 2010 Apr 21-23;11(Suppl.1):9(abstract O22) 14. Journal of Infectious Diseases 2013 207(12):1850-1856