Master Protocols in Neonatal Infections:

Pharmacokinetic, Safety and Outcome Assessment

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Declaration of interests

- My employers have received funds for clinical studies from: Roche, Chiesi, Johnson & Johnson, Pfizer, EC FP7, NIHR, BLISS, MRC, AMR
- My employers receive funds for consultancy from Chiesi, BMS, Novartis, Shire, Janssen, Grunenthal
- Chair, European Network for Paediatric Research at the European Medicines Agency
- Co-Director, International Neonatal Consortium
- Coordinator, European Paediatric Clinical Trials Research Infrastructure

Topics

State of the art

- Systematic reviews of extant protocols

Components of a master protocol

Design of a master protocol

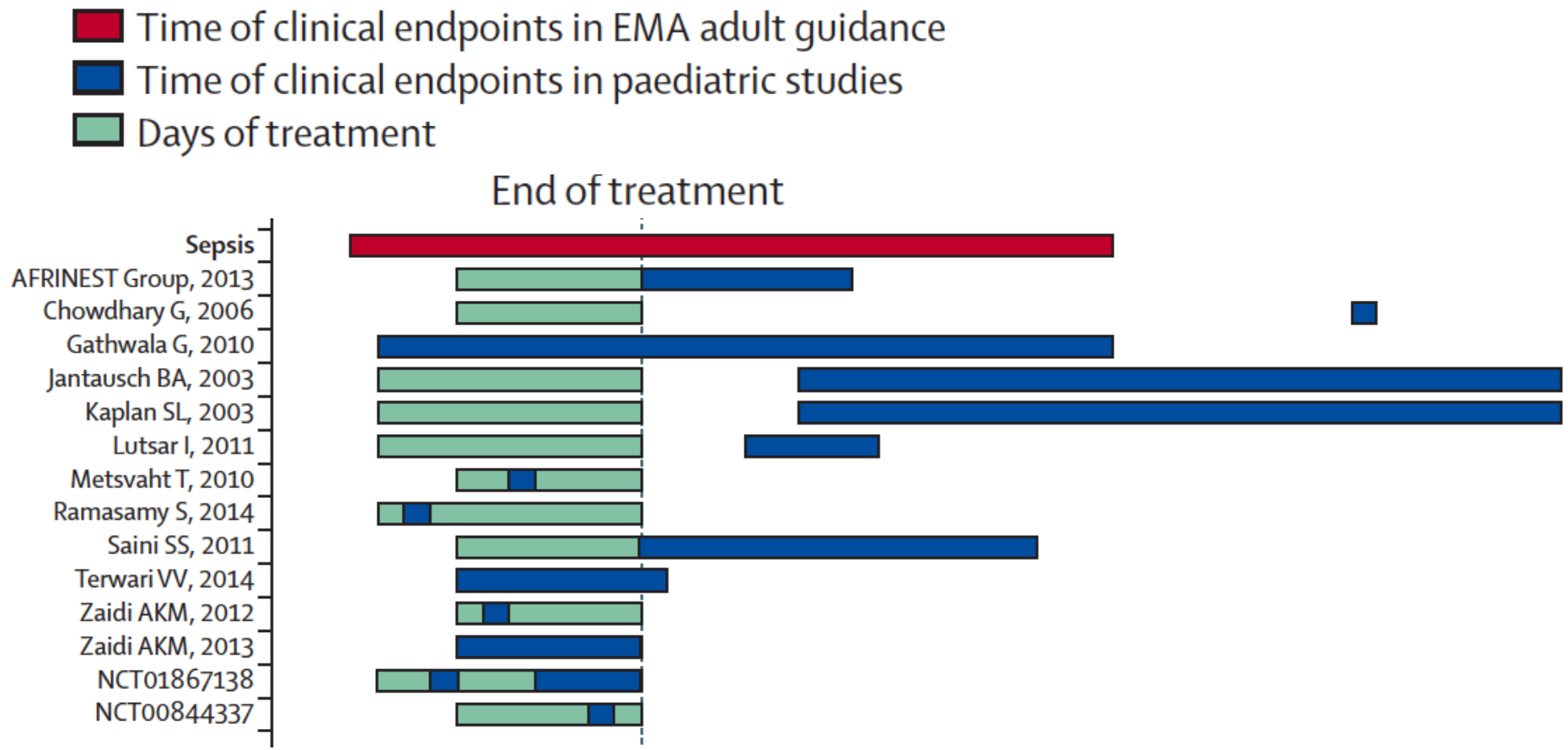
State of the art

Harmonisation in study design and outcomes in paediatric antibiotic clinical trials: a systematic review

Laura Folgori, Julia Bielicki, Beatriz Ruiz, Mark A Turner, John S Bradley, Daniel K Benjamin Jr, Theoklis E Zaoutis, Irja Lutsar, Carlo Giaquinto, Paolo Rossi, Mike Sharland

Lancet Infect Dis 2016; 16: e178–89

State of the art



Lancet Infect Dis 2016; 16: e178–89

Components of a master protocol

Need alignment of:

Inclusion criteria

- EMA consensus statement etc.

Target groups

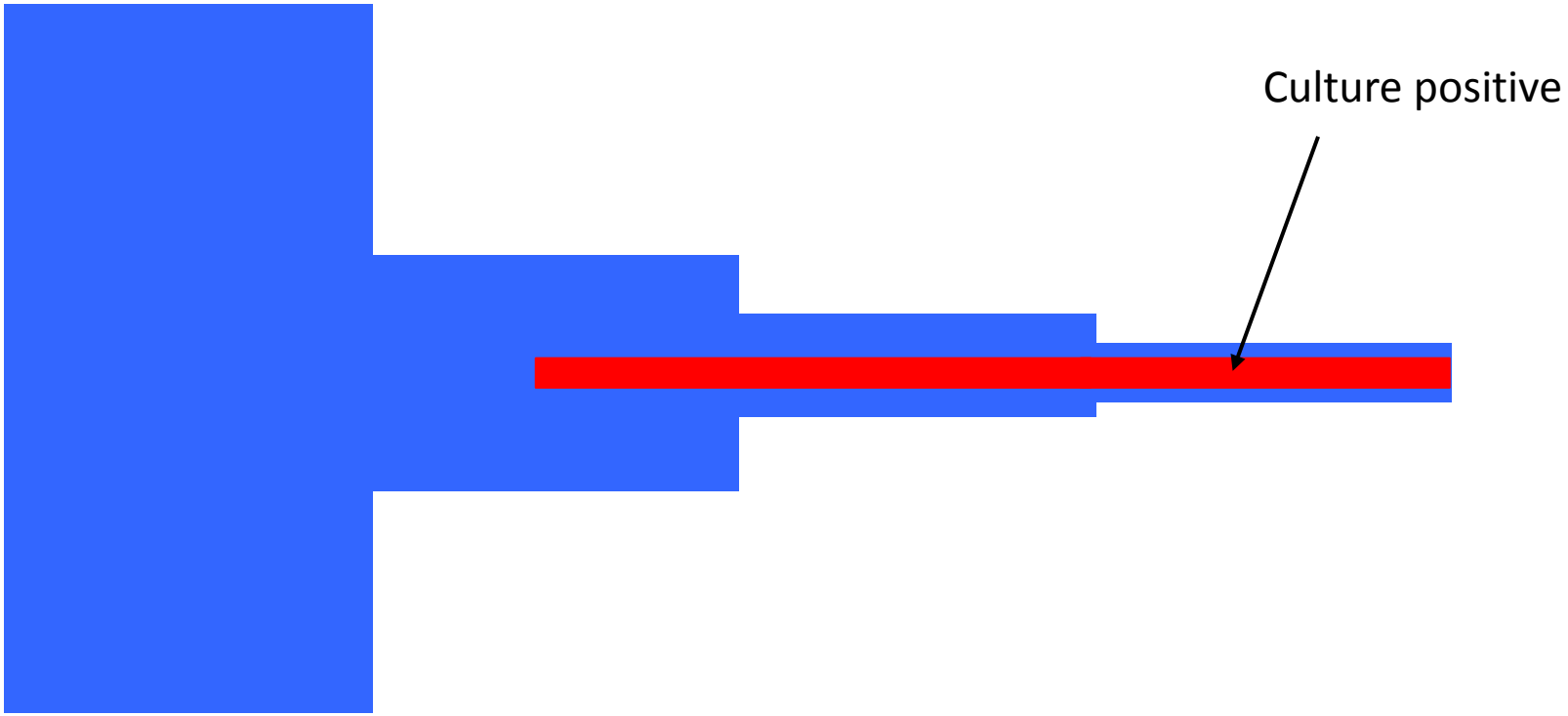
- Empiric / Confirmed / Rescue

Outcomes

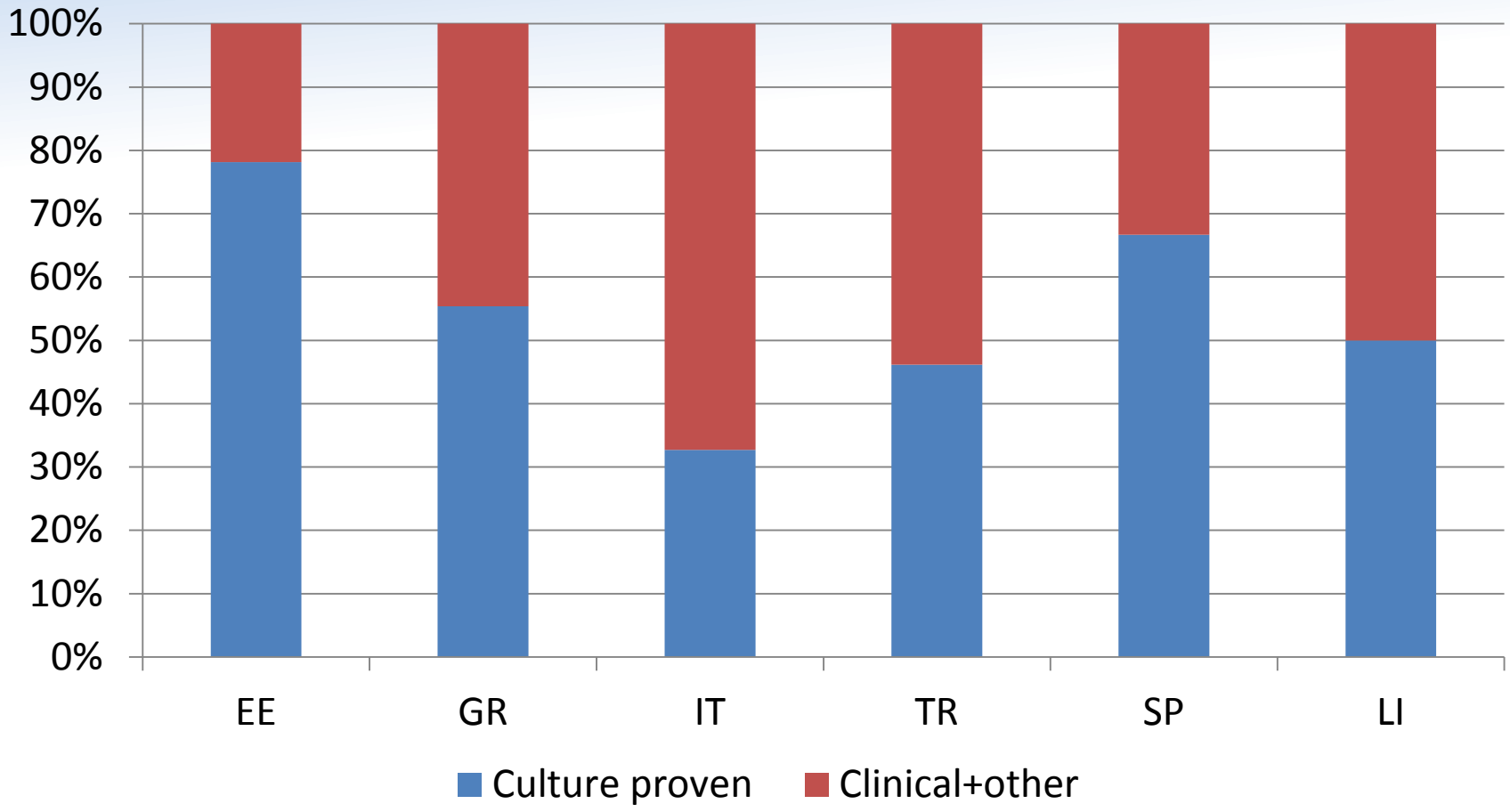
Methodology

- Clinical / Microbiology / PK

Target groups



Percentage of culture proven LOS in different countries



Target groups

Target	Strengths	Weaknesses
Empiric	Complete	Post-randomisation imbalance Bias Loss of numbers Bacteria not known
Confirmed	Bacteria known (if culture positive) Enriched for infection	Previous treatment may affect efficacy and safety signals
Rescue	Bacteria known (if culture positive) Enriched for resistant bacteria	Previous treatment may affect efficacy and safety signals Clinical variation in timing

Target groups

	Preterm	Term
Early onset		
Late onset		
Specific • NEC • Meningitis • VAP • BPD		

Issues

Marked variation between settings in:

- Microbiology
- Standard of care
- Thresholds for moving between confirmed and rescue
  - Protocol deviations

Goals of a master protocol

Develop PK models

Percentage Attainment of a PK/PD target

Assess Efficacy

- Clinical
- Microbiological

Assess Safety

- Descriptive
- Causal

PK and PD data

Sample collection (generally acceptable)

Storage and transfer

Assays

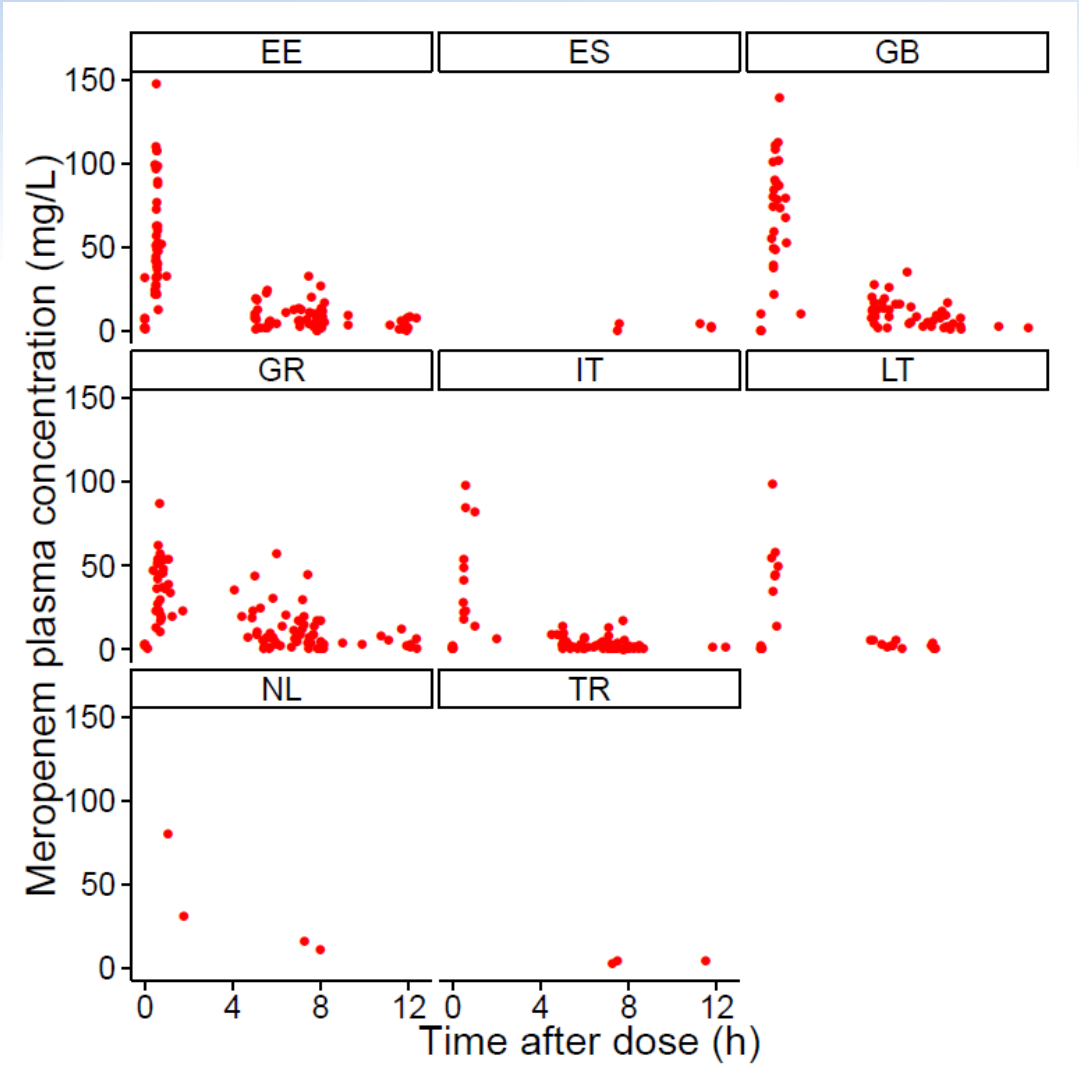
TDM

Analysis

Warehousing

Covariates

Plasma concentration of meropenem by country



Safety data

Background events

- Prematurity
- Term conditions

Drug specific

- Predictable
- Unpredictable

Infection specific

Safety data

Background events

- Prematurity
- Term conditions

Drug specific

- Predictable
- Unpredictable

Infection specific

Definitions
Severity
Causality

Efficacy Outcomes

Components

- Alive or dead
- Resolution of clinical features
- Resolution of microbiological features
- No change in therapy
- No new microbiological concerns

Choice of outcomes

Issues include

- Feasibility
- Timing in the study
- Influence of co-medication (e.g. medicines with some G+ and G- activity)
- Utility
- Balance between pre and post approval

Difficulties with Efficacy as the primary outcome

Ascertainment

Culture negative cases

Other treatments

- especially before randomisation

Confirmed cases are not common

Specific resistant bacteria are rare

Master protocol designs: 1

Design	Approach	Output	Comments
Each centre evaluates one antibiotic that is compatible with local needs • sites selected for the antibiotics they **currently** use	Each antibiotic is studied in several centres and in one or more target groups	Population PK model that incorporates covariates from multiple centres and target groups	Could be combined with PD targets
	All antibiotics are studied consistently	Efficacy data also available	Safety surveillance could include all babies in the centre (with consent)

Master protocol designs: 2

Design	Approach	Output	Comments
Each centre compares more than one antibiotic • Sites selected according to the antibiotics they are **prepared to use**	Randomised for a single target group • one of empiric, confirmed or rescue • Could vary between centres according to preferences	Comparative data • For target attainment • For efficacy	Could be a comparison to standard of care • which may differ Could be a comparison between two agents
	Need to ensure adequate numbers of comparators		Safety surveillance could include all babies in the centre (with consent)

Key assumptions

Data can be pooled across sites

- PK warehouse
- Stratification by
  - Site
  - GA band
  - Target group

Common comparator

- May be difficult
- “Network analysis”

Conclusions

Master protocols can be developed

- PK data can be pooled
- Safety issues are generic to neonates
- Outcomes may be problematic
- Comparisons may be problematic

Please work with Europe and other jurisdictions