Adjunctive Rifampicin to Reduce Early mortality from STaphylococcus aureus bacteraemia: final results from the multi-centre, randomised, blinded, placebo-controlled ARREST trial

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Background

- *Staphylococcus aureus* bacteraemia is one of the most common and serious community and hospital-acquired bacterial infections worldwide
- Optimal antimicrobial treatment remains uncertain: <1,600 participants enrolled in RCTs of antimicrobial therapy over the last 50 years[1]
- The ARREST trial (ISRCTN37666216) therefore tested the hypothesis that adjunctive rifampicin would enhance early killing of *S. aureus*, sterilise infected foci/blood faster, and thereby reduce the risk of dissemination, metastatic infection and death from *S. aureus* bacteraemia

1) Thwaites *et al*. LID 2011

ARREST trial design

Adults (≥18 years) with *S. aureus* (meticillin-susceptible or resistant (MRSA)) bacteraemia, ≤96 hours of active antibiotic therapy, and without contraindications to rifampicin, receiving standard antibiotic therapy in 29 UK NHS Hospitals

Randomized 1:1

2 weeks' active rifampicin

2 weeks' blinded placebo

- Rifampicin/placebo: 600mg or 900mg; once or twice daily; oral or IV

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- Rifampicin/placebo: 600mg or 900mg; once or twice daily; oral or IV
- Follow-up through 12 weeks
  - Clinical assessments day 0, 3, 7, 10, 14, then weekly until the earlier of discharge/w12
  - Blood cultures days 3 and 7; CRP days 3, 7, 10 and 14; LFTs day 3 and 10
  - Final week 12 visit conducted face-to-face where possible; otherwise by telephone or via general practitioner records; vital status to 2 years.
- **Primary endpoint**: bacteriologically-confirmed failure or recurrence through 12 weeks
  - Failure: symptoms and signs of infection ongoing for >14 days
  - Recurrence: symptoms/signs after >7 days of clinical improvement

Baseline characteristics (N=758)

n (%) or median (IQR)

Characteristic	Placebo N=388	Rifampicin N=370	Total N=758
Male	246 (63.4%)	249 (67.3%)	495 (65.3%)
Age (years)	66 (51,76)	64 (49,76)	65 (50,76)
Mode of acquisition of infection			
Community acquired	240 (61.9%)	245 (66.2%)	485 (64.0%)
Nosocomial infection (≥48h post admission)	76 (19.6%)	56 (15.1%)	132 (17.4%)
Healthcare associated (all other)	72 (18.6%)	68 (18.4%)	140 (18.5%)
MRSA	22 (5.7%)	28 (7.6%)	50 (6.6%)
Active injecting drug use (N=751)	41 (10.6%)	42 (11.4%)	83 (10.9%)
Charlson comorbidity score	2 (0,3)	1 (0,3)	2 (0,3)
Cancer	60 (15.5%)	66 (17.8%)	126 (16.6%)
Chronic lung disease	42 (10.8%)	48 (13.0%)	90 (11.9%)
Moderate or severe renal disease	80 (20.6%)	58 (15.7%)	138 (18.2%)
Diabetes	119 (30.7%)	109 (29.5%)	228 (30.1%)

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n (%) or median (IQR)

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Main focus/foci of infection			
Deep focus	**159 (41.0%)**	**142 (38.4%)**	**301 (39.7%)**
Native heart valve	16 (4.1%)	17 (4.6%)	33 (4.4%)
Native joint	34 (8.8%)	29 (7.8%)	63 (8.3%)
Prosthetic heart valve/device	5 (1.3%)	9 (2.4%)	14 (1.8%)
Implanted vascular device	23 (5.9%)	13 (3.5%)	36 (4.7%)
Deep tissue infection/abscess*	94 (24.2%)	82 (22.2%)	176 (23.2%)
Non-deep focus	**229 (59.0%)**	**227 (61.4%)**	**456 (60.2%)**
Central or peripheral line	67 (17.3%)	63 (17.6%)	130 (17.2%)
Skin/soft tissue (excluding wounds)	66 (17.0%)	72 (19.5%)	138 (18.2%)
Surgical wound	15 (3.9%)	10 (2.7%)	25 (3.3%)
Pneumonia or urinary tract infection	31 (4.1%)	30 (4.0%)	61 (8.0%)
Not established	67 (17.3%)	72 (19.5%)	139 (18.3%)

* including vertebral bone/disc or other bone infection, epidural or intraspinal empyema, infected intravascular thrombus, brain infection

Receipt of randomised trial drug
n (%) or median (IQR)

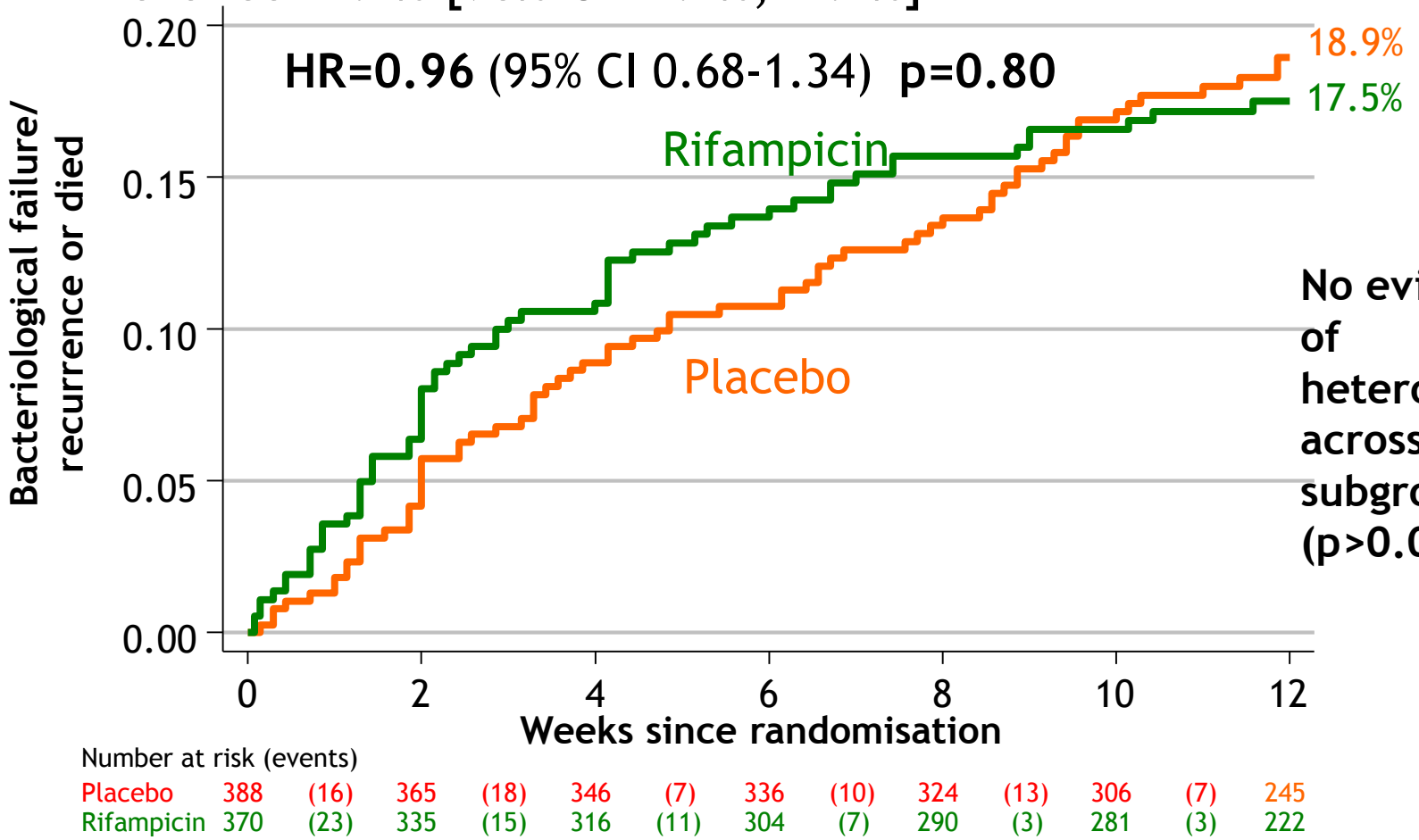
		Placebo N=388	Rifampicin N=370	Total N=758
Initiated trial drug		380 (97.9%)	364 (98.4%)	744 (98.2%)
Hours from start of active antibiotic therapy		69.2 (48.5,85.0)	67.6 (44.8,85.5)	68.0 (47.2,85.4)
Initial route:	IV	51 (13.1%)	45 (12.2%)	96 (12.7%)
	Oral	329 (84.8%)	319 (86.2%)	648 (85.5%)
Initial daily dose:	600 mg	74 (19.1%)	75 (20.3%)	149 (19.7%)
	900mg	306 (78.9%)	289 (78.1%)	595 (78.5%)
Initial frequency:	once daily	175 (45.1%)	173 (46.8%)	348 (45.9%)
	twice daily	205 (52.8%)	191 (51.6%)	396 (52.2%)
Days on trial drug		**13.0 (11.3,13.5)**	**12.6 (6.0,13.2)**	**12.8 (7.9,13.4)**

Other antibiotics
n (%) or median (IQR)

	Placebo N=388	Rifampicin N=370	Total N=758
Backbone antibiotics included			
anti-staphylococcal penicillin (ASP)	335 (86.3%)	306 (82.7%)	641 (84.6%)
glycopeptide	187 (48.2%)	191 (51.6%)	378 (49.9%)
Days on active antibiotics	30 (17,44)	28 (17,45)	29 (17,45)
Open-label rifampicin after discontinuing trial drug	53 (13.7%)	33 (8.9%)	86 (11.3%)
Days to open rifampicin	14.3 (7.4,25.3)	12.9 (3.6,16.8)	13.9 (6.6,18.5)

Bacteriological failure/recurrence or death through 12 weeks

- 62 events rifampicin vs 71 events placebo
- Difference -1.4% [95% CI -7.1%,+4.2%]

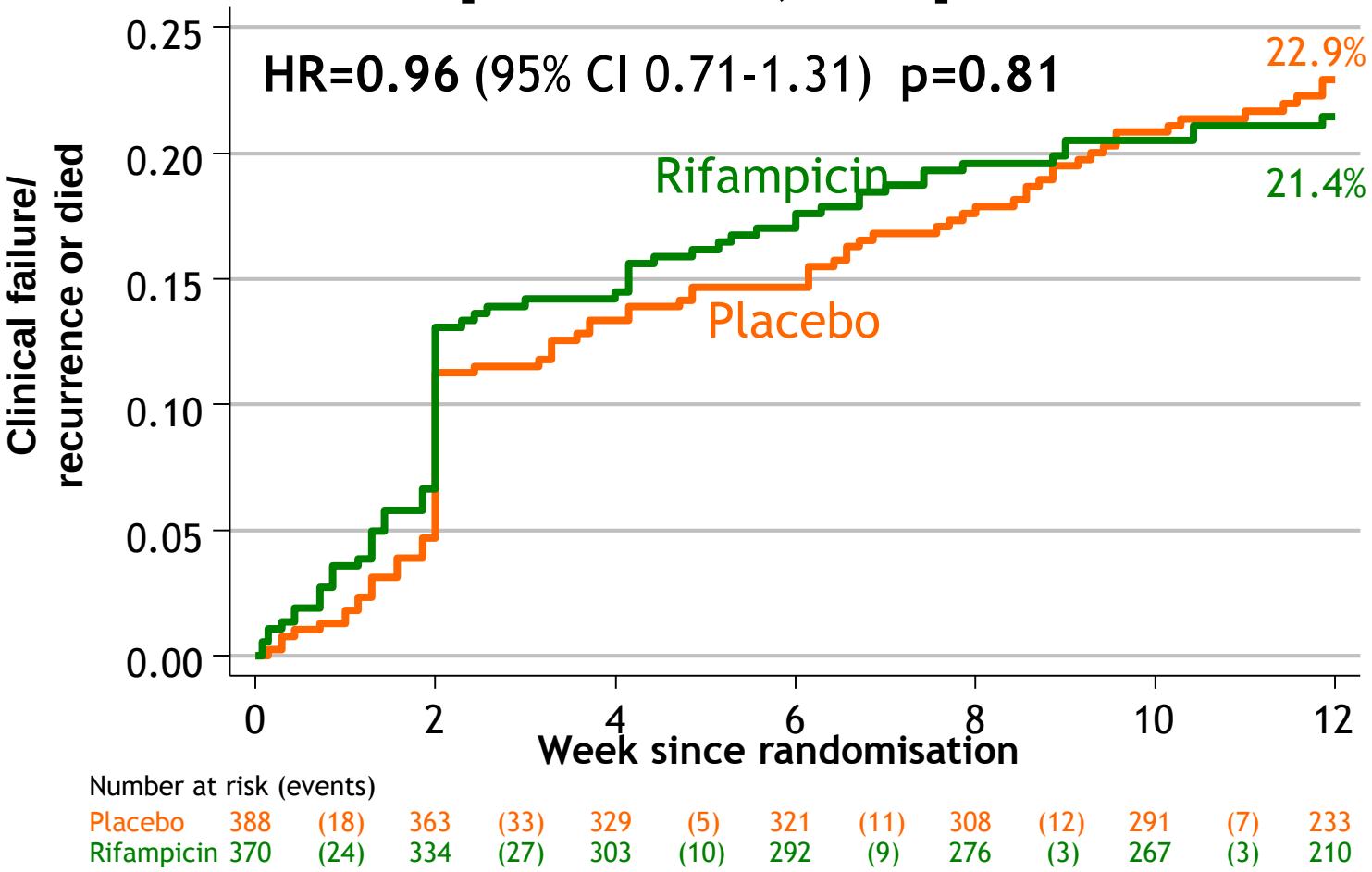


No evidence of heterogeneity across 18 subgroups (p>0.05)

- 65 (8.6%) not assessed for signs/symptoms after 11 weeks: only 39 (5.1%) had unknown vital status

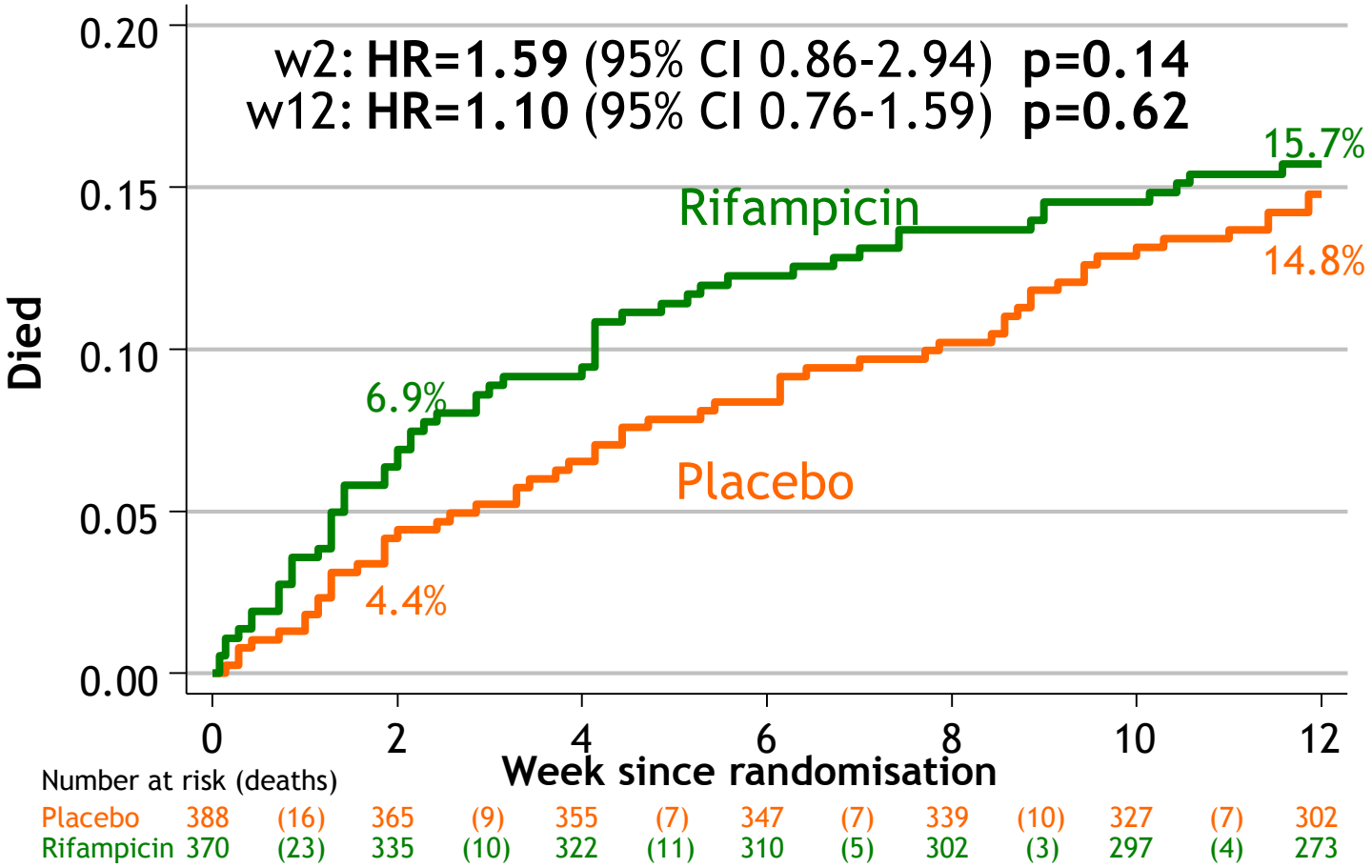
Clinical failure/recurrence or death through 12 weeks

- 76 events rifampicin vs 86 events placebo
- Difference -1.5% [95% CI -7.5%,+4.6%]



Mortality through 12 weeks

- 56 deaths rifampicin vs 56 deaths placebo
- Difference +0.9% [95% CI -4.3%,+6.1%]



- 28 rifampicin vs 28 placebo definitely or probably *S. aureus*-related

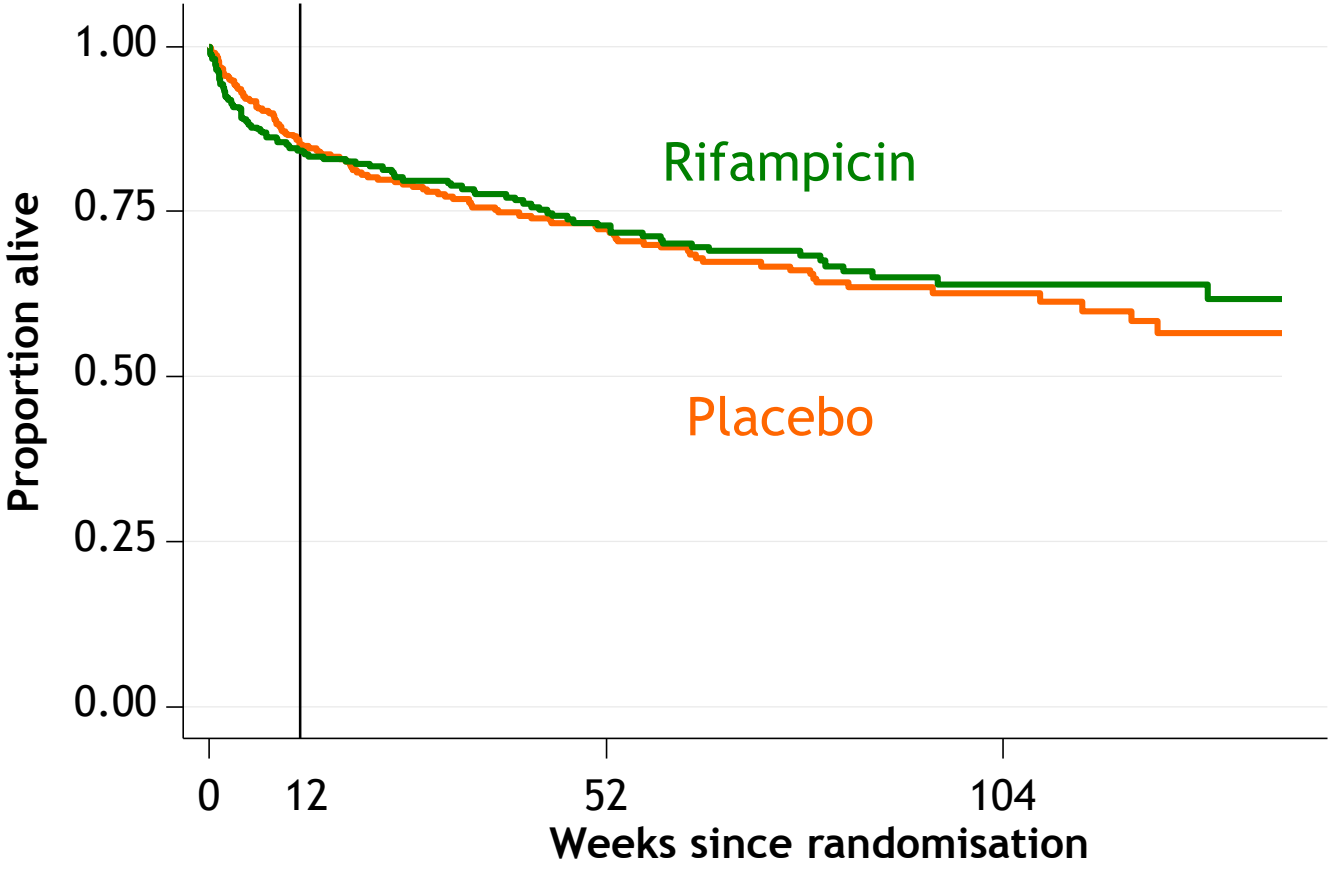
Failures and recurrences determined by Independent Endpoint Review Committee

	Bacteriological			Clinical		
	Placebo	Rifampicin	p	Placebo	Rifampicin	p
Total	71	62	0.80	86	76	0.81
Failure	5	4	0.81	24	21	0.94
Recurrence	16	3	0.01	22	8	0.01
Death without either	50	55	0.31	38	45	0.22
Total failures/recurrences	21	7		46	29	

Number needed to treat to prevent one bacteriologically proven recurrence = 29

Number needed to treat to prevent one clinical recurrence = 26

Survival to 104 weeks from randomisation



Number at risk						
Placebo	388	(91)	161	(17)	55	(4)
Rifampicin	370	(83)	142	(13)	49	(1)

Safety outcomes

- No evidence of overall difference in SAEs (p=0.18) or Grade 3/4 AEs (p=0.37), with exception of more acute kidney injury in rifampicin group
- More antibiotic-modifying AEs with rifampicin (63 (17.0%)) than placebo (39 (10.1%)) (p=0.007)
- More drug-interactions reported with rifampicin (24 (6.5%)) than placebo (6 (1.5%)) (p=0.0005)

Only 2 (0.5%) developed rifampicin resistant *S. aureus* bacteraemia (p=0.24) during treatment

Conclusions

- Adjunctive rifampicin did not reduce death or bacteriologically confirmed treatment failure or relapse within 12 weeks
- Rifampicin complicated management: increased need to change antibiotic therapy and increased drug-drug interactions
- There is, however, evidence of some biological activity: small but significant reduction in disease recurrences
- But 26 patients to receive rifampicin to prevent one recurrence, and no evidence recurrence influences longer-term survival

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