INHALE WP3: Results of a multi-centre randomised controlled trial (INHALE) testing the utility of rapid multiplex PCR at point-of-care for the antibiotic management of hospital-acquired and ventilator-associated pneumonia in critical care.

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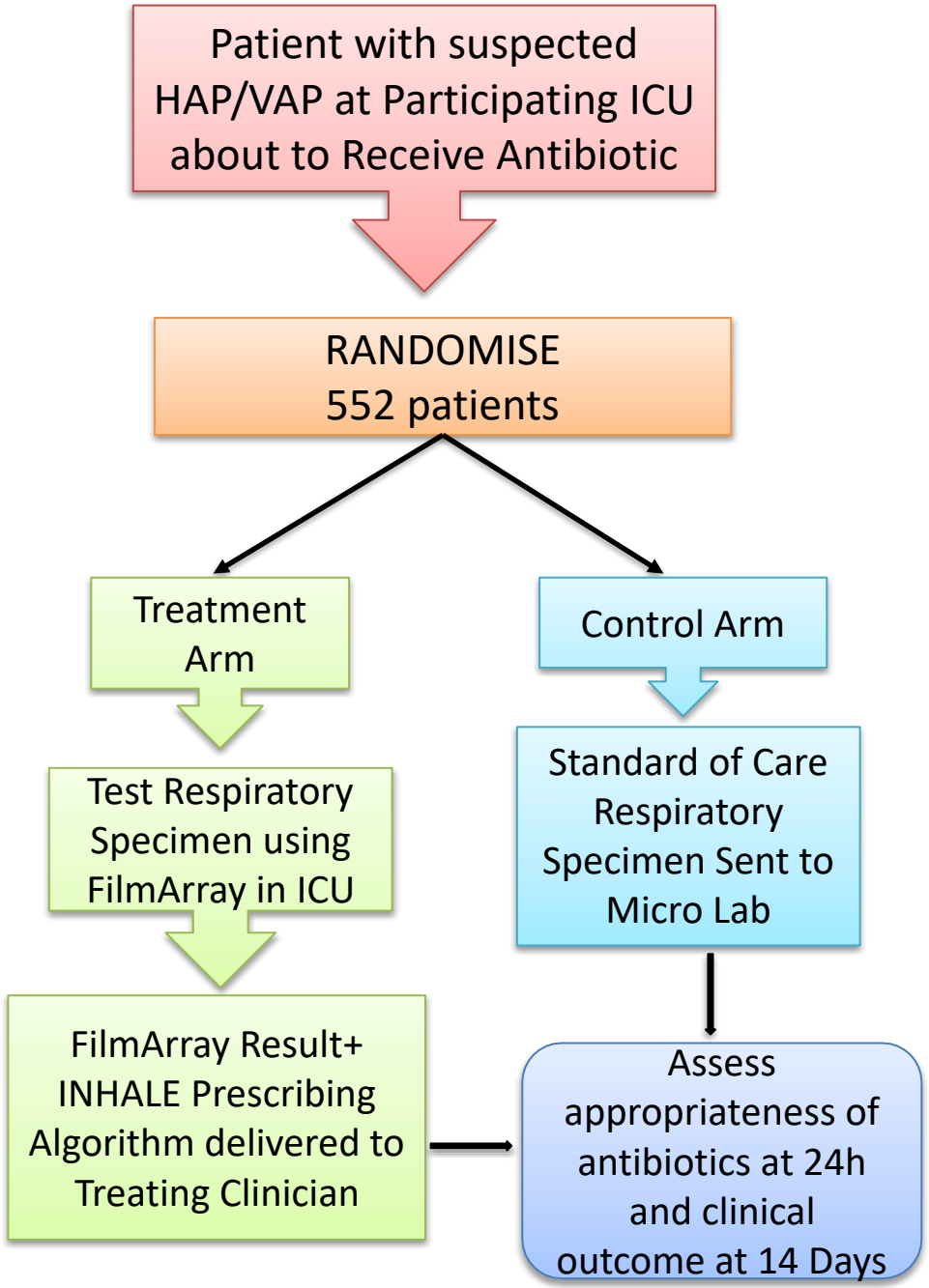
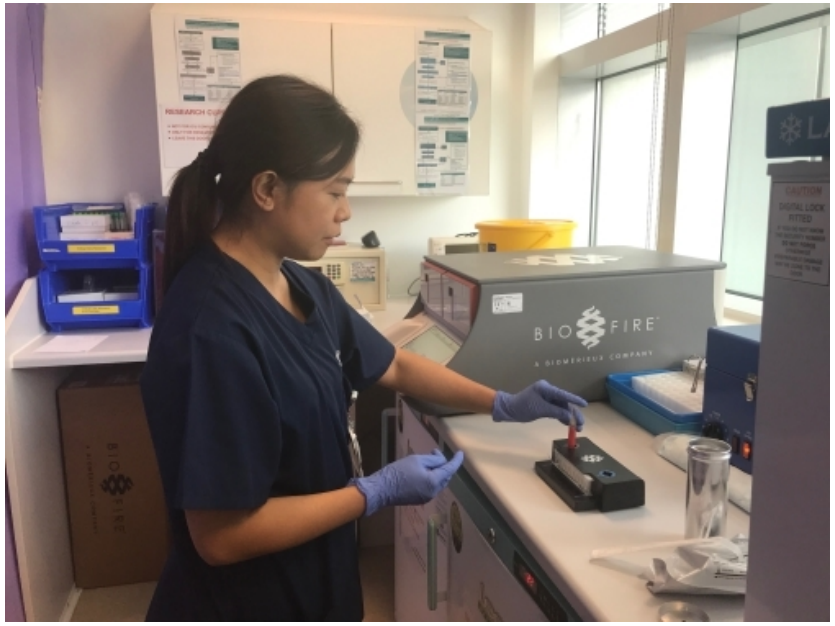
Conflicts of Interest Disclosure

Dr. Enne has received speaking honoraria, consultancy fees, and/or in-kind contributions from the following diagnostic companies:
Curetis
GmbH, bioMérieux, Inflammatix Inc and Oxford Nanopore Technologies

INHALE WP3 RCT

Aim: To test whether rapid diagnostics for diagnosis of HAP and VAP can improve antimicrobial stewardship in ICU

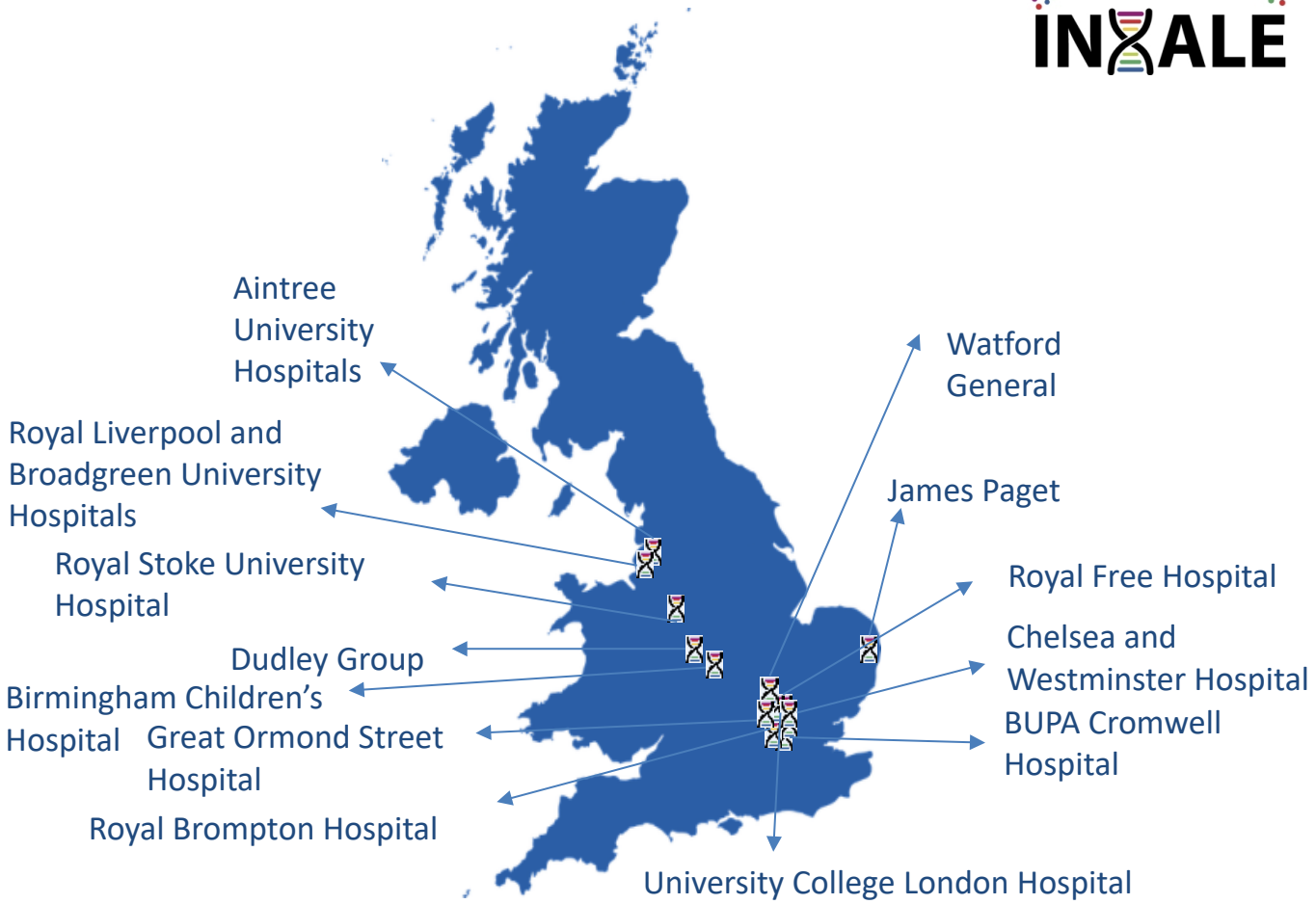




FilmArray Torch Pneumonia Panel placed at Point of Care within Intensive Care Units

INHALE WP3 RCT

- Biofire FilmArray Pneumonia Panel chosen for RCT based on its laboratory diagnostic performance
  - 70 min turnaround
  - Broad range of target pathogens
- Pragmatic real-world study design
- 14 Critical Care Units in England representing diverse case-mix
  - Tertiary referral
  - District general
  - Paediatric
- Recruitment Jul 2019 – Aug 2021



Enne *et al.* 2022. *Thorax* http://dx.doi.org/10.1136/thoraxjnl-2021-216990

Primary Outcomes

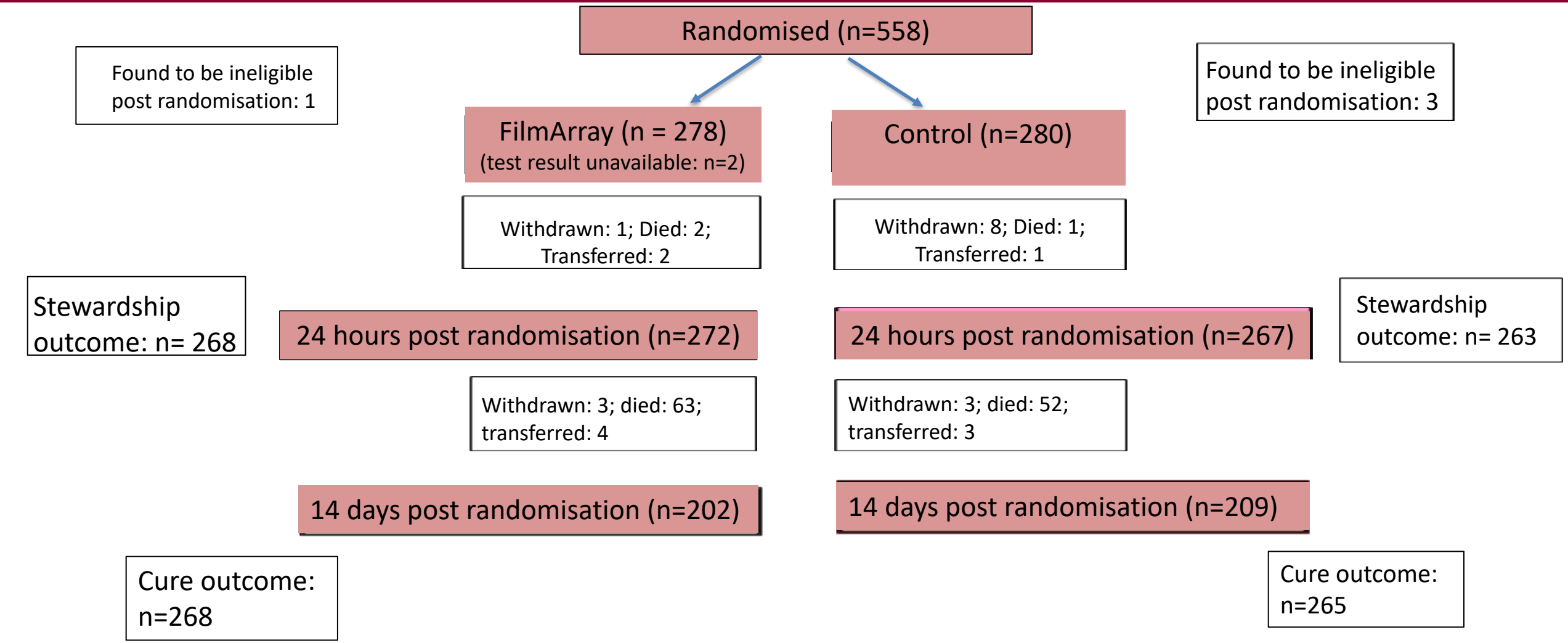
Two *co-primary* outcomes were used:

1. **Non-inferiority** in clinical cure of pneumonia at 14 days post randomisation
   Cure of pneumonia defined as: Absence of (i) death where the pneumonia was considered causative or at least contributory, (ii) septic shock (except when associated with a documented non-respiratory infection) and (iii) relapse of the pneumonia.

2. **Superiority** outcome of Improvement in antimicrobial stewardship at 24 hours post randomisation (measured as % of patients on active and proportionate antibiotics)

Protocol published: High *et al.* 2021. *Trials* **22**:680

Participant Flow



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Baseline Characteristics - Demographics

	Intervention (n = 276)	Control (n = 269)
Male	184 (66.7%)	189 (70.3%)
Age		
Adults (mean age)	82.6% (58.2 years)	83.6% (59.4 years)
Children < 18 years (mean age)	17.4% (2.3 years)	16.4% (2 years)
Ethnicity		
White - any	176 (63.7%)	182 (67.6%)
Mixed race – any	4 (1.4%)	6 (2.2%)
Asian	36 (13.0%)	28 (10.4%)
Black	18 (6.5%)	15 (5.6%)
Not stated	36 (13.0%)	20 (7.4%)
Other	6 (2.2%)	14 (5.2%)
ICU Admission Reason		
Medical	194 (70.3%)	190 (70.6%)
Surgical	59 (21.4%)	52 (19.3%)
Trauma	16 (5.8%)	20 (7.4%)
Other	7 (2.5%)	7 (2.6%)

Baseline Characteristics – Co-morbidities

Co-morbidity	Intervention (n = 276)	Control (n = 269)
Covid-19 at randomisation	93 (33.7%)	90 (33.5%)
Prior blood stream infection	7 (2.5%)	18 (6.7%)
Cancer - haematological	11 (4.0%)	12 (4.5%)
Cancer – solid tumor	35 (12.7%)	28 (10.4%)
COPD	29 (10.5%)	22 (8.2%)
Chronic Lung Disease	58 (21.0%)	52 (19.3%)
Chronic Kidney Disease	15 (5.4%)	15 (5.6%)
Diabetes	55 (19.9%)	56 (20.8%)
Chronic Liver Disease	8 (2.9%)	17 (6.3%)
Cardiovascular	126 (45.7%)	128 (47.6%)
Abdominal	30 (10.9%)	26 (9.7%)
Congenital	12 (4.3%)	11 (4.1%)
Mental health	26 (9.4%)	29 (10.8%)

Primary Outcome – Antibiotic Stewardship

Participants on active and proportionate antibiotics at 24h

Intervention arm 205/268 = 76.5%

Control arm 147/263 = 55.9%

Difference in proportions:

0.21 (95% CI 0.13 – 0.28) p <0.001

Primary Outcome – Clinical Cure

Participants judged to be cured of pneumonia 14 days post-randomisation (intention to treat analysis).

Intervention arm 150/268 participants = 55.9%

Control arm 171/265 participants = 64.7%

Difference in proportions -0.06 (CI -0.15 to 0.02)

Non-inferiority margin of 13% not met.

Antibiotic Stewardship Related Secondary Outcomes

Outcome	Intervention	Control	Difference in proportions/OR (95%CI)
On active antibiotics at 24h	91.4%	77.6%	0.13 (0.07 – 0.20)*
On active and proportionate antibiotics at 72h	73.4%	58.8%	0.15 (0.07 – 0.23)*
On active antibiotics at 72h	91.3%	81.6%	0.10 (0.04 – 0.16)*
On narrow spectrum antibiotics at 24h	17.3%	16.5%	0.005 (-0.06 – 0.07)
On narrow spectrum antibiotics at 72h	28.8%	23.6%	0.05 (-0.02 – 0.13)

* Denotes statistically significant difference at 5% level

Clinical Secondary Outcomes

Outcome	Intervention	Control	Difference in proportions/OR (95%CI)
Mortality	31.3%	28.8%	0.05 (-0.01 – 0.11)
Antibiotic diarrhoea	9.9%	5.5%	0.06 (0.04 – 0.09)*
C. diff infection	1.1%	1.9%	-0.01 (-0.03 – 0.02)
Septic shock	14.1%	12.1%	0.03 (-0.01 – 0.07)
Secondary pneumonia	9.5%	12.1%	-0.11 (-0.13 – -0.09)*
Ventilator free days (all)	2 days	2 days	0.98 (0.72 – 1.35)
Ventilator free days (survivors)	11 days	9 days	1.1 (0.77 – 1.58)
Length of stay (all)	11 days	13 days	0.95 (0.83 – 1.09)
Length of stay (survivors)	14 days	14 days	

* Denotes statistically significant difference at 5% level

SOFA Organ Dysfunction Score Progression in Adults

Outcome	Intervention	Control
Baseline SOFA score (Mean (SD))	6.9 (2.9) n = 228	7.4 (3.0) n = 226
SOFA score at Day 7	6.0 (3.9)	5.7 (3.9)
Change in SOFA score (baseline - Day 7)	-1.0 (3.3)	-1.7 (3.3)
SOFA Score at Day 14	5.4 (4.4)	5.4 (4.1)
Change in SOFA score (baseline - Day 14)	-1.5 (3.9)	-1.9 (3.9)
Ventilator free days (all)	**Estimate of difference**	**95% CI**
Change in SOFA score (Day 7 – baseline)	0.58	0.00, -1.15
Adjusted change in SOFA score (Day 7 – baseline)	0.52	-0.04, -1.08
Change in SOFA score (Day 14 – baseline)	0.28	-0.41, -0.97
Adjusted Change in SOFA score (Day 14 – baseline)	0.35	-0.31, -1.00

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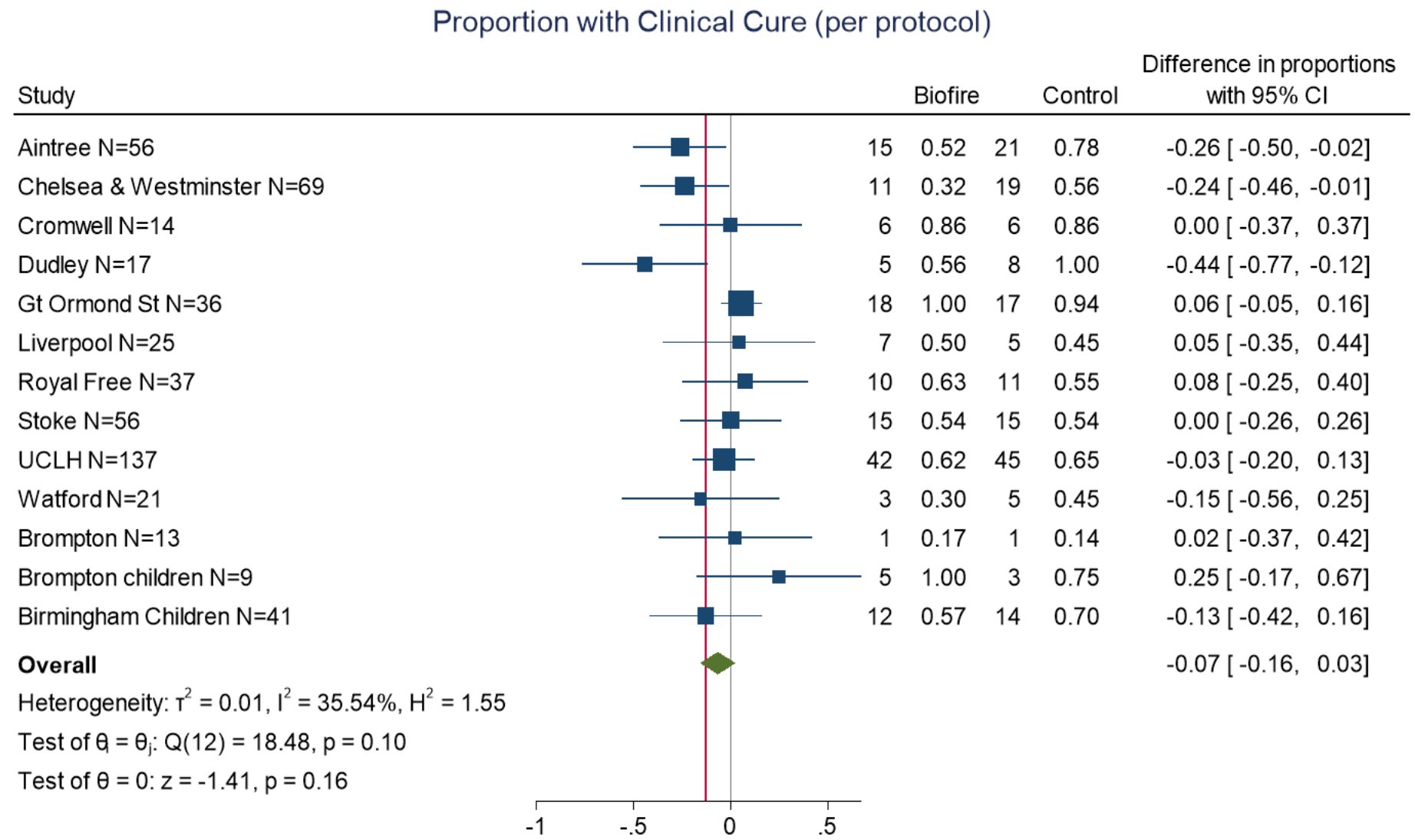
Further Analysis of Clinical Cure

Micro Committee Category at 24h	Neg/Pos for pathogen	Intervention (n = 264)		Control (n = 262)	
		Pneumonia not cured	Pneumonia Cured	Pneumonia not cured	Pneumonia Cured
Neither active nor proportionate	Neg	5 (62.5%)	3 (37.5%)	2 (40%)	3 (60%)
Active & not proportionate	Neg	5 (45.5%)	6 (54.5%)	8 (57.1%)	6 (42.9%)
Active & proportionate	Neg	30 (49.2%)	31 (50.8%)	21(47.7%)	23 (52.3%)
Neither active nor proportionate	Pos	5 (33.3%)	10 (66.6%)	23 (43.4%)	30 (56.6%)
Active & not proportionate	Pos	10 (34.5%)	19 (65.5%)	13 (30.2%)	30 (69.8%)
Active & proportionate	**Pos**	**59 (42.1%)**	**81 (57.9%)**	**26 (25.2%)**	**77 (74.8%)**

Clinical Cure by Site



Conclusions

- Significant improvements in antibiotic stewardship were achieved in the intervention arm compared to the control arm at both 24h and 72h.
- Equivalence of clinical cure was not demonstrated at 14 days.
- Other clinical measures such as mortality, length of stay, ventilator free days and SOFA at 14 days showed no significant difference between arms.
- The difference in clinical cure occurred in the patient group judged to receive active and proportionate treatment and who had a pathogen found. There was a moderate site-specific effect.
- Analyses are ongoing to understand drivers for the clinical cure result.

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Secondary Outcomes

- ICU/CCU length of stay – time from randomisation to discharge from ICU/critical care
- Number of ventilator-free days within 21 days after randomisation (VAP participants only surviving 21 days post randomisation)
- Mortality - death from any cause within 28 days of randomisation
- Incidence of septic shock – within 21 days of randomisation.
- Change in SOFA (ΔSOFA) score from randomisation to 7 days post-randomisation (adults)
- Change in PELOD-2 (ΔPELOD_2) score from randomisation to 7 days post randomisation (children)
- Change in pSOFA (ΔpSOFA) score from randomisation to 7 days post-randomisation (children)
- % of participants on antibiotics active/inactive against the pathogen(s) found at 24 and 72h from randomisation
- % of participants on proportionate/disproportionate antibiotics in relation to pathogen(s) found at 24 and 72h from randomisation
- % of participants on narrow-spectrum antimicrobials at 24 and 72 h from randomisation
- % of participants with specific adverse events associated with antibiotics within 21 days from randomisation
- % of participants that contract a secondary pneumonia within 21 days from randomisation
- Total antibiotic usage in Defined Daily Dose (DDD)s at 21 days post randomisation (all conditions)
- Inpatient stay related costs

Eligible Participants Randomised per Site