Combination antibiotic therapy against drug-resistant Gram-negative bacteria: where the evidence stands

Guest speaker: Evelina Tacconelli

Moderator: Gavin Barlow

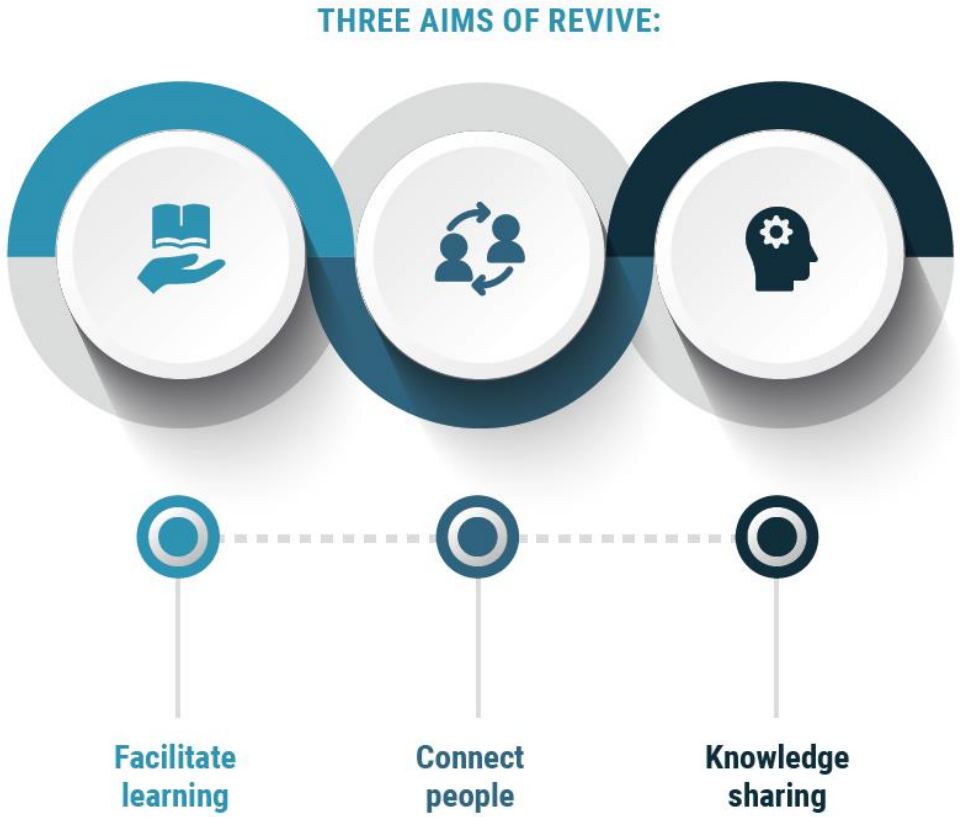
Host: Victor Kouassi (GARDP)

8 September 2021

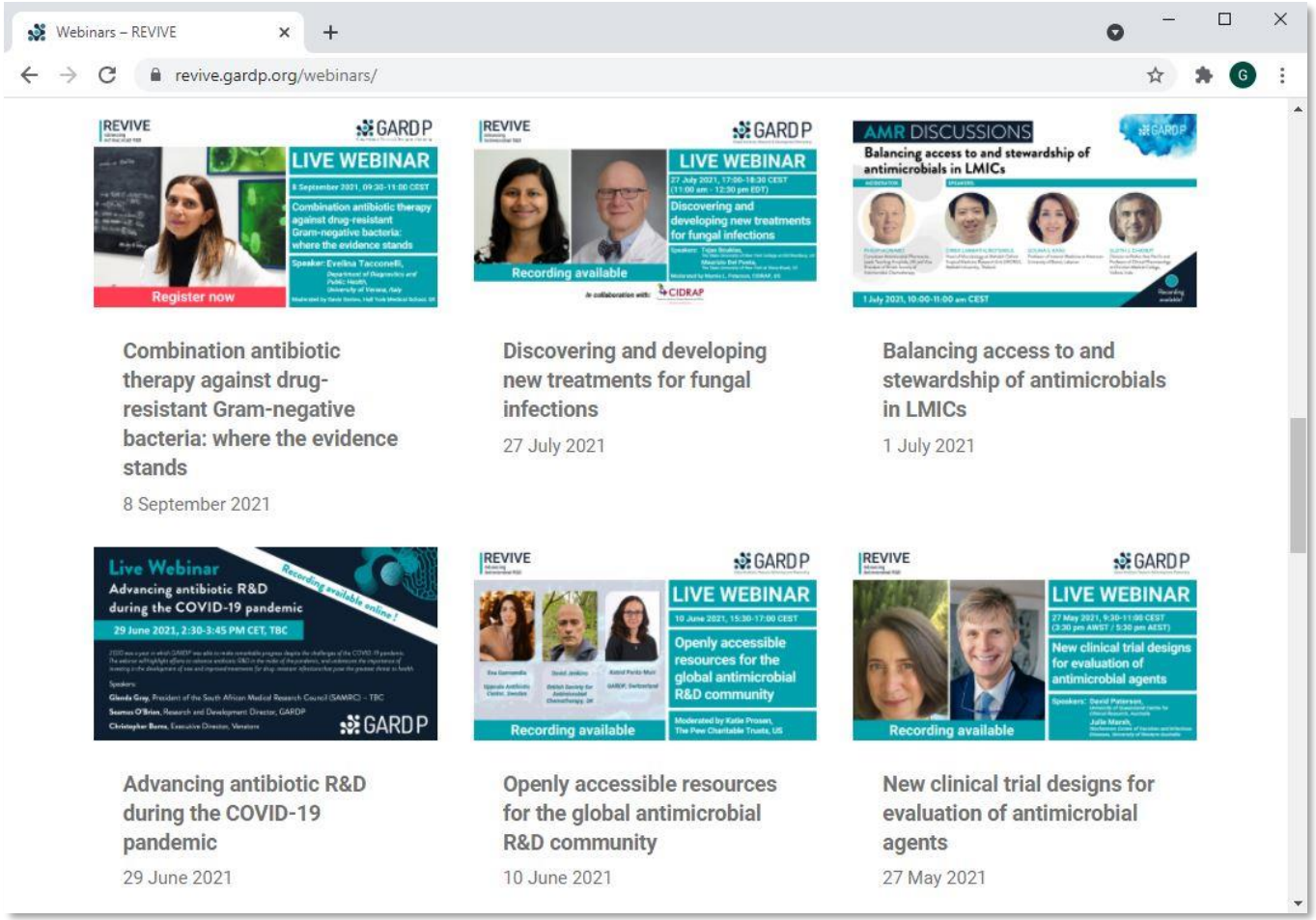
GARDP
Global Antibiotic Research & Development Partnership

REVIVE

An online space to connect and support the antimicrobial discovery, research, and development community

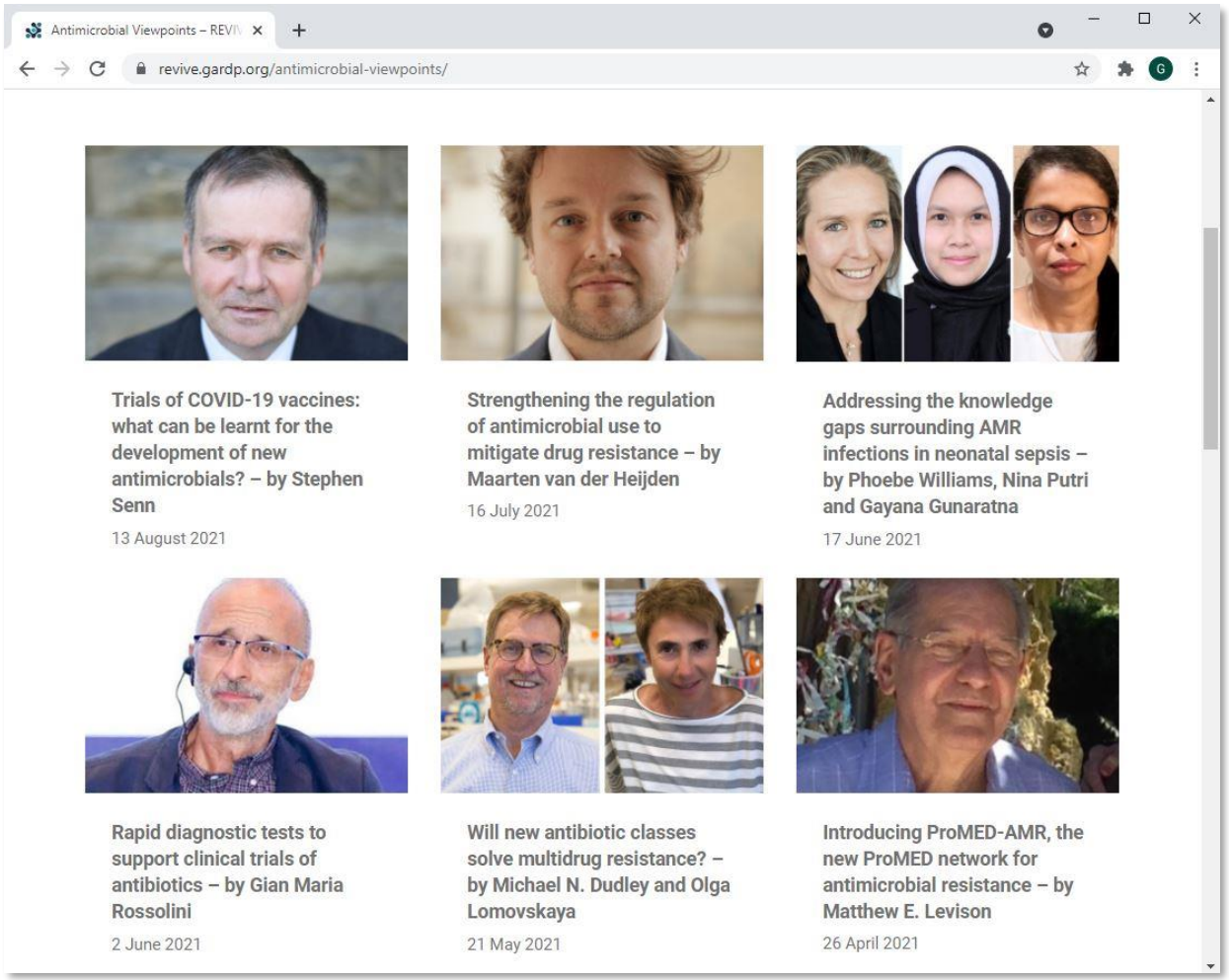


Webinar recordings



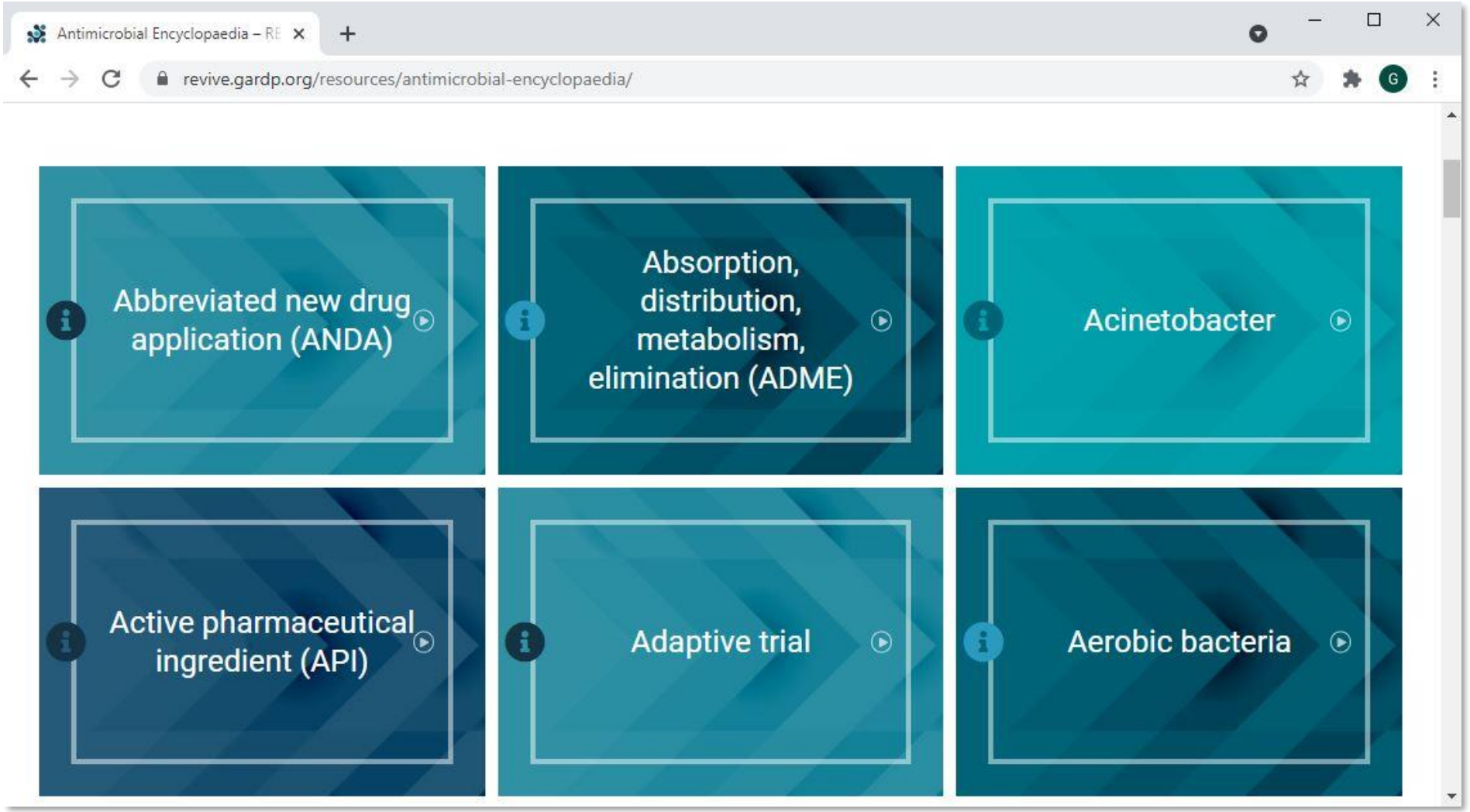
revive.gardp.org/webinars

Antimicrobial Viewpoints



revive.gardp.org/antimicrobial-viewpoints

Antimicrobial Encyclopaedia



revive.gardp.org/resources/antimicrobial-encyclopaedia

Today’s speakers

Combination antibiotic therapy against drug-resistant Gram-negative bacteria: where the evidence stands

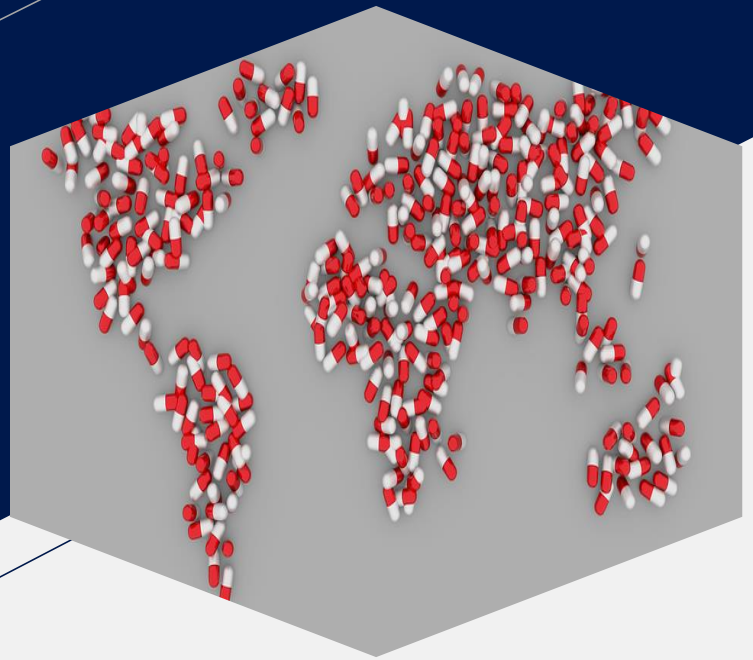
Evelina Tacconelli
Director of the Infectious Diseases Unit
Verona University Hospital (Italy)

Moderator:
Gavin Barlow
Senior Clinical Lecturer in Infection
Hull York Medical School (UK)

Evelina Tacconelli

Evelina Tacconelli is Director of the Infectious Diseases Section at Verona University Hospital, Italy, and lecturer for Antimicrobial Resistance at the University of Tübingen, Germany.

Evelina coordinated the WHO priority list of antibiotic resistant bacteria for the research and development of new effective antibiotics as well as the WHO project on limitations of estimates of the burden of antibiotic resistant infections within the GLASS (Global Surveillance of Resistant Severe Infections) project. She is Chair of the European Committee for Infection Control (EUCIC), and a WHO and ECDC consultant for infection control and antimicrobial stewardship. Evelina has a wealth of experience in the participation and coordination of European projects and networks focused on antimicrobial resistance.



Combination antibiotic therapy against drug-resistant Gram-negative bacteria: where the evidence stands

Evelina Tacconelli

ID-CARE (Infectious Diseases Center for trAnslational Research)

University of Verona, Italy

DZIF Research Clinical Unit - Translational Unit on Healthcare-associated and Antibiotic-resistant Bacterial Infections

Tübingen University, Germany

Declaration of interest (DOI)

2016-2021

- Horizon 2020
- German Center Infectious Diseases Research (DZIF)
- Innovative Medicine Inititiative (IMI)
- Joint Programming Initiatives on Antimicrobial Resistance (JPIAMR)
- WHO
- GARDP
- ESCMID

Preliminary Considerations

Definition of combination

- Treatment with >1 antibiotic

Target Drugs

- Colistin – Fosfomicin - Tigecycline – Carbapenems - Aminoglycosides
- Ceftazidime-avibactam
- Meropenem-vaborbactam
- Imipenem-cilastatin-relebactam
- Aztreonam-avibactam - Ceftolozane-tazobactam - Cefiderocol

Guidance documents or reviews not pharma-funded

- IDSA, CID 2021 - BSAC / HIS / BIAWP, JAC 2018 - PIN, JAC 2020
- ESCMID, 2021

GARDP-COHERENCE project

Empiric therapy

Molecular characterization of resistance

ESCMID Guidelines for the treatment of infections caused by MDR-GNB
Paul, Tacconelli, Rodriguez Baño and the ESCMID MDR-GL Experts Panel *Coming soon*

ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Target bacteria

Priority for R&D of new, effective antibiotics

Panel: WHO priority list for research and development of new antibiotics for antibiotic-resistant bacteria

Multidrug-resistant and extensively-resistant *Mycobacterium tuberculosis*[25]

Other priority bacteria

Priority 1: critical
- *Acinetobacter baumannii*, carbapenem resistant
- *Pseudomonas aeruginosa*, carbapenem resistant
- Enterobacteriaceae, carbapenem resistant, third-generation cephalosporin resistant

Priority 2: high
- *Enterococcus faecium*, vancomycin resistant
- *Staphylococcus aureus*, methicillin resistant, vancomycin resistant
- *Helicobacter pylori*, clarithromycin resistant
- *Campylobacter* spp, fluoroquinolone resistant
- *Salmonella* spp fluoroquinolone resistant
- *Neisseria gonorrhoeae*, third-generation cephalosporin resistant, fluoroquinolone resistant

Priority 3: medium
- *Streptococcus pneumoniae*, penicillin non-susceptible
- *Haemophilus influenzae*, ampicillin resistant
- *Shigella* spp, fluoroquinolone resistant

FIGURE 1

Tacconelli, Lancet Infect Dis 2017

Road map

- Short introduction
- Real-life prescription habits
- In vitro evidence
- Clinical evidence
- Experts´ opinion
- Final considerations

Antibiotic prescribing is *per se* a complex action

Patient

- Symptoms
- Source of infection
- Comorbidities
- Risk for future infections

Bacteria

- Sensitivity pattern
- Risk of relapse
- Risk of development of new resistance

Drug

- Penetration
- Side effects
- Selection of resistance
- Mono vs combi

Society

- Ward colonisation pressure
- Risk of resistance in community

Increasing resistance to new released antibiotics

COMBACTE-MAGNET EPI-Net Central Data Repository (last update Nov 2020) and PubMed search (12.07.2021)

Antibiotic	In vitro Resistance Overall number of publications (Publications from Industry driven surveillance)**	In vivo Resistance Overall number of publications (Publications from Industry funded study / projects)
Ceftaroline	12 (5, last data from 2018)	1 (--)
Ceftazidime-avibactam*	46 (5, last data from 2018)	74 (--)
Ceftolozane-tazobactam	34 (2, last data from 2018)	58 (--)
Meropenem-vaborbactam	5 (--)	7 (--)

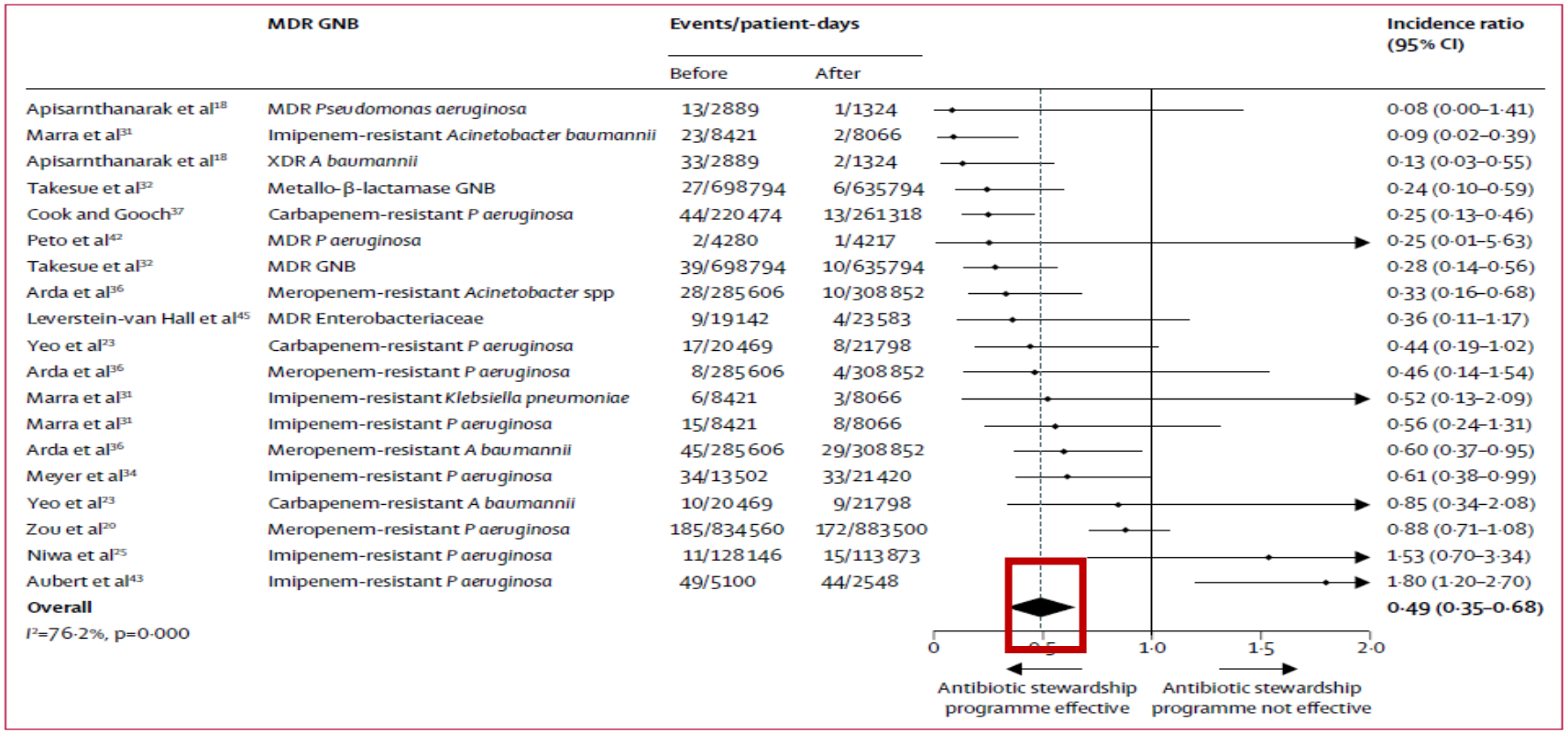
*one outbreak reported

** ATLAS, SMART, SIDERO-WT

Source: https://epi-net.eu/

Antibiotic stewardship (ATBS)
Evidence: 32 studies; 9 056 241 patient-days; 159 estimates of IRs

ATBS intervention was associated with a reduction of incidence of MDR-GNB by 51% (IR 0·49, 95% CI 0·35–0·68; p<0·0001)



	MDR GNB	Events/patient-days		Incidence ratio (95% CI)
		Before	After	
Apisarnthanarak et al[18]	MDR *Pseudomonas aeruginosa*	13/2889	1/1324	0·08 (0·00–1·41)
Marra et al[31]	Imipenem-resistant *Acinetobacter baumannii*	23/8421	2/8066	0·09 (0·02–0·39)
Apisarnthanarak et al[18]	XDR *A baumannii*	33/2889	2/1324	0·13 (0·03–0·55)
Takesue et al[32]	Metallo-β-lactamase GNB	27/698794	6/635794	0·24 (0·10–0·59)
Cook and Gooch[37]	Carbapenem-resistant *P aeruginosa*	44/220474	13/261318	0·25 (0·13–0·46)
Peto et al[42]	MDR *P aeruginosa*	2/4280	1/4217	0·25 (0·01–5·63)
Takesue et al[32]	MDR GNB	39/698794	10/635794	0·28 (0·14–0·56)
Arda et al[36]	Meropenem-resistant *Acinetobacter* spp	28/285606	10/308852	0·33 (0·16–0·68)
Leverstein-van Hall et al[45]	MDR Enterobacteriaceae	9/19142	4/23583	0·36 (0·11–1·17)
Yeo et al[23]	Carbapenem-resistant *P aeruginosa*	17/20469	8/21798	0·44 (0·19–1·02)
Arda et al[36]	Meropenem-resistant *P aeruginosa*	8/285606	4/308852	0·46 (0·14–1·54)
Marra et al[31]	Imipenem-resistant *Klebsiella pneumoniae*	6/8421	3/8066	0·52 (0·13–2·09)
Marra et al[31]	Imipenem-resistant *P aeruginosa*	15/8421	8/8066	0·56 (0·24–1·31)
Arda et al[36]	Meropenem-resistant *A baumannii*	45/285606	29/308852	0·60 (0·37–0·95)
Meyer et al[34]	Imipenem-resistant *P aeruginosa*	34/13502	33/21420	0·61 (0·38–0·99)
Yeo et al[23]	Carbapenem-resistant *A baumannii*	10/20469	9/21798	0·85 (0·34–2·08)
Zou et al[20]	Meropenem-resistant *P aeruginosa*	185/834560	172/883500	0·88 (0·71–1·08)
Niwa et al[25]	Imipenem-resistant *P aeruginosa*	11/128146	15/113873	1·53 (0·70–3·34)
Aubert et al[43]	Imipenem-resistant *P aeruginosa*	49/5100	44/2548	1·80 (1·20–2·70)
Overall				**0·49 (0·35–0·68)**
I^2=76·2%, p=0·000				

Figure 2: **Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of MDR GNB**
GNB=Gram-negative bacteria. MDR=multidrug-resistant. XDR=extensively drug-resistant.

The reduction in the incidence of the MDR GNB was also confirmed in the subgroup of studies focusing on carbapenem resistance (43%; 0·57, 0·40–0·81; p=0·0018)

Baur & Tacconelli Lancet Infect Dis 2017

1956

PRINCIPLES AND PROBLEMS OF COMBINED ANTIBIOTIC THERAPY

By Stephen D. Elek, M.D., Ph.D., D.P.H.
St. George's Hospital Medical School

Conclusions

The indiscriminate use of 'shot-gun therapy' is undesirable. Many of the newer antibiotics have pharmacological properties which restrict their usefulness. These have to be weighed against the possible advantages which may accrue from their use in combinations. The fuller understanding of the way in which antibiotics help to bring about a cure indicates that combinations should not be given blindly in the hope that it will deal with any microbic infection. Combinations should be reserved for particular problems, in which they are capable of achieving results unobtainable by single drugs. This, however, requires not only the identification of the infecting organism, but also careful laboratory tests which can forecast the usefulness or otherwise of various combinations.

Pediatrics, June 1958

SPECIAL ARTICLE

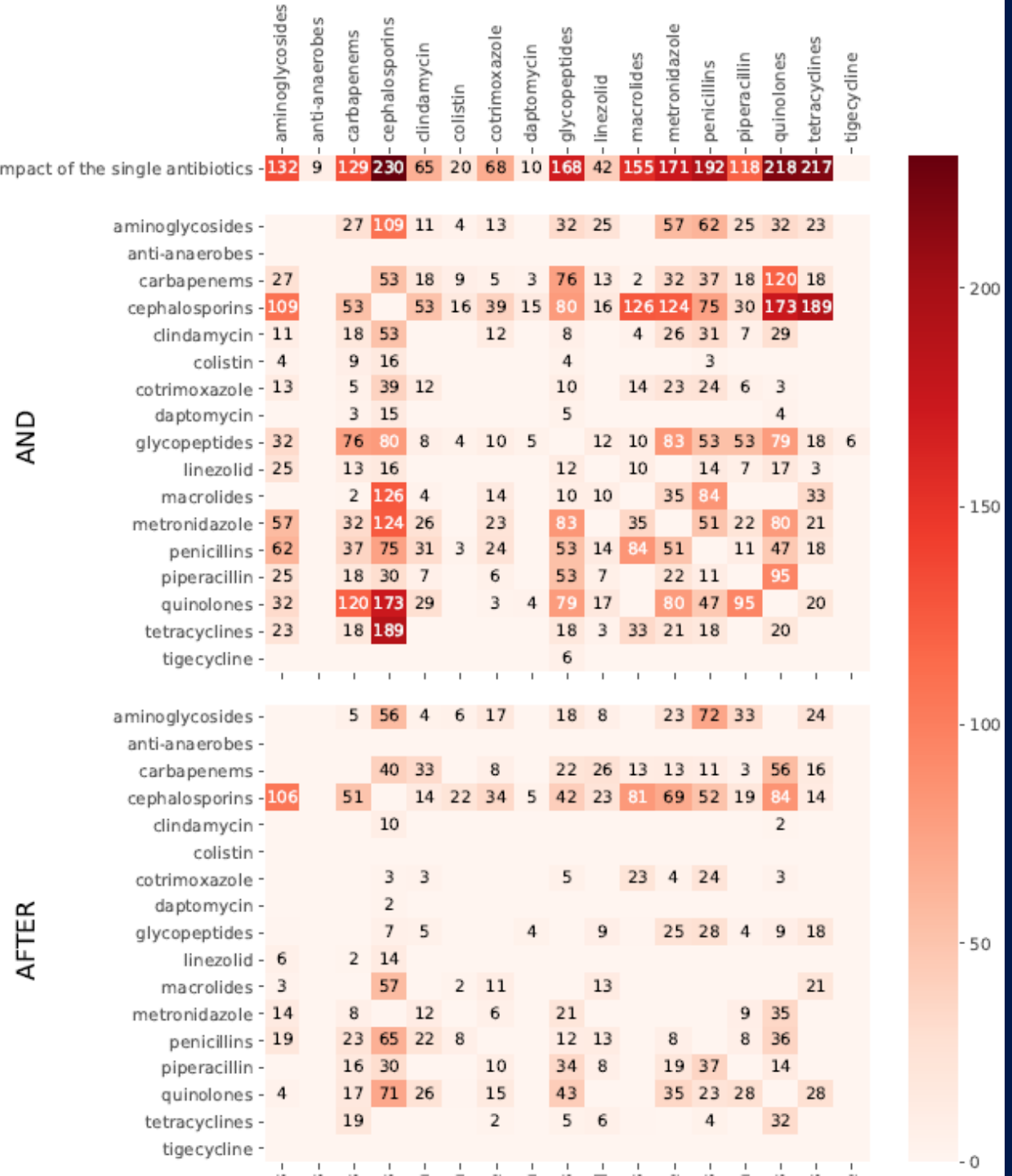
CURRENT STATUS OF COMBINED ANTIBIOTIC THERAPY

By Charles V. Pryles, M.D.
Department of Pediatrics, Boston University School of Medicine, and the Pediatric Service, Boston City Hospital

.. many physicians are using uncritically and without analysis, antimicrobials in varying combinations.

In view, therefore, of the increasing trend toward the use and misuse of antibiotic agents in combinations, it appears appropriate to review the problem and to examine critically the attendant benefits and dangers that may accrue from the use of combined antimicrobials.

1. **Broaden the Spectrum**
2. **Delay the Emergence of Bacteria Resistant**
3. **May Be Synergistic**



Machine learning applied to antibiotic therapy
Tacconelli, CMI 2019

10,034 patients

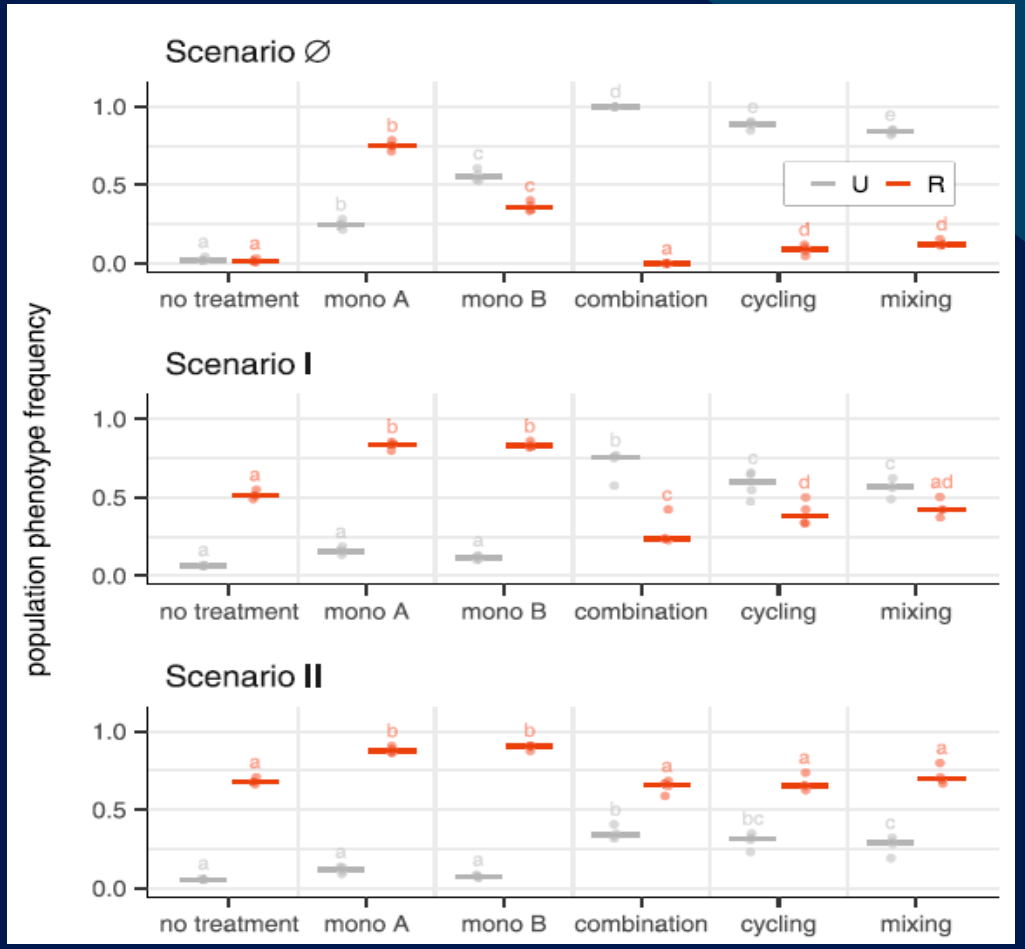
22.345 days antibiotic theray

28,322 rectal swab samples

- The impact of an antibiotic on new intestinal colonisation with ESBL GN varied depending on whether used as mono or combi and on previous antibiotic exposure
  1. Cephalosporin monotherapy in patients who had not received antibiotics within 72 hours
  2. Tetracycline monotherapy
  3. Penicillins monotherapy

Comparing treatment strategies to reduce antibiotic resistance in an in vitro epidemiological setting

- To assess multidrug treatment strategies *in vitro* using a robotic liquid handling platform.
- The framework was used to study resistance evolution and spread implementing epidemiological population dynamics for treatment, transmission, and patient admission and discharge.
- The authors performed massively parallel experimental evolution over up to 40 days and complemented it with a computational model to infer the underlying population-dynamical parameters.
- Combination therapy outperforms monotherapies, as well as cycling and mixing, in minimizing resistance evolution and maximizing uninfecteds, as long as there is no influx of double resistance into the focal treated community.



Angst, PNAS 2021

COHERENCE

COmbination t**HER**apy to treat sepsis due to carbapenem-resistant Gram negative bacteria in adult and pediatric population

Evide**NCE** and common practice

GARDP
Global Antibiotic Research & Development Partnership

Laura Piddock
Francoise Franceschi
Sally Ellis

UNIVERSITÀ di VERONA

Elda Righi
Alessia Savoldi
Elena Carrara
Evelina Tacconelli
Margherita Chiamenti
Damiano Bragantini
Paolo Cattaneo
Dario Menghin
Gloria Pellizzari
Gabriel Levi Hara

Kamilia Abdelraouf
Maurizio Sanguinetti - Giulia Menchinelli
Christian Giske
Mike Sharland
Thomas Lodise
Johan Mouton
Luigia Scudeller - Chiara Rebuffi

COHERENCE

OBJECTIVES

- To comprehensively summarize the evidence on the available antibiotic options for the treatment of sepsis sustained by CR-GNB (*Acinetobacter spp*., *P. aeruginosa* and *Enterobacteriaceae*), including data
  - *in vitro*
  - *in vivo* (animal)
  - on humans

- To investigate the prescription habits and attitudes of clinicians usually dealing with the treatment of CR-GNB in both pediatric and adult populations from a global perspective

Savoldi, BMC Infect Dis 2021; Carrara, CMI 2021; Scudeller, Int J Antimicr Agents 2021

The *in vitro* perspective

STUDY DESIGN

Systematic review and Network meta-analysis

- **pharmacokinetic/pharmacodynamic** (PK/PD)
- **time–kill** (TK) **studies**

examining the in vitro efficacy of antibiotic combinations against CR-GNB

OUTCOMES

Primary outcome: ***in vitro* synergy** based on the effect size (ES)

- high: ES ≥ 0.75
- moderate: 0.35 < ES < 0.75
- low: ES ≤ 0.35
- absent: ES = 0.

Secondary outcome: **bactericidal effect and re-growth rate**

Scudeller & Tacconelli, Int J Antimicr Agents 2021

Results

Most commonly analysed antibiotic combination for TK and PK/PD studies for the most clinically relevant CR Gram negative bacteria

- ✓ Over **180 combination regimens** from 136 studies were included
- ✓ The most frequently analysed classes were polymyxins and carbapenems

Bacterium/antibiotic combination	TK study	PK/PD study	Total of studies
Acinetobacter baumannii			
Polymyxins + carbapenems	42	7	49
Polymyxins + rifampicin	20	1	21
Carbapenems + rifampicin	14	0	14
Polymyxins + tigecycline	13	2	15
Carbapenems + sulbactam	13	3	16
Total	102	13	115
Klebsiella pneumoniae			
Polymyxins + carbapenems	52	3	55
Double carbapenem	26	1	27
Polymyxins + rifampicin	17	1	18
Polymyxins + fosfomycin	6	5	11
Polymyxins + tigecycline	7	1	8
Total	108	11	119
Pseudomonas aeruginosa			
Carbapenems + aminoglycosides	25	2	27
Carbapenems + fluoroquinolones	22	1	23
Fluoroquinolones + cephalosporins	18	0	18
Polymyxins + carbapenems	8	3	11
Fluoroquinolones + aminoglycosides	10	0	10
Total	83	6	89

Scudeller & Tacconelli, Int J Antimicr Agents 2021

Acinetobacter baumannii

In vitro synergy of antibiotic combinations against A. baumannii assessed by PK/PD and TK studies

Antibiotic regimen	Assay	No. of strains	No. of studies	No. of tests	ES	95% CI	Synergy rate
Colistin + meropenem	PK/PD	3	1	4	0.40	0.00–0.95	Positive trend
Colistin + rifampicin	PK/PD	2	1	4	0.91	0.44–1.00	High
Colistin + tigecycline	PK/PD	4	1	2	0.63	0.24–0.95	Moderate
Imipenem + tobramycin	PK/PD	1	1	3	1.00	0.38–1.00	High
Meropenem + amikacin	PK/PD	1	1	1	0.00	0.00–0.79	No synergy
Polymyxin B + tigecycline	PK/PD	4	1	2	0.08	0.00–0.43	Positive trend
Colistin + ampicillin/sulbactam	TK	2	1	1	0.00	0.00–0.66	No synergy
Colistin + ampicillin/sulbactam + rifampicin	TK	2	1	1	0.50	0.09–0.91	Moderate
Colistin + doripenem	TK	16	2	3	0.39	0.00–0.94	Positive trend
Colistin + imipenem	TK	10	2	2	0.39	0.07–0.76	Moderate
Colistin + meropenem	TK	24	3	4	0.87	0.48–1.00	High
Colistin + rifampicin	TK	24	5	7	0.75	0.41–0.99	High
Colistin + sulbactam	TK	18	1	1	0.56	0.34–0.75	Moderate
Colistin + tigecycline	TK	6	1	2	0.89	0.61–1.00	High
Colistin + trimethoprim/sulfamethoxazole	TK	4	1	1	1.00	0.51–1.00	High
Doripenem + amikacin	TK	8	1	1	0.13	0.02–0.47	Low
Doripenem + sulbactam	TK	18	1	1	0.28	0.12–0.51	Low
Imipenem + rifampicin	TK	4	2	3	0.72	0.00–1.00	Positive trend
Imipenem + tigecycline	TK	5	1	1	0.80	0.38–0.96	High
Meropenem + ampicillin/sulbactam	TK	2	1	1	0.50	0.09–0.91	Moderate
Meropenem + aztreonam	TK	5	1	1	0.00	0.00–0.43	No synergy
Polymyxin B + amikacin	TK	2	1	1	1.00	0.34–1.00	High
Polymyxin B + ampicillin/sulbactam	TK	2	1	1	0.00	0.00–0.66	No synergy
Polymyxin B + imipenem	TK	2	1	1	0.50	0.09–0.91	Moderate
Polymyxin B + meropenem	TK	4	2	2	0.82	0.23–1.00	High
Polymyxin B + meropenem + ampicillin/sulbactam	TK	2	1	1	0.50	0.09–0.91	Moderate
Polymyxin B + meropenem + rifampicin	TK	2	1	1	0.50	0.09–0.91	Moderate
Polymyxin B + rifampicin	TK	33	2	2	0.53	0.32–0.73	Moderate
Polymyxin B + tigecycline	TK	33	2	2	0.34	0.16–0.55	Low

Scudeller & Tacconelli, Int J Antimicr Agents 2021

Klebsiella pneumoniae

In vitro synergy of antibiotic combinations against K.pneumoniae assessed by PK/PD ans TK studies

Antibiotic regimen	Assay	No. of strains	No. of studies	No. of tests	ES	95% CI	Synergy rate
Ceftazidime/avibactam + amikacin	PK/PD	3	1	1	0.33	0.06–0.79	Low
Ceftazidime/avibactam + aztreonam	PK/PD	1	1	1	1.00	0.21–1.00	High
Colistin + doripenem	PK/PD	1	1	4	0.50	0.00–1.00	Positive trend
Colistin + fosfomycin	PK/PD	8	3	5	0.58	0.28–0.86	Moderate
Polymyxin B + fosfomycin	PK/PD	4	2	4	1.00	0.66–1.00	High
Meropenem + tigecycline	PK/PD	5	1	1	0.40	0.12–0.77	Moderate
Ceftazidime/avibactam + colistin	TK	16	1	1	0.25	0.10–0.49	Low
Colistin + doripenem	TK	62	5	6	0.50	0.28–0.71	Moderate
Colistin + ertapenem	TK	9	1	2	0.38	0.10–0.70	Moderate
Colistin + fosfomycin	TK	2	1	21	0.60	0.41–0.78	Moderate
Colistin + gentamicin	TK	26	2	2	0.31	0.14–0.50	Low
Colistin + meropenem	TK	9	2	2	0.12	0.00–0.46	No synergy
Colistin + meropenem + tigecycline	TK	6	1	1	0.00	0.00–0.39	No synergy
Colistin + rifampicin	TK	25	2	2	1.00	0.95–1.00	High
Colistin + tigecycline	TK	10	2	3	0.42	0.00–0.98	Positive trend
Colistin + tobramycin	TK	4	1	2	0.37	0.05–0.76	Moderate
Doripenem + ertapenem	TK	12	1	1	0.00	0.00–0.24	No synergy
Doripenem + gentamicin	TK	26	2	2	0.15	0.03–0.32	Low
Imipenem + amikacin	TK	4	1	1	1.00	0.51–1.00	High
Meropenem + amikacin	TK	4	1	1	1.00	0.51–1.00	High
Meropenem + ertapenem	TK	21	1	1	0.43	0.24–0.63	Moderate
Meropenem + gentamicin	TK	13	1	1	0.00	0.00–0.23	No synergy
Meropenem + tigecycline	TK	13	1	1	0.00	0.00–0.23	No synergy
Meropenem + tigecycline + gentamicin	TK	13	1	1	0.00	0.00–0.23	No synergy
Polymyxin B+ doripenem	TK	1	1	4	1.00	0.51–1.00	High
Polymyxin B + imipenem	TK	2	1	3	1.00	0.67–1.00	High
Polymyxin B + meropenem	TK	25	6	50	0.45	0.36–0.53	Moderate

Scudeller & Tacconelli, Int J Antimicr Agents 2021

Pseudomonas aeruginosa

In vitro synergy of antibiotic combinations against *P. aeruginosa* assessed by PK/PD and TK studies

Antibiotic regimen	Assay	No. of strains	No. of studies	No. of tests	ES	95% CI	Synergy rate
Ceftazidime/avibactam + amikacin	PK/PD	3	1	1	0.33	0.06–0.79	Low
Colistin + doripenem	PK/PD	3	2	6	0.57	0.03–1.00	Moderate
Imipenem + amikacin	PK/PD	1	1	2	1.00	0.21–1.00	High
Ceftolozane/tazobactam + colistin	TK	4	1	1	0.50	0.15–0.85	Moderate
Ceftolozane/tazobactam + aztreonam	TK	4	1	1	0.00	0.00–0.49	No synergy
Ceftolozane/tazobactam + amikacin	TK	4	1	1	0.00	0.00–0.49	No synergy
Colistin + imipenem	TK	2	1	2	0.67	0.08–1.00	Moderate
Colistin + meropenem	TK	7	1	4	0.43	0.16–0.75	Moderate
Imipenem + amikacin	TK	87	4	7	0.35	0.23–0.47	Low
Imipenem + tobramycin	TK	2	1	8	0.39	0.04–0.80	Moderate
Meropenem + amikacin	TK	63	2	1	0.43	0.31–0.55	Moderate

Scudeller & Tacconelli, Int J Antimicr Agents 2021

Linking in vitro data with clinical data…

A. baumannii

Most consistently reported synergism: **colistin/rifampicin (**PK/PK and TK studies)

Synergism between a polymyxin with either a carbapenem or tigecycline was not always shown

Assessed in clinical trials with no impact on mortality

K. pneumoniae

Most consistently reported synergism: polymyxin/rifampicin

The benefit of this combination **has not been assessed in a RCT for this pathogen**

Fosfomycin with polymyxin is a potential promising option to consider, showing not only synergism but also increased bactericidal activity

P. aeruginosa

Aminoglycoside with imipenem showed **increased synergism** (*e.g.* imipenem and amikacin) and **bactericidal activity** (*e.g*. imipenem/amikacin)

Although this combination is often used in clinical practice as empirical therapy in bloodstream infections, limitations are represented by aminoglycoside nephrotoxicity and their limited lung penetration

The clinical perspective
Systematic reviews and meta-analyses

- A 2014 SR found that the majority of studies on CRE did not show statistically significant differences in mortality or treatment failures between combination therapy and monotherapy.
- However, 3 studies (194 patients with bacteraemia), demonstrated a significantly lower mortality with combination therapy, colistin/polymyxin B or tigecycline combined with a carbapenem.
- A 2019 SR in a subgroup analysis revealed lower mortality with combination therapy with at least two in-vitro active antibiotics, in blood stream infections, and CR-GN.
- No mortality difference was seen in case-control studies (n=6) and RCTs (n=2). Cure rates did not differ regardless of study type. The RCTs had a high and unknown risk of bias, respectively. 16.7% (1/6) of case-control studies and 37.8% (17/45) of cases series/cohort studies were of good quality, whereas quality was poor in the remaining studies.

Falagas, Antimicrob Agents Chemother 2014; Schmidt, Scient rep 2019

Where is the evidence from clinical data

Methods

- Systematic review from January 1945 until December 2018 for observational comparative and non-comparative studies and randomized trials examining any antibiotic option for CR-GNB.
- Studies were included if reporting microbiologically-confirmed infection caused by target microorganism, reporting at least one of the study outcomes, and definitive antibiotic treatment.
- Carbapenem-resistance was defined as phenotypically-detected in vitro resistance to at least one of the following carbapenems: doripenem, ertapenem, imipenem, meropenem.
- Bayesian network meta-analysis approach was selected for quantitative synthesis to explore feasibility of pooling data on antibiotic regimens

Outcomes

Primary outcomes were 30-day and attributable mortality.

Savoldi & Tacconelli, BMC Infect Dis 2021

Summary of results

- A total of 6306 records were retrieved
- 134 studies including 11,546 patients
  - 54 studies were on Acinetobacter
  - 52 on Enterobacteriales
  - 21 on mixed Gram-negative
  - 7 on Pseudomonas
- 9 RCTs; 19 prospective cohorts, 89 retrospective cohorts, and 17 case series
- 41 studies multicentric

- 92 distinct antibiotic regimens identified
- **47 of them (51%) not reporting any details on numbers, type, dosage and in vitro activity of the included antibiotics**
- Heterogeneous and scattered reporting of key-clinical and microbiological variables
- The NMAs could not be performed for any of the selected outcome given the presence of too many disconnected components

Savoldi & Tacconelli, BMC Infect Dis 2021

Antibiotic regimens assessed in the included studies stratified by bacterial phenotype and number of patients

Patients	Total	Acinetobacter	Enterobacteriaceae	Mixed Gram Negative	Pseudomonas
Undefined	5,863	1,364	2,585	1,806	108
Single-antibiotic regimen					
Aminoglycoside	174	39	96		39
BLBLIs	46				46
Carbapenem	97		97		
Cefepime	88				88
Ceftazidime/avibactam	120		107	13	
Ceftolozane/tazobactam	12				12
Fosfomycin	8		8		
Meropenem/Vaborbactam	50		50		
Polymyxin	2,383	1,066	252	976	89
Sulbactam	142	142			
TMP-SMX	12		12		
Tetracycline	21	21			
Tigecycline	416	221	179	16	
Dual-antibiotic regimen					
Aminoglycoside + Carbapenem	37		37		
Aminoglycoside + Fosfomycin	11		11		
Aminoglycoside + Polymyxin	42		42		
Aminoglycoside + Sulbactam	8	8			
Aminoglycoside + Tetracycline	20	20			
Aminoglycoside + Tigecycline	73	13	60		
BLBLIs + Polymyxin	27	17			10
BLBLIs + Cefepime	24		24		
Carbapenem + Ertapenem	73		73		
Carbapenem + Fosfomycin	41		16		25
Carbapenem + Polymyxin	608	388	134	50	36
Carbapenem + Rifampin	20	20			
Carbapenem + Sulbactam	180	180			
Carbapenem + Tigecycline	48	28	20		
Fosfomycin + Polymyxin	5		5		
Fosfomycin + Tigecycline	22		22		
Glycopeptide + Polymyxin	71	29		42	
Polymyxin + Rifampin	246	246			
Polymyxin + Sulbactam	153	153			
Polymyxin + Tetracycline	7			7	
Polymyxin + Tigecycline	210	88	103	19	
Triple-antibiotic regimen					
Aminoglycoside + Carbapenem + Tigecycline	9		9		
Aminoglycoside + Fosfomycin + Tigecycline	32		32		
Aminoglycoside + Polymyxin + Tigecycline	6		6		
Carbapenem + Ertapenem + Polymyxin	14		14		
Carbapenem + Fosfomycin + Polymyxin	24				24
Carbapenem + Fosfomycin + Tigecycline	8		8		
Carbapenem + Glycopeptide + Polymyxin	4	4			
Carbapenem + Polymyxin + Rifampin	24			24	
Carbapenem + Polymyxin + Tigecycline	33		33		
Carbapenem + Polymyxin + Tigecycline	15	15			
Polymyxin + Rifampin + Tigecycline	19	19			

Among the 92 regimens, 13 were single-, 21 were dual, and 11 were triple-antibiotic regimens.

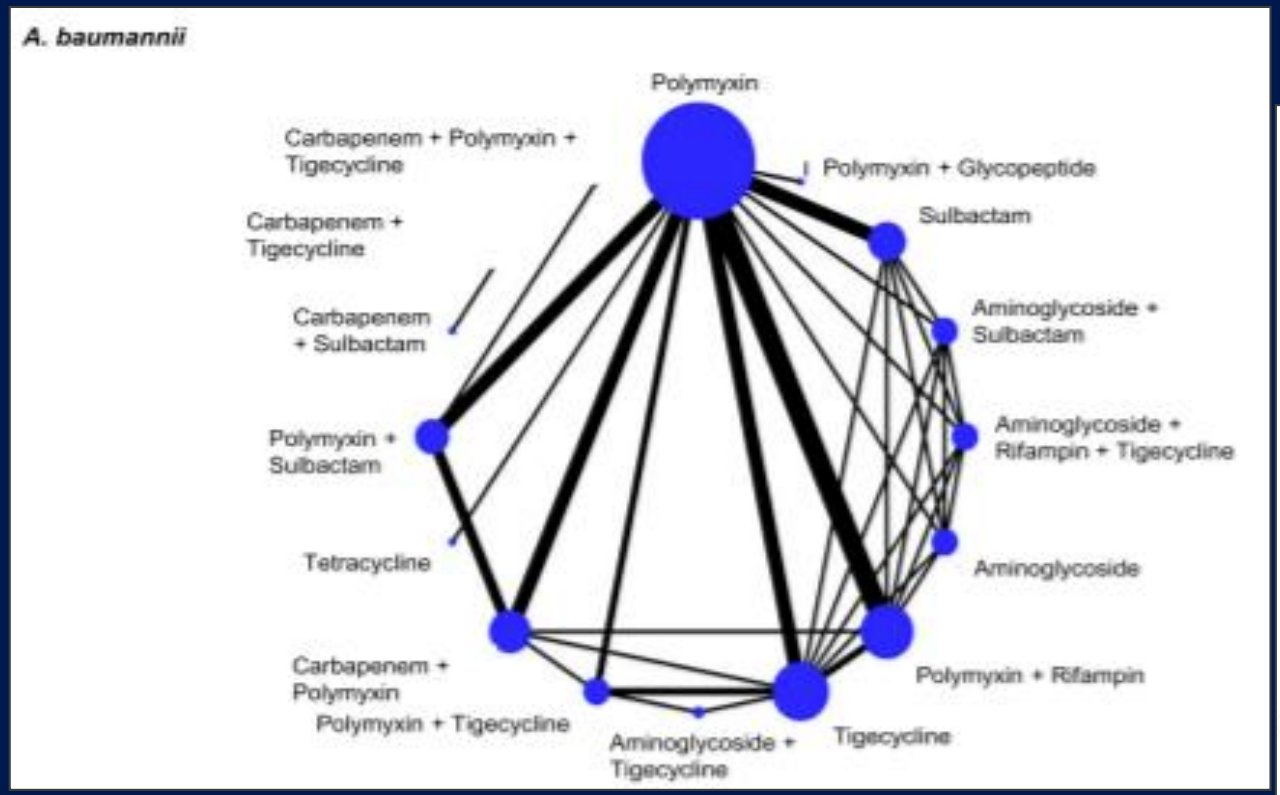
- Polymyxin was the most prescribed antibiotic class both alone and in combination for each bacterial phenotype.

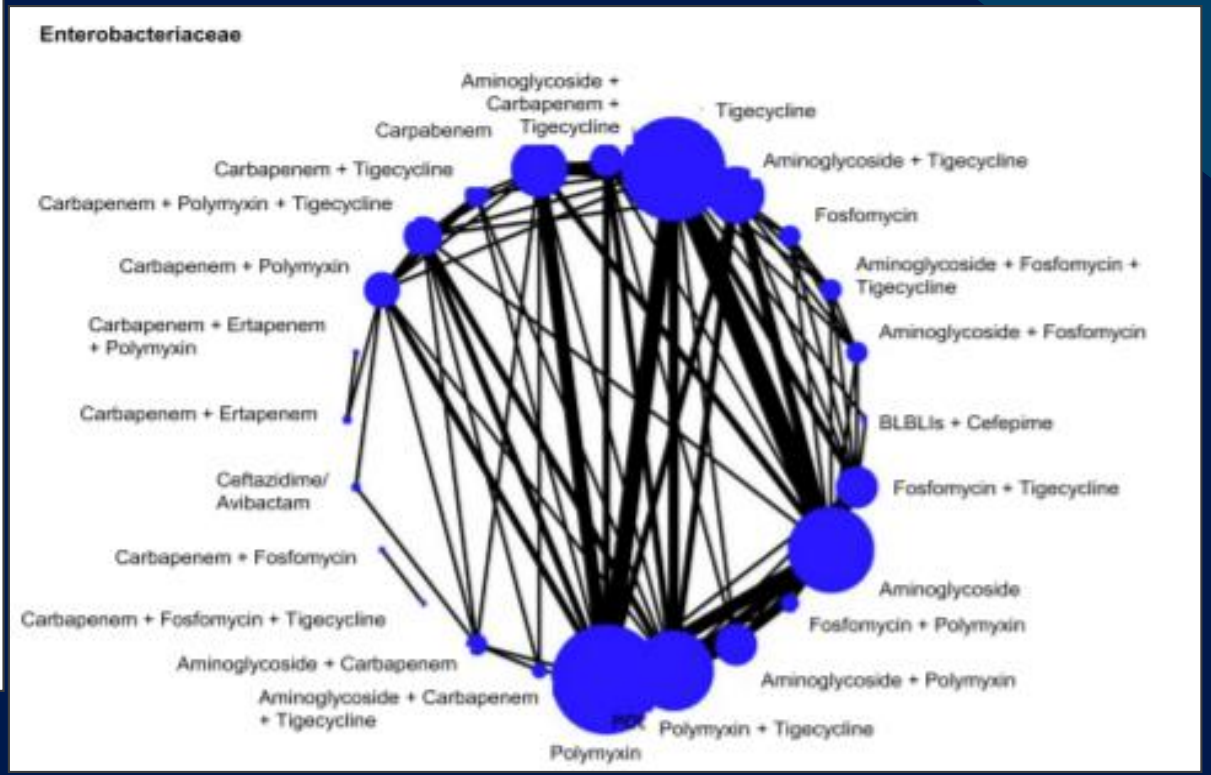
- The most frequently assessed antibiotic regimens were:

- polymyxin plus carbapenem (608 patients)
- carbapenem plus rifampin (246 patients)
- polymyxin plus tigecycline (210 patients)

Savoldi & Tacconelli, BMC Infect Dis 2021

Network geometry of outcome mortality assessed for each bacterial phenotype: *A. baumannii and* Enterobacteriales



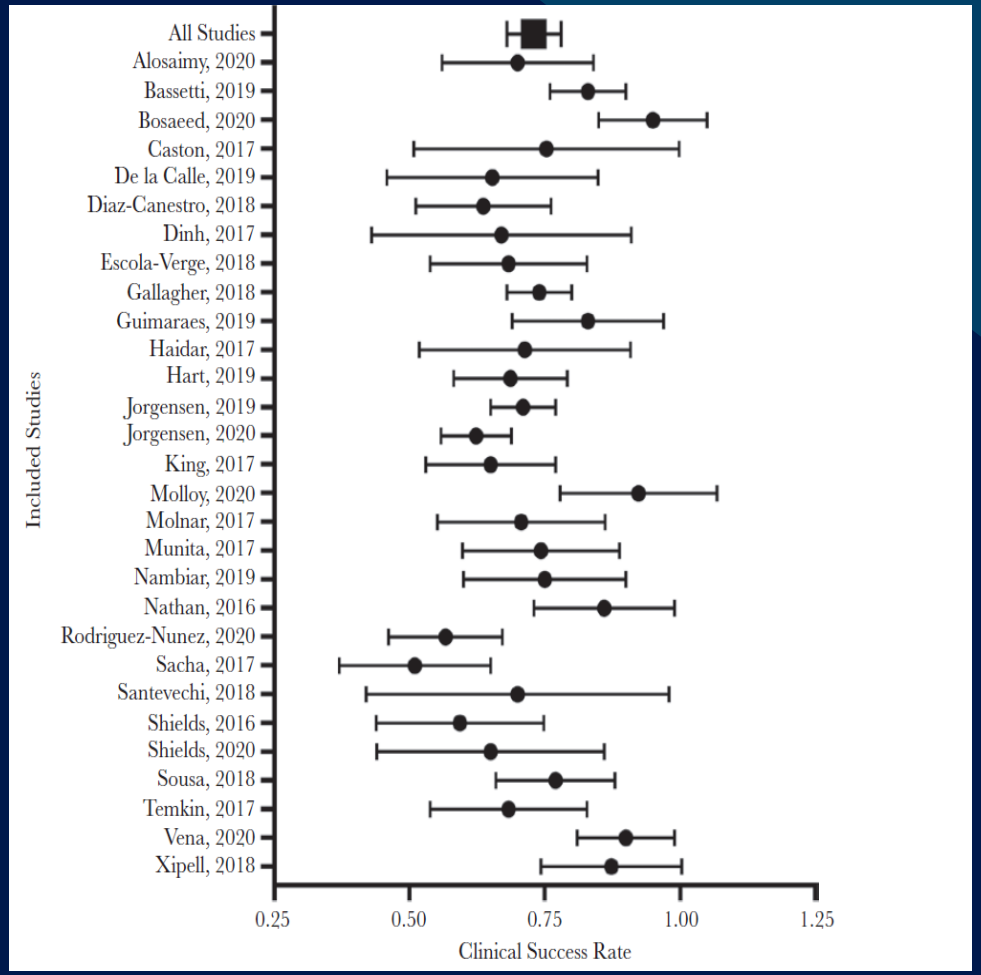


Savoldi & Tacconelli, BMC Infect Dis 2021

1. The SR included 97 distinct antibiotic regimens reflecting the lack of standardization in clinicians' prescribing.
2. Overall, the studies had a median sample size of 49, a figure which is considerably low considering the estimated sample of several hundreds or even thousands of patients that are needed for reliably assessing independent association of one antibiotic regimen with mortality in observational studies.
3. The quality of the studies was low. The included RCTs were generally of better quality, but did not contribute significantly to the overall analysis. In particular, the trials on new antibiotics showed important limitations related to the inclusion of very small sample size and the use of heterogeneous comparison groups.
4. In patients with CR-GNB infections, especially those with critical illness, comorbidities and baseline severity of disease are known to be major contributors to the final outcomes. However, the systematic review showed that only 21 comparative observational studies included an adjusted analysis for these confounders, whereas the remaining studies were generally too small to allow for adjustment.

Systematic reviews and meta-analyses Ceftazidime/ Avibactam, Ceftolozane/Tazobactam, and Meropenem/ Vaborbactam

- 29 publications including 1620 patients
- Pneumonia was the predominant infection type (49.8%)
- MDRPA was the major pathogen treated (65.3%)
- The pooled clinical success rate was 73.3% (95% CI, 68.9%–77.5%)
- Resistance to new drugs was reported in 8.9% of the population



Wilson, Open Forum Infect Dis 2021

The prescribers' perspective

36-item questionnaire addressing the following aspects of antibiotic prescribing:

- Diagnostic and therapeutic availability
- Preferred antibiotic strategies and rationale for selecting combination therapy

Adjusted by respondent's background, number of cases treated, availability of diagnostics, and income category

1012 respondents from 95 countries

	Respondents,
WHO region	
Africa	64 (6·0)
Americas	205 (20·5)
Eastern Mediterranean	116 (11·5)
Europe	444 (44·0)
South East Asia	95 (9·3)
Western Pacific	88 (8·7)
Total	1012 (100)
Patients' age	
Adults	867 (85·6)
Paediatric population	145 (14·3)
Children	110 (10·9)
Neonates	35 (3·5)
Total	1012 (100)
Income category	
High-income countries	512 (50·6)
Upper-middle income countries	296 (29·2)
Lower-middle-income/Low-income countries	204 (20·1)
Total	1012 (100)
Prescribing frequency[a]	
Low-rate prescribers	257 (25·4)
Medium-rate prescribers	416 (41·1)
High-rate prescribers	283 (28·0)
Not specified	56 (5·5)
Total	**1012 (100)**

Carrara & Tacconelli, CMI 2021

Availability of diagnostic tools for detecting CR-GNB and time needed to inform laboratories by income category

Diagnostic tool	HIC (*n* = 469; 45·8%)	UMIC (*n* = 268; 26·3%)	LMIC/LIC (*n* = 171; 27·9%)	Overall (*n* = 908)	p value
Standard AST	373 (75·2%)	238 (82·6%)	156 (76·3%)	767 (77·5%)	NS
MALDI-TOF	277 (58·8%)	61 (17·7%)	15 (2·8%)	353 (32·4%)	<0·001
Rapid phenotypic test from blood isolates	142 (32·3%)	61 (21·1%)	15 (1·5%)	218 (20·8%)	<0·001
NAAT	217 (47·2%)	45 (15·4%)	21 (9·6%)	283 (28·4%)	<0·001
In all CR-GNB strains	157 (26·6%)	16 (6·4%)	11 (5·8%)	184 (15·5%)	<0·001
only in selected cases	60 (20·6%)	29 (9·1%)	10 (3·7%)	12·9 (99)	0·008
Internal testing facilities not available	34 (5·3%)	38 (14·0%)	25 (21·7%)	10· 6 (97)	<0·001

Time to positive blood cultures	Income category; *n* (%) of country			p value
	HIC (*n* = 500; 51·5%)	UMIC (*n* = 282; 27·2%)	LMI/LIC (*n* = 191; 25·3%)	
Within 36 hours	172 (41·2%)	70 (21·6%)	51 (20·8%)	0·01
Within 48 hours[a]	349 (73·2%)	139 (40·0%)	93 (42·5%)	<0·001
Within 72 hours[a]	463 (80·1%)	224 (52·0%)	139 (59·8%)	<0·001
Within 96 hours[a]	494 (99·1%)	260 (91·8%)	174 (80·4%)	<0·001
More than 96 hours	6 (0·9%)	22 (8·2%)	17 (19·6%)	<0·001

Carrara & Tacconelli, CMI 2021

The “concept of combination therapy”

1. According to respondents, ‘combination therapy’ must include antibiotics that retain some degree of in vitro activity (321/783; 42% of respondents) or be synergic (290/783; 38% of respondents).
2. Twenty per cent of respondents (150/783) conceived ‘combination therapy’ as the simple association of two or more antibiotic compounds, regardless of their potential in vitro activity

Disagreement among respondents clearly reflects the lack of a standardized definition for ‘combination therapy’ also in clinical studies, with the result that there can be a misinterpretation and poor generalizability of study results

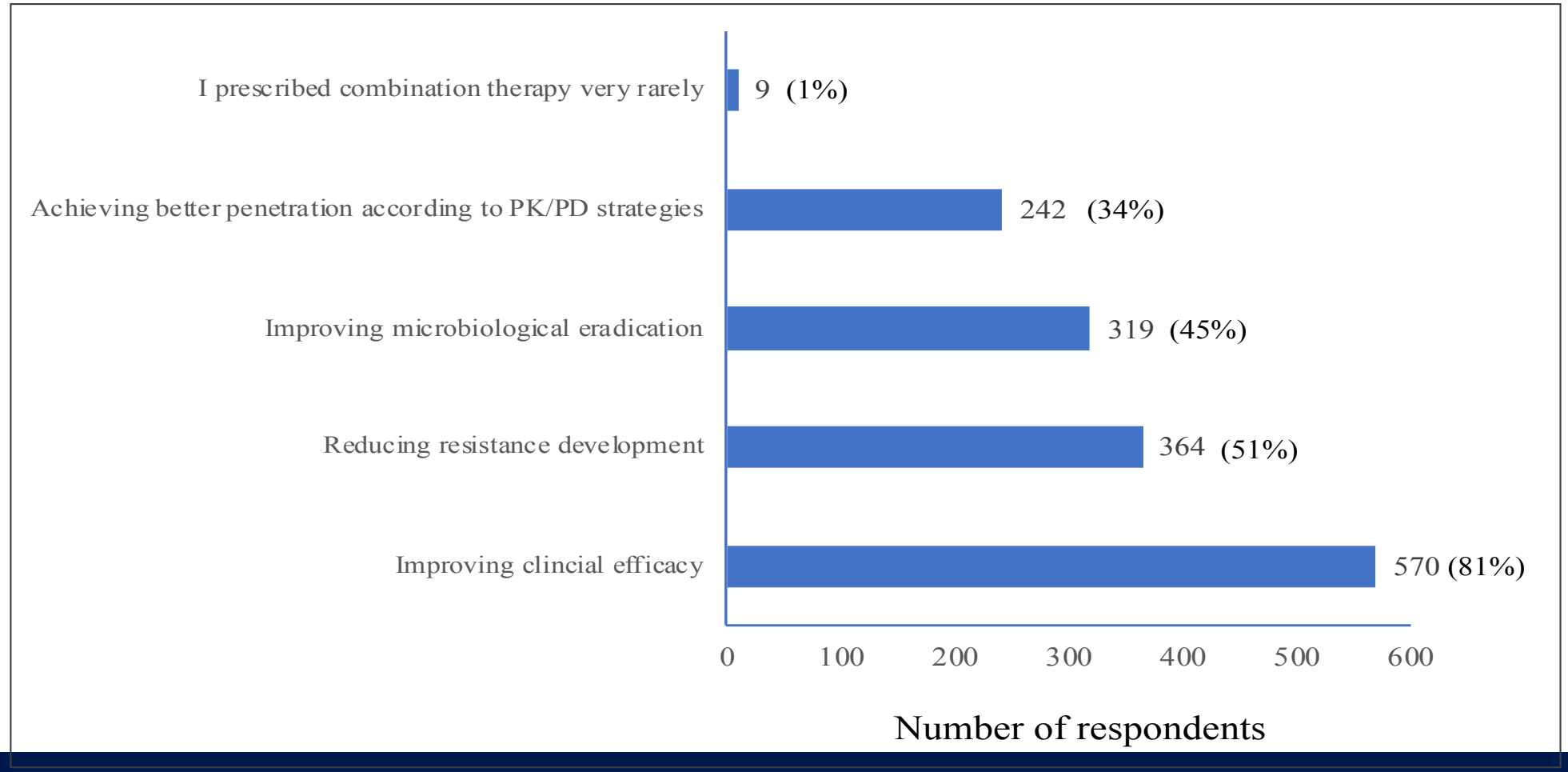
Carrara & Tacconelli, CMI 2021

Respondents' prescription strategies

- **Combination of two antibiotics** (35%-45% of respondents depending on sepsis sources or bacterial species) was the preferred strategy and a carbapenem plus a polymyxin the most prescribed
- The number of regimens ranged **from 40 regimens in CR-Acinetobacter spp. to more than 100 regimens in CR-Enterobacteriales**
- **Single antibiotic therapy** was considered especially for CR-Acinetobacter spp. and CR-Pseudomonas spp. (23%-37% and 26%-35% of respondents, respectively, depending on the sepsis source)
- **Combination of three antibiotics** was regarded as the preferred strategy by a lower number of respondents (15%-20% depending on sepsis sources or pathogen type)

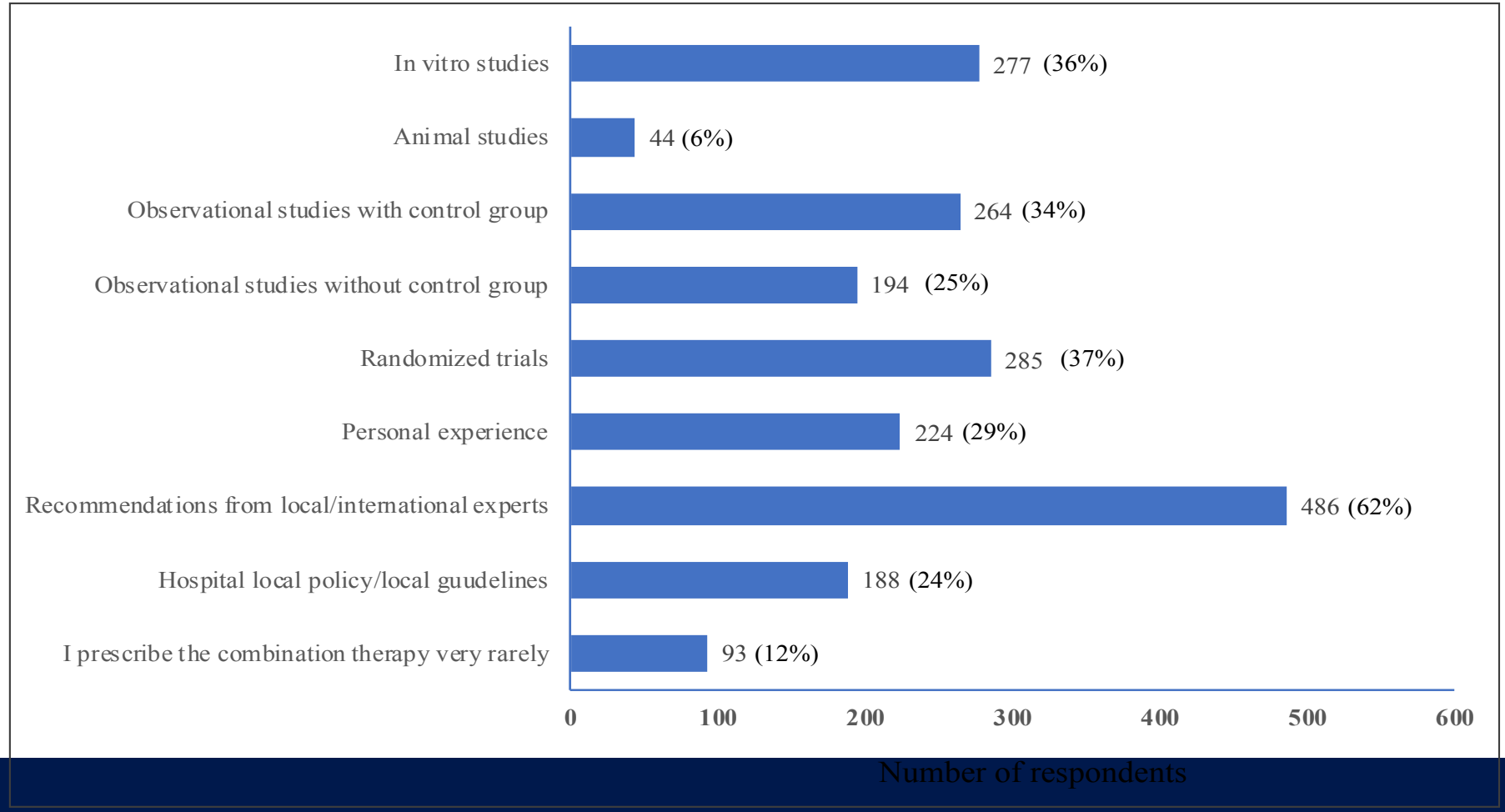
Carrara & Tacconelli, CMI 2021

Reasons supporting the use of combination therapy



Carrara & Tacconelli, CMI 2021

Type of evidence supporting the use of combination therapy



Carrara & Tacconelli, CMI 2021

Carbapenem-resistant Enterobacterales
Carbapenem-combination therapy

AIDA trial

- Randomised controlled superiority trial
- BSI, VAP, HAP or urosepsis caused by CR-GN
- I.v. colistin (9-million unit LD, followed by 4·5 million units x2) vs colistin with meropenem (2-g prolonged infusion x3)
- Primary outcome: 14-d clinical failure
- 406 patients randomized
- Most patients had pneumonia or bacteraemia (87%) caused by A. baumannii (77%)
- No significant difference between colistin monotherapy (79%) and combination therapy (73%) for clinical failure (risk difference –5·7%, 95% CI –13·9 to 2·4; risk ratio [RR] 0·93, 95% CI 0·83–1·03).

OVERCOME trial

- Colistin monotherapy versus colistin-meropenem combination therapy in patients with severe infections caused by CR-GNB, mainly HAP/VAP and BSI.
- High-dose extended-infusion meropenem was used.
- ++CRAB
- Subgroup analysis of patients with CRE infections did not show statistically significant differences in 28-day mortality

Paul, LID 2018; Kaye, ECCMID 2021

INCREMENT

- In the retrospective INCREMENT cohort such combination therapy was associated with lower 30-day mortality among patients with CPE BSIs at high risk for death (INCREMENT score 8-15, N=166, adjusted HR 0.56 [95% CI 0.34-0.91]), but not among patients with lower INCREMENT scores (N=177, adjusted OR 1.21 [95% CI 0.56-2.56]).
- *Patients with urinary or biliary tree infections and reduced acuity of infection on presentation may be safely trialled on single directed therapy (if available)*
- Lower efficacy of a single drug regimen with these drugs has been attributed to the often-suboptimal dosage and the unsuitable PK/PD profile for some infection sites.

Variable	Score
Severe sepsis or septic shock	5 pts
Pitt score ≥6	4 pts
Charlson comorbidity index ≥2	3 pts
Source of BSI other than urinary or biliary tract	3 pts

Gutierrez-Gutierrez, LID 2017

Observational studies

- Italian cohort study of patients BSIs and non-bacteremic infections due to KPC-producing K. pneumoniae, combination therapy including a carbapenem was associated with lower 14-day mortality when the meropenem MICs were <8 mg/L.

- A continuation and reanalysis of same cohort showed a similar association between high-dose carbapenem-containing combinations (6 g/day, 3 hours infusion) and 14-day survival compared to non-carbapenem containing combinations, even when the MICs were higher (>16 mg/L).

Tumbarello, JAC 2015; Giannella Intern J Ant Chemoth 2018

Double-carbapenem combination therapy

- The rationale for using double-carbapenem therapy for treating CRE infections is based on higher affinity of ertapenem for carbapenemases and a hypothesis that consumption of the carbapnemases by ertapenem will allow for the action of the other carbapenem. In-vitro data for synergistic interactions are conflicting.
- Two observational studies from Italy and one from the USA suggested better survival in patients with invasive KPC infections treated with a double carbapenem regimen when compared to other regimens, even with high carbapenem MICs.
  - Major limitations: small sample size and multiple combination

Erdem, ARIC 2020; Oliva, CMI 2016; Cancelli, BioMed research international. 2018;De Pascale Critical Care 2017; Venugopalan, Infect Dis 2017

Cefiderol and cefta-avibactam vs combination

- CREDIBLE-CR trial: 150 patients with proven/suspected CR-GNB infections; cefiderocol versus BAT (mostly polymyxin based combination) ++ HAP/VAP and BSI - not powered to conduct specific hypothesis testing
- Mortality was higher in the cefiderocol arm at 28 days (24.8% with cefiderocol vs. 18.4%)
  - Clinical and microbiological efficacies of cefiderocol vs. BAT were similar
  - Post-hoc subgroup analyses revealed that the mortality difference was observed among patients with CRAB infections
- Retrospective cohorts enrolled a total of 824 patients from three countries (USA, Spain and Italy) and compared ceftazidime-avibactam in combination with other antibiotics vs ceftazidime-avibactam monotherapy, showing no difference in mortality and clinical failure in mixed infections caused by KPC and OXA-48 producer

Bassetti, LID 2021; Tumbarello, CID 2019 & 2021; King, AAC 2017; Shields, AAC 2018; De la Calle 2019

Ceftazidime-avibactam in combination with aztreonam

- A prospective study was conducted including 102 patients with MBL-producing CPE bacteremia (82 NDM-producing and 20 VIM-producing strains) treated with ceftazidime-avibactam in combination with aztreonam compared to other in-vitro covering therapies, mostly combinations.
    - The isolates were mostly non-susceptible to aztreonam alone. Using propensity-score adjusted multivariable regression, the study showed a significant independent association between ceftazidime-avibactam-aztreonam and lower 30-day mortality (HR 0.37, 95% CI 0.13-0.74), clinical failure and length of hospital stay

Karlowsky, AAC 2017; Sader, AAC 2018; Falcone, CID 2021

Combination of imipenem-relebactam

- The RESTORE IMI-1 reports non-inferior clinical outcomes with imipenem/cilastatin/relebactam versus imipenem/cilastatin plus colistin but is predominantly tested against CR-PA.
- Effectiveness in non-Pseudomonas organisms remains unclear.
- There are currently no data to inform whether combination therapy prevents or promotes emergence of resistance in this setting.

Motsch, CID 2020

Summary of evidence for CRE infections

- **There is no clear evidence that combination of antibiotics** (i.e., the use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, or polymyxin) is more effective than monotherapy for the treatment of infections caused by CRE
- For patients with **severe infections** caused by CRE susceptible in-vitro **only to polymyxins, aminoglycosides, tigecycline or fosfomycin**, or in the case of non-availability of new BLBLs, there is **moderate evidence for the treatment with more than one drug** active in-vitro
- There is low evidence that **high-dose extended-infusion meropenem-polymyxin combination therapy is more effective than polymyxin monotherapy** in the treatment of severe infections caused by CRE, mainly **KPC-producing *K. pneumoniae*, with MICs ≤8 mg/L**
- There is moderate evidence for **ceftazidime-avibactam in combination with aztreonam** against BSI caused by **MBL-producing CPE**.
- There is no evidence on the effectiveness of combination of double carbapenems over the monotherapy
- Expert opinion / **stewardship principles**:
  - No combination for patients with non-severe infections
  - Use monotherapy chosen among the in-vitro active drugs, on an individual basis and according to the source of infection

Carbapenem-resistant Acinetobacter baumannii
Colistin-carbapenem combination therapy

AIDA trial

- Randomised controlled superiority trial
- BSI, VAP, HAP or urosepsis caused by CR-GN
- I.v. colistin vs colistin with meropenem
- Primary outcome: clinical failure at 14 days after randomisation.
- 406 patients randomized
- Most patients had pneumonia or bacteraemia (87%) caused by A. baumannii (77%)
- No significant difference between colistin monotherapy and combination therapy for clinical failure
- The addition of meropenem to colistin did not improve clinical failure in severe A baumannii infections

OVERCOME trial

- Double-blind RCT comparing colistin monotherapy with colistin-meropenem combination for HAP/ VAP and BSI caused by CR-GNB
- Mostly patients with CRAB of infections
- Mortality at 28 days was similar for colistin monotherapy 76/165 (46%) and colistin-meropenem 69/163 (42%), p=0.5.

Paul, LID 2018; Kaye, ECCMID 2021

Colistin-rifampin combination therapy

- A multicenter, parallel, randomized, open-label clinical trial enrolled 210 patients , mostly pneumonia
- No advantage to colistin-rifampin over colistin monotherapy at 30-day mortality
- A significant increase of microbiologic eradication rate was observed in the colistin plus rifampicin arm (P = .034). No difference was observed for infection-related death and length of hospitalization
- A RCT included 43 patients in ICU with VAP showing no difference between combination and monotherapy with respect to in-hospital mortality and microbiological failure

Durante-Mangoni, CID 2013; Aydemir, Epidemiol Infect 2013

Other combinations
Double covering with carbapenems

- Colistin-vancomycin
  - Retrospective observational study, 57 patients in ICU mostly with CRAB pneumonia - No difference in mortality
  - Retrospective observational study, 42 patients in ICU – No difference in mortality
- Colistin-fosfomycin
  - RCT including 94 patients, usually resistant to fosfomycin – No difference in mortality
- Double covering
  - RCT Colistin + ampicillin-sulbactam vs. colistin: 49 patients in ICU with VAP - advantage to combination therapy with respect to clinical failure, but no difference in 28-day mortality
  - Observational studies (polymyxin, aminoglycoside, tigecycline, sulbactam combinations) showed an association between colistin monotherapy and mortality.

Sirijatuphat R, AAC 2014; Garnacho-Montero, Chemotherapy 2013; Petrosillo, AAC 2014

Summary of evidence for CRAB infections

- There is no evidence for the combination colistin-meropenem or colistin-rifampin
- There is a very low quality evidence for the combination with two in-vitro active antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations)
- Experts´ opinion /**stewardship principles**
  - Combination therapy in infections with a meropenem MIC ≤8 mg/L, using high-dose extended-infusion carbapenem dosing, preferably administered through extended or continuous infusion
  - Combination therapy for pan-resistant CRAB isolates (resistant also to colistin), with the least resistant antibiotic/s based on MICs

Carbapenem-resistant Pseudomonas aeruginosa
Polymyxin-based combination therapy

RCT

- AIDA: 21 patients with MDR-PA
- OVERCOME: 43 patients with MDR-PA
- No difference

Observational studies

- 114 patients with HAP/VAP monotherapy associated with higher mortality (aOR 6.63, 95% CI 1.99 to 22.05)
- Subgroup of XDR-PA mortality was lower for combinations (14/15 dead with monotherapy vs. 0/3 with combinations)
- Subgroup of 68 patients with MDR-PA- No difference

Paul, LID 2018; Kaye, ECCMID 2021; Khawcharoenporn, IJAA 2014; Rigatto, AAC 2015; Falagas IJAA 2010

Ceftolozane-tazobactam monotherapy vs combination with colistin or an aminoglycoside

- Retrospective cohort study /MDR or XDR *P. aeruginosa* infections. There was no difference in cure, defined as clinical and microbiological cure at day 7, between patients given ceftolozane-tazobactam monotherapy (14/21, 66.7%) and those treated with ceftolozane-tazobactam in combination with colistin or an aminoglycoside (21/35, 60%), without adjustment
- The study found no significant difference in development of resistance to ceftolozane-tazobactam during therapy between monotherapy and combination therapy.
- An observational study including 200 patients and compared ceftolozane-tazobactam and imipenem-cilastatin-relebactam to combination regimens have not shown the latter to have added value

Díaz-Cañestro, EJCMID 2018; Pogue, CID 2019

Summary of evidence for CRPA infections

- There is **no evidence to choose a combination therapy when susceptibility to a preferred β-lactam agent has been demonstrated**
- Expert opinion /**stewardship principles**:
  - Use two in vitro active drugs (polymyxins, aminoglycosides, or fosfomycin), in patients with severe infections, or monotherapy for non-severe, chosen among the drugs active in vitro, on an individual basis and according to the source of infection

FINAL CONSIDERATIONS

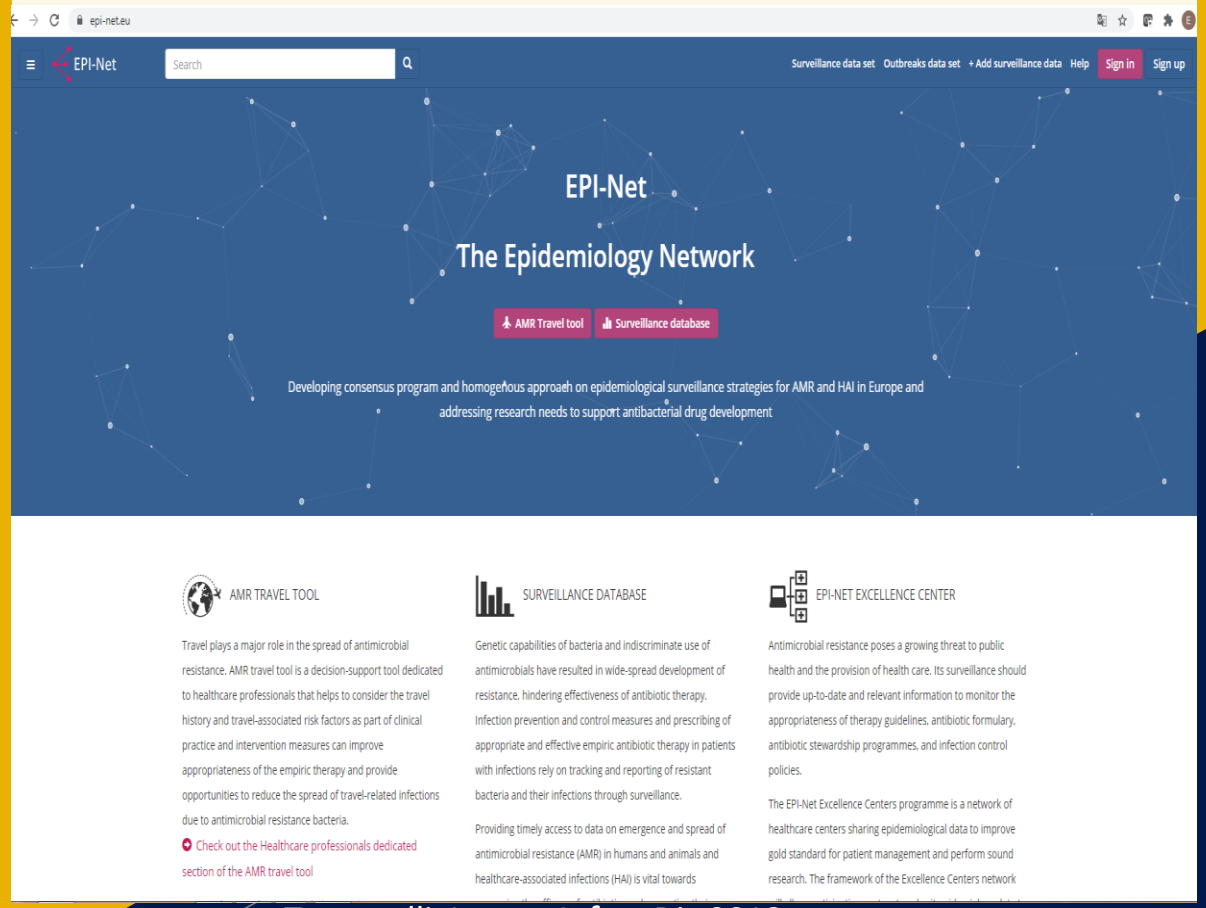
Improve

- Evidence
- Surveillance
- Stewardship
- Infection prevention and control
- Diagnostics (evidence & availability)
- In vitro and PK/PD studies for new antibiotics

Why after so many years we accept low quality or lack of evidence?

- The incidence of MDR Gram negative infections is, in many countries, a substantial threat for public health and the rights of citizens for equal healthcare standard
- The lack of evidence cannot be justified as a problematic recruitment or difficult diagnosis
- Countries like Italy and Greece with the highest number of cases did not lead neither organised any multicenter high level clinical trial on combination therapy for MDR-GNB infections
- There is an urgent need to invest in trials infrastructures and medical education not only at national level but with the support of international stakeholders and funding bodies
- We need to reconsider the process of publication and define some minimum criteria for quality for observational studies which should be respected by all scientific journals
- The impact of low quality observational studies can be enormous in terms of quality of care received by the patients

https://epi-net.eu/publications/



Tacconelli, Lancet Infect Dis 2018

Checklist on how to implement stewardship

- Hospital
- Ambulatory setting
- Veterinary clinic
- Long term care facility

jpiamr
Joint Programming Initiative on Antimicrobial Resistance

ND4BB COMBACTE MAGNET

JAC 2020 Dec 6;75(Suppl 2)

Downloadable checklists from the website

Area for research

- Agreement on definition for combination therapy and for invasive, severe and non severe infections, and at-risk
- The available in vitro and in vivo data could be used to inform new clinical trials and push forward the research of PK/PD data for the last resirt new drugs
- Combination therapy for severe infections including association of “old” drugs
- Salvage treatments for susceptible MDR
- Optimization and duration of therapy

“Well, that’s just how we do things here… It’s how we’ve always done it… It’s best that you don’t rock the boat…”

- The burden of MDR Gram negatives infections cannot be accepted any more as “unavoidable”
- Reducing such a burden can be achieved only with a coordinated effort of preventive measures, stewardship approaches, and active R&D for new drugs
- We need to develop trials infrastructure linked with educational modules in particular in countries with the highest burden
- A change in the status quo can be achieved only with the participation of all actors and the support of major stakeholders and the European Commission

..evolution followed by revolution…

@EveTacconelli
Evelina.Tacconeli@univr.it
Evelina.Tacconelli@med.uni-tuebingen.de

ID-CARE

https://www.id-care.net/

Several research positions available!

Today’s speakers

Combination antibiotic therapy against drug-resistant Gram-negative bacteria: where the evidence stands

Evelina Tacconelli
Director of the Infectious Diseases Unit
Verona University Hospital (Italy)

Moderator:
Gavin Barlow
Senior Clinical Lecturer in Infection
Hull York Medical School (UK)

New webinars will be announced very soon.

Registration link and more information will be available on:
revive.gardp.org/webinars

Thank you for joining us