Clinical trial platforms for new and neglected antimicrobials

Guest speakers: Jesús Rodríguez-Baño & Julia Bielicki

Moderator: Marc Bonten

Host: Shirine Derakhshani (GARDP)

20 September 2023

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Global Antibiotic Research & Development Partnership

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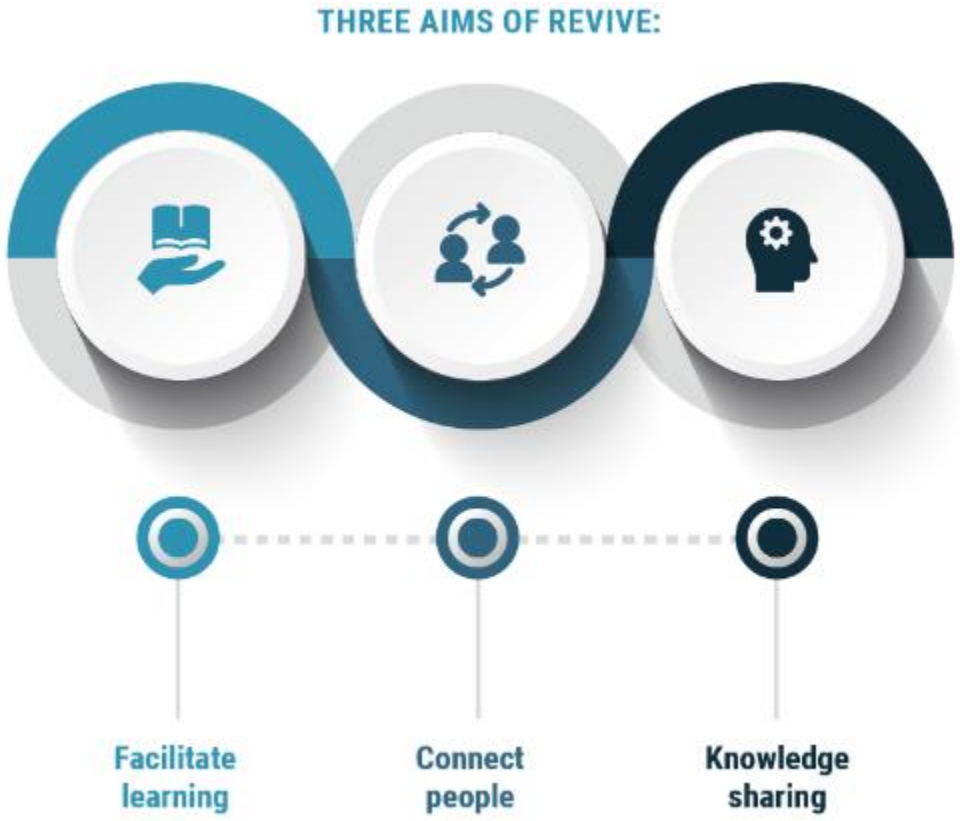

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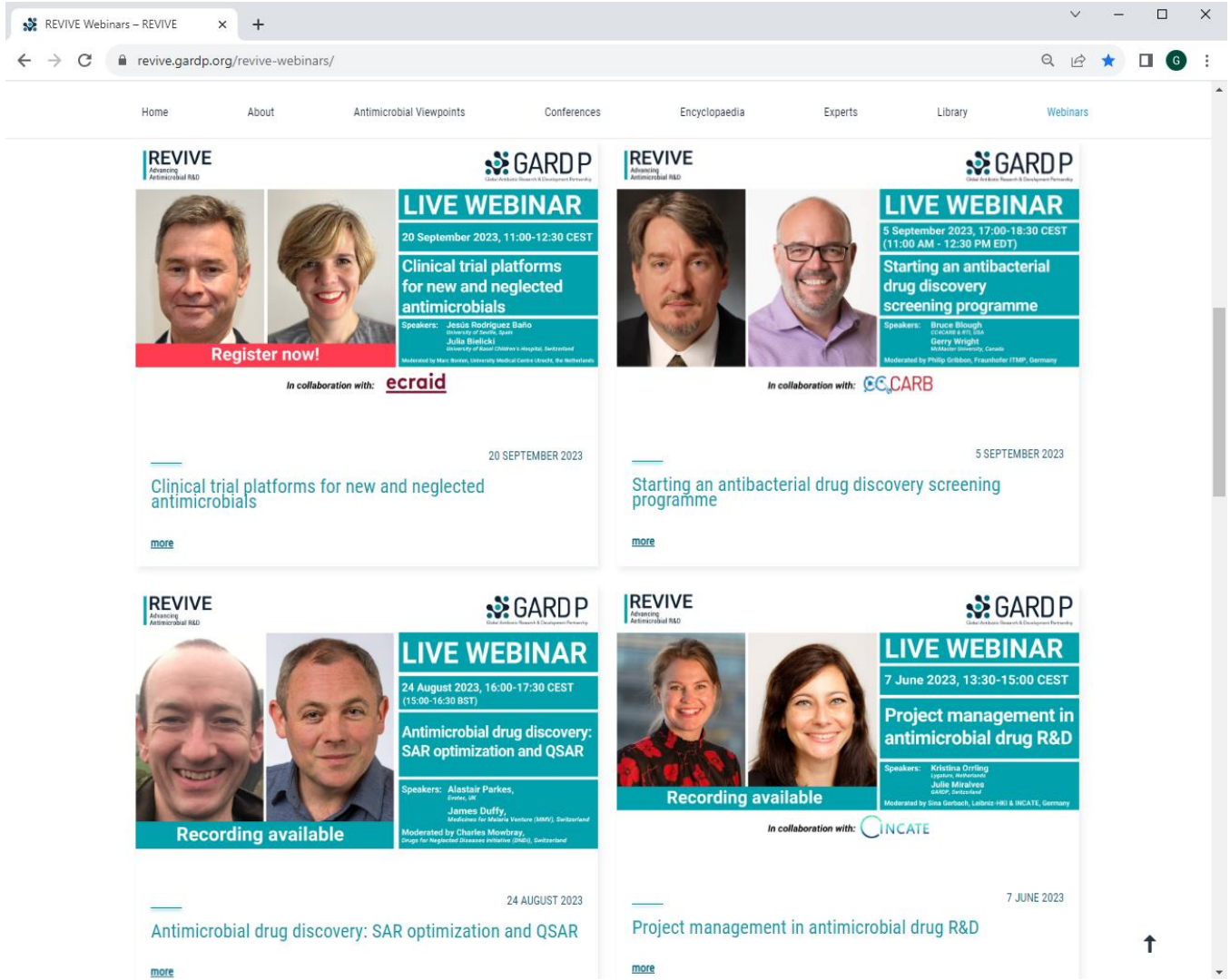

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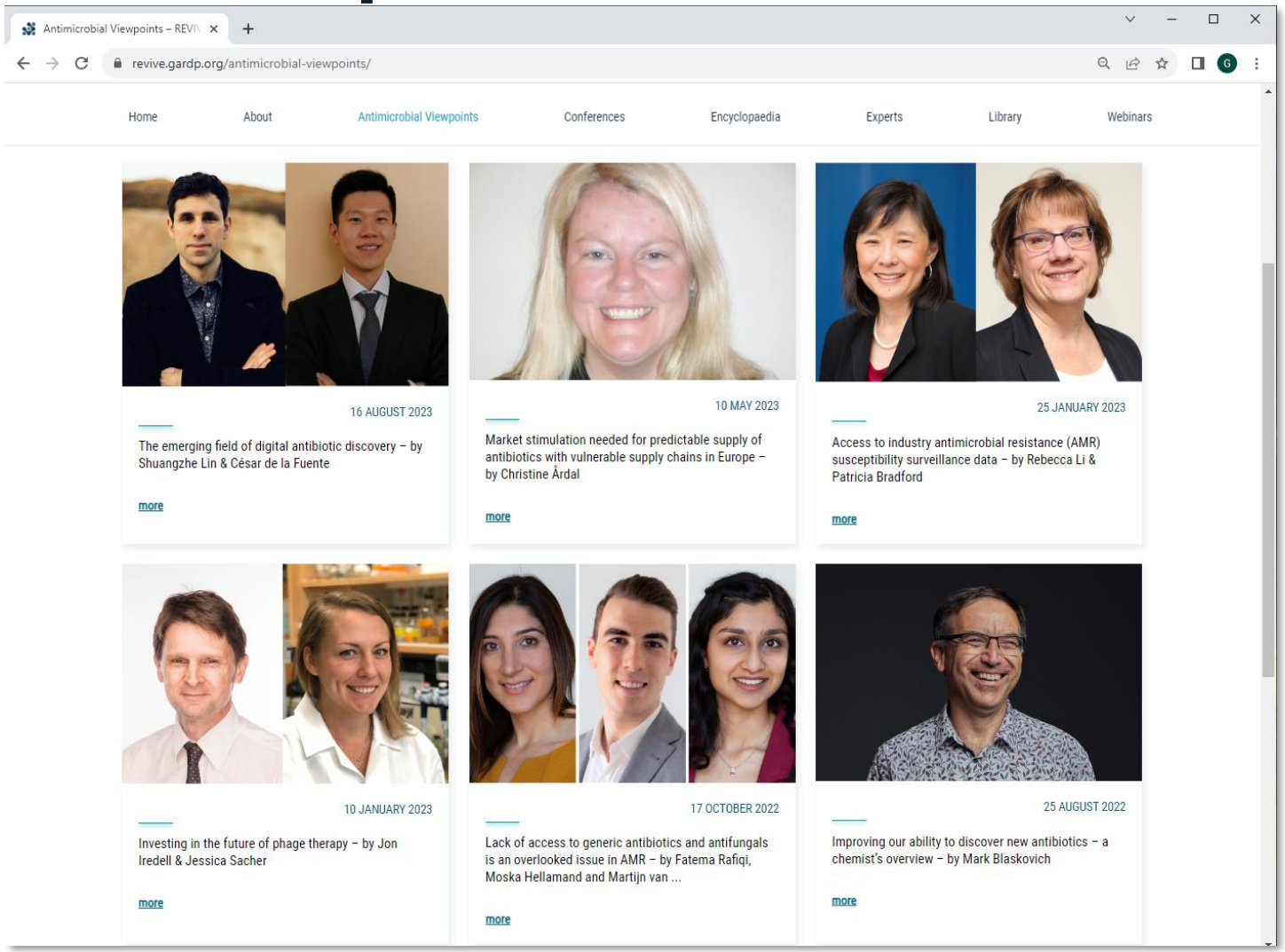

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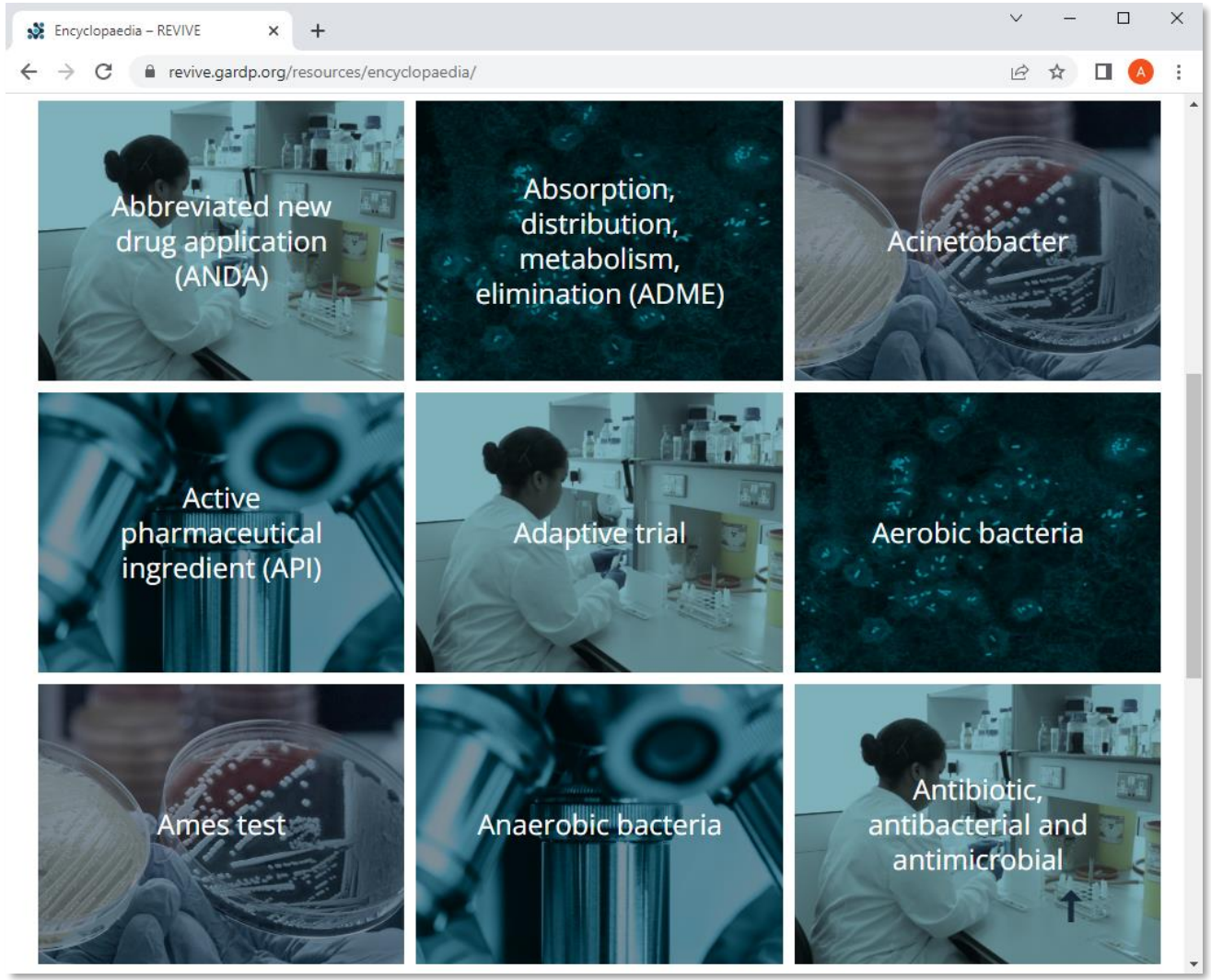

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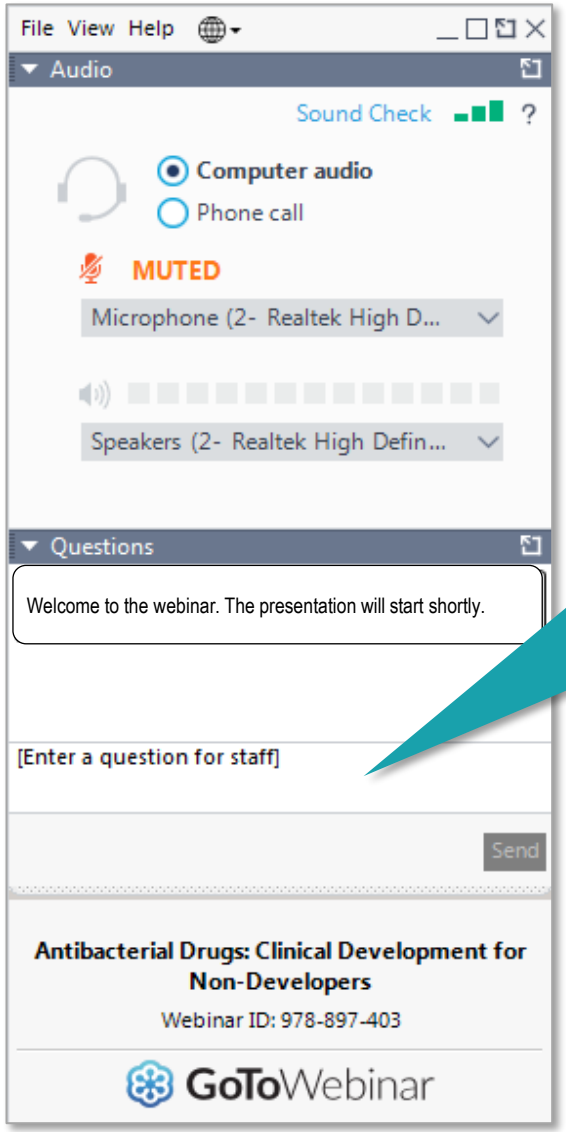
If your question is addressed to a specific speaker, please include their name when submitting the question.



The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

This webinar was developed in collaboration with Ecraid.

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https://www.ecraid.eu/

Today’s speakers

Clinical trial platforms for new and neglected antimicrobials

Jesús Rodríguez-Baño
Professor of medicine,
University of Seville (Spain)
&
Infectious Diseases division,
Hospital Universitario Virgen Macarena (Spain)

Julia Bielicki
Senior consultant in paediatric infectious diseases,
University of Basel Children’s Hospital (Switzerland)
&
Reader in paediatric infectious diseases,
St George’s, University of London (UK)

Moderator:
Marc Bonten
Professor of molecular epidemiology of infectious diseases,
University Medical Centre Utrecht (The Netherlands)

Jesús Rodríguez-Baño

Jesús Rodríguez-Baño is a specialist in Internal Medicine and has an expert degree in Epidemiology and Clinical Research. He is Past-President of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Editor of *Clinical Microbiology and Infection*.

He is Head of the Infectious Diseases Division at Hospital Universitario Virgen Macarena (HUVM) and Full Professor of Medicine at the University of Seville, Spain.

Jesús has authored more than 400 peer-reviewed articles and has been a leader or partner in several research projects funded by the European Union. He was member of the Scientific Advisory Board of the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) of the European Union.

His areas of interest include antimicrobial resistance (clinical epidemiology, control and treatment), antimicrobial use, bloodstream infections, UTI and healthcare-associated infections.

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Trials in cUTI
Opportunities from POS-cUTI/ecraid

Jesús Rodríguez-Baño

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Conflicts of interest

- None
- (Funding from Innovative Medicines Initiative, European Union + EFPIA)

Areas of interest for randomized controlled trials (RCTs) in complicated urinary tract infections (cUTI)

- Diagnostics
  - Aetiology – rapid identification of pathogen / susceptibility
  - Biomarkers
- Treatment
  - Drugs (new, neglected)
  - Other management aspects
- Stewardship
  - Duration of treatment
  - Oral treatment for febrile/bacteraemic infections
- Prevention

Pivotal trials in cUTI for new drugs registration

- Frequent ("easy indication" for anti-gram negatives)
  - High probability of success for beta-lactams, fluoroquinolone (FQ), aminoglycoside (AG)
- Typically two-arms (new vs standard), non-inferiority
- Recommendations from regulatory agencies
  - Inclusion and exclusion criteria
  - Endpoints
  - Non-inferiority margin

Regulatory agencies recommendations for RCTs in cUTI

	European Medicines Agency EMA	U.S. Food and Drug Administration FDA
UTI signs/symptoms	Minimum no.	At least 2
Criteria for complicated	Urinary retention or obstruction; catheter	Functional or anatomical; catheter
Pyelonephritis	Yes (30-70%)	Yes (30-70%)
Exclusions	Prostatitis, ileal loop, V-R reflux	Prostatitis, renal Tx, ileal loop, drug prophylaxis, recent pelvis trauma
Endpoint	Clinical and microbiological response (microbiological intention-to-treat population – ITTp)	Clinical and microbiological response
Non-inferiority margin	10%	10%

Issues with regulatory agencies recommendations

- Mixed of different infection types, severity, etc.
- Exclusion of complex patients
- Underrepresentation of multidrug-resistant/extensively drug-resistant (MDR/XDR) bacteria
- Protocols different from real clinical practice

Heterogeneity of Recent Phase 3 Complicated Urinary Tract Infection Clinical Trials

Simon Portsmouth, MD, FRCP,[1] Almasa Bass, PharmD,[2] Roger Echols, MD, FIDSA,[3] and Glenn Tillotson, PhD, FIDSA[4]

[1]Shionogi Inc, Florham Park, New Jersey, USA, [2]UCB, Durham, North Carolina, USA, [3]ID3C Consultants, Easton Connecticut, USA, [4]GST Micro LLC, Richmond, Virginia, USA

Open Forum Infectious Diseases®2021

Results. Microbiologic modified intent-to-treat sample size, age, proportions of female patients, acute pyelonephritis (AP), *Escherichia coli* and other pathogens at baseline, protocol-specified switch to oral antibiotic, and the noninferiority margin were compared. Outcome data included clinical response, microbiologic eradication, and composite outcomes, including a subset of patients with AP.

Conclusions. A study design can follow regulatory guidelines but still have variable populations. The proportion of AP within a study varied greatly and influenced population demographics (age, gender) and baseline microbiology. A smaller proportion of AP resulted in an older patient population, fewer females, less *E coli*, and lower proportions of patients achieving success. Fluoroquinolones and piperacillin/tazobactam should be reconsidered as active comparators given the high rates of resistance to these antibiotics.

Medical needs in cUTI

- Options for “difficult to treat” pathogens
  - Extended Spectrum Beta-Lactamase (ESBL)/AmpC or carbapenemase-producing Enterobaterales
  - Difficult-to-treat *P. aeruginosa, A. baumannii*
- Efficacy/safety in complex infections and specific populations
  - Prostatitis, renal abscess, chronic urinary tract obstruction, chronic transcutaneous catheters, ileal loops…
  - Renal transplant, very elderly
- Antimicrobial stewardship
  - Strategies for empirical treatment
  - Oral step down, treatment duration
  - Neglected drugs
  - Ecological impact of different drugs

RCT with new drugs for carbapenem-resistant Gram negative bacteria

Drug	Randomized trials	No. of patients
CAZ-AVI	None	-
MER-VAB	TANGO-II (Wunderink, Infect Dis Ther 2018)	32 vs 15
IMI-REL	RCT: RESTORE-IMI 1 (Motsch, CID 2019)	21 vs 10
PLAZOMICIN	RCT: CARE (McKinnel, NEJM 2019)	17 vs 20
ERAVACYCLINE	None	-
CEFIDEROCOL	RCT: CREDIBLE (Bassetti, Lancet Infect Dis 2020)	101 vs 49

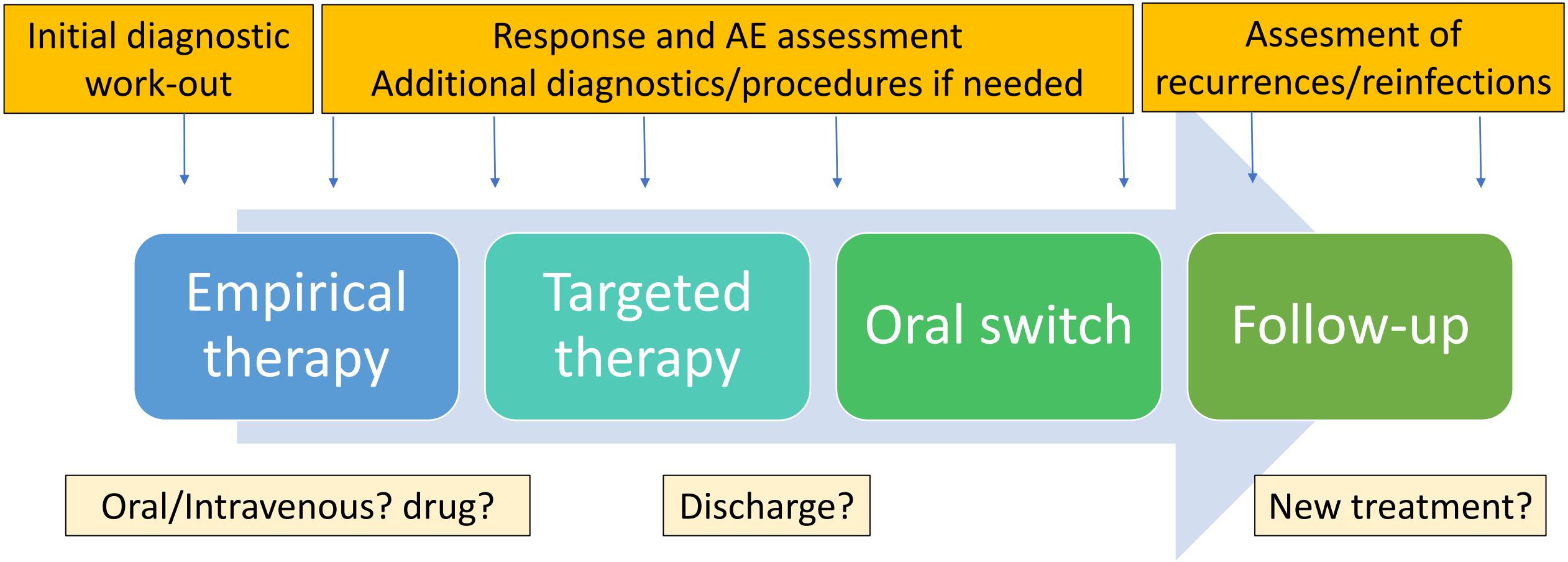
Neglected “oldies”

- Aminoglycosides
- Fosfomycin
- Temocillin

What to improve in RCT design for cUTI

- Better selection of patients
- Pragmatic protocols (real practice)
- Efficient designs
- Relevant research question (medical needs)
- Individualised therapy
- Outcomes: patients' preferences; ecological impact

Pragmatic trials: reflecting the clinical pathway and real-life resources



Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant *Escherichia coli* Bacteremic Urinary Tract Infections
A Randomized Clinical Trial

Jesús Sojo-Dorado, MD, PhD; Inmaculada López-Hernández, MD, PhD; Clara Rosso-Fernandez, MD, PhD; Isabel M. Morales, MD, PhD; Zaira R. Palacios-Baena, MD, PhD; Alicia Hernández-Torres, MD, PhD; Esperanza Merino de Lucas, MD, PhD; Laura Escolà-Vergé, MD, PhD; Elena Bereciartua, MD; Elisa García-Vázquez, MD, PhD; Vicente Pintado, MD, PhD; Lucía Boix-Palop, MD; Clara Natera-Kindelán, MD, PhD; Luisa Sorlí, MD, PhD; Nuria Borrell, MD, PhD; Livia Giner-Oncina, PharmD, PhD; Concha Amador-Prous, MD, PhD; Evelyn Shaw, MD, PhD; Alfredo Jover-Saenz, MD; Jose Molina, MD; Rosa M. Martínez-Alvarez, MD; Carlos J. Dueñas, MD; Jorge Calvo-Montes, MD; Jose T. Silva, MD, PhD; Miguel A. Cárdenes, MD; María Lecuona, MD, PhD; Virginia Pomar, MD, PhD; Lucía Valiente de Santis, MD; Genoveva Yagüe-Guirao, MD, PhD; María Angeles Lobo-Acosta, MD; Vicente Merino-Bohórquez, PharmD; Alvaro Pascual, MD, PhD; Jesús Rodríguez-Baño, MD, PhD; and the REIPI-GEIRAS-FOREST group

JAMA Network Open. 2022;5(1):e2137277.

Protocol adapted to real-life management for target therapy

- Active (48h) and non-active empirical drugs allowed
- Very limited exclusion criteria
- Switch to oral drugs or parenteral ertapenem according to AST in comparator arm
- Follow-up similar to standard practice

Table 1. Baseline Characteristics of Patients in the Modified Intention-to-Treat Population[a]

Characteristic	Patients, No. (%) Receiving fosfomycin (n = 70)	Receiving comparator (n = 73)
Age, median (IQR), y	69 (62-81)	73 (62-84)
Sex		
Women	34 (48.6)	39 (53.4)
Men	36 (51.4)	34 (46.6)
Charlson Comorbidity Index score[b]		
Median (IQR)	1 (0-3)	2 (1-3)
≥3	22 (31.4)	22 (30.1)
Congestive heart failure[c]	8 (11.4)	11 (15.1)
Chronic pulmonary disease[c]	12 (17.1)	11 (15.1)
Diabetes[c]	19 (27.1)	19 (26.0)
Chronic kidney disease[c]	9 (12.9)	14 (19.2)
Cancer[c]	14 (20.0)	16 (21.9)
Full dependence for basic activities	4 (5.7)	6 (8.2)
Urinary catheter at enrollment	21 (30.0)	22 (30.1)
Invasive procedure in the urinary tract in previous month[d]	12 (17.1)	4 (5.5)
Immunosuppressive drugs	7 (10.0)	9 (12.3)
Oral antibiotic therapy after intravenous therapy with study drug	60 (85.7)	48 (65.7)
Oral drug used		
Fosfomycin trometamol	60 (85.7)	1 (1.4)[j]
Cefuroxime axetil	0	28 (38.3)
Amoxicillin-clavulanic acid	0	7 (9.6)
Trimethoprim-sulfamethoxazole	0	7 (9.6)
Ciprofloxacin	0	5 (6.8)
Parenteral ertapenem after study drug	0	13 (17.8)

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Table 2. Patients Reaching CMC and Reasons for Not Reaching It

	Patients, No./total No. (%)			
	Receiving fosfomycin	Receiving comparator	Risk difference (1-sided 95% CI)[a]	*P* value, 1-sided
CMC at TOC among MITT (measures of success)				
All patients	48/70 (68.6)	57/73 (78.0)	−9.4 (−21.5 to ∞)	.10
Patients with ceftriaxone-susceptible isolates[b]	25/31 (80.6)	27/31 (87.0)	−6.4 (−21.7 to ∞)	.24
Patients with ceftriaxone-resistant isolates[b]	23/39 (59.0)	30/42 (71.4)	−12.4 (−29.8 to ∞)	.12
Reasons for not reaching CMC at TOC among MITT (measures of failure)				
Clinical or microbiological failure				
All patients	10/70 (14.3)	14/73 (19.7)	−5.4 (−∞ to 4.9)	.19
Patients with ceftriaxone-susceptible isolates[b]	3/31 (9.7)	4/31 (12.9)	−3.2 (−∞ to 10.0)	.34
Patients with ceftriaxone-resistant isolates[b]	7/39 (17.9)	10/42 (23.8)	−8.9 (−∞ to 6.9)	.25
Other reasons				
Withdrawn because of adverse events	6/70 (8.5)[c]	0/73 (0)	8.5 (−∞ to 13.9)	.006
Missed assessment at TOC	3/70 (4.2)	2/73 (2.7)	1.5 (−∞ to 6.5)	.31
TOC assessed but urine culture at TOC not available	3/70 (4.2)	0/73 (0)[d]	4.2 (−∞ to 8.1)	.03

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Table 3. Analysis of Secondary End Points

	Patients, No./total No. (%)[a]			
	Receiving fosfomycin	Receiving comparators	Risk difference (1-sided 95% CI)[b]	*P* value, 1-sided
Measure of success				
Clinical cure at TOC (CEP)				
All patients	59/61 (96.7)	64/71 (90.1)	6.6 (−0.2 to ∞)	.05
Patients with ceftriaxone-susceptible isolates	29/29 (100)	29/31 (93.5)	6.5 (−1.1 to ∞)	.08
Patients with ceftriaxone-resistant isolates	30/32 (93.8)	35/40 (87.5)	6.3 (−5.2 to ∞)	.18
Microbiological cure at TOC (MEP)				
All patients[c]	48/58 (82.8)	59/69 (85.5)	−2.7 (−13.3 to ∞)	.33
Patients with ceftriaxone-susceptible isolates	25/28 (89.3)	29/31 (93.5)	−4.2 (−18.4 to ∞)	.28
Patients with ceftriaxone-resistant isolates	23/30 (76.6)	30/38 (78.9)	−2.3 (−18.9 to ∞)	.41

Original Investigation | Infectious Diseases

Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant *Escherichia coli* Bacteremic Urinary Tract Infections

A Randomized Clinical Trial

Sojo-Dorado J et al *JAMA Network Open.* 2022;5(1):e2137277.

Acquisition of rectal colonisaton with ceftriaxone or meropenem-R bacteria

- Fosfomycin 0/21 p=0.01
- Comparators 4/17 (23.5%)

Conclusions

- Fosfomycin is effective;
- Caution with heart failure (>80 yo, chronic heart failure or renal insufficiency)
- Potential ecological advantage

Fosfomycin Vs Ciprofloxacin as Oral Step-Down Treatment for *Escherichia coli* Febrile Urinary Tract Infections in Women: A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial

Thijs ten Doesschate,[1,2] Sander Kuiper,[3,4] Cees van Nieuwkoop,[3] Robert-Jan Hassing,[5] Tom Ketels,[5] Suzan P. van Mens,[6] Wouter van den Bijllaardt,[7] Akke K. van der Bij,[8] Suzanne E. Geerlings,[9] Ad Koster,[10] Evert L. Koldewijn,[11] Judith Branger,[12] Andy. I. M. Hoepelman,[1] Cornelis. H. van Werkhoven,[2] and Marc J. M. Bonten[2]; on Behalf of the FORECAST Study Team[a]

Clinical Infectious Diseases® 2021;XX(XX):1–9

Difference in clinical cure: 9.6% (95% CI: -8.8 - 28.0)

- Fosfomycin 36/48 (75.0%)
- Ciprofloxacin 30/46 (65.2%)

Table 2. Secondary End Points of the Intention-to-Treat Population

Secondary End Point	Fosfomycin (n = 48)	Ciprofloxacin (n = 49)	Risk Difference (95% Confidence Interval/*P* Value)
6–10 days post-end of therapy			
Microbiological cure	29/37 (78.4%)	33/35 (94.3%)	–16.2% (–32.7% to –0.0%)
30–35 days post-end of therapy			
Clinical cure	35/47 (74.5%)	33/44 (75.0%)	0.4% (–18.4% to 17.6%)
Reinfection	4/47 (8.5%)	7/44 (15.9%)	–7.8% (–22.3% to 6.6%)
Relapse	2/47 (4.3%)	0/44	5.2% (–4.0% to 14.3%)
Additional antibiotic therapy for presumed urinary tract infection	6/47 (12.8%)	7/44 (15.9%)	–3.4% (–18.6% to 11.9%)
Length of hospital stay, mean (SD), days	4.4 (1.2)	5.4 (2.5)	*P* = .9156[a]
Hospital readmission (any cause)	3/48 (6.3%)	1/49 (2.0%)	5.0% (–5.3% to 15.2%)
Absenteeism days[b] mean (SD)	3.0 (6.7)	2.5 (7.0)	*P* = .5508[c]
Intensive care unit admission[a]	1/48 (2.1%)	0/49	2.9% (–5.3% to 11.0%)
Mortality (any cause)	2/48 (4.2%)	0/49	5.4% (–3.3% to 14.0%)
Mortality (probably related)	0/48	0/49	NA

Effectiveness of fosfomycin trometamol as oral step-down therapy for bacteraemic urinary tract infections due to MDR *Escherichia coli*: a post hoc analysis of the FOREST randomized trial

Sojo-Dorado et al, JAC 2023

Oral fosfomycin trometamol as step-down therapy for febrie/bacteraemic UTI

Study	Design	Infections studied	No. of patients with FOF (no. with bacteraemia)	Frequency of FOF 3 g dose	Days of previous IV therapy in FOF group	Comparator (no. of patients)	Clinical cure rate	Microbiological cure rate	Relapse rate
Wald-Dickler[18]	Retrospective cohort	cUTI including pyelonephritis	110 (7)	3 g q24h: 29 3 g q48h: 59 3 g q72h: 22	0 days: 15 1–3 days: 38 4–5 days: 44 ≥6 days: 13	ETP (212)	FOF: 65.4%[a] ETP: 64.1%[a] aOR 1.21 (95% CI: 0.68–2.16)	Not provided	FOF: 34.5% ETP: 26.8%
Ten Doesschate[9]	Randomized trial	Febrile UTI due to *E. coli* in women	48 (25)	3 g q24h	Mean (SD): 3.4 (1.1)	CIP (49)	FOF: 75%[b] CIP: 65.2%[b]	FOF: 78.4% CIP: 94.3%	FOF: 4.2% CIP: 0
FOREST	Ad hoc analysis of randomized trial	Bacteraemic UTI due to MDR *E. coli*	61 (61)	3 g q48h	Median (IQR): 5 (5–6)	CXM (28), AMC (7), SXT (7), CIP (5)	FOF: 93.4%[c] COMP: 91.4%[c] aOR: 1.97 (95% CI: 0.31–12.47)	FOF: 78.6% COMP: 87.2%	FOF: 15% COMP: 4.3%

The clinical and microbiological efficacy of temocillin versus cefotaxime in adults with febrile urinary tract infection, and its effects on the intestinal microbiota: a randomised multicentre clinical trial in Sweden

Charlotta Edlund, Anders Ternhag, Gunilla Skoog Ståhlgren, Petra Edquist, Åse Östholm Balkhed, Simon Athlin, Emeli Månsson, Maria Tempé, Jakob Bergström, Christian G Giske, Håkan Hanberger, on behalf of the Temocillin Study Group*

Lancet Infect Dis 2021

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- Primary outcome: colonisation with 3rd-generation cephalosporin-R Enterobacterales and/or toxin-producing *C. difficile*
- Secondary outcomes:
  - Clinical and bacteriological response
  - Early and late response
  - Response in predefined subgroups

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Lancet Infect Dis 2021

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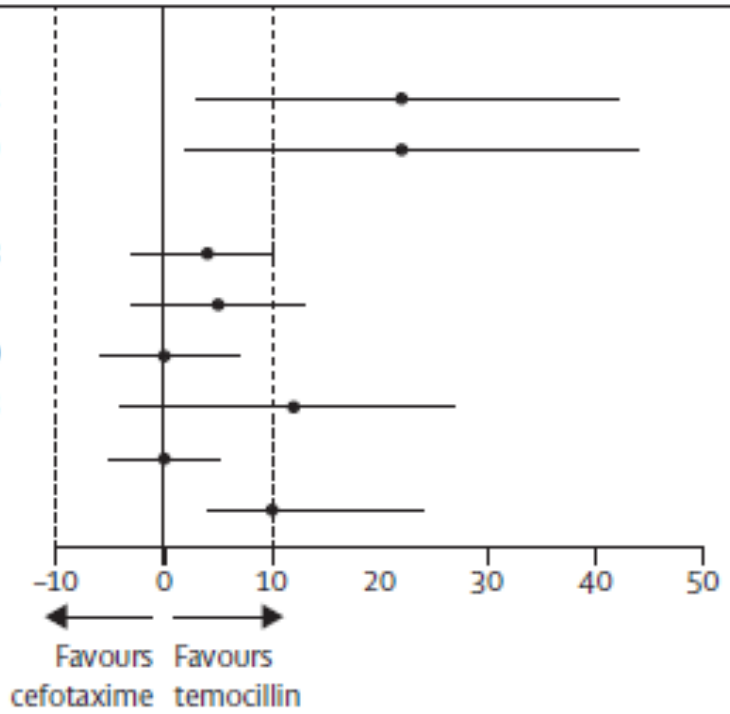
	Temocillin (N=77), (n/N)	Cefotaxime (N=75), (n/N)	Risk difference (95% CI)
Superiority primary endpoints			
Disturbance in gut microbiota (mITT)	18 (26%)/68	30 (48%)/62	22% (3% to 42%)
Disturbance in gut microbiota (PP)	17 (26%)/65	29 (49%)/59	22% (2% to 44%)
Non-inferiority secondary endpoints (PP)			
Early clinical response	68 (97%)/70	59 (94%)/63	4% (-3% to 10%)
Late clinical response	59 (97%)/61	54 (92%)/59	5% (-3% to 13%)
Early bacteriological response, per patient	55 (98%)/56	49 (98%)/50	0% (-6% to 7%)
Late bacteriological response, per patient	49 (91%)/54	38 (79%)/48	12% (-4% to 27%)
Early bacteriological response, per urinary pathogen	61 (98%)/62	56 (98%)/57	0% (-5% to 5%)
Late bacteriological response, per urinary pathogen	55 (92%)/60	45 (82%)/55	10% (4% to 24%)



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Randomised trials at the level of the individual

Jay J H Park, Nathan Ford, Denis Xavier, Per Ashorn, Rebecca F Grais, Zulfiqar A Bhutta, Herman Goossens, Kristian Thorlund, Maria Eugenia Socias, Edward J Mills

Lancet Glob Health 2021;
9: e691–700

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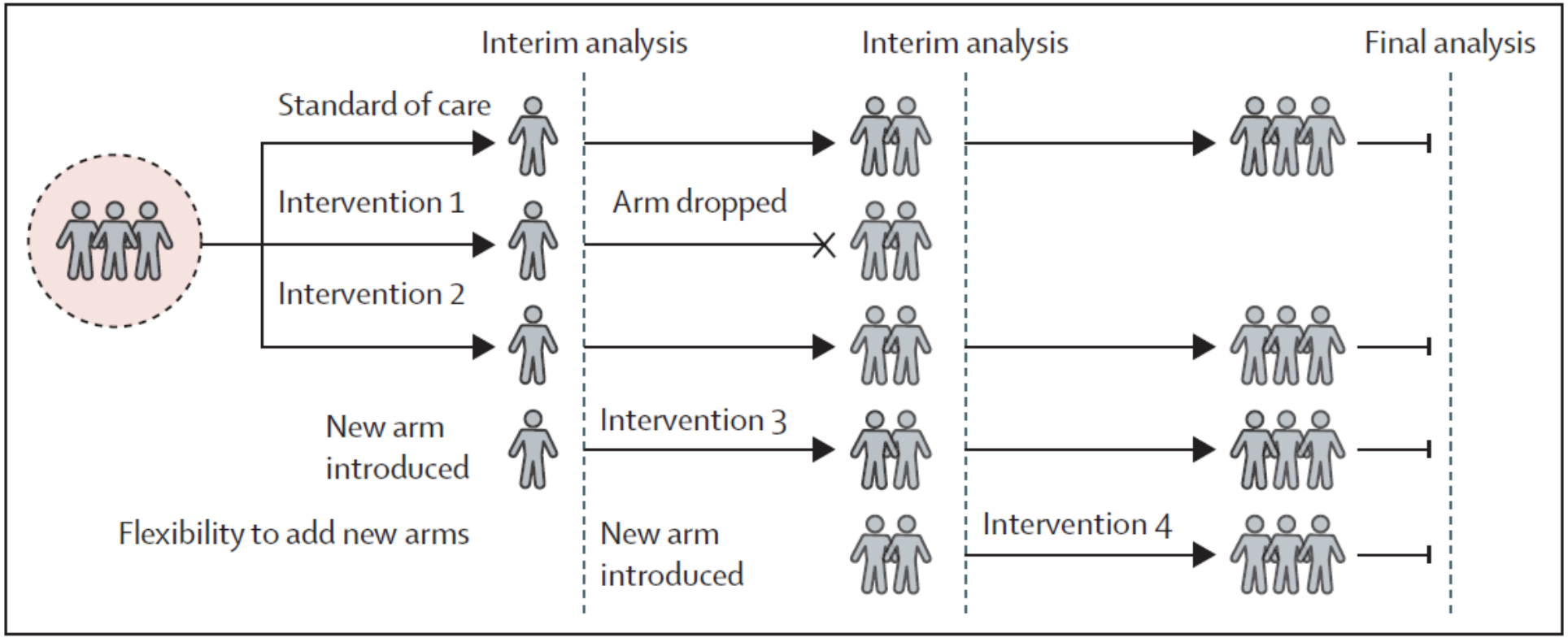
Platform trial



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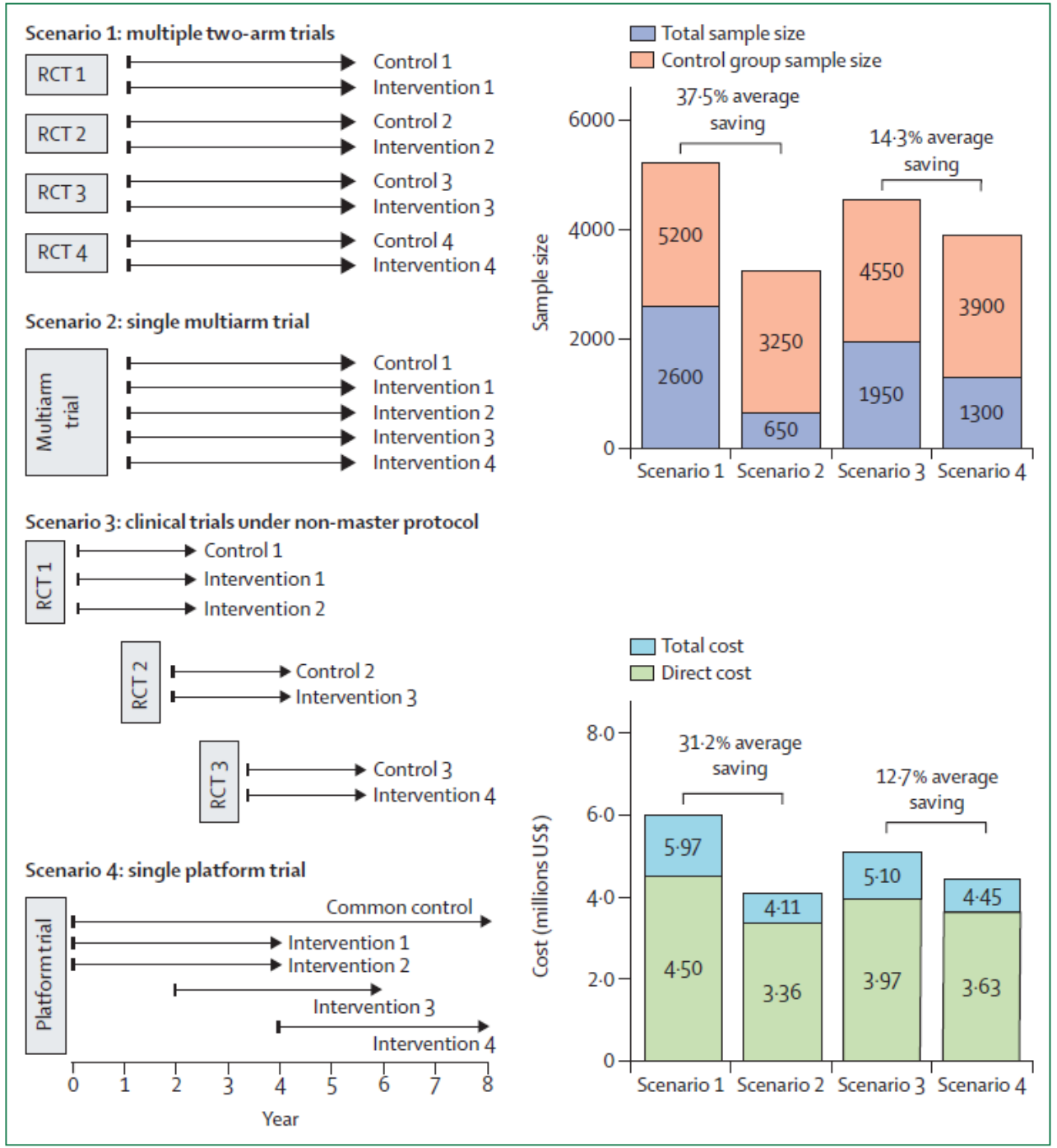
Randomised trials at the level of the individual

Jay J H Park, Nathan Ford, Denis Xavier, Per Ashorn, Rebecca F Grais, Zulfiqar A Bhutta, Herman Goossens, Kristian Thorlund, Maria Eugenia Socias, Edward J Mills

Lancet Glob Health 2021;
9: e691–700



Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)

Clinical Infectious Diseases® 2015;61(5):800–6

Scott R. Evans,[1] Daniel Rubin,[2] Dean Follmann,[3] Gene Pennello,[4] W. Charles Huskins,[5] John H. Powers,[6,7] David Schoenfeld,[8] Christy Chuang-Stein,[9] Sara E. Cosgrove,[10] Vance G. Fowler Jr,[11] Ebbing Lautenbach,[12] and Henry F. Chambers[13]

- Mortality
- Clinical cure
- Microbiological cure
- Recurrence/reinfection
- Length of stay, readmission
- Colonization/superinfection by multidrug-resistant organisms (MDRO)
- Adverse events (mild to severe)

→ Desirability of outcome ranking (DOOR)

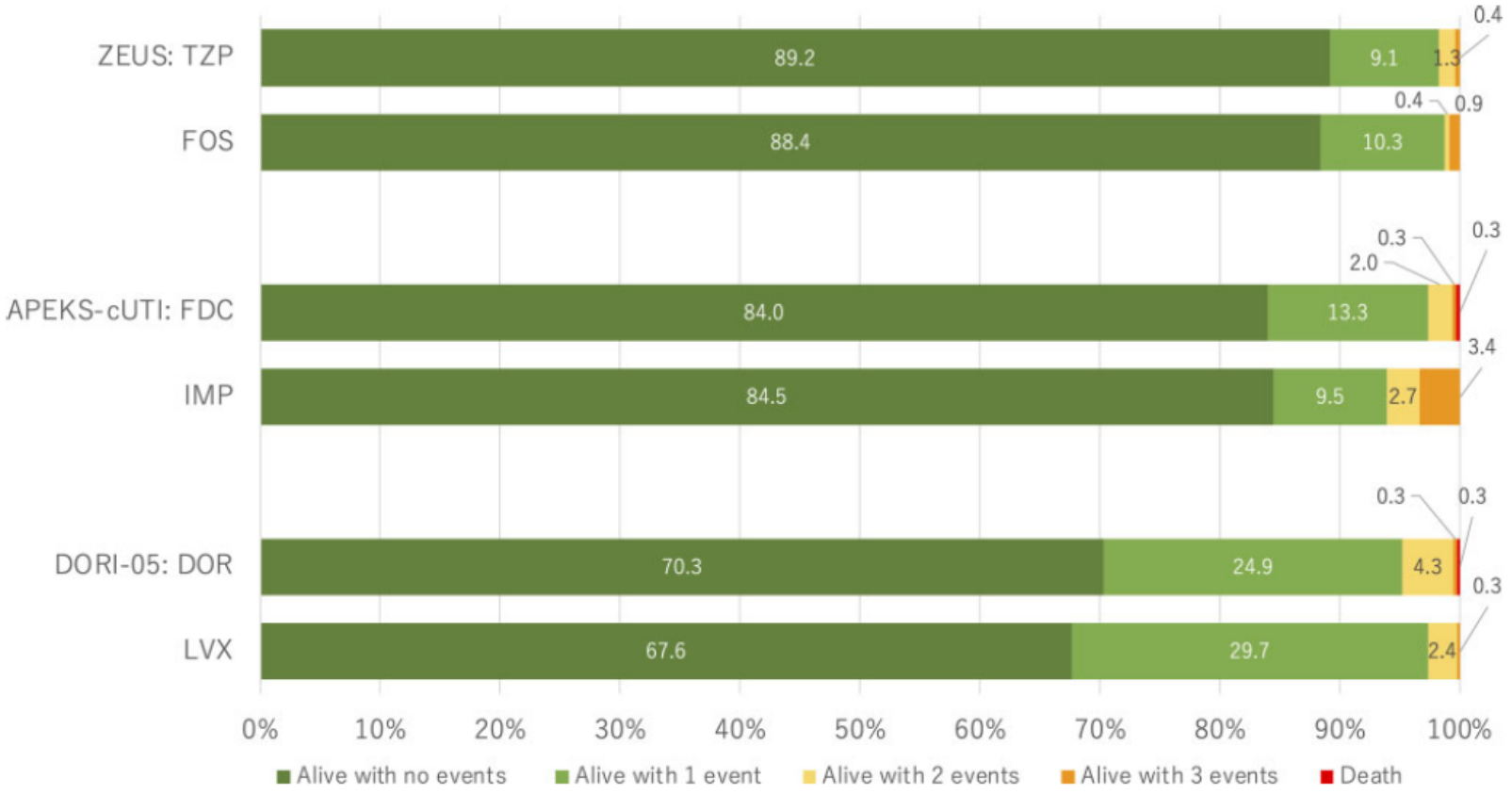
↓

Probability of having a better DOOR

Improving Traditional Registrational Trial End Points: Development and Application of a Desirability of Outcome Ranking End Point for Complicated Urinary Tract Infection Clinical Trials

Clin Infect Dis 2022

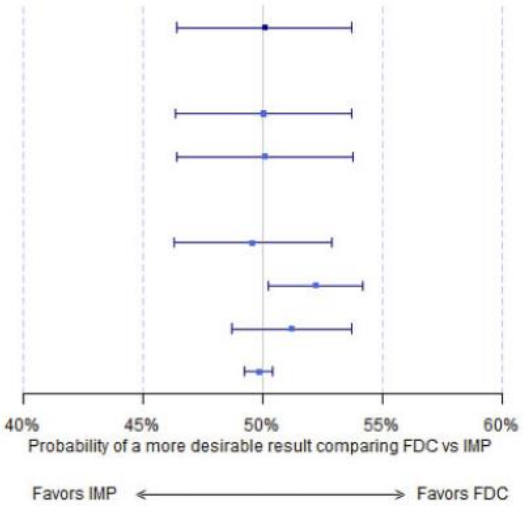
Jessica Howard-Anderson,[1] Toshimitsu Hamasaki,[2] Weixiao Dai,[2] Deborah Collyar,[3] Daniel Rubin,[4] Sumathi Nambiar,[5] Tori Kinamon,[4] Carol Hill,[6] Steven P. Gelone,[7] David Mariano,[7] Takamichi Baba,[8] Thomas L. Holland,[6,9] Sarah B. Doernberg,[10] Henry F. Chambers,[10] Vance G. Fowler Jr,[6,9] Scott R. Evans,[2] Helen W. Boucherand[11]; on behalf of the Antibacterial Resistance Leadership Group



Howard-Anderson et al, Clin Infect Dis 2022

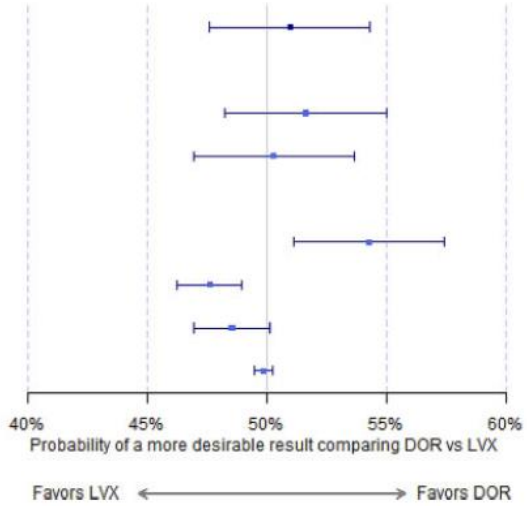
B APEKS-cUTI

	FDC (N = 300) n (%)	IMP (N = 148) n (%)	DOOR probability (95% CI)
DOOR			**50.1% (46.4%, 53.7%)**
Prioritized DOOR			
Prioritized Efficacy			50.0% (46.4%, 53.7%)
Prioritized Safety			50.1% (46.4%, 53.8%)
DOOR components			
Absence of clinical response	39 (13.0%)	18 (12.2%)	49.6% (46.3%, 52.9%)
Infectious complications	3 (1.0%)	8 (5.4%)	52.2% (50.2%, 54.2%)
SAE	15 (5.0%)	11 (7.4%)	51.2% (48.7%, 53.7%)
Death	1 (0.3%)	0 (0.0%)	49.8% (49.3%, 50.4%)



C DORI-05

	DOR (N = 374) n (%)	LVX (N = 374) n (%)	DOOR probability (95% CI)
DOOR			**51.0% (47.6%, 54.3%)**
Prioritized DOOR			
Prioritized Efficacy			51.6% (48.3%, 55.0%)
Prioritized Safety			50.3% (46.9%, 53.7%)
DOOR components			
Absence of clinical response	81 (21.7%)	113 (30.2%)	54.3% (51.1%, 57.4%)
Infectious complications	23 (6.1%)	5 (1.3%)	47.6% (46.2%, 49.0%)
SAE	25 (6.7%)	14 (3.7%)	48.5% (46.9%, 50.1%)
Death	1 (0.3%)	0 (0.0%)	49.9% (49.5%, 50.2%)



Personalised randomised controlled trial designs—a new paradigm to define optimal treatments for carbapenem-resistant infections

A Sarah Walker*, Ian R White*, Rebecca M Turner, Li Yang Hsu, Tsin Wen Yeo, Nicholas J White, Mike Sharland*, Guy E Thwaites*

Lancet Infect Dis 2021

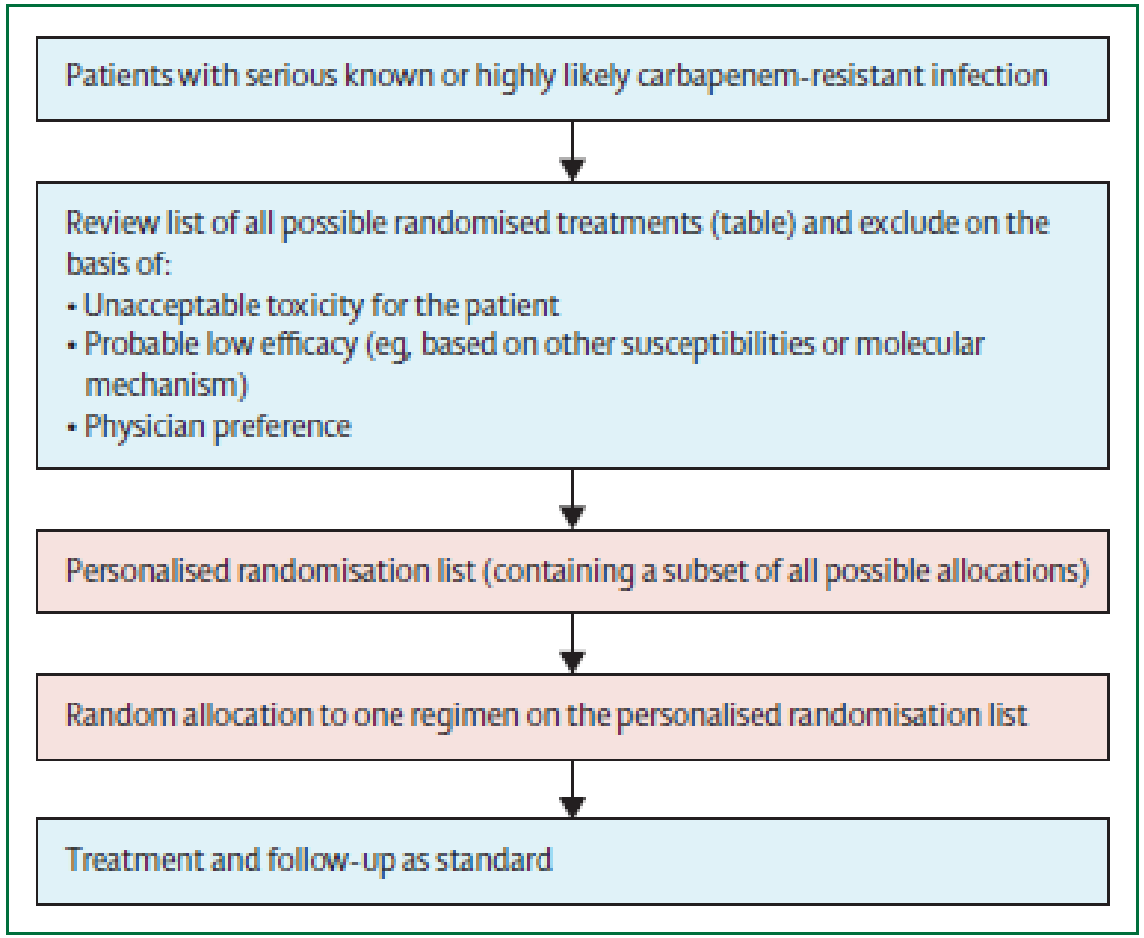


Figure 1: **Proposed flow diagram of participants through the trial**

	Patient 1: moderate renal impairment (creatinine clearance <40mL/min)	Patient 2: history of myocardial infarction	Patient 3: meropenem MIC ≥64	Patient 4: ventilator-acquired or hospital-acquired pneumonia	Patient 5: *Pseudomonas aeruginosa* infection	Patient 6: known class B (NDM, IMP, VIM) infection	Patient 7: presence of 6S ribosomal RNA methyltransferases (encoding aminoglycoside resistance)*	Patient 8: history of moderate to severe allergy to cephalosporins
A: plazomicin	No or maybe†	Yes	Yes	Yes	Yes	No	No	Yes
B: ceftazidime plus avibactam	No or maybe†	Yes	Yes	Yes	Yes	No	Yes	No
C: cefiderocol	Maybe†	Yes	Yes	Yes	Yes	Yes	Yes	No
D: high-dose meropenem‡	Maybe†	Yes	No	Yes	Yes	Yes	Yes	Yes
E: polymyxin B with or without zidovudine	No or maybe†	Yes	Yes	No	Yes	Yes	Yes	Yes
F: high-dose meropenem‡ plus ertapenem	Maybe†	Yes	No	Yes	No	Yes	Yes	Yes
G: high-dose meropenem‡ plus imipenem	No or Maybe†	Yes	No	Yes	Yes	Yes	Yes	Yes
H: high-dose meropenem‡ plus polymyxin B with or without zidovudine	No or maybe†	Yes	No	No	Yes	Yes	Yes	Yes
I: high-dose meropenem‡ plus high-dose tigecycline	Maybe†	No	No	Yes	No	Yes	Yes	Yes
J: high-dose meropenem‡ plus fosfomycin	Maybe†	Yes	No	Yes	Yes	Yes	Yes	Yes
K: high-dose tigecycline§ plus polymyxin B with or without zidovudine	No or maybe†	No	Yes	No	No	Yes	Yes	Yes
L: high-dose tigecycline§ plus fosfomycin	Maybe†	No	Yes	Yes	No	Yes	Yes	Yes
M: fosfomycin plus polymyxin B with or without zidovudine	No or maybe†	Yes	Yes	No	Yes	Yes	Yes	Yes

MIC=minimum inhibitory concentration. NDM=New Delhi metallo-β-lactamase. IMP=imipenemase. VIM=Verona integron metallo-β-lactamase. *Based on plausibility as assessed by high MIC.
†Dose adjustments required in patients with renal impairment, which might or might not be assessed as feasible in an individual patient; patient weight or surface area and creatinine are important variables, given their likely effect on drug exposure to the treatment outcome. ‡By use of continuous or prolonged infusion (>3 h); 2 g delivered every 8 h. §200 mg loading dose and 100 mg maintenance dose every 12 h.

Table: **Example of possible regimens for personalised randomised trial design**

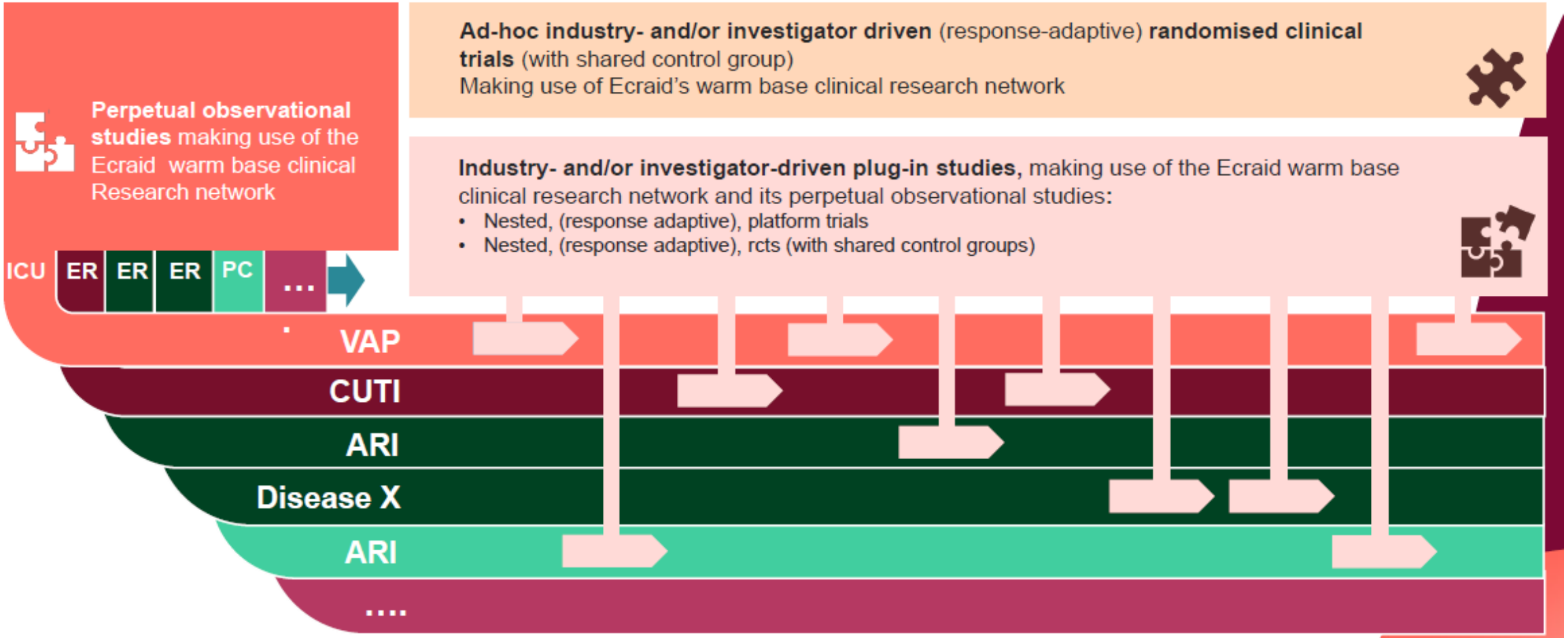
Walker SA et al. Lancet Infect Dis 2021

ecraid

Perpetual observational studies making use of the Ecraid warm base clinical Research network

Ad-hoc industry- and/or investigator driven (response-adaptive) **randomised clinical trials** (with shared control group)
Making use of Ecraid's warm base clinical research network

Industry- and/or investigator-driven plug-in studies, making use of the Ecraid warm base clinical research network and its perpetual observational studies:
- Nested, (response adaptive), platform trials
- Nested, (response adaptive), rcts (with shared control groups)



ICU = Intensive Care Unit
ER = Emergency Room
PC = Primary Care

VAP = Ventilator Associated Pneumonia
CUTI = Complicated Urinary tract Infections

ARI = Acute Respiratory Infections
ARBO = Arthropod-borne infectious diseases

= individual plug-in study making use of the POS

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POS-cUTI: OBJECTIVES

- Overarching objective
  - To build a sustainable European network to facilitate clinical studies in cUTI
- Strategical objectives
  - To evaluate best practices related to patient enrolment and data collection
  - To collect information supporting the design of innovative clinical trials
  - To align local practices in diagnosing and treating cUTI
- Scientific objectives
  - To describe the patient population with cUTI and the microbiological aetiology of cUTI
  - To delineate the outcomes of patients with cUTI (cure/failure, mortality, length of stay)
  - To identify the outcome predictors overall and in subgroups
  - To describe variations in current practices in treating cUTI in the study sites.

nb. POS : Perpetual Observational Study

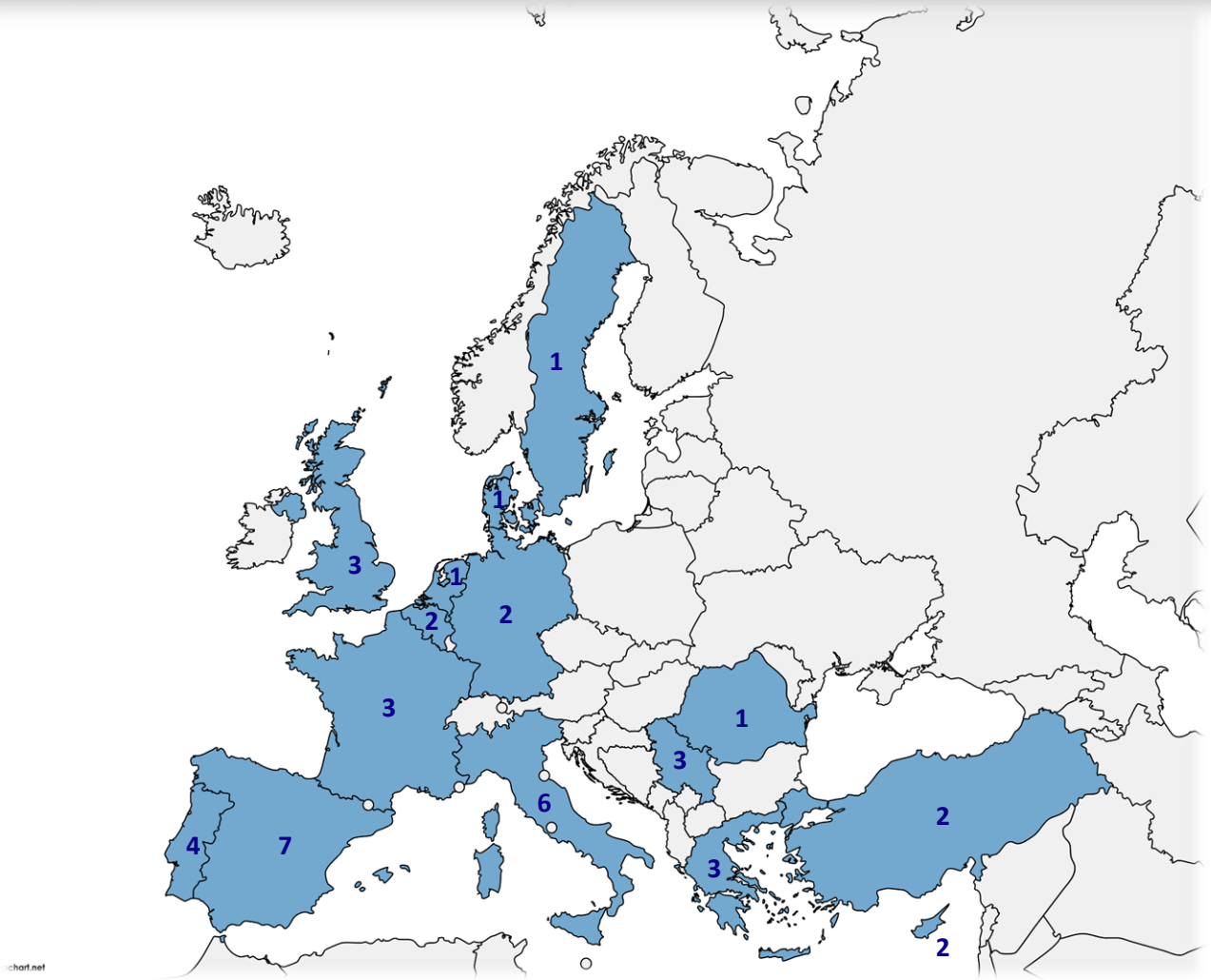
POS-cUTI

- High number of sites, recruiting 50-100 cUTI cases per year
- Observational, prospective cohort
- Informed consent
- Criteria, follow-up and data similar to RCT but simplified
- Quality monitoring
- Preservation of isolates depending on local resources

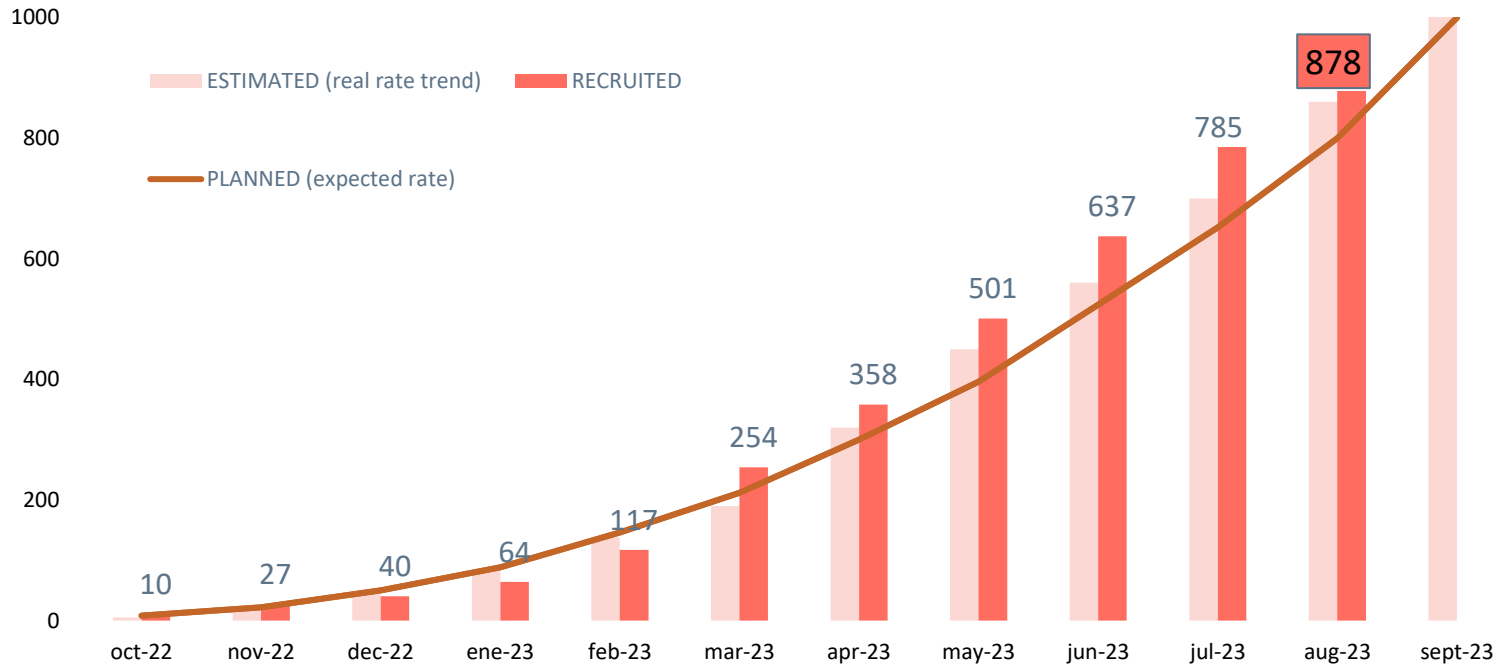
POS-cUTI: recruiting sites

Countries and number of sites:
(41 sites and 15 countries)

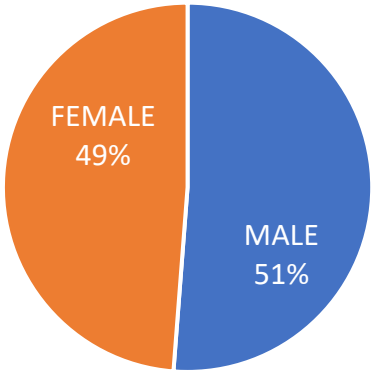
1. BELGIUM: 2
2. CYPRUS: 2
3. DENMARK: 1
4. FRANCE: 3
5. GERMANY: 2
6. GREECE: 3
7. ITALY: 6
8. THE NETHERLANDS: 1
9. PORTUGAL: 4
10. ROMANIA: 1
11. SERBIA: 3
12. SPAIN: 7
13. SWEDEN:1
14. TURKEY: 2
15. UK: 3

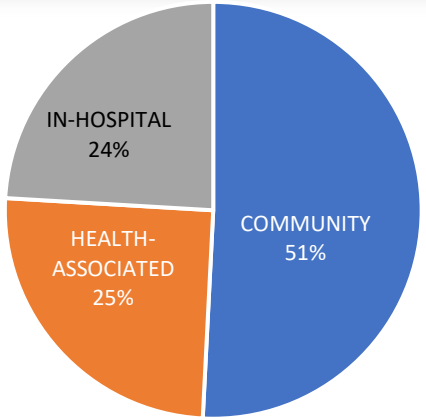


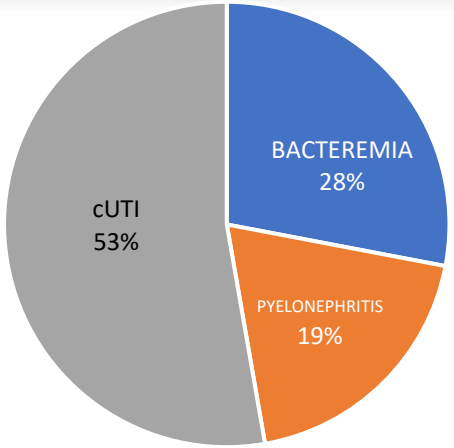
POS-cUTI: recruitment



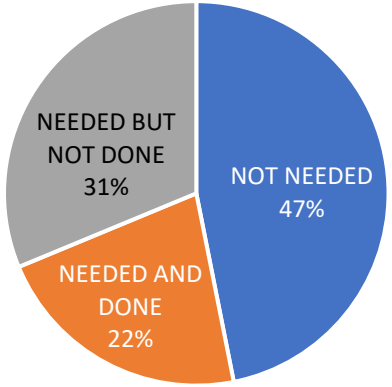
POS-cUTI: summary of data (June 2023, n=600)

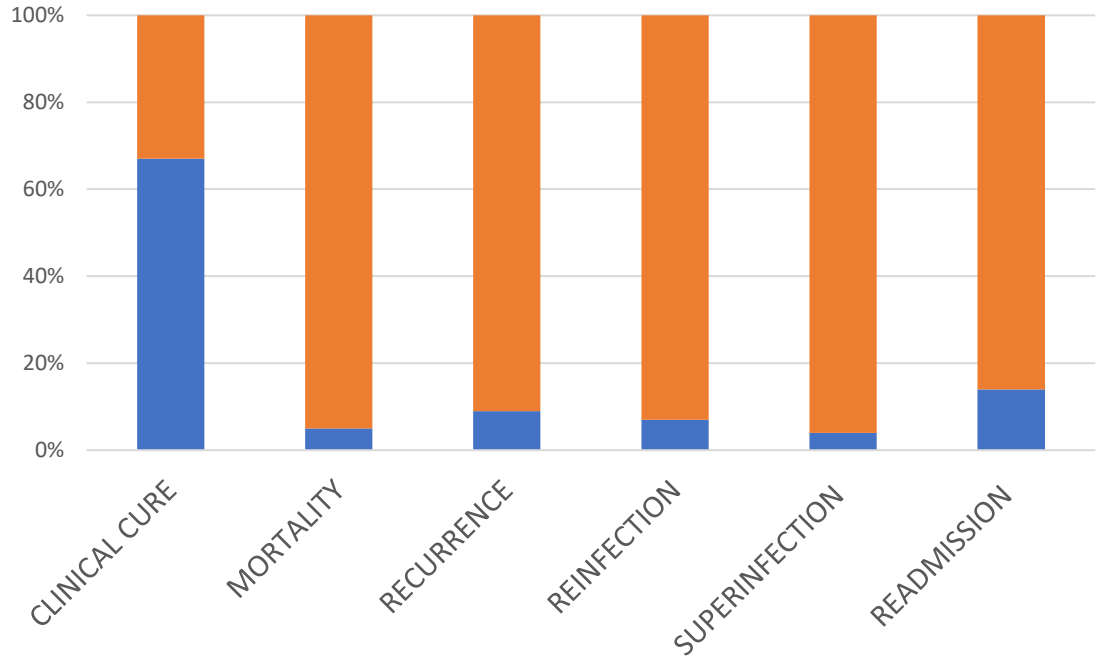




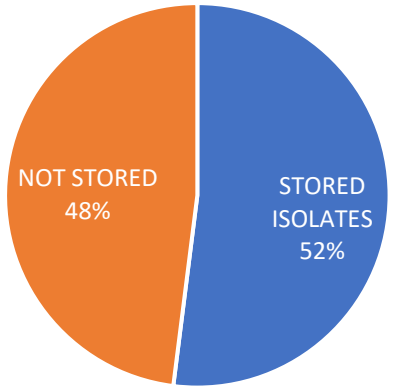


SOURCE CONTROL





MICROBIOLOGICAL SAMPLES



Conclusions

- Important medical questions in cUTI to be answered
- Innovative designs may allow
  - Higher efficiency (simple size, procedures, several questions)
  - Wider applicability of results
- ECRAID POS-cUTI may be instrumental for the design and development of innovative trials

Acknowledgments:

POS-cUTI team at HUVM

Jose Bravo
Almudena Serna
Elisa Moreno
Elena Rubio
Lydia Barrera
Francesco Cogliati
Inés Portillo
Pablo Martínez
Natalia Maldonado
Belén Gallego
Sandra de la Rosa
Virginia Palomo
Mercedes Delgado

Investigators from all sites!

ecraid network

Julia Bielicki

Julia Bielicki is a consultant in Paediatric Infectious Diseases and Infection Prevention and Control at the University of Basel Children's Hospital, and heads the hospital's Paediatric Research Centre, engaged in several large-scale national and international projects.

She is also a Reader and senior PI at the Centre for Neonatal and Paediatric Infection, St George's, University of London. Furthermore, Julia is the working group lead for severe bacterial infections and AMR at Penta and is involved in developing a national antimicrobial stewardship programme in Switzerland.

Julia's research focuses on observational and interventional studies to improve the use of antibiotics to treat neonates and children. She has a particular interest in 'best in class' antibiotic use and prescribing practices as well as innovative approaches to infection prevention and control in low-and-middle-income countries (LMICs) with high prevalence of multidrug-resistant bacteria. To date she has authored or co-authored over 100 papers and book chapters.

SNIP-AFRICA

SNIP-AFRICA

GARDP REVIVE Webinar

Planning for change: Severe Neonatal Infection Platform – AFRICA (SNIP-AFRICA)

Panellist

Julia A Bielicki

Scientific co-ordinator

St George's, University London

SNIP-AFRICA (Project No. 101103201) is supported by the Global Health EDCTP3 and its members (the European Union and the EDCTP Association).

Global Health EDCTP3

Penta Child Health Research

SNIP-AFRICA

How to interpret platform in the context of SNIP

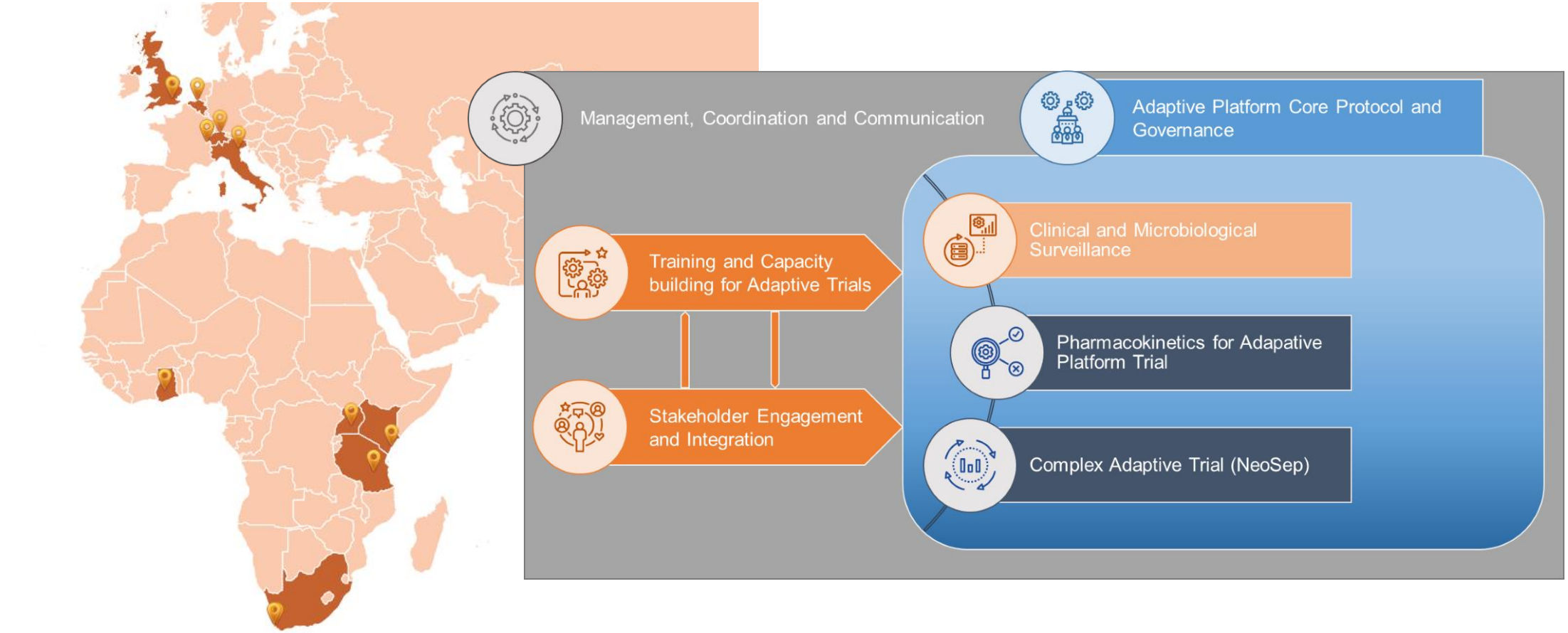
- Can test multiple primary questions within one core protocol with multiple associated domains governed by their protocols
- Combines opportunity of conducting gold-standard clinical trials (CTs) with adaptations to emerging evidence and agents of interest
- Is “planned to be flexible” but references an overarching patient population, disease or outcome assessment
- Can accommodate a range of innovative designs under a coherent governance structure

SNIP-AFRICA

SNIP-AFRICA objectives

Build	Build a sustainable architecture and governance structure
Implement	Implement an adaptive trial in the 'Extended Spectrum Beta-Lactamase (ESBL) drug-regimen' domain
Conduct	Conduct pharmacokinetic studies in the 'dose' domain
Survey	Survey neonatal sepsis epidemiology and management
Provide	Provide training on innovative CTs and neonatal sepsis
Engage	Engage with families, clinicians and regulators

SNIP-AFRICA consortium



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Clinical trials 1: PRECISION

Open label, single arm, opportunistic study to evaluate the pharmacokinetics and safety of colistin and colistin loading dose in neonates, infants, and children less than 2 years

- Co-development of Pharmacokinetics (PK) appendix for neonatal and infant antibiotic dose finding or confirmation
- Development of electronic case report forms (eCRFs) to facilitate standardised data collection
- Development of a template for pharmacometrics analysis plan

Clinical trials 2: NeoSep1 - SNIP

An open label randomised controlled trial comparing novel combination and currently used antibiotic regimens for the empiric treatment of neonatal sepsis

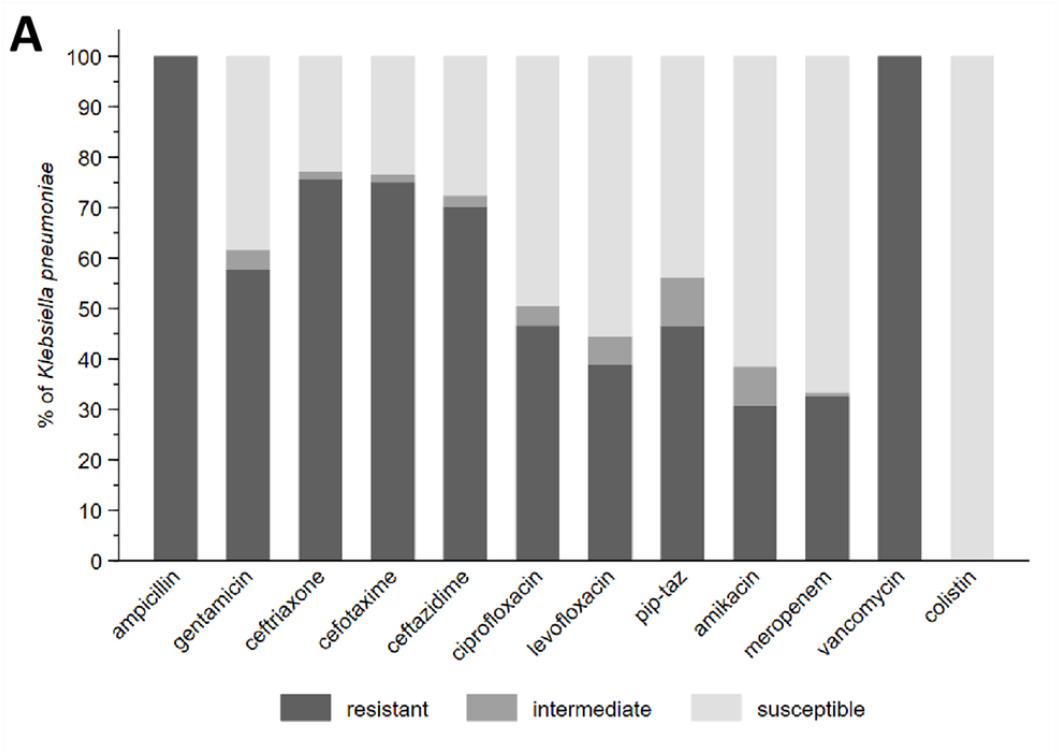
- Co-development of appendix for the ESBL drug regimen domain
- Development of eCRFs and web-enabled data collection

Why is NeoSep1 needed?

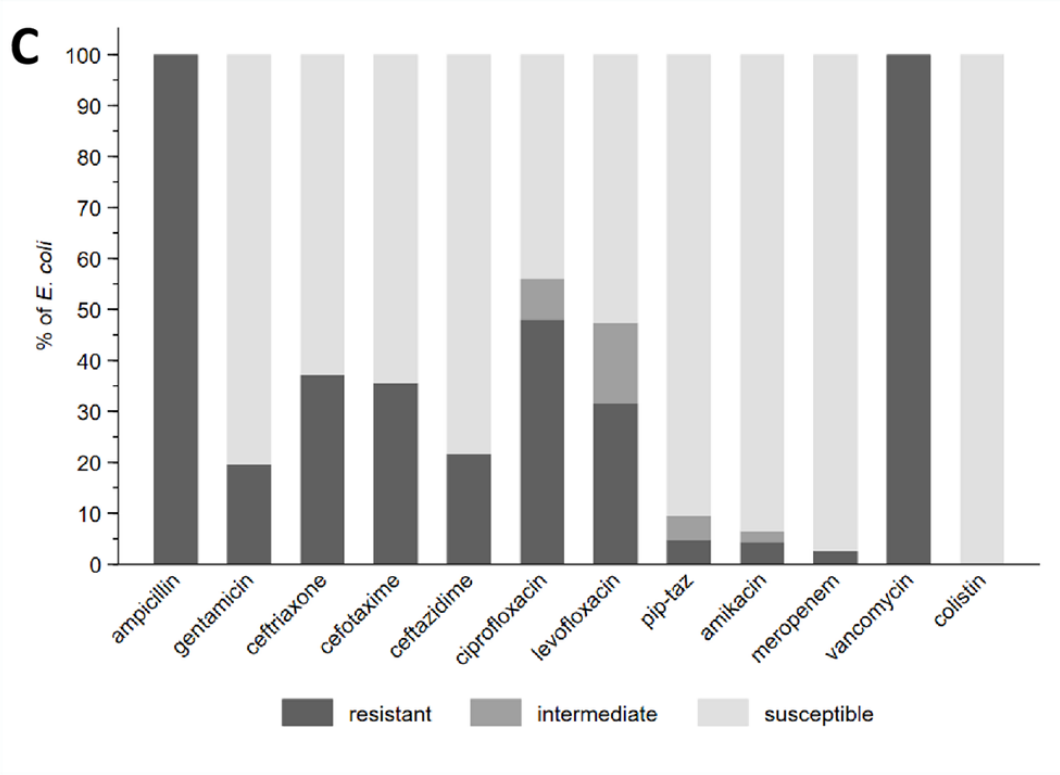
- Disproportionate burden of AMR in neonates
- Increasing antimicrobial resistance to WHO recommended therapy
- Estimated 214,000 neonatal sepsis deaths/year due to multidrug resistance (MDR) organisms
- *Enterobacterales* & extended spectrum beta-lactamases (ESBL) dominate

Findings from NeoOBS

Resistance among *K. pneumoniae*



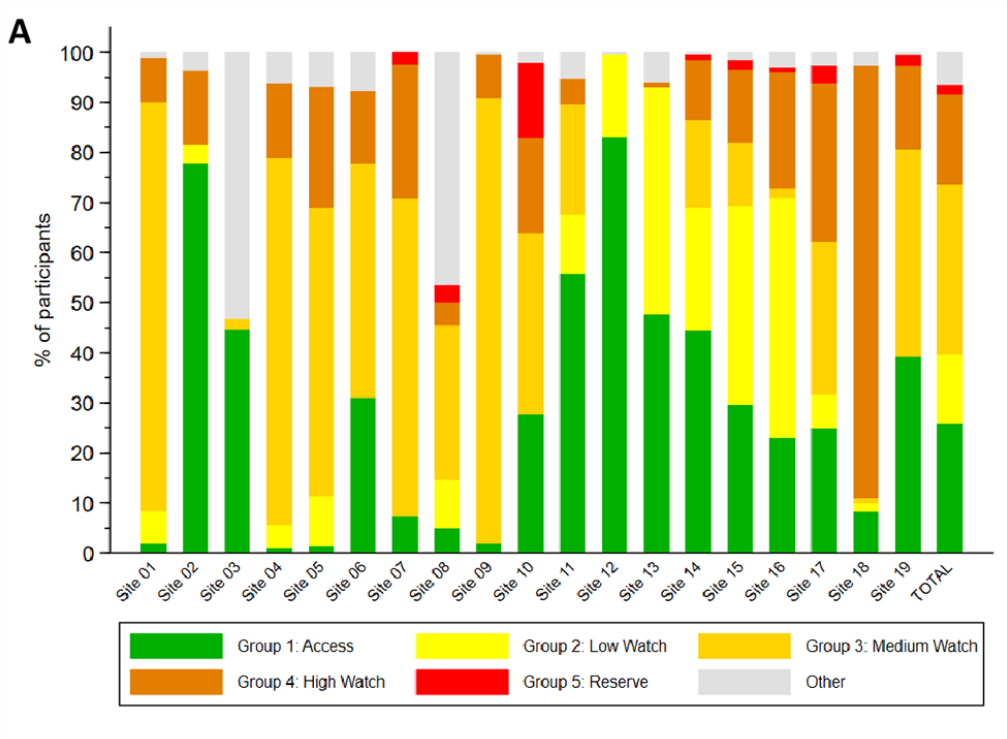
Resistance among *E. coli*



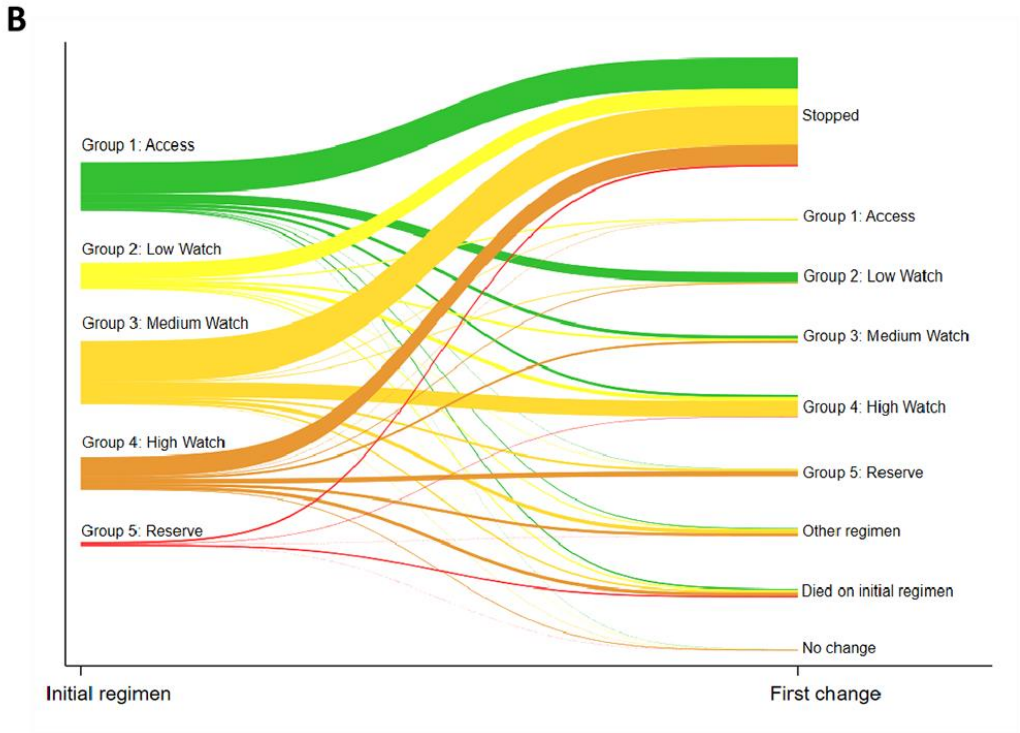
Russel, Stöhr, Bielicki et al. Plos Med. 2023

Findings from NeoOBS

Deviations from WHO guidance



Frequent escalation and switching



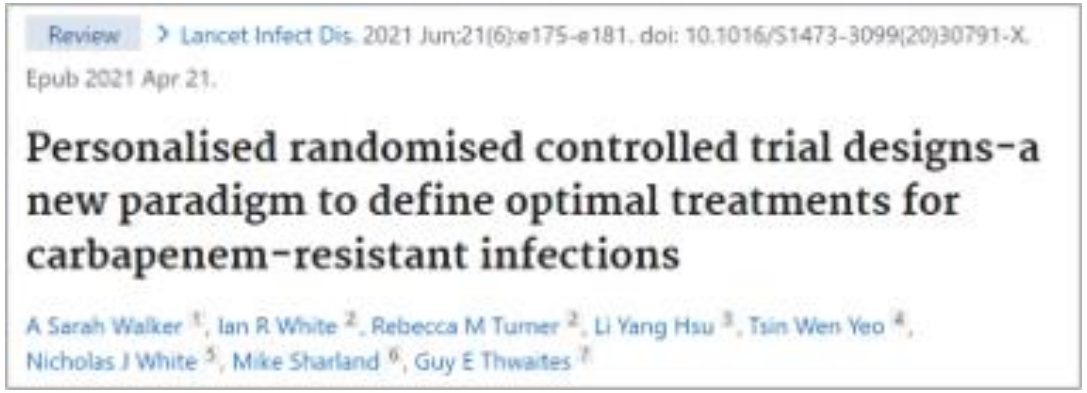
Russel, Stöhr, Bielicki et al. Plos Med. 2023

Challenges of NeoSep1

- Neonatal sepsis challenging to identify & define
- Multiple bacterial aetiologies & increasing AMR
- No single “accepted” standard of care
- Primary analysis as pairwise comparison with standard of care (SOC) inappropriate

PRACTical – NeoSep1

- Personalized selection of regimens + network meta-analysis approach
- Sequential Multiple Assignment Randomisation (SMART) design to allow escalation to second line randomised options
- Sites decide the range of acceptable 1st and 2nd line options
- NeoSep Severity Score to define high risk population & Recovery Score to define response

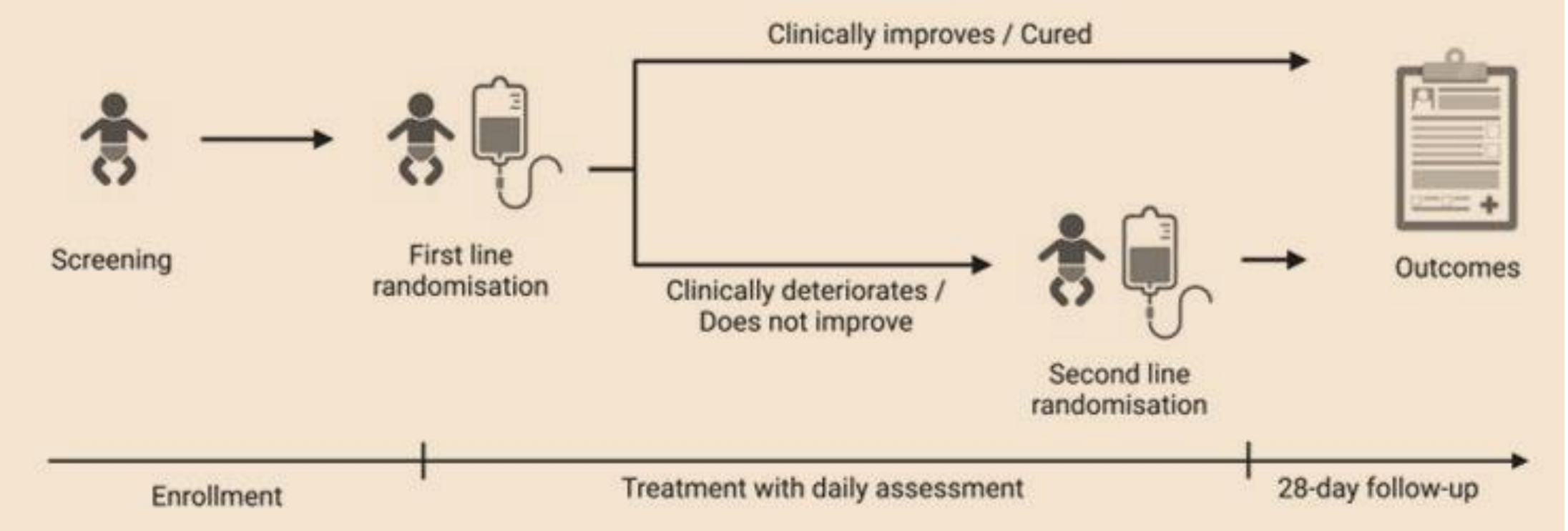


Review > Lancet Infect Dis. 2021 Jun;21(6):e175-e181. doi: 10.1016/S1473-3099(20)30791-X. Epub 2021 Apr 21.

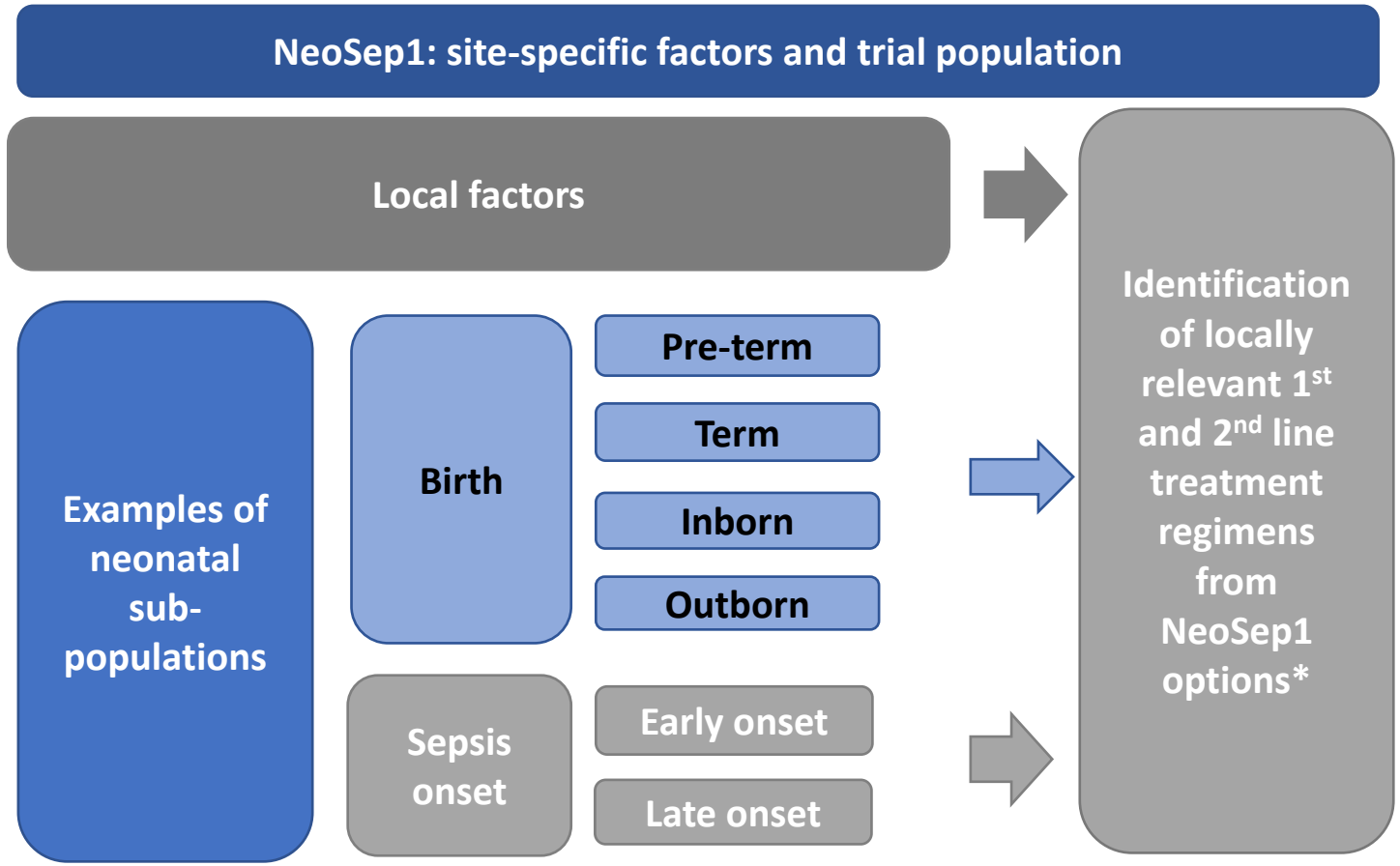
Personalised randomised controlled trial designs-a new paradigm to define optimal treatments for carbapenem-resistant infections

A Sarah Walker [1], Ian R White [2], Rebecca M Turner [2], Li Yang Hsu [3], Tsin Wen Yeo [4], Nicholas J White [5], Mike Sharland [6], Guy E Thwaites [7]

Trial schema NeoSep1



Example – adaptations in NeoSep1



*** Local protocols and practice, not centrally determined**

1st and 2nd randomisation options may include *any of the following regimens*

Treatment regimens options: 1st randomisation	Treatment regimens options: 2nd randomisation
Ampicillin + gentamicin*	Cefotaxime or ceftriaxone
Cefotaxime or ceftriaxone	Fosfomycin + amikacin
Fosfomycin + amikacin	Fosfomycin + flomoxef
Fosfomycin + flomoxef	Flomoxef + amikacin
Flomoxef + amikacin	Piperacillin-tazobactam
Piperacillin-tazobactam	Piperacillin-tazobactam + amikacin
Piperacillin-tazobactam + amikacin	Ceftazidime
Ceftazidime	Ceftazidime + amikacin
Ceftazidime + amikacin	Meropenem
Meropenem	Locally selected therapy

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NeoSep1

*ampicillin can be substituted for cloxacillin, benzylpenicillin or amoxicillin dependent on local penicillin policy/availability

Note: glycopeptides, metronidazole, antifungals and antivirals may be added to any regimen as deemed clinically necessary

WHO recommended regimens or broad spectrum antibiotics for neonatal use

Novel regimens

Locally selected therapy

1st and 2nd randomisation options may include *any of the following regimens*

Treatment regimens options: 1st randomisation	Treatment regimens options: 2nd randomisation
Ampicillin + gentamicin*	Cefotaxime or ceftriaxone
Cefotaxime or ceftriaxone	Fosfomycin + amikacin
Fosfomycin + amikacin	Fosfomycin + flomoxef
Fosfomycin + flomoxef	Flomoxef + amikacin
Flomoxef + amikacin	Piperacillin-tazobactam
Piperacillin-tazobactam	Piperacillin-tazobactam + amikacin
Piperacillin-tazobactam + amikacin	~~Ceftazidime~~
~~Ceftazidime~~	Ceftazidime + amikacin
Ceftazidime + amikacin	Meropenem
Meropenem	Locally selected therapy

SNIP-AFRICA

NeoSep1

*ampicillin can be substituted for cloxacillin, benzylpenicillin or amoxicillin dependent on local penicillin policy/availability

Note: glycopeptides, metronidazole, antifungals and antivirals may be added to any regimen as deemed clinically necessary

WHO recommended regimens or broad spectrum antibiotics for neonatal use

Novel regimens

Locally selected therapy

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NeoSep1

Treatment regimens options: 1st randomisation	Treatment regimens options: 2nd randomisation
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Cefotaxime or ceftriaxone	Fosfomycin + amikacin
Fosfomycin + amikacin	Fosfomycin + flomoxef
Fosfomycin + flomoxef	Flomoxef + amikacin
Flomoxef + amikacin	Piperacillin-tazobactam
Piperacillin-tazobactam	Piperacillin-tazobactam + amikacin
Piperacillin-tazobactam + amikacin	
	Ceftazidime + amikacin
Ceftazidime + amikacin	Meropenem
Meropenem	Locally selected therapy

*ampicillin can be substituted for cloxacillin, benzylpenicillin or amoxicillin dependent on local penicillin policy/availability

Note: glycopeptides, metronidazole, antifungals and antivirals may be added to any regimen as deemed clinically necessary

WHO recommended regimens or broad spectrum antibiotics for neonatal use

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NeoSep1

Treatment regimens options: 1st randomisation	Treatment regimens options: 2nd randomisation
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Cefotaxime or ceftriaxone	Fosfomycin + amikacin
Fosfomycin + amikacin	Fosfomycin + flomoxef
Fosfomycin + flomoxef	Flomoxef + amikacin
Flomoxef + amikacin	Piperacillin-tazobactam
Piperacillin-tazobactam	Piperacillin-tazobactam + amikacin
Piperacillin-tazobactam + amikacin	
	Ceftazidime + amikacin
Ceftazidime + amikacin	Meropenem
Meropenem	Locally selected therapy

*ampicillin can be substituted for cloxacillin, benzylpenicillin or amoxicillin dependent on local penicillin policy/availability

Note: glycopeptides, metronidazole, antifungals and antivirals may be added to any regimen as deemed clinically necessary

WHO recommended regimens or broad spectrum antibiotics for neonatal use

Novel regimens

Locally selected therapy

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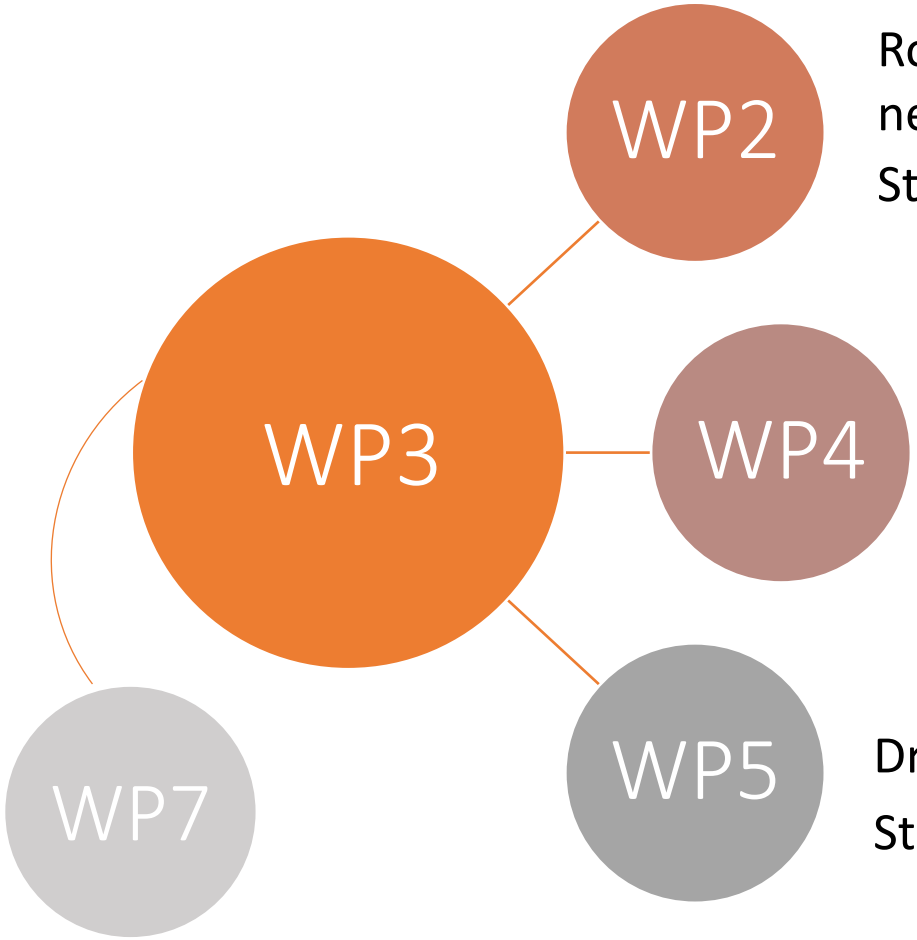
Platform structure - 1



Routine clinical screening and data capture protocol for suspected neonatal sepsis and blood culture (BC) isolates

Standardised approach to data collection and presentation

PK appendix for neonatal and infant dose finding and confirmation

Standardised approach to data collection and analysis

Drug-regimen in ESBL high-prevalence settings domain appendix

Standardised approach to data collection and analysis

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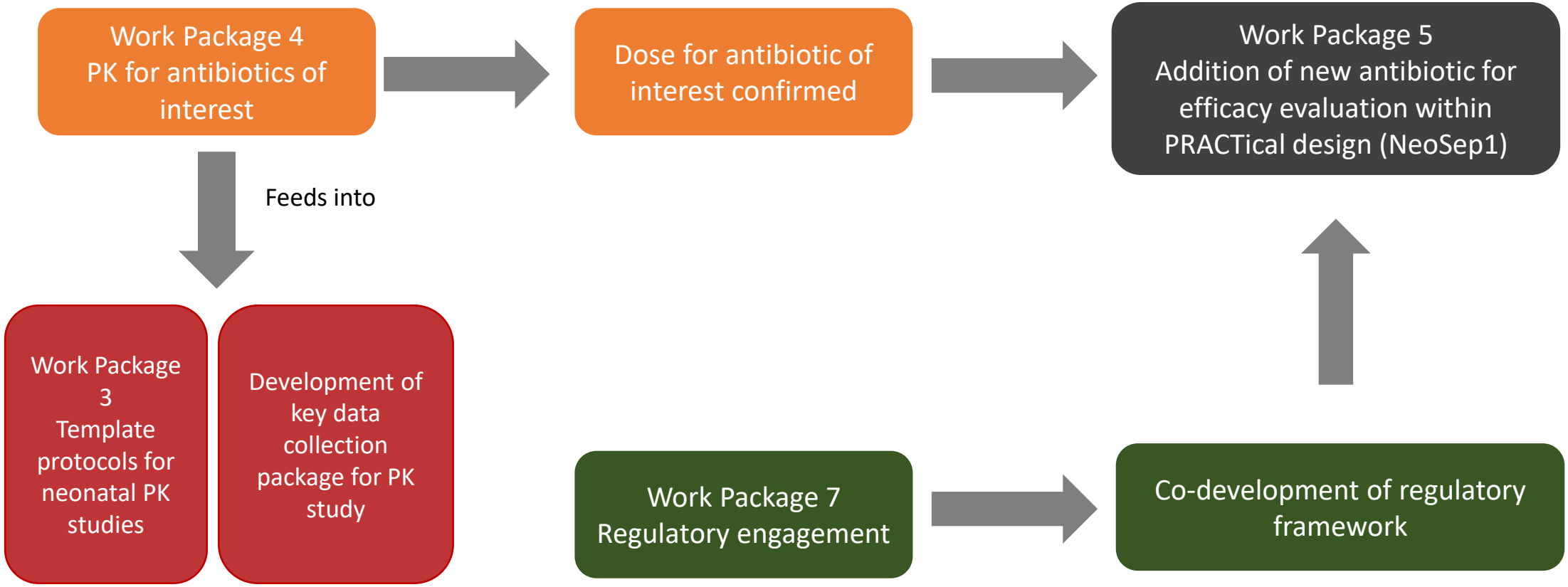
Work Package 4
PK for antibiotics of interest
Dose for antibiotic of interest confirmed
Work Package 5
Addition of new antibiotic for efficacy evaluation within PRACTical design (NeoSep1)
Feeds into
Work Package 3
Template protocols for neonatal PK studies
Development of key data collection package for PK study
Work Package 7
Regulatory engagement
Co-development of regulatory framework

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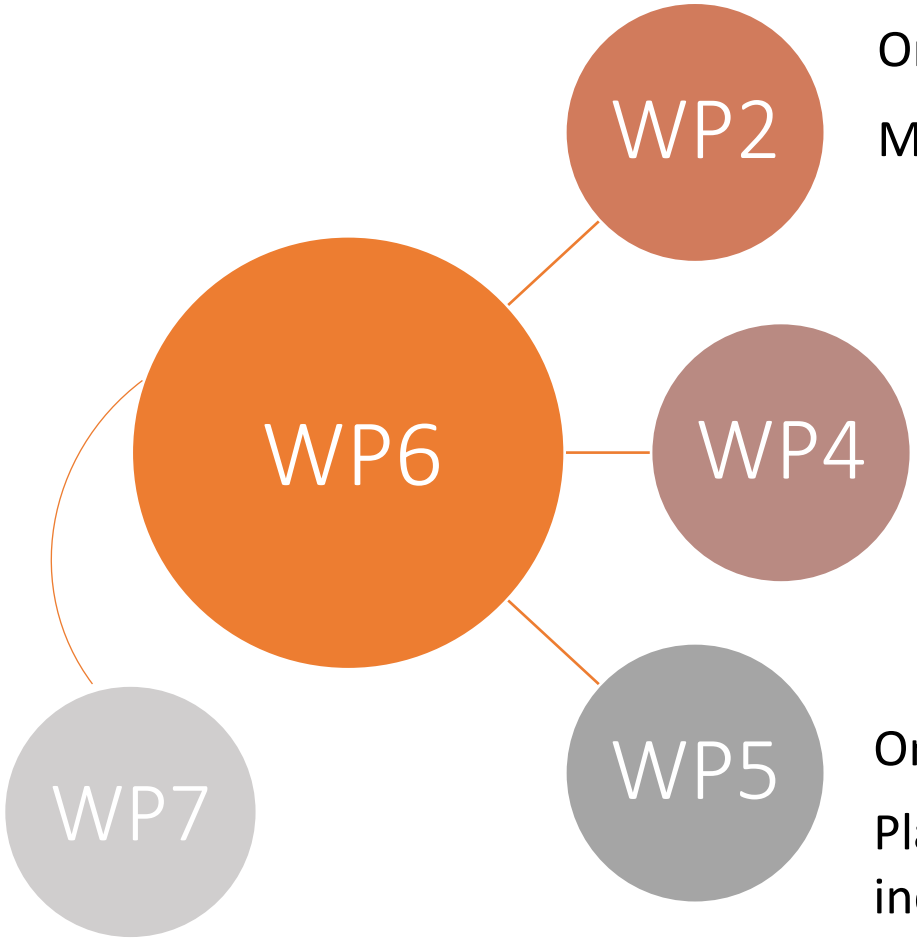
Platform structure - 2



Online training: Laboratory practice and workflow

Microbiological laboratory techniques (basic and advanced)

Online training: Pharmacometric modelling and simulation approaches

Pharmacokinetic assays and associated laboratory techniques

Online training: Methodology and implementation of CTs

Planning, implementation and management of trials, including data management (DM)

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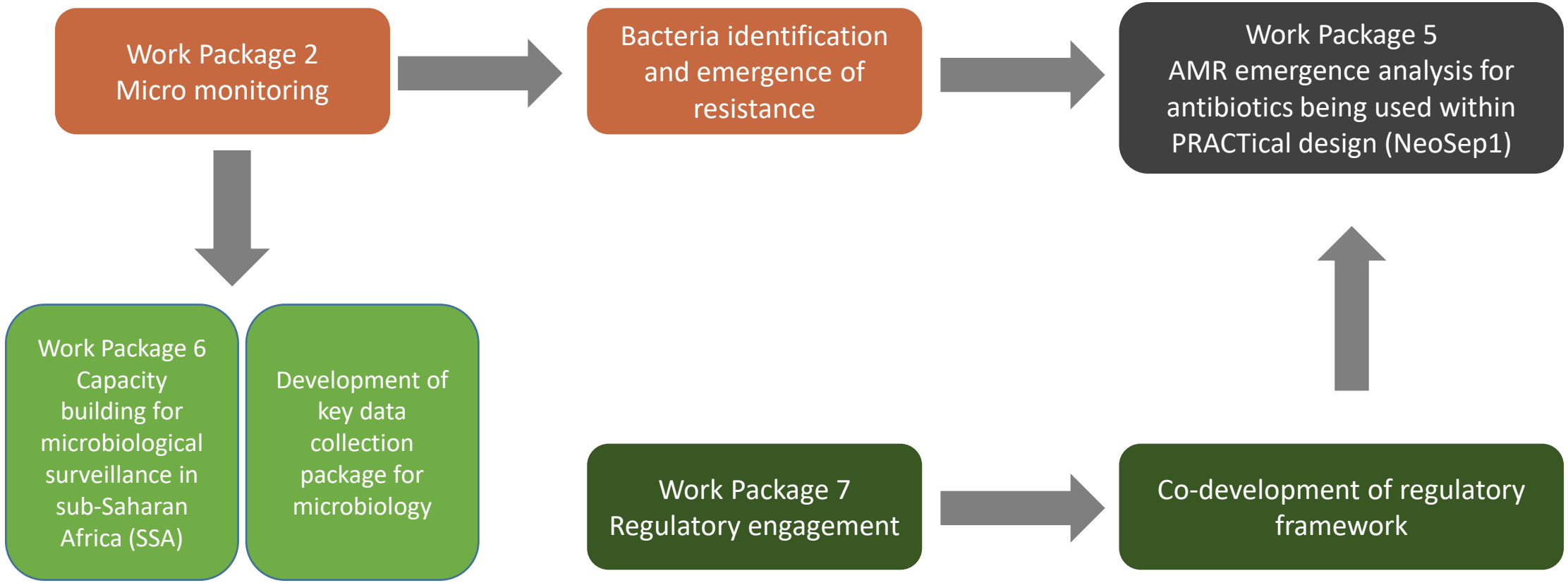
Work Package 2
Micro monitoring
Bacteria identification and emergence of resistance
Work Package 5
AMR emergence analysis for antibiotics being used within PRACTical design (NeoSep1)
Work Package 6
Capacity building for microbiological surveillance in sub-Saharan Africa (SSA)
Development of key data collection package for microbiology
Work Package 7
Regulatory engagement
Co-development of regulatory framework

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Promote African contributions to a global severe childhood infection trials platform, building on methods and approaches developed within the project

Consolidate advanced trial and associated expertise and capacity in the Consortium through South-North and South-South collaboration

Rapidly **generate** actionable evidence to improve antibiotic treatment of neonatal sepsis in Africa and ultimately reduce associated mortality and morbidity

Foster research innovation to address treatment of neonatal and, in the future, paediatric infections with epidemic potential in a timely way

Combine surveillance and pharmacokinetic studies, as well as basket, umbrella and adaptive elements to support efficient research implementation and evidence generation

Address multiple domains of neonatal sepsis antimicrobial treatment to maximise the chances of identifying effective and ineffective approaches, including targeted to infant and setting factors

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THANK YOU

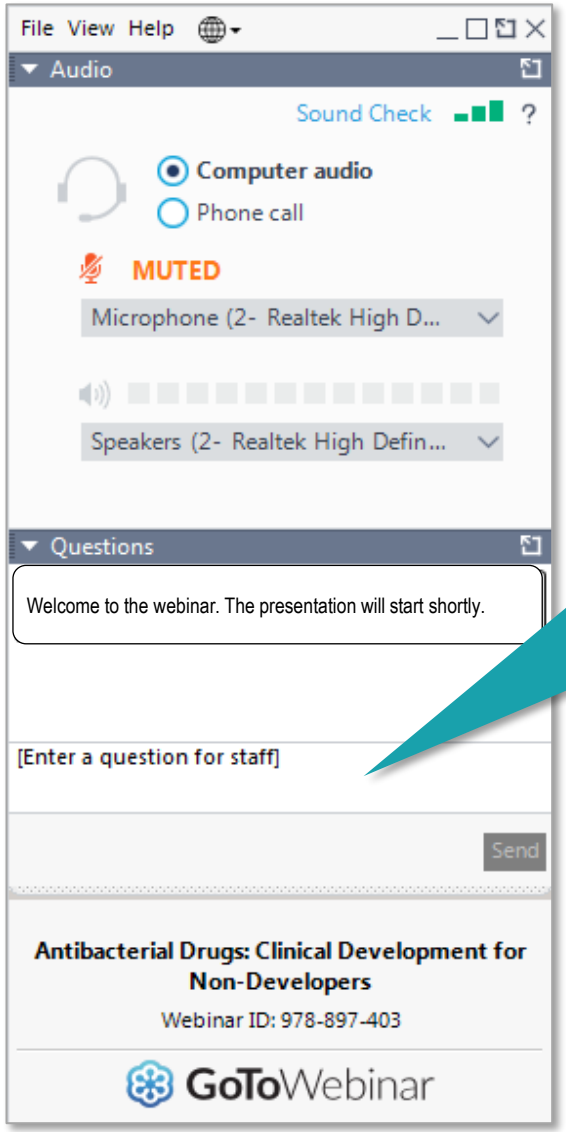
SNIP-AFRICA (Project No. 101103201) is supported by the Global Health EDCTP3 and its members (the European Union and the EDCTP Association).

Global Health EDCTP3

Penta Child Health Research

How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.



The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

Today’s speakers

Clinical trial platforms for new and neglected antimicrobials

Jesús Rodríguez-Baño
Professor of medicine,
University of Seville (Spain)
&
Infectious Diseases division,
Hospital Universitario Virgen Macarena (Spain)

Julia Bielicki
Senior consultant in paediatric infectious diseases,
University of Basel Children’s Hospital (Switzerland)
&
Reader in paediatric infectious diseases,
St George’s, University of London (UK)

Moderator:
Marc Bonten
Professor of molecular epidemiology of infectious diseases,
University Medical Centre Utrecht (The Netherlands)

Join us for our next webinars!

Wednesday 27 September 2023, 14:00-15:00 CEST

Antibiotic shortages: causes, consequences, and solutions

Speakers : Esmita Charani, Jennifer Cohn, Kopano Klaas & Chaitanya Koduri

Thursday 12 October 2023, 14:00-15:00 CEST

AMR Discussion webinar:
Market interventions to improve access to antibiotics for resistant infections

Speakers :

- Procurement interventions: Brenda Waning (GDF)
- Market intelligence, sharing and coordination: Wesley Kreft (i+Solutions)
- Financial instruments: Hema Srinivasan (MedAccess)
- Exploring how economic and procurement tools can improve access to antibiotics in LMICs: Kim Faure (SECURE)

Registration links and more information soon available on:
revive.gardp.org/webinars

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- On Twitter and LinkedIn

Thank you for joining us