

# Emulating the MERINO randomised control trial using data from an observational cohort and trial of rapid diagnostic (BSI-FOO)

## Supplementary material

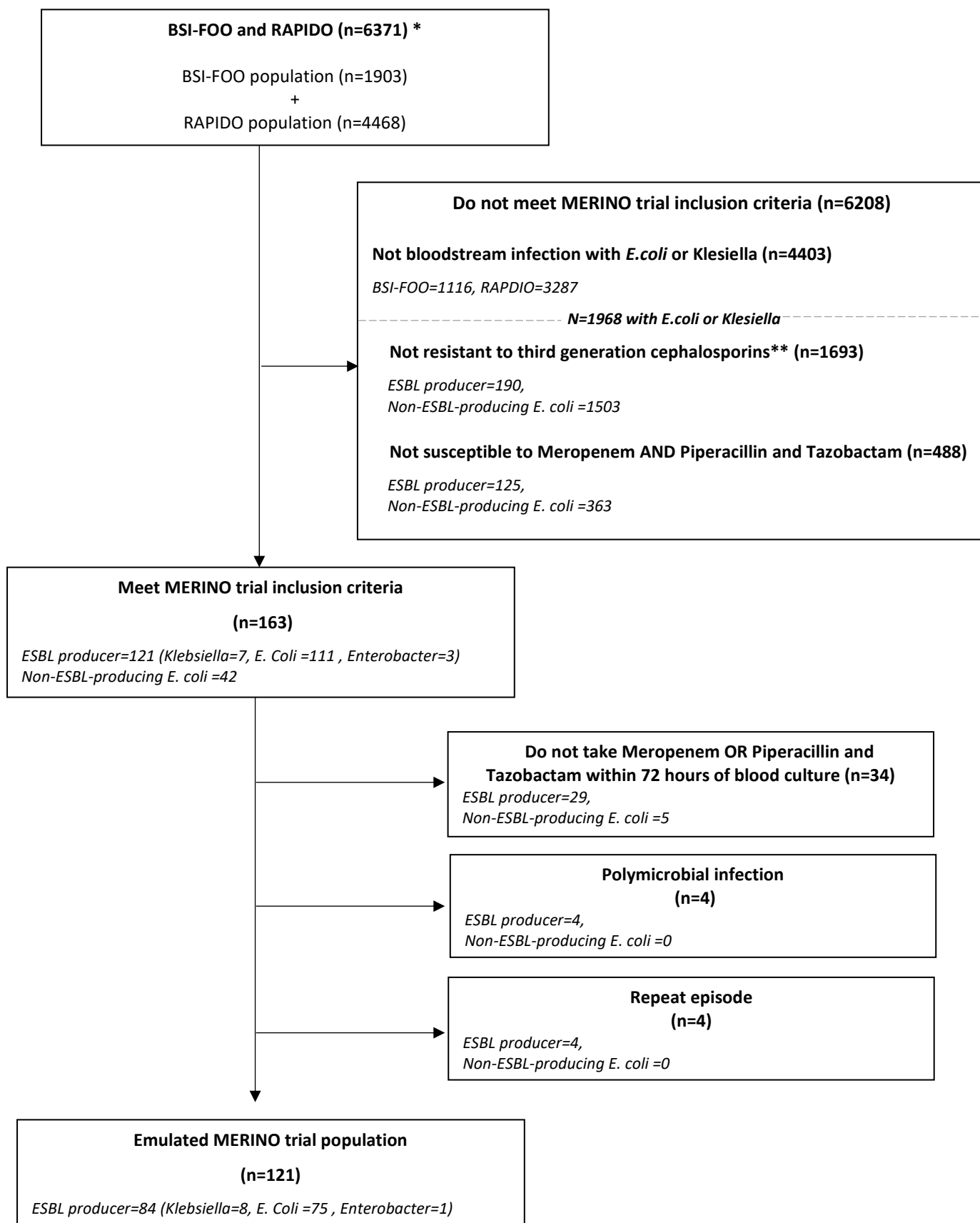
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## Supplementary Figure S1 Flowchart



\* All BSI-FOO/RAPIDO participants were ages 18 years and over and RAPIDO participant provided informed consent

\*\* Ceftriaxone OR Cefotaxime

**Supplementary Table S1**      **Duration and time to receipt of emulated intervention**

	Meropenem (n=39)		Piperacillin-Tazobactam (n=82)		Overall (n=121)	
	n	%	n	%	n	%
	<b>Time to receipt of allocated drug</b>					
Median hours (IQR)	38 (8, 54)		5 (0, 19)		7 (1, 32)	
<b>Total duration of allocated drug *</b>						
Median days (IQR)	7 (4, 8)		3 (2, 5)		4 (2, 7)	
<b>Duration category</b>						
Died within 4 days	1/39 (2.6%)		7/82 (8.5%)		8/121 (6.6%)	
Intervention received <4 days	7/39 (17.9%)		37/82 (45.1%)		44/121 (36.4%)	
Intervention received ≥4 days	31/39 (79.5%)		38/82 (46.3%)		69/121 (57.0%)	
In combination with other active drug	4/39 (10.3%)		15/82 (18.3%)		19/121 (15.7%)	
Allocated drug only	27/39 (69.2%)		23/82 (28.0%)		50/121 (41.3%)	
<b>Crossover</b>						
Switch to other intervention during follow-up	1/39 (2.6%)		39/82 (47.6%)		40/121 (33.1%)	

\* Total duration of study drug in MERINO (Median, IQR): Meropenem = 6 days (5, 9); Piperacillin-Tazobactam = 6 days (5, 10)

**Abbreviations:** IQR=Interquartile range

Supplementary Table S2

Baseline characteristics of patients in the MERINO trial analysis population vs. emulated trial population

	MERINO trial analysis population				Emulated trial population				
	Piperacillin-Tazobactam		Meropenem		Piperacillin-Tazobactam		Meropenem		
	(n=188)		(n=191)		(n=82)		(n=39)		
	n	%	n	%	n	%	n	%	
<b>Organism</b>									
E. coli	162/188	86.2%	166/191	86.9%	77/82	93.9%	36/39	92.3%	
Klebsiella	26/188	13.8%	25/191	13.1%	5/82	6.1%	3/39	7.7%	
<b>Stratification *</b>									
<b>E1:</b> E. coli, less severe	159/188	84.6%	162/191	84.8%	74/79	93.7%	32/35	91.4%	
<b>E2:</b> E. coli, more severe	3/188	1.6%	3/191	1.6%	1/79	1.3%	0/35	0.0%	
<b>K1:</b> Klebsiella, less severe	23/188	12.2%	25/191	13.1%	4/79	5.1%	3/35	8.6%	
<b>K2:</b> Klebsiella, more severe	3/188	1.6%	1/191	0.5%	0/79	0.0%	0/35	0.0%	
<b>Patient measures</b>									
Age (years)	Median (IQR)	70.0	(55.0, 78.0)	69.0	(59.0, 78.0)	74.5	(63.0, 84.0)	70.0	(54.0, 82.0)
Male		101/188	53.7%	97/191	50.8%	46/82	56.1%	15/39	38.5%
Weight (kg) <sup>a</sup>	Mean (SD)	67.2	18.1	69.3	19.3	70.0	15.9	72.1	24.6
<b>Acquisition **</b>									
Hospital-acquired		52/188	27.7%	46/191	24.1%	35/82	42.7%	16/39	41.0%
Health-care associated		55/188	29.3%	61/191	31.9%				
Community associated		81/188	43.1%	84/191	44.0%	47/82	57.3%	23/39	59.0%
<b>Source of infection</b>									
Bone and joint						0/82	0.0%	1/39	2.6%
Gastrointestinal system						10/82	12.2%	6/39	15.4%

Intra-abdominal infection		34/188	18.1%	28/191	14.7%				
Line infection – central venous line						1/82	1.2%	1/39	2.6%
Vascular catheter-related		3/188	1.6%	3/191	1.6%				
Lower respiratory tract						1/82	1.2%	1/39	2.6%
Reproductive tract						0/82	0.0%	1/39	2.6%
Skin and soft tissue		4/188	2.1%	1/191	0.5%	0/82	0.0%	1/39	2.6%
Surgical site infection		8/188	4.3%	4/191	2.1%	1/82	1.2%	0/39	0.0%
Systemic Infection						0/82	0.0%	1/39	2.6%
Urinary tract infection		103/188	54.8%	128/191	67.0%	46/82	56.1%	20/39	51.3%
Pneumonia		9/188	4.8%	3/191	1.6%				
Mucositis/neutropenia		12/188	6.4%	7/191	3.7%				
Musculoskeletal		1/188	0.5%	0/191	0.0%				
Other		2/188	1.1%	1/191	0.5%				
Site uncertain		12/188	6.4%	16/191	8.4%	23/82	28.0%	7/39	17.9%
<b>Other patient measures</b>									
Surgery requiring overnight stay within									
past 14 (MERINO) or 7 (BSI-FOO) days		19/188	10.1%	14/191	7.3%	3/82	3.7%	2/39	5.1%
ICU admission		13/188	7.0%	14/191	7.3%	6/82	7.3%	4/39	10.3%
Charlson score <sup>b</sup>	Median (IQR)	2.0	(1.0, 4.0)	2.0	(1.0, 4.0)	3.0	(2.0, 4.0)	4.0	(2.0, 5.0)
Pitt score <sup>c</sup>	Median (IQR)	1.0	(0.0, 2.0)	1.0	(0.0, 2.0)	1.0	(0.0, 2.0)	0.0	(0.0, 2.0)
Neutropenia		16/188	8.5%	9/191	4.7%	11/79	13.9%	2/38	5.3%
Urinary catheter/nephrostomy ***		51/188	27.1%	37/191	19.4%	21/59	35.6%	7/32	21.9%
Moderate-sever renal dysfunction		31/188	16.5%	30/191	15.7%	51/81	63.0%	21/37	56.8%
Diabetes		59/188	31.4%	79/191	41.4%	25/82	30.5%	10/39	25.6%

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Liver disease	12/188	6.4%	18/191	9.4%	13/69	18.8%	5/31	16.1%
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\* Severity definition: More severe= nonurinary source and Pitt score >4. Less Severe= Urinary source, or nonurinary source and Pitt score  $\leq$ 4.

\*\* Hospital acquired if date of blood culture is >48 hours after date of admission in BSI-FOO. Data on healthcare associated infections was not collected in BSI-FOO.

\*\*\* Urinary catheter only in BSI-FOO

<sup>a</sup> Data missing for 57 BSI-FOO patients (14 Meropenem, 43 Piperacillin-Tazobactam)

<sup>b</sup> Data missing for 29 BSI-FOO patients (10 Meropenem, 19 Piperacillin-Tazobactam)

<sup>c</sup> Data missing for 12 BSI-FOO patients (4 Meropenem, 8 Piperacillin-Tazobactam)

**Abbreviations:** IQR=Interquartile range, SD= Standard deviation, ICU=Intensive care unit

**Supplementary Table S3** Baseline characteristics of patients by emulated trial intervention, inverse probability weighted

		Meropenem (n=39)		Piperacillin-Tazobactam (n=82)	
		n	%	n	%
<b>Patient measures</b>					
Age	Median (IQR)	72.0 (62.0, 80.0)		73.0 (63.0, 83.0)	
Male		31 (50.8%)		30 (48.5%)	
Body Mass Index	Mean (SD)	27.1 (9.4)		24.7 (4.8)	
<b>Patient medical history</b>					
Chemotherapy in month before date 0		1 (1.6%)		12 (20.1%)	
Any tumour within last 5 years		21 (35.1%)		21 (35.6%)	
Surgery requiring overnight stay within 7 days before date 0		2 (2.8%)		2 (3.1%)	
Burn requiring admission within 7 days before date 0		0 (0.0%)		0 (0.0%)	
Cardiac arrest within 7 days before date 0		0 (0.0%)		0 (0.0%)	
Renal support within 7 days before date 0		4 (6.9%)		1 (2.4%)	
Myocardial infarction within 7 days before date 0		9 (14.9%)		7 (11.3%)	
<b>Infection severity measures</b>					
Temperature (°C) at time 0	Median (IQR)	38.2 (37.8, 38.8)		38.2 (37.4, 38.7)	
INR	Median (IQR)	1.3 (1.2, 1.9)		1.2 (1.1, 1.4)	
eGFR (mL/min/1.73m <sup>2</sup> )	Median (IQR)	44.0 (25.0, 70.0)		50.0 (29.0, 80.0)	
Neutrophil count at day 0 or closest (x10 <sup>9</sup> /L)	Median (IQR)	10.7 (6.9, 13.7)		10.7 (3.6, 15.6)	

Systolic BP at day 0 or closest (mmHg)	Mean (SD)	120.8 (21.8)	118.3 (29.0)
On IV fluids at day 0		21 (34.9%)	25 (41.7%)
On ventilation at day 0		5 (8.5%)	6 (9.6%)
On vasopressor drugs at day 0		3 (5.1%)	2 (3.2%)
Systemic corticosteroids in last 24 hours		5 (8.9%)	5 (8.9%)
EWS score nearest to day 0		2.0 (2.0, 6.0)	2.0 (1.0, 3.0)

### Patient comorbidities at date 0

Congestive heart failure		7 (12.3%)	8 (12.8%)
Peripheral vascular disease		6 (9.1%)	7 (11.6%)
Cerebrovascular disease		17 (27.7%)	14 (23.6%)
Hemiplegia		0 (0.0%)	3 (5.2%)
Dementia		5 (9.0%)	6 (10.0%)
COPD		6 (9.5%)	9 (14.6%)
Connective tissue disease		4 (6.5%)	4 (6.6%)
Peptic ulcer disease		15 (24.3%)	4 (6.6%)
Ascites		2 (3.1%)	3 (4.3%)
Diabetes:			
None		48 (79.2%)	42 (69.0%)
Without organ damage		9 (14.4%)	14 (21.7%)
With organ damage		4 (6.5%)	6 (9.3%)
Child-Pugh score	Median (IQR)	7.0 (6.0, 8.0)	6.0 (6.0, 9.0)
Charlson score	Median (IQR)	4.0 (2.0, 5.0)	3.0 (2.0, 4.0)
Abscess at time 0		0 (0.0%)	2 (3.8%)



Infected foreign body at time 0	1 (1.9%)	0 (0.0%)
Surgical prosthesis time 0	0 (0.0%)	1 (1.2%)

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**Source of infection**

Bone and joint	2 (3.9%)	0 (0.0%)
Gastrointestinal system	12 (19.7%)	8 (13.7%)
Line infection – central venous line	1 (1.7%)	1 (1.0%)
Lower respiratory tract	1 (1.6%)	1 (1.0%)
Reproductive tract	1 (1.6%)	0 (0.0%)
Skin and soft tissue	3 (5.0%)	0 (0.0%)
Surgical site infection	0 (0.0%)	1 (1.0%)
Systemic Infection	2 (2.6%)	0 (0.0%)
Urinary tract infection	31 (51.9%)	33 (54.2%)
Site uncertain	7 (12.0%)	18 (29.1%)

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**Lines and catheters**

Central line present at time 0	8 (16.4%)	10 (23.9%)
Peripheral line present at time 0	24 (49.0%)	22 (53.4%)
Urinary catheter present at time 0	6 (11.9%)	17 (40.2%)

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**Organisational factors**

Centre:

A	7 (11.1%)	5 (7.6%)
B	16 (26.0%)	14 (23.0%)
C	18 (29.1%)	21 (35.1%)

D	8 (13.7%)	8 (13.5%)
E	10 (16.2%)	11 (17.7%)
F	1 (1.0%)	0 (0.0%)
G	2 (3.0%)	2 (3.1%)
Ward specialty on day 0:		
Medicine	30 (50.2%)	37 (60.5%)
Critical care	4 (6.7%)	5 (8.3%)
Major surgery	21 (34.6%)	12 (20.0%)
Minor surgery	0 (0.0%)	1 (2.3%)
Other	5 (8.5%)	5 (8.9%)

**Notes:** Date and time 0 = date/time of sampling for blood culture

**Abbreviations:** IQR=Interquartile range, SD= Standard deviation, INR=International normalised ratio, eGFR=Estimated glomerular filtration rate, BP=Blood pressure, IV=Intravenous, EWS=Early warning score, COPD=Chronic obstructive pulmonary disease