

CREDITS

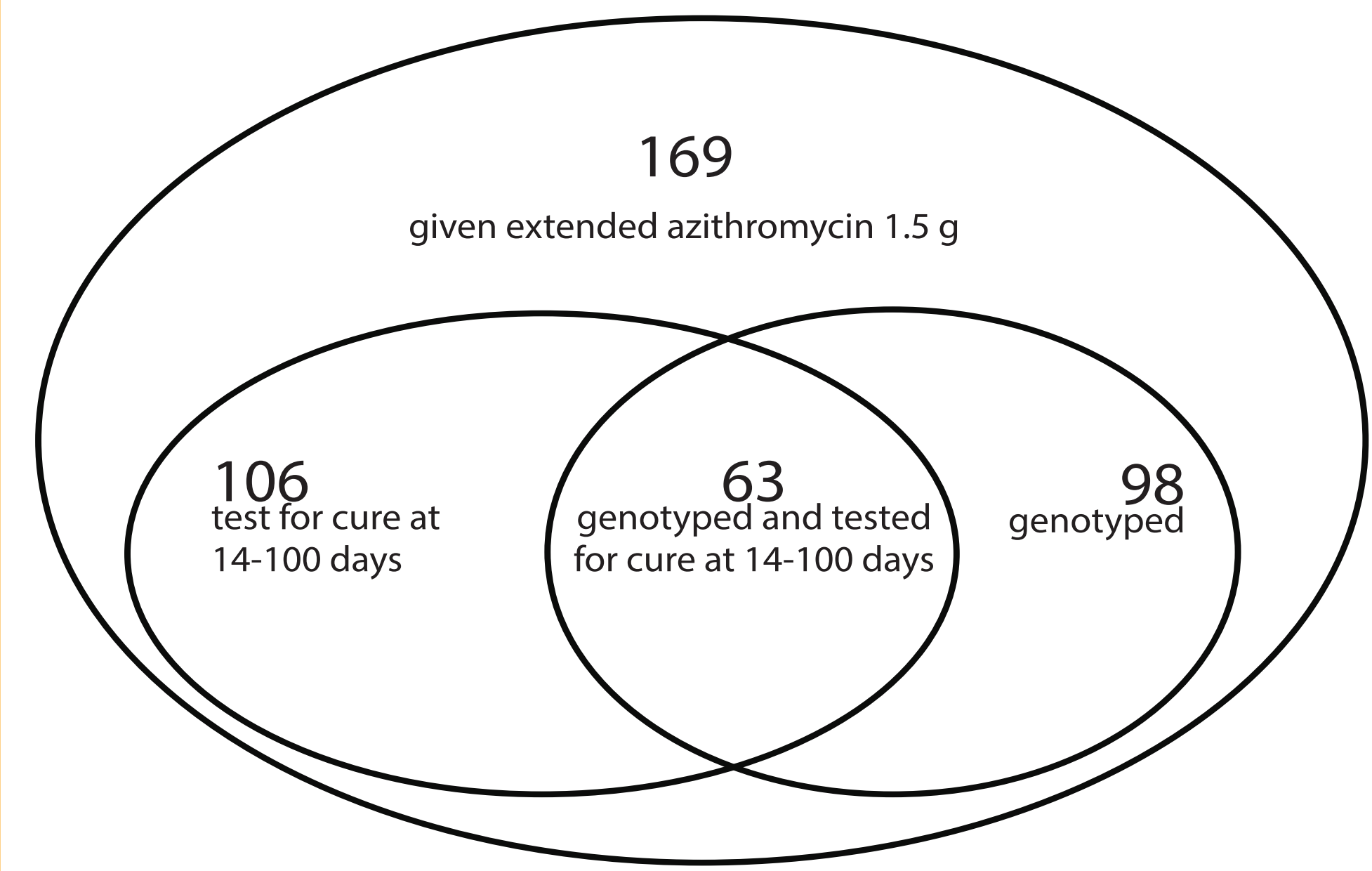
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AIM:

We aimed to evaluate the effect of azithromycin 1.5g over five days for *M. genitalium* urethritis on proportions with microbiological cure or with selection of macrolide resistance.

METHODS:

- Retrospective review of electronic medical records (October 2013 – June 2015) with comparison to men with urethritis selected from a previously reported prospective case-series² of *M. genitalium* infections (2012-2013, historical controls).
- From 169 men with *M. genitalium* urethritis treated with 1.5g extended azithromycin, we selected 106 who had a test of cure (polymerase chain reaction targeting 16S ribosomal RNA) 14 – 100 days after start of treatment (Figure 1).
- Pre and post-treatment macrolide resistance mutations (MRM) were detected by sequencing the 23S gene in 98 patients with available samples (Figure 1).
- Information on sexual risk factors and the risk of post-treatment reinfection was extracted from case notes.



RESULTS:

- No difference between proportions cured by azithromycin 1.5g - 62/106 [58% (95%CI, 49, 68)] vs azithromycin 1g - 56/107 [52% (95%CI, 42%, 62%)] P=0.34
- No difference between proportions of wildtype 23S rRNA (presumed macrolide sensitive) infections cured after azithromycin 1.5g and 1g: 82% for both (Table 1).
- There was no difference between 1.5g and 1g in the proportions of wildtype infections with post-treatment macrolide resistance mutations: 4/34 [12%* (95%CI, 3%, 27%)] and 11/60 [18% (95%CI, 10%, 30%)], respectively P=0.40. *Two wildtype treatment failures from 2013-2015 could not be sequenced.
- Pre-treatment resistance was detected in 51/98 [52% (95%CI, 42%, 62%)] cases in 2013-2015 vs 47/107 [44%(95%CI, 34%, 54%)] in 2012-13, P=0.25.
- In 2013-2015, pre-treatment resistance was detected in 26/34 gay/bisexual men (76%) compared to 25/64 heterosexual men (39%), P<0.001.
- Wildtype infections that were not cured had a higher bacterial load than those that were, and resistant infections that were cured had a lower bacterial load (Fig 2).
- When treatment failed, bacterial load was lower in post-treatment samples (mean log₁₀ 2.2) than in pre-treatment samples (log₁₀ 3.3, p<0.01) (Figure 3).
- Treatment failure was strongly associated with pre-treatment macrolide resistance and less so with being a gay or bisexual man (Table 2). Reinfection risk and sex overseas were not associated with treatment failure.

Table 1. Pre-treatment resistance, selected resistance and outcomes after a single dose of azithromycin 1g in 2012-2013², or extended azithromycin 1.5g over five days in 2013-2015, for men with *M. genitalium* urethritis.

	1.5g over 5 days		1g single dose		P value
	n/N	% (95% CI)	n/N	% (95% CI)	
Proportion cured	62/106	58 (49, 68)	56/107	52 (42, 62)	0.34
Pretreatment resistance					
Overall	51/98	52 (42, 62)	47/107	44 (34, 54)	0.25
Heterosexual	25/64	39 (27, 52)	31/77	40 (29, 52)	0.90
Gay/bisexual men	26/34	76 (59, 89)	16/30	53 (34, 72)	0.05
Proportion of each pretreatment genotype cured					
Wildtype	28/34	82 (65, 92)	49/60	82 (70, 90)	1.0
Resistant	4/29	14 (8, 35)	7/47	15 (6, 28)	0.90
Post-treatment resistance	4/34	12 (3, 27)	11/60	18 (10, 30)	0.40

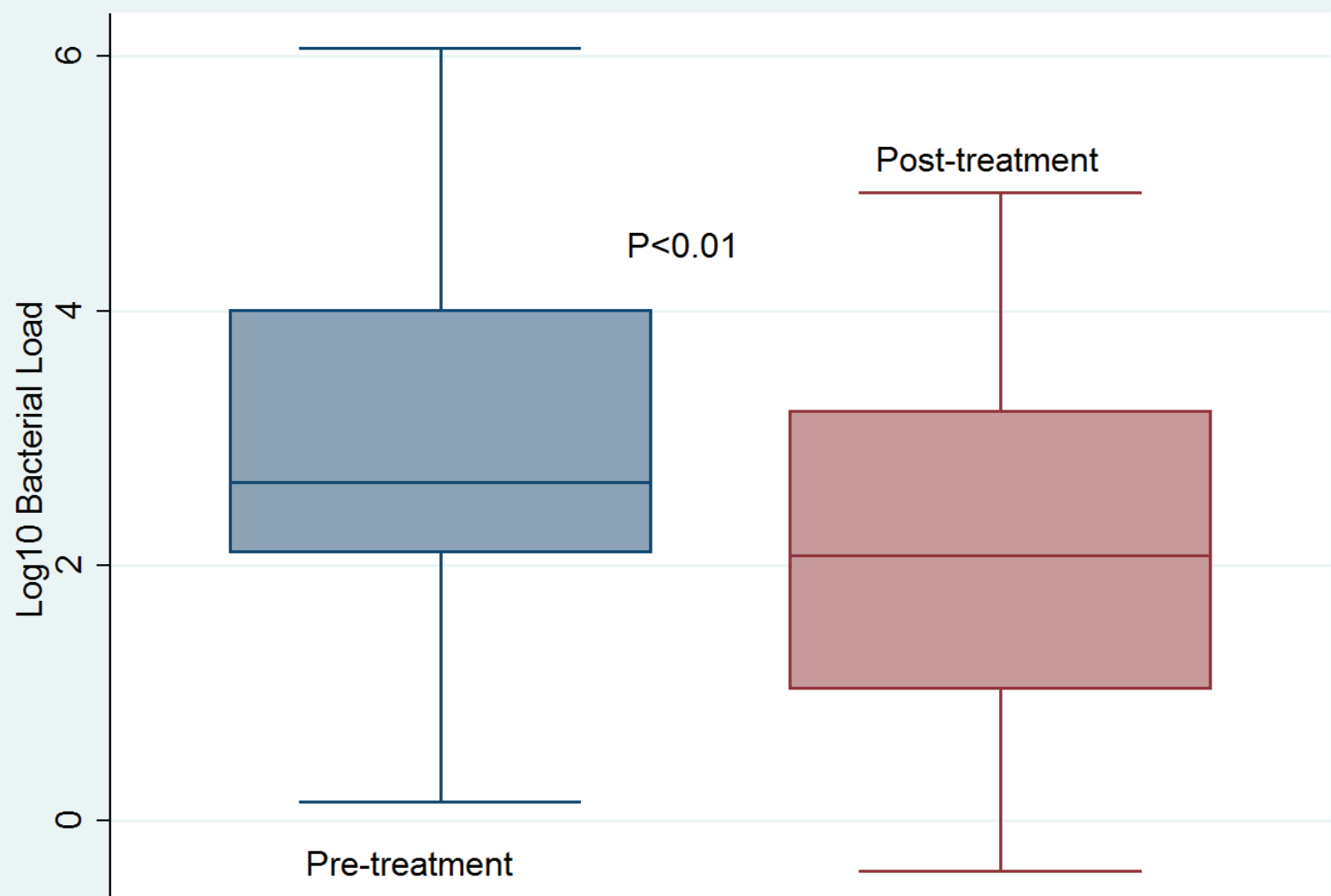
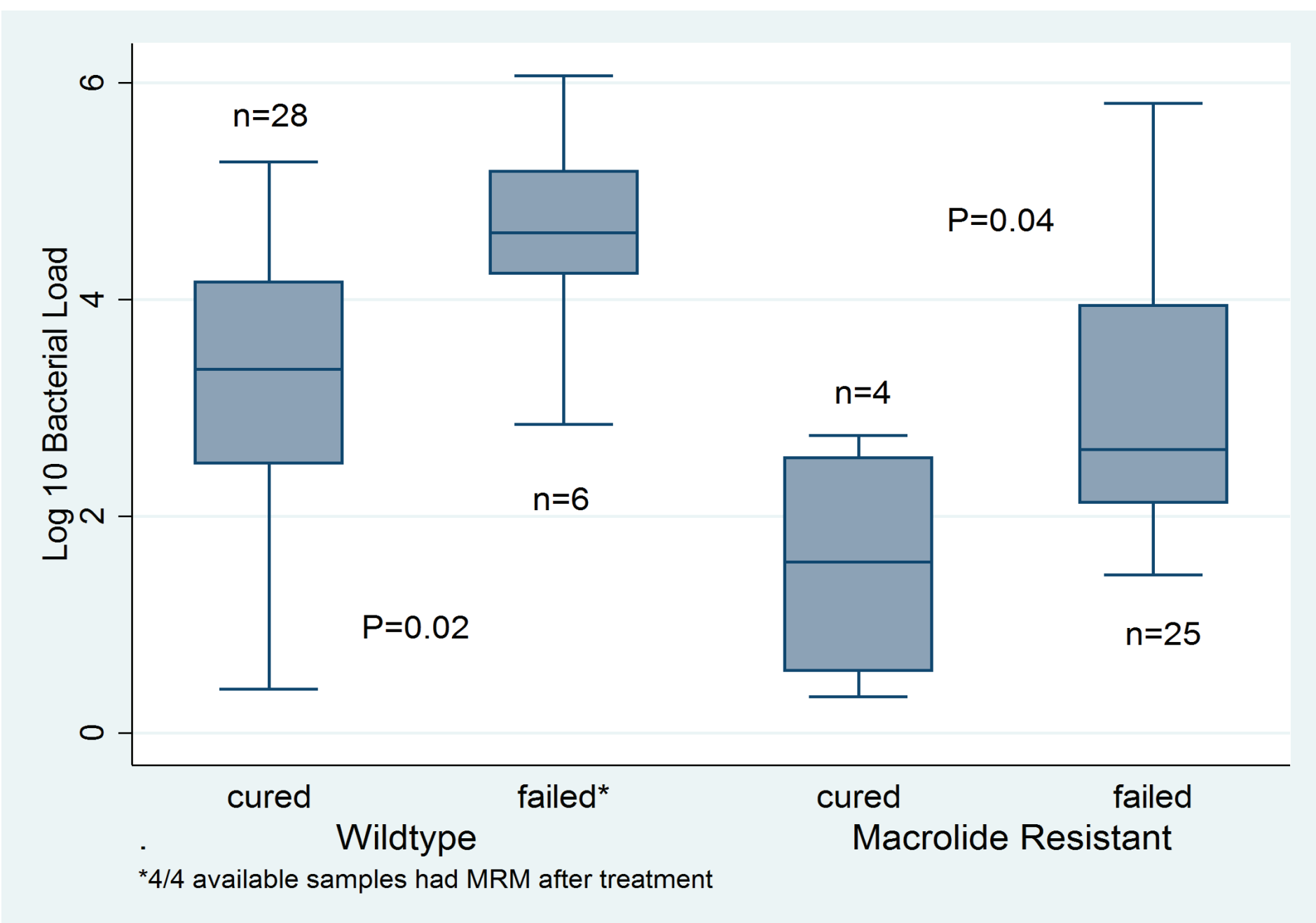


Table 2. Predictors of failure of extended azithromycin 1.5g for urethral *M. genitalium*.

Patient group	Unadjusted OR (95% CI)	P value	Adjusted OR ¹ (95% CI)	P value
Pre-treatment Genotype				
Wildtype	reference		reference	
Resistant	29.2 (7.4, 115.4)	<0.001	24.2 (5.7, 102.3)	<0.001
Bacterial load ²	1.1 (0.9, 1.3)	0.3		
Sexual preference				
Heterosexual	reference		reference	
Gay/bisexual	5.6 (1.4, 13.0)	<0.001	4.9 (1.1, 21.1)	0.04
Previous azithromycin recorded				
No	reference		reference	
Yes	4.4 (1.1, 17.8)	0.04	0.8 (0.1, 6.6)	0.9
Sex outside Australia				
No	reference			
Yes	1.0 (0.4, 2.5)	1.0		
Number of partners in past 3 months				
OR per additional partner	1.2 (1.0, 1.4)	0.03	1.1 (0.8, 1.5)	0.4
Risk of reinfection ³				
No	reference			
Yes	1.6 (0.4, 6.9)	0.5		

1. Odds ratio (OR) for treatment failure, adjusted for sexual preference and pre-treatment resistance mutations.
2. OR per log₁₀ increase in bacterial load in pretreatment sample.
3. Sex between treatment and test of cure with new or pre-existing partners.

CONCLUSIONS:

Extended azithromycin 1.5g was not more effective than a single 1g dose at achieving cure of *M. genitalium* urethritis and did not reduce the selection of macrolide resistance. New approaches for the treatment of *M. genitalium* urethritis are required.

REFERENCES:

- In press. *Clinical Infectious Diseases* 2016
- Bissessor M et al. *Clinical Infectious Diseases* 2015; 60(8): 1228-36

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ACKNOWLEDGMENT:

Jimmy Twin for laboratory work.