Antibiotic trials in Paediatrics: NeoMero and NeoVanc

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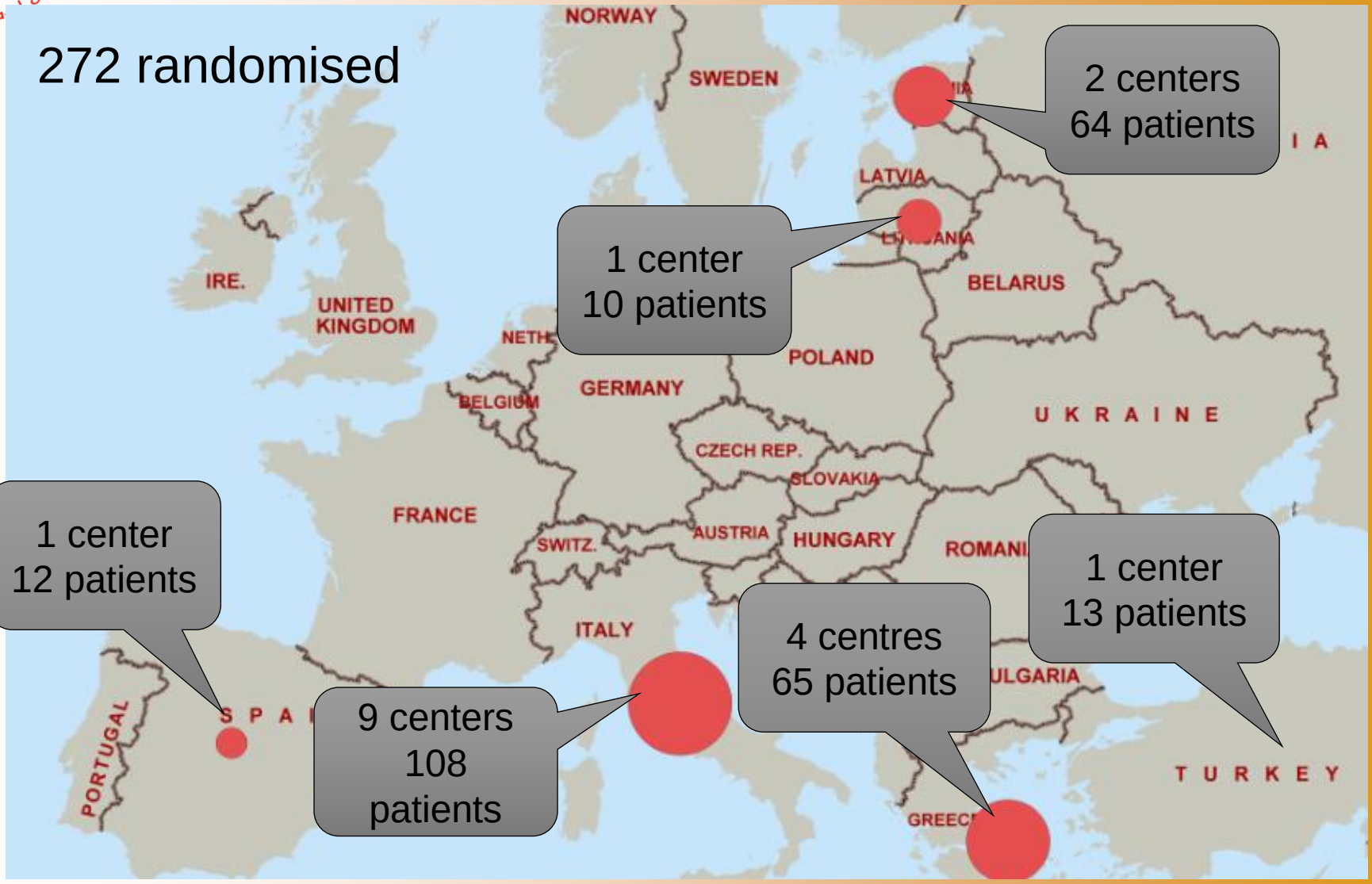
Background

- >95% of premature neonates in NICU receive antibiotics
- Dosing regimen is based on expert opinion rather than clinical trials
- Studies in LOS have been conducted >30 years ago
- We have conducted NeoMero1 and are conducting NeoVanc3

NeoMero1: Methodology

- An open label, multicenter, pan-European, randomised active-comparator controlled phase III superiority trial
- 550 subjects (275 subjects per group)
  - Mortality 15%
  - Ineligibility rate 25%
- Stratification
  - Based on SOC regimen
  - Based on AB therapy prior to randomisation or not
- SOC predefined:
  - Ampicillin + gentamicin
  - Cefotaxime + gentamicin
- PK samples were collected in meropenem and mucosal samples in all patients

03.09-2012 – 30.11.2014



Primary endpoint: Favourable outcome at TOC

- infant is alive

  AND

- resolution or significant improvement of all abnormalities that defined LOS

  AND

- microbiological eradication or presumed eradication

  AND

- no change in the AB treatment allocated at randomisation (duration 11 ± 3 days)

  AND

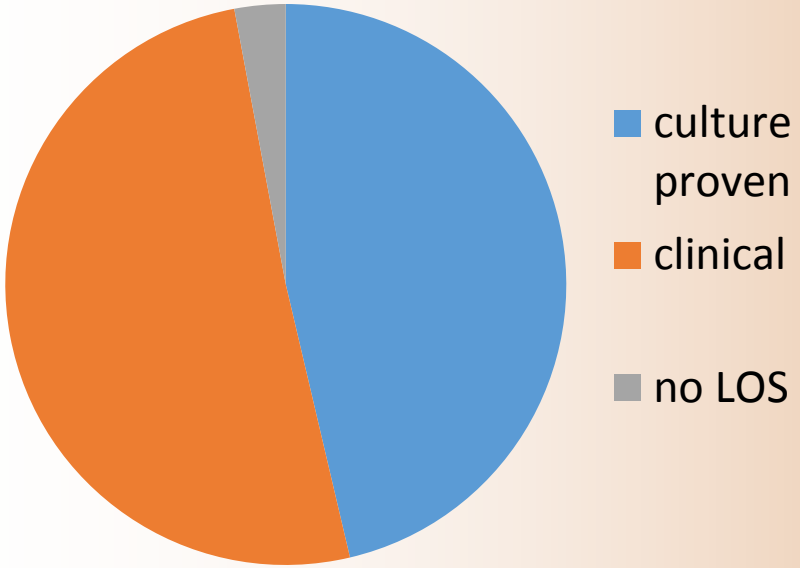
- no new abnormalities suggestive to LOS or microorganism identified

Medical history: demographics

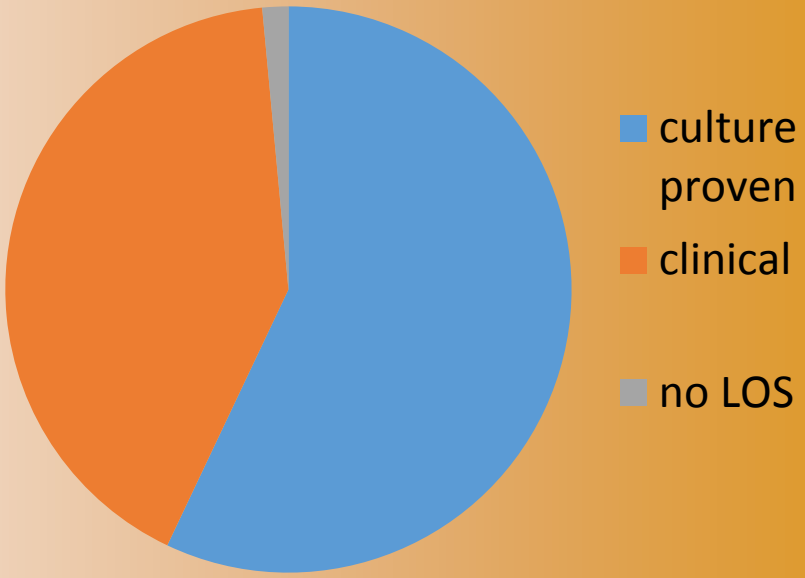
Characteristic	Meropenem N = 136 (%)	SOC N = 135 (%)
Demographics		
Median GA weeks (IQR)	31.6 (26.4 - 37.3)	30.6 (27.0 - 36.3)
-<28 weeks	41 (30)	41 (30)
-28-32 weeks	31 (23)	38 (28)
-32-37 weeks	26 (19)	23 (17)
-≥37 weeks	38 (28)	33 (24)
Median PNA days (IQR)	16 (8 - 30)	16 (8 - 30)
Median PMA	34.5 (30.5 - 40.7)	33.8 (29.9 - 40.1)
PMA > 44 weeks n (%)	5 (4)	6 (4)
Male n (%)	72 (53)	72 (53)
Median (IQR) birth weight (g)	1540 (840 - 2830)	1340 (850 - 2530)
-BW <1000g (n)	45 (33)	51 (38)
-BW <1500g (n)	67 (49)	80 (59)
-BW >2500g (n)	43 (32)	37 (27)
SGA *n (%)	33 (24)	34 (25)

Distribution of patients based diagnosis

Meropenem
N = 136



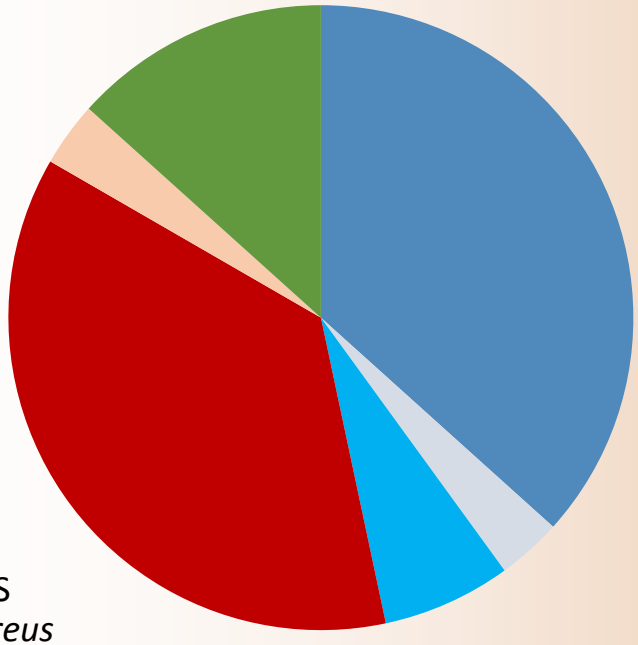
SOC
N = 135



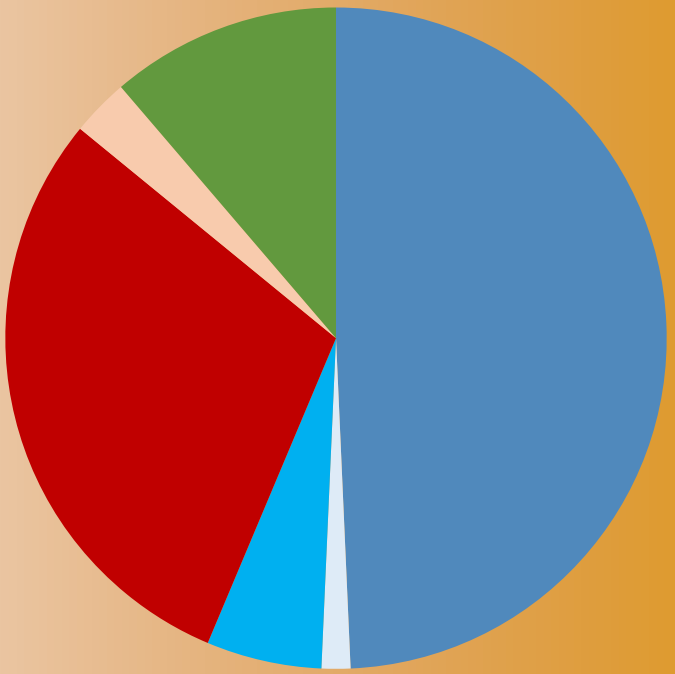
LOS – late onset sepsis
SOC – standard of care

Causative organisms of LOS

Meropenem
N = 63 (49%)



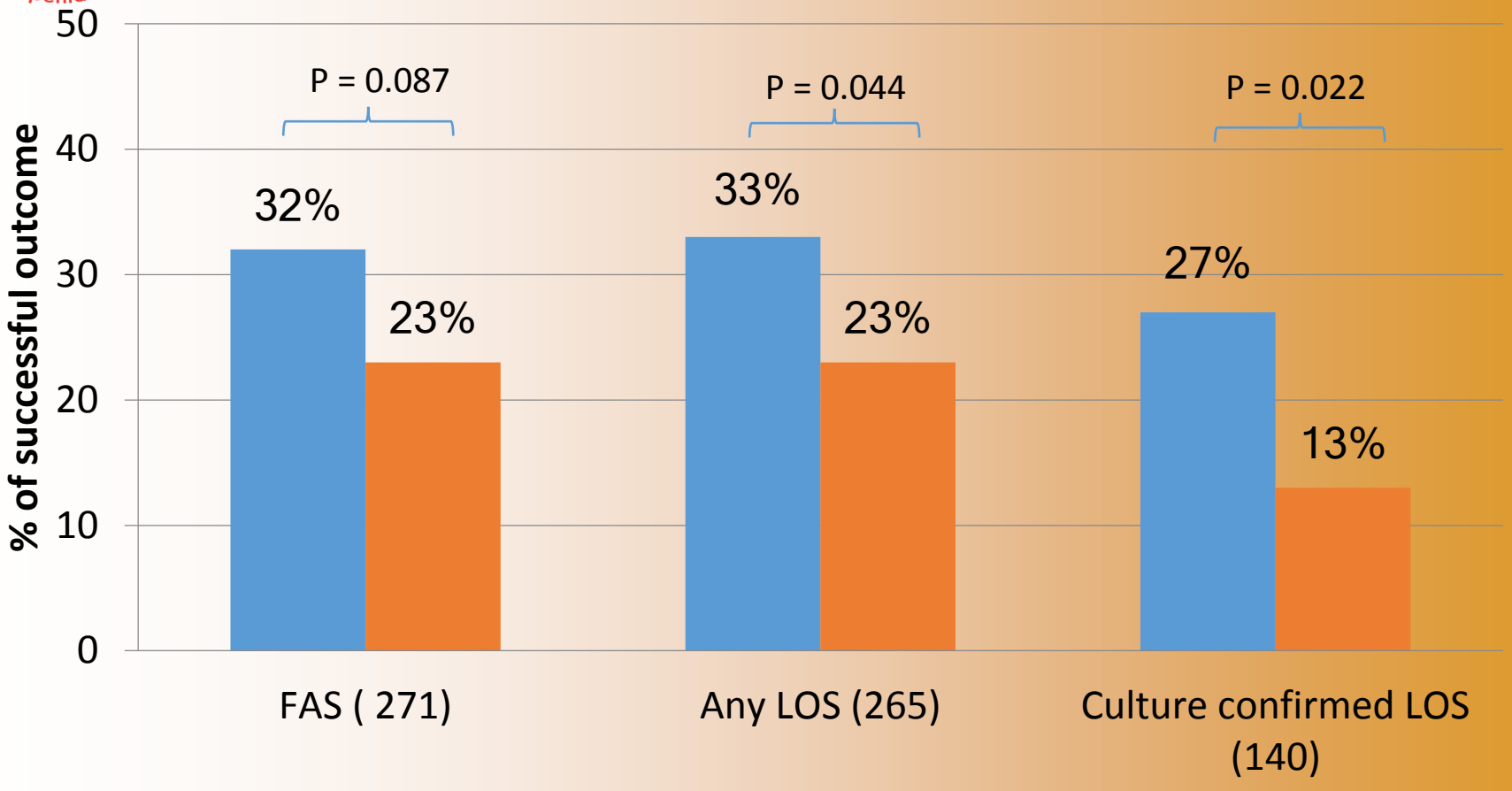
SOC
N = 77 (57%)



- CONS
- *S.aureus*
- Other G+
- *Enterobacteriaceae*
- Non-fermentative
- Mixed

CONS – coagulase negative staphylococci
SOC – standard of care
LOS – late onset sepsis

Primary outcome:
Success rate at TOC visit (2+/-1 day of EOT)



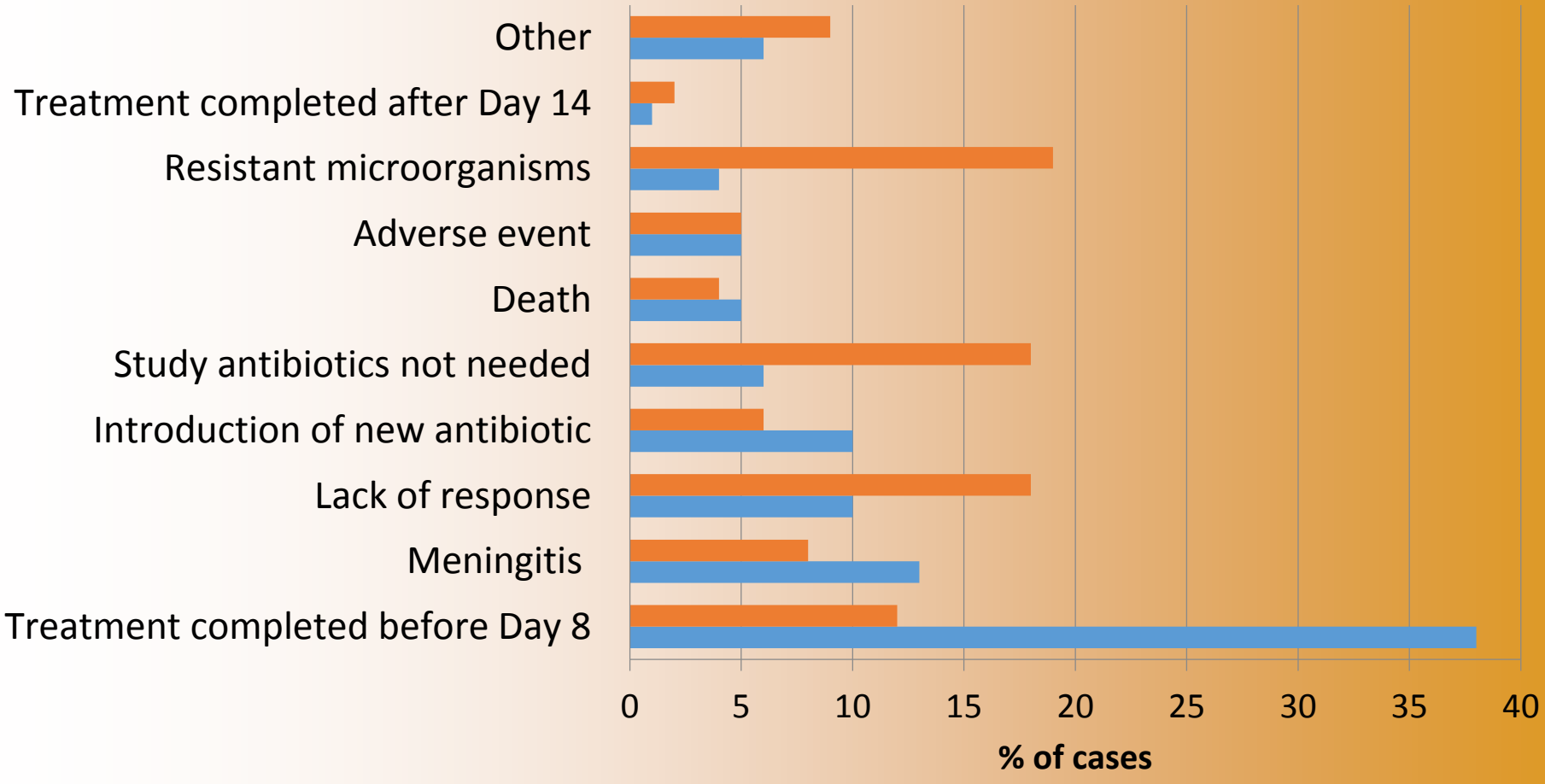
FAS – full analysis set
LOS – late onset sepsis
AT – allocated therapy
SOC – standard of care

Reasons for failure: FAS population

	Meropenem	SOC
Failure outcome	**92 (68%)**	**104 (77%)**
-Modification of allocated therapy	78 (57%)	85 (63%)
-Clinical signs not resolved and/or microbiological failure	29 (21%)	31 (23%)
-Death	10 (7%)	6 (4%)
- Antibiotics not started or not allowed antibiotics given	2 (1%)	10 (7%)

FAS – full analysis set

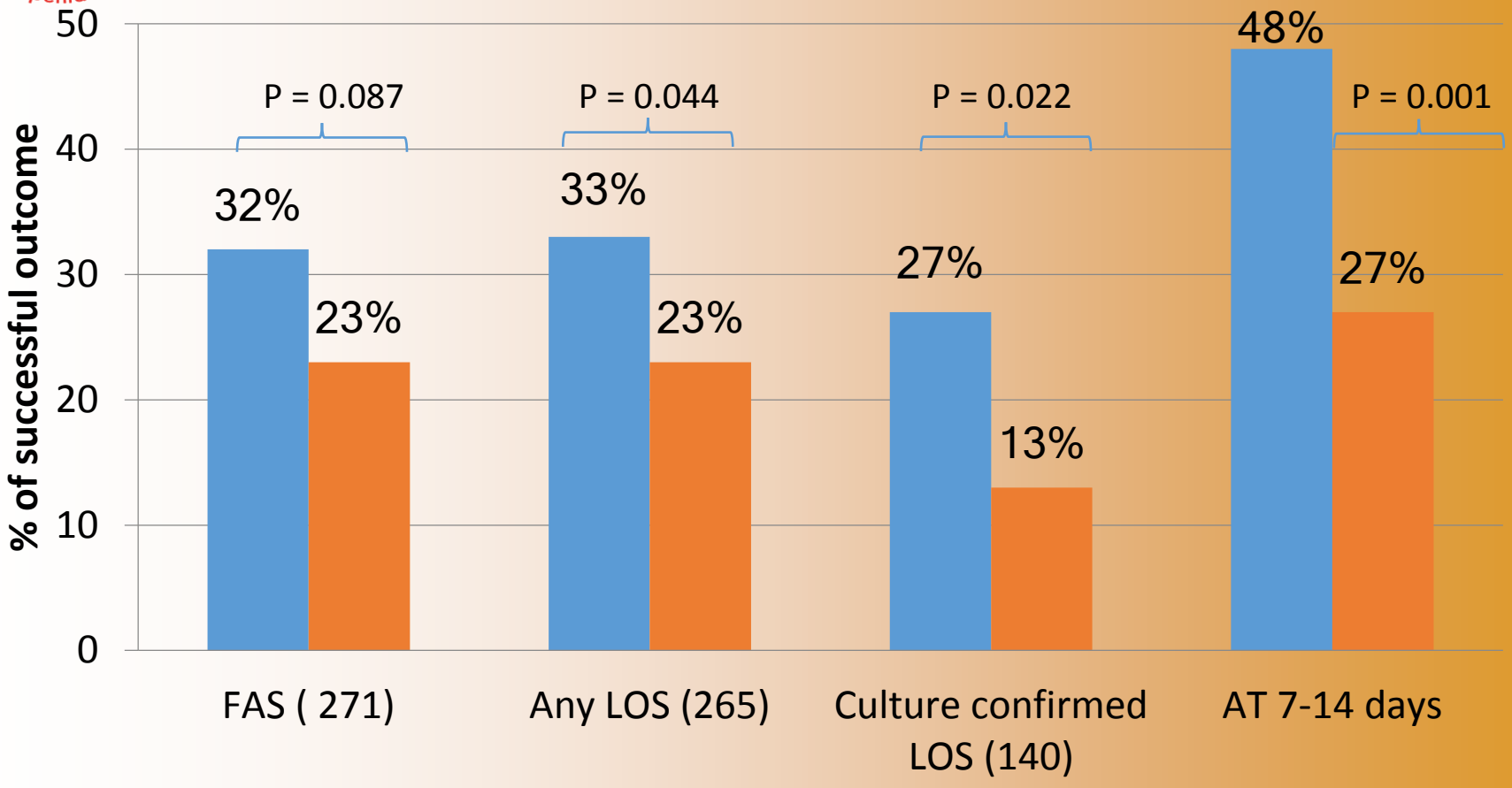
Reasons for modification of allocated therapy



N = 78 in meropenem
N = 85 in SOC

SOC – standard of care

Primary outcome: Success rate at TOC



FAS – full analysis set
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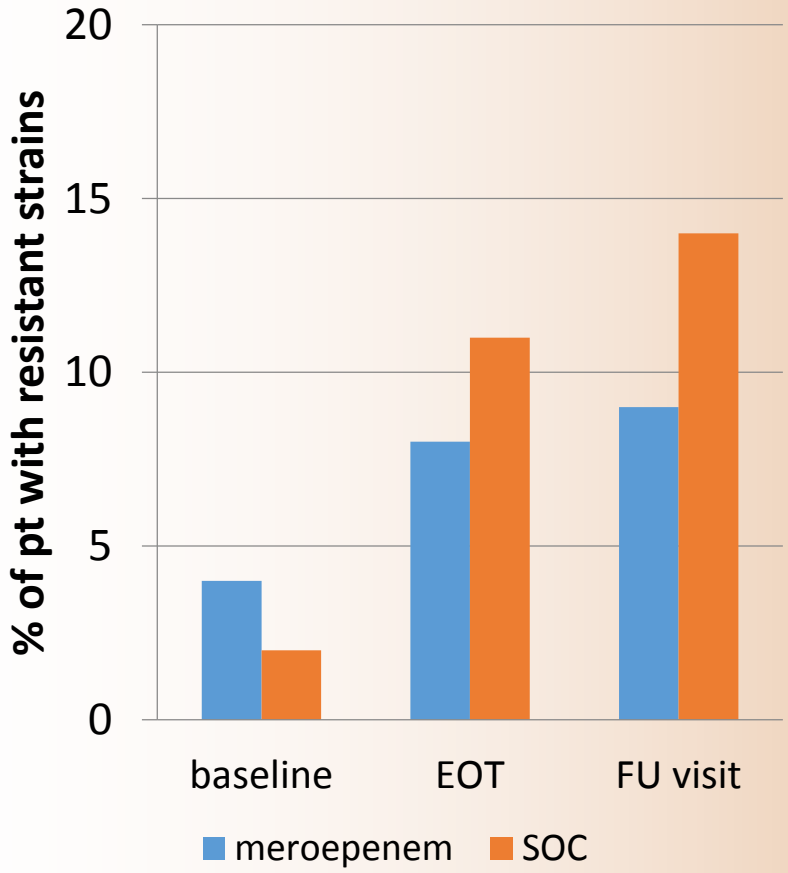
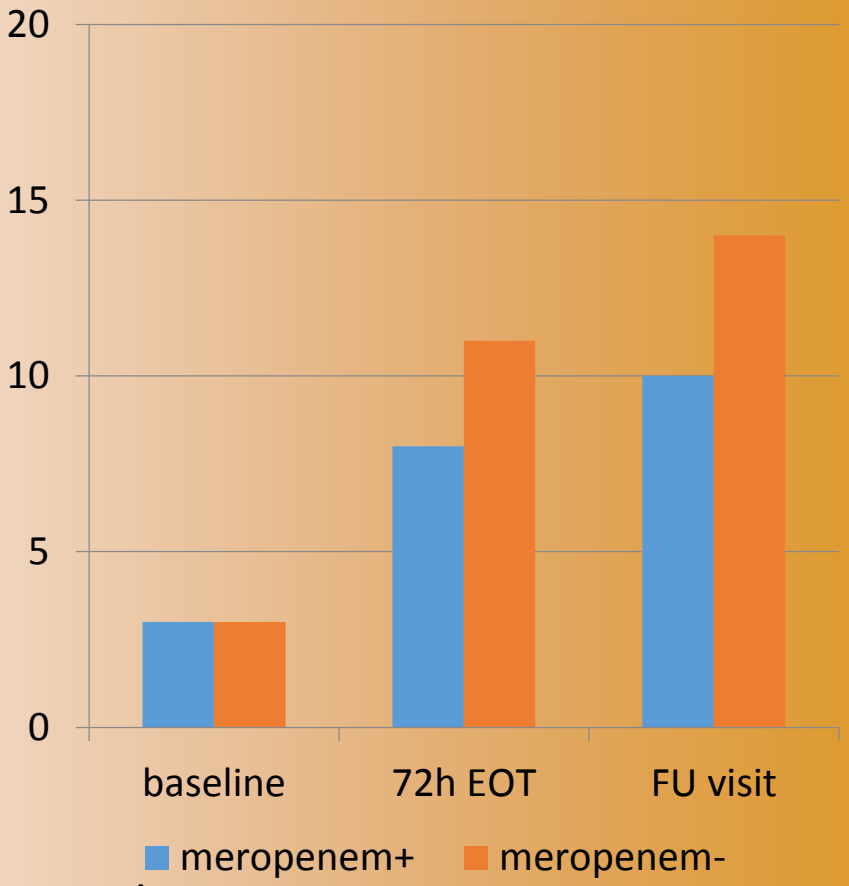
Cumulative percentage of patients with CRGNO in rectal swab

Meropenem vs SOC

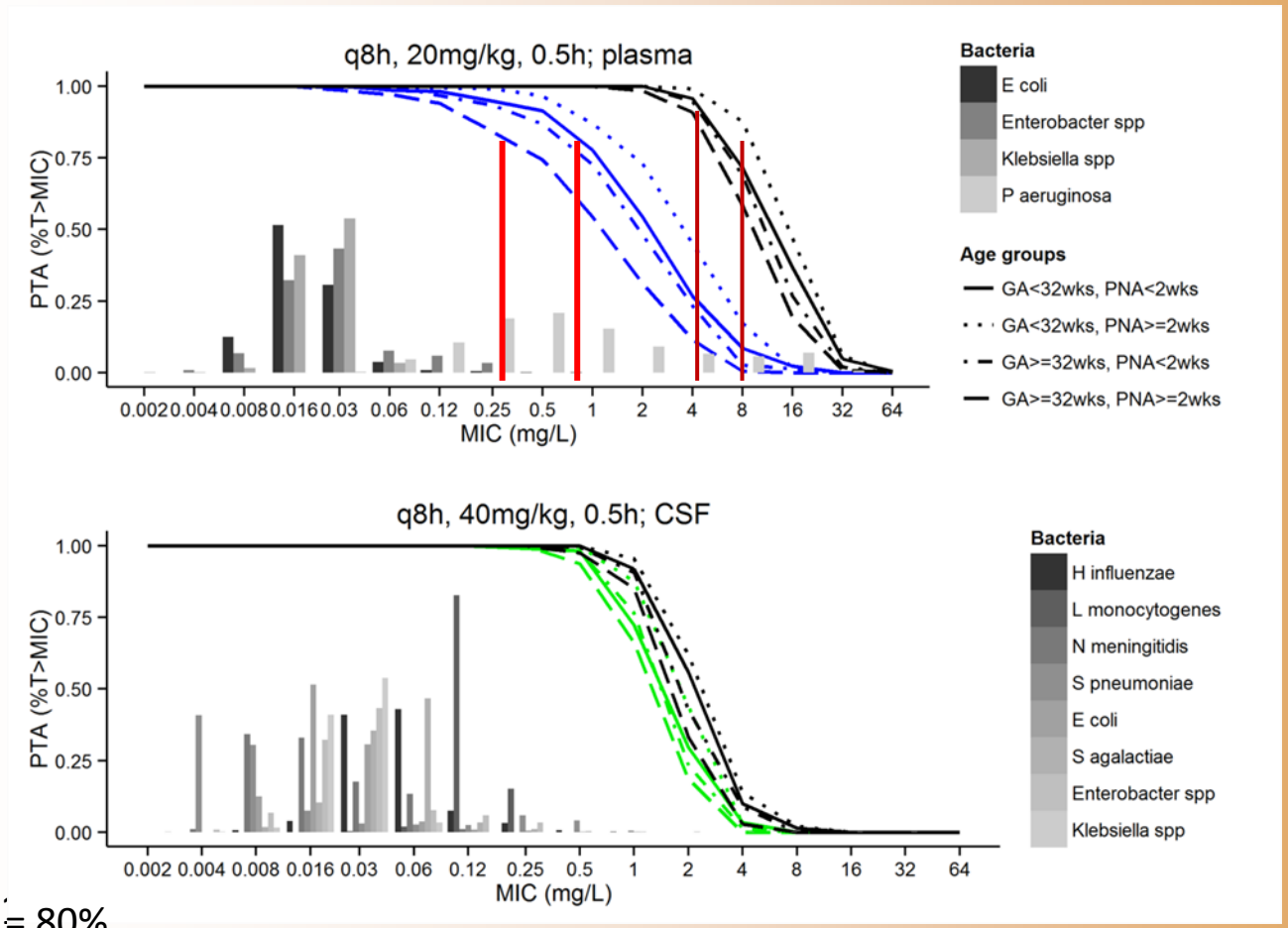


Meropenem yes vs no



CRGNO – carbapenem resistant Gram-negative organisms

Probability of target attainment: T>MIC = 40% (blue) ja T>MIC = 100% (black)



PTA = 80%

Main conclusions of NM1

- Meropenem treatment was not superior to SOC in terms of primary endpoint at TOC
- Meropenem mono-therapy was more efficacious than SOC in patients with culture-proven LOS, resulted in slightly shorter treatment duration
- Meropenem did not select for carbapenem resistant Gram-negative microorganisms
- Meropenem therapy is an alternative for treatment of LOS especially in patients infected with resistant Gram-negative organisms

St George's University of London

PIDRG
Paediatric Infectious Diseases Research Group

neoVanc

PENTA - ID
www.penta-id.org

Louise Hill

INSTITUTE FOR INFECTION & IMMUNITY

NeoVanc programme

- **NeoVanc-1-** Hollow fibre infection and rabbit models (Ramos-Martín V, *et al*. J Antimicrob Chemother. 2016;71(4):992-1002)
- **NeoVanc-2 -** Population PK meta-analysis of previous neonatal, vancomycin pharmacokinetics data
- **NeoVanc-3 –** Randomised open label study optimised vs SOC

NeoVanc-3

Treatment of LOS caused by Gram-pos microorganisms

Optimised treatment

- 5 days

- Bolus 25mg/kg

+

- Maintenace dose 15 mg/kg
  - q12 (≤35PMA)
  - q8h (>35PMA)

Non-inferiority study

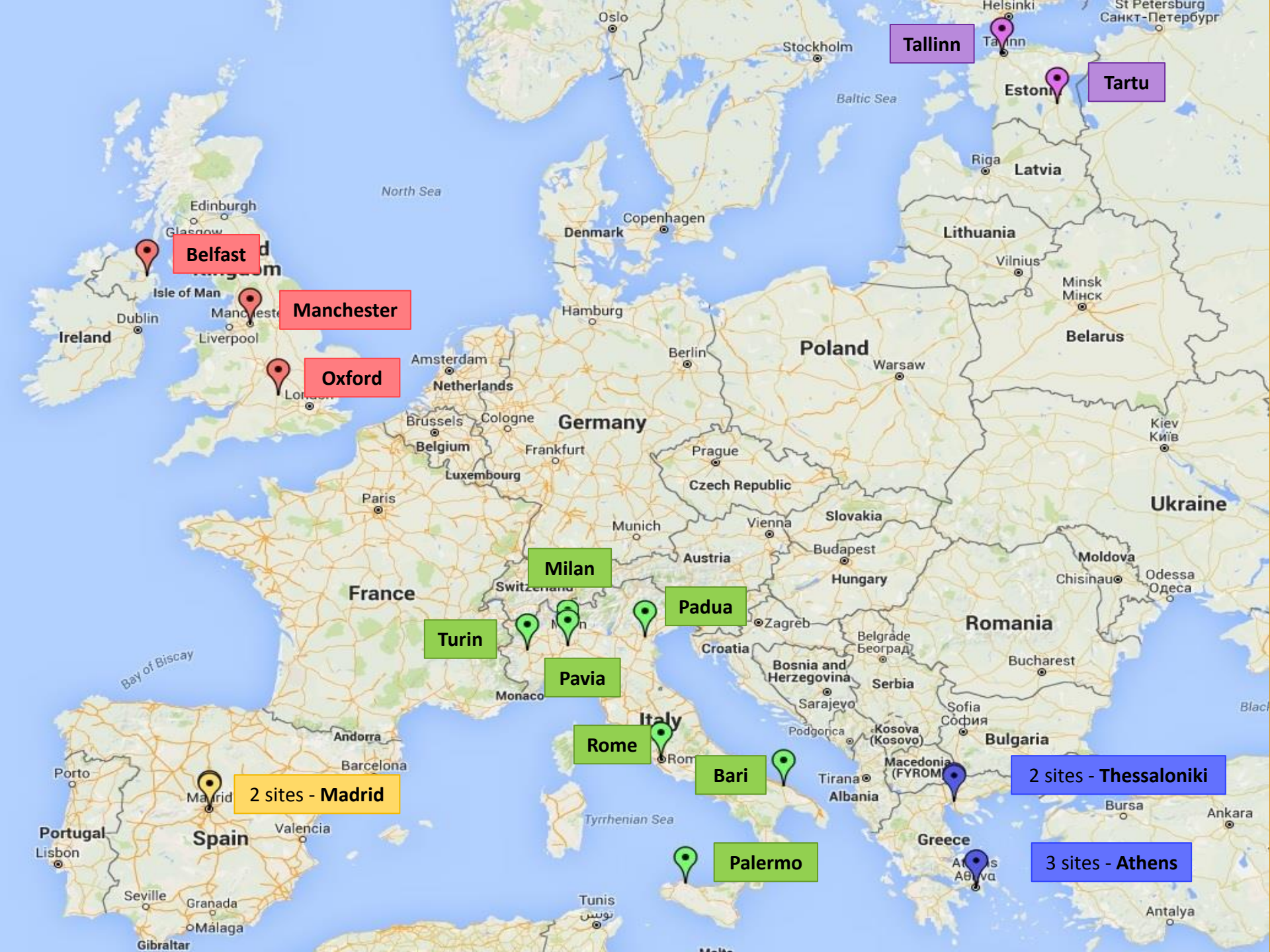
Standard treatment (B-Book 2011)

- 10 days

- Dose 15mg/kg
  - q24h (<29 PMA)
  - q12h (29-35 PMA)
  - q8h (>35PMA)

Recruitment

- 300 participants is planned to be enrolled from five EU countries
  - Estonia, Greece, Italy, Spain, the United Kingdom
  - At least 30% of recruits should be < 29 weeks postmenstrual age (PMA) at randomisation
- Recruitment
  - Recruitment open in
    - Tartu (EST) – 3 participants enrolled
    - Tallinn (EST) – 2 participants enrolled
    - Rome (IT) – 6 participants enrolled (1 withdrawal of consent)
  - Over 18 months


Tallinn
Tartu
Belfast
Manchester
Oxford
Milan
Padua
Turin
Pavia
Rome
Bari
2 sites - Madrid
2 sites - Thessaloniki
Palermo
3 sites - Athens
Oslo
Stockholm
Helsinki
Baltic Sea
North Sea
Latvia
Lithuania
Belarus
Poland
Denmark
Copenhagen
Hamburg
Berlin
Warsaw
Netherlands
Amsterdam
Germany
Belgium
Brussels
Cologne
Frankfurt
Luxembourg
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Odessa
Bucharest
Belgrade
Sarajevo
Sofia
Tirana
Podgorica
Kosovo
Macedonia

Conclusions

- Multinational, pan-European trials are feasible but they are very complex
- Diagnostic criteria selected well patients with LOS but did not allow to distinguish between Gram-positive and Gram-negative infection
- Networking across Europe and different specialitis is a key for success