NUS National University of Singapore | Saw Swee Hock School of Public Health

Challenges in the Treatment of Drug-Resistant Gram-Negative Infections

Hsu Li Yang

June 2022

Disclosure

Research Funding:

- MSD
- Pfizer
- AstraZeneca
- Janssen-Cilag

Advisory Board:

- Janssen-Cilag (Doripenem)
- Pfizer (vaccines, antimicrobials)
- MSD (vaccines)

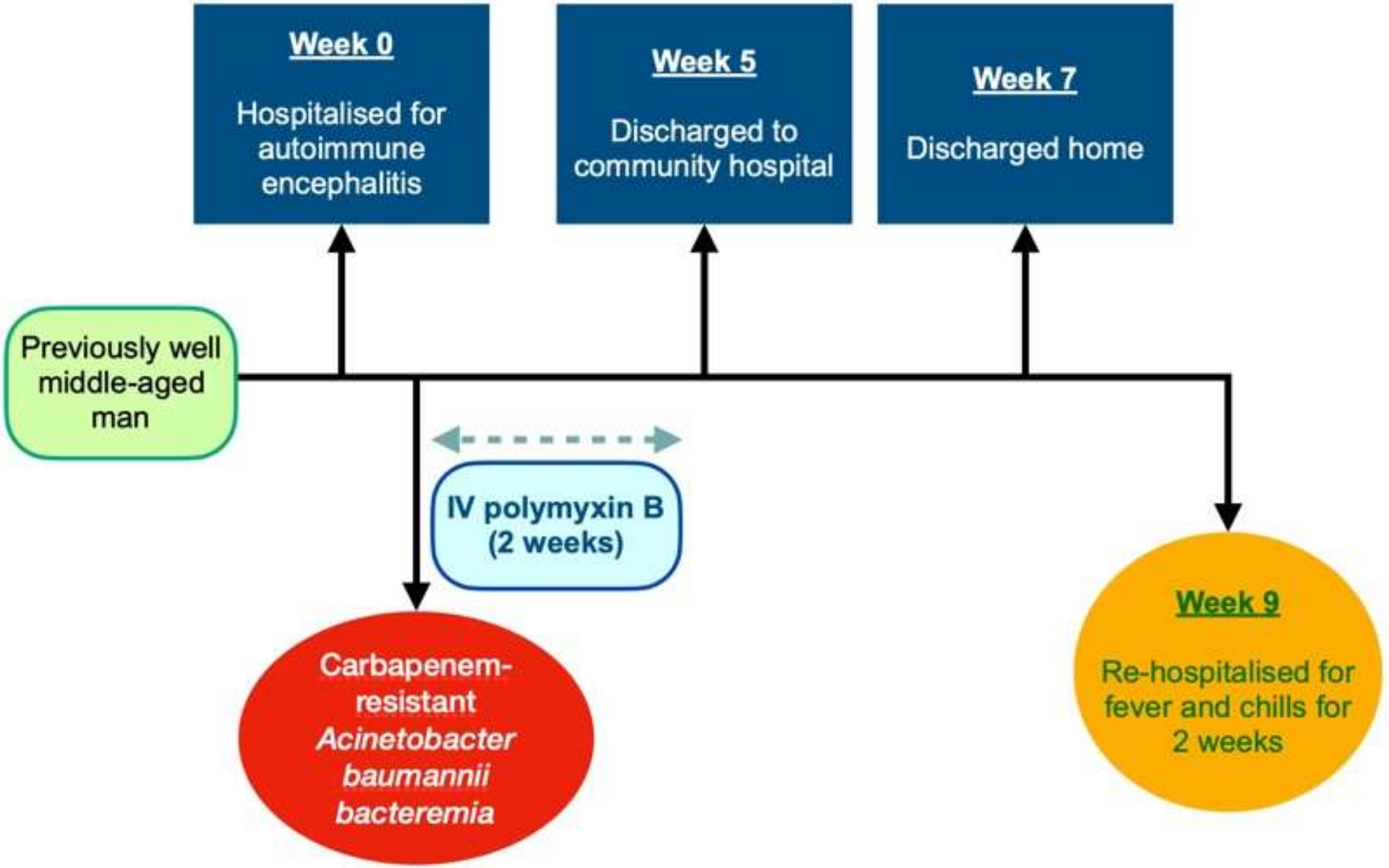
Educational grants:

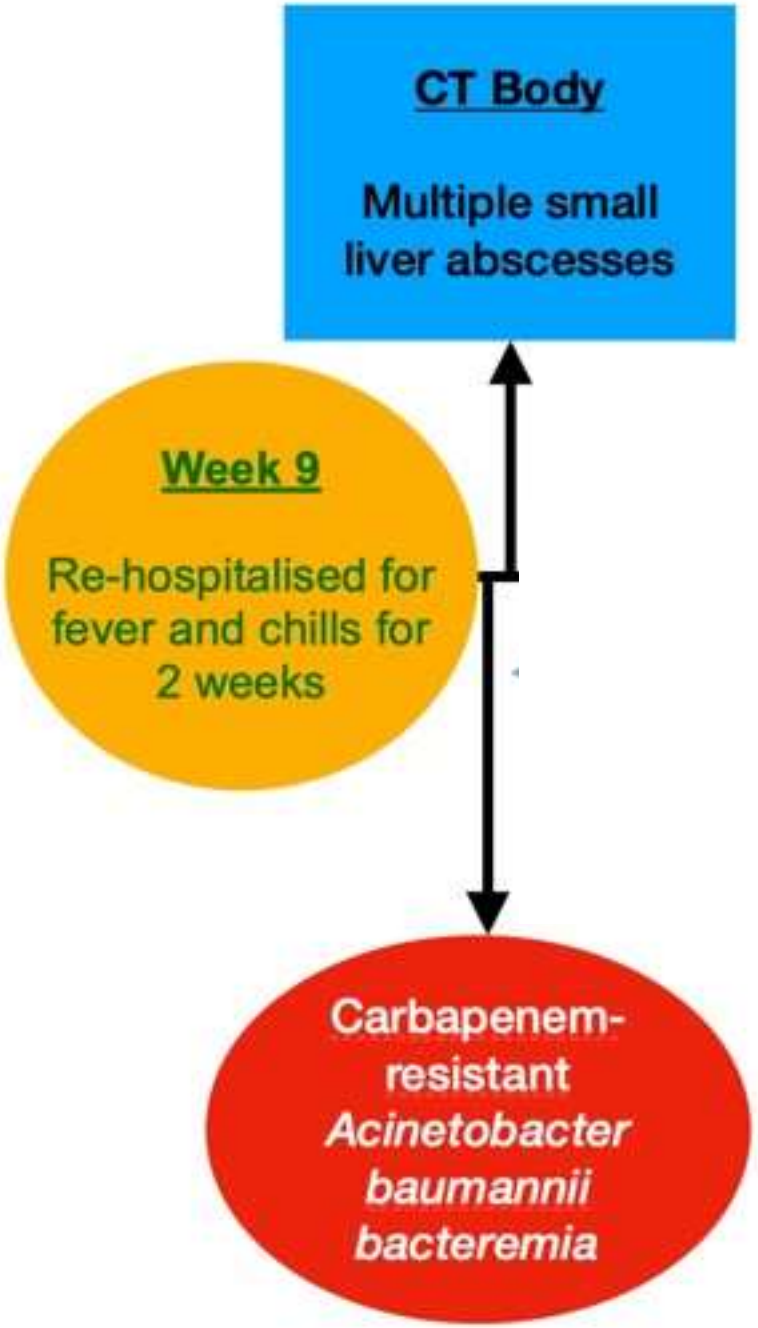
- Pfizer
- BioMerieux
- MSD

Overview

- A Difficult Case
- AMR & the Antibiotic Pipeline
- Key drug-resistant bacterial pathogens: Carbapenem-resistant Gram-negative bacteria (CR-GNB)
- Treatment guidelines
  - Combination vs mono-therapy for CR-GNB
- Conclusion

A Difficult Case





Susceptibility Testing Results (*A. baumannii*)	
Ampicillin/sulbactam	Resistant
Ceftazidime	Resistant
Piperacillin/Tazobactam	Resistant
Meropenem	Resistant
Ciprofloxacin	Resistant
Trimethoprim/Sulfamethoxazole	Resistant
Amikacin	Resistant
Tigecycline	Resistant
Polymyxin B	**S (MIC = 0.38)**

CT Body

Multiple small liver abscesses

Week 9

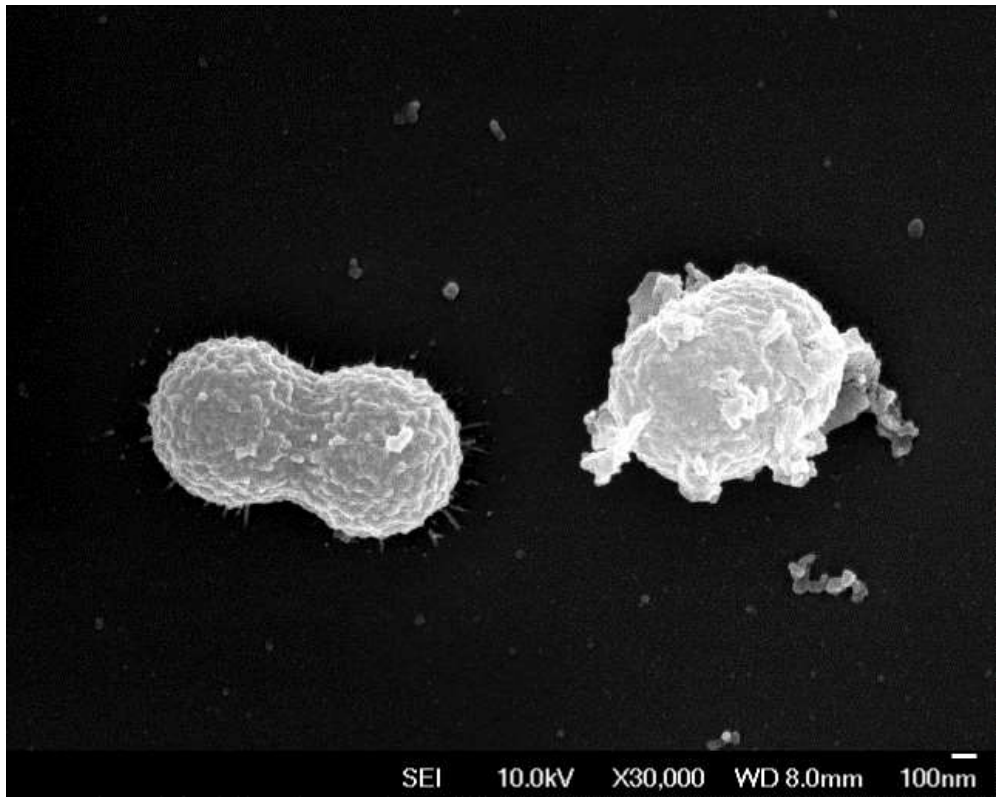
Re-hospitalised for fever and chills for 2 weeks

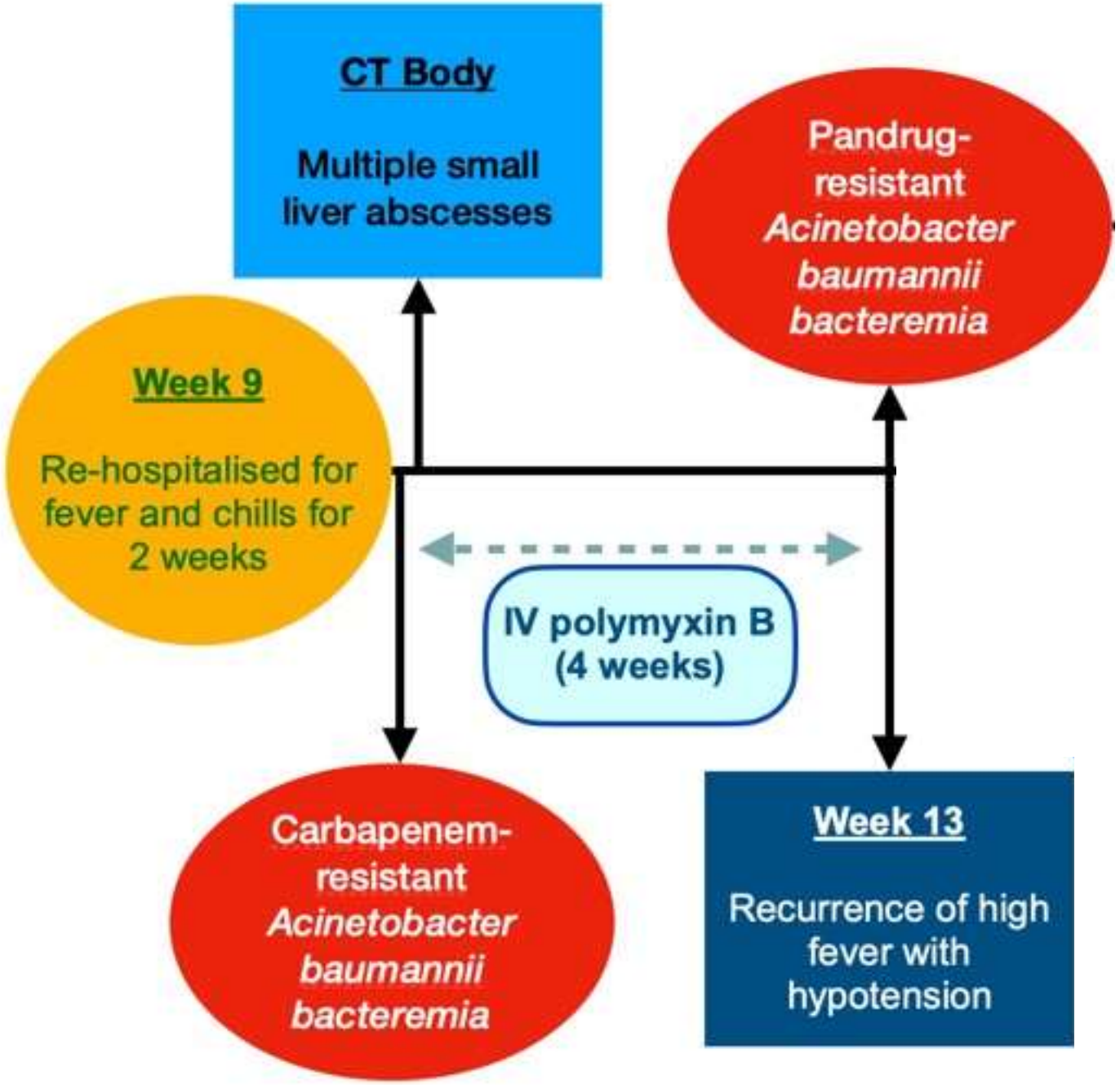
IV polymyxin B (4 weeks)

Carbapenem-resistant *Acinetobacter baumannii* bacteremia

Week 13

Recurrence of high fever with hypotension





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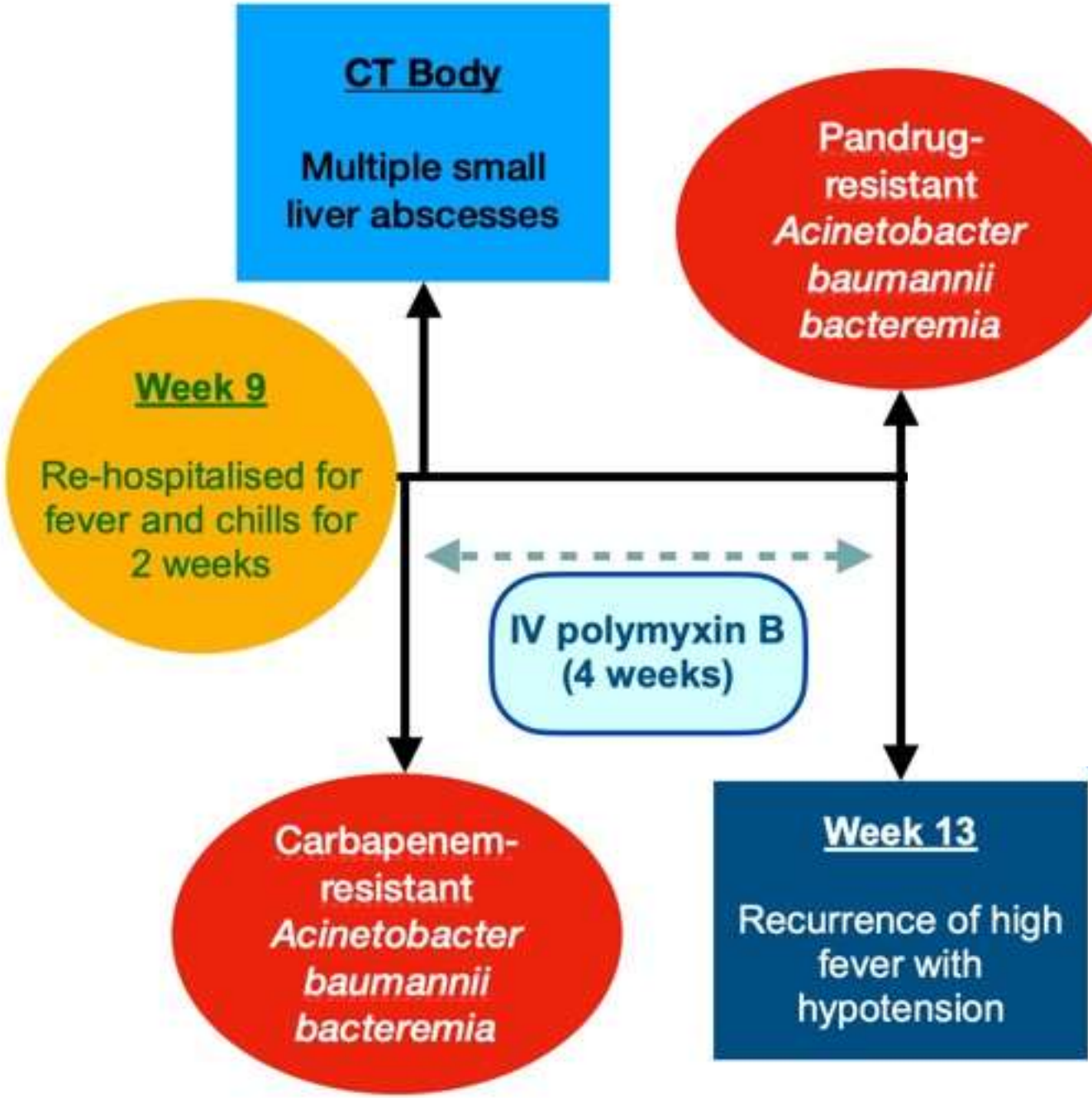
Meropenem	Resistant
Ciprofloxacin	Resistant
Trimethoprim/ Sulfamethoxazole	Resistant
Amikacin	Resistant
Tigecycline	Resistant
Polymyxin B	**R (MIC = 256)**



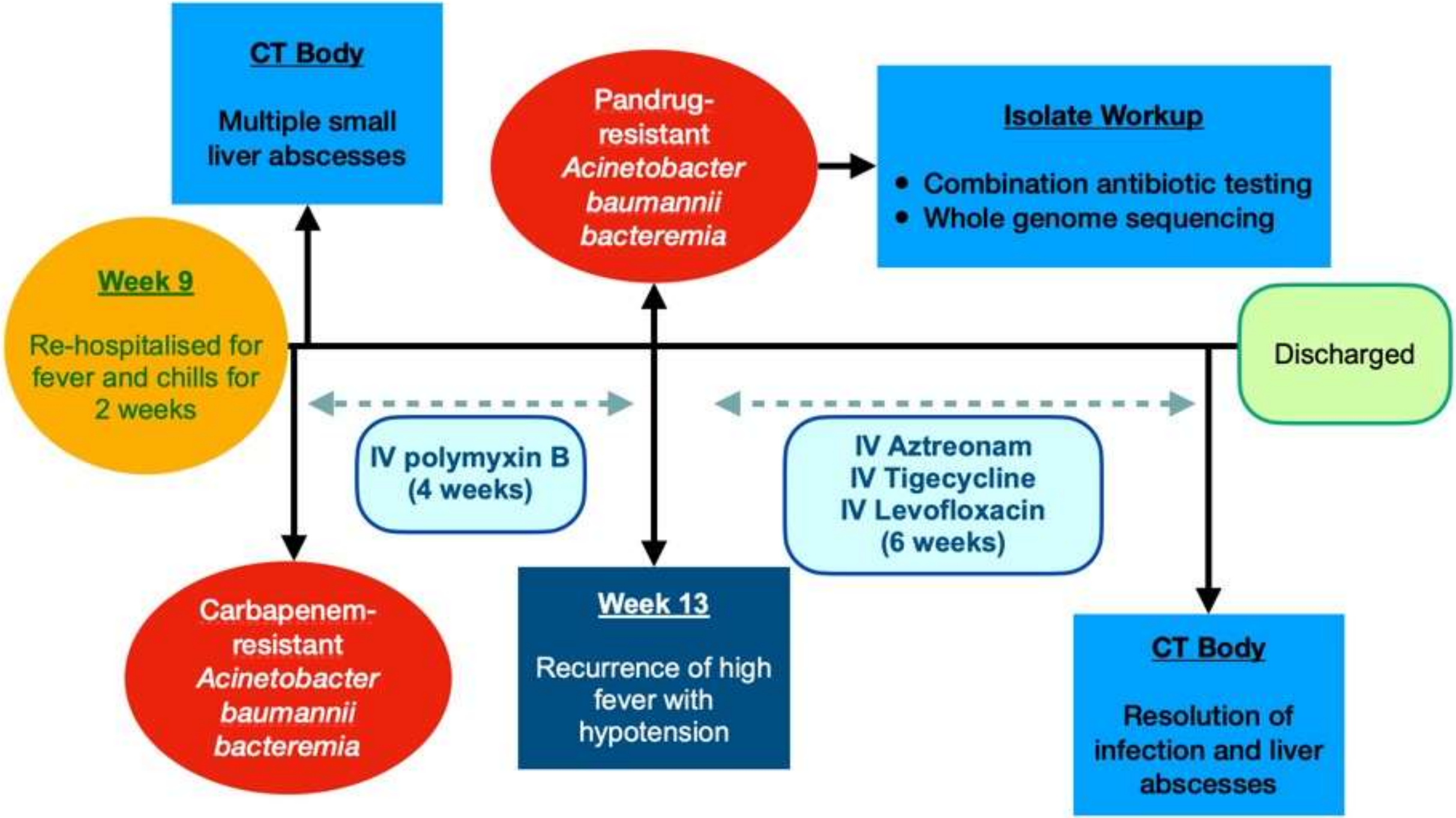
PLOS ONE

RESEARCH ARTICLE

Using an Adenosine Triphosphate Bioluminescent Assay to Determine Effective Antibiotic Combinations against Carbapenem-Resistant Gram Negative Bacteria within 24 Hours

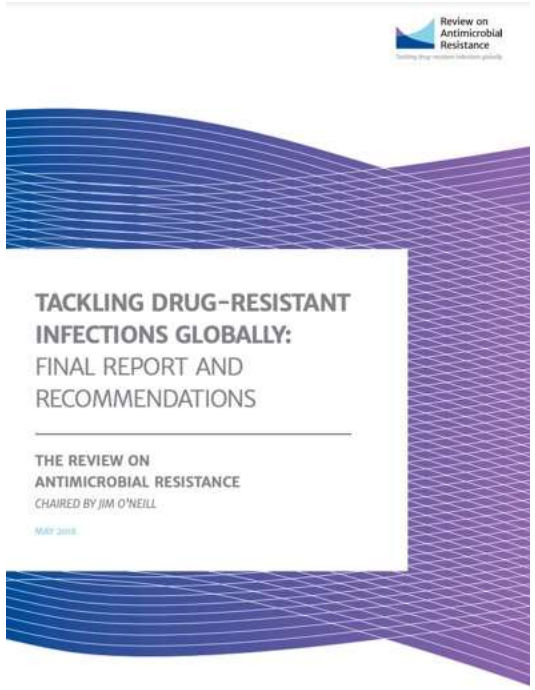
Yiying Cai[1], Hui Leck[1], Tze Peng Lim[1], Jocelyn Teo[1], Winnie Lee[1], Li Yang Hsu[2], Tse Hsien Koh[3], Thuan Tong Tan[4], Thean-Yen Tan[5], Andrea Lay-Hoon Kwa[1,6,7]*

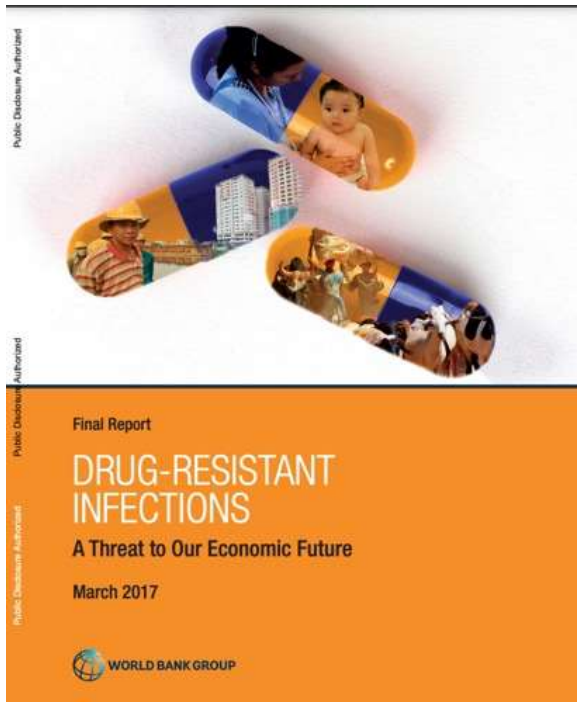
1 Department of Pharmacy, Singapore General Hospital, Singapore, Singapore, **2** Department of Infectious Diseases, National University Health Systems, Singapore, Singapore, **3** Department of Pathology, Singapore General Hospital, Singapore, Singapore, **4** Department of Infectious Diseases, Singapore General Hospital, Singapore, Singapore, **5** Department of Laboratory Medicine, Changi General Hospital, Singapore, Singapore, **6** Emerging Infectious Diseases, Duke-NUS Graduate Medical School, Singapore, Singapore, **7** Pharmacy, Faculty of Science, National University of Singapore, Singapore, Singapore


CT Body
Multiple small liver abscesses
Pandrug-resistant Acinetobacter baumannii bacteremia
Isolate Workup
Combination antibiotic testing
Whole genome sequencing
Week 9
Re-hospitalised for fever and chills for 2 weeks
Discharged
IV polymyxin B (4 weeks)
IV Aztreonam
IV Tigecycline
IV Levofloxacin
(6 weeks)
Carbapenem-resistant Acinetobacter baumannii bacteremia
Week 13
Recurrence of high fever with hypotension
CT Body
Resolution of infection and liver abscesses

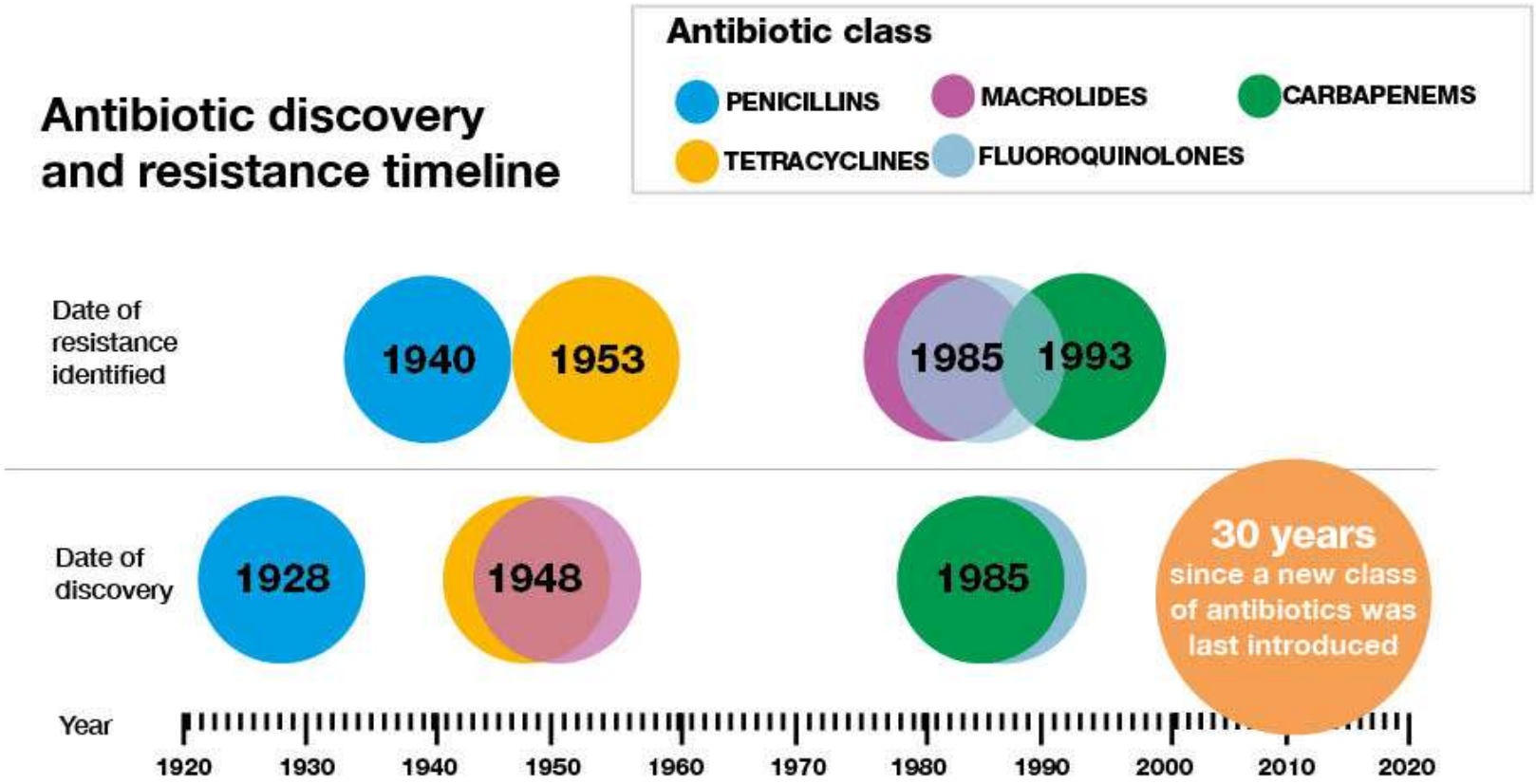
Antimicrobial Resistance

- One of the world's greatest public health threats
  - ≈1.2 million deaths in 2019
  - ≈10 million deaths per year by 2050
  - Annual global GDP fall of 1.1% - 3.8% by 2050





Antibiotic Pipeline



https://www.gov.uk/government/publications/health-matters-antimicrobial-resistance/health-matters-antimicrobial-resistance

Tracking the Global Pipeline of Antibiotics in Development, March 2021

ISSUE BRIEF March 9, 2021 Topics: Antibiotics Projects: Antibiotic Resistance Read time: 6 min

Antibiotics in Development Since 2014

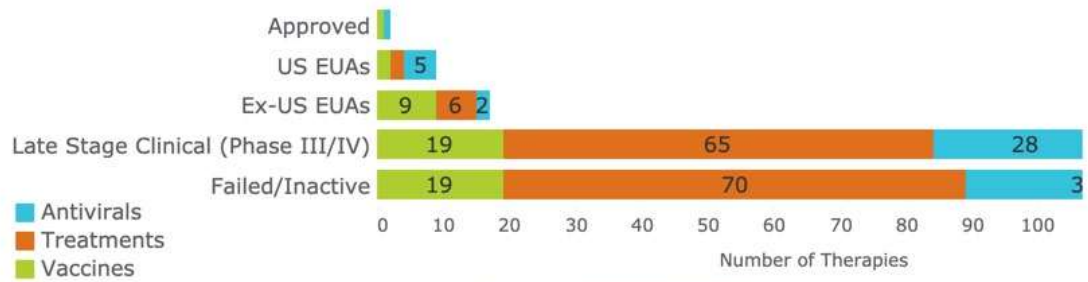
Biotechnology Innovation Organization

The COVID-19 Late Stage Clinical Pipeline by Phase and Strategy

Hover over each color to see the development strategy and use the development phase filter below to view only

Clinical Development Phase Filter

(Multiple values)



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Carbapenem-Resistant Gram-Negative Infections Top the List of AMR Threats

WHO priority pathogens list for R&D of new antibiotics

Priority 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

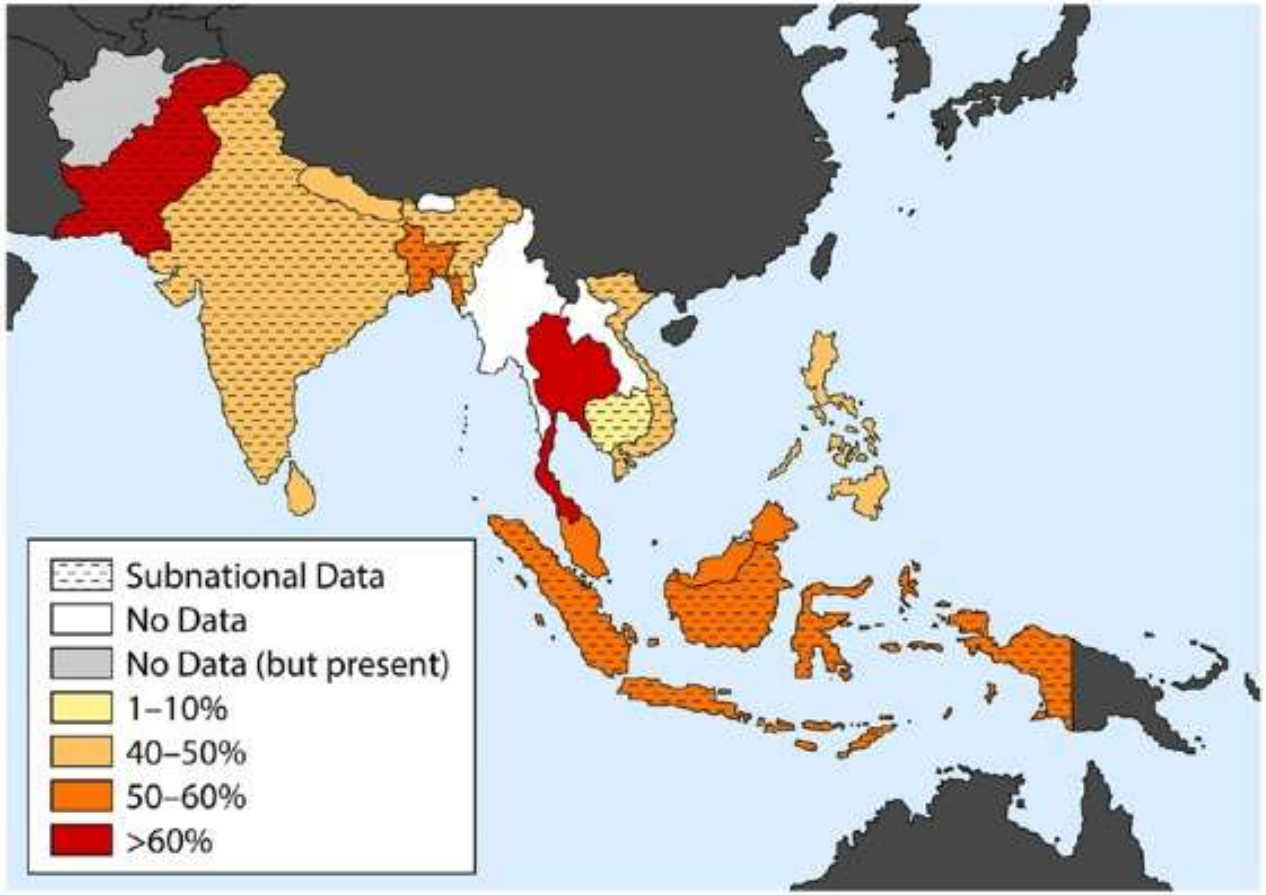
- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

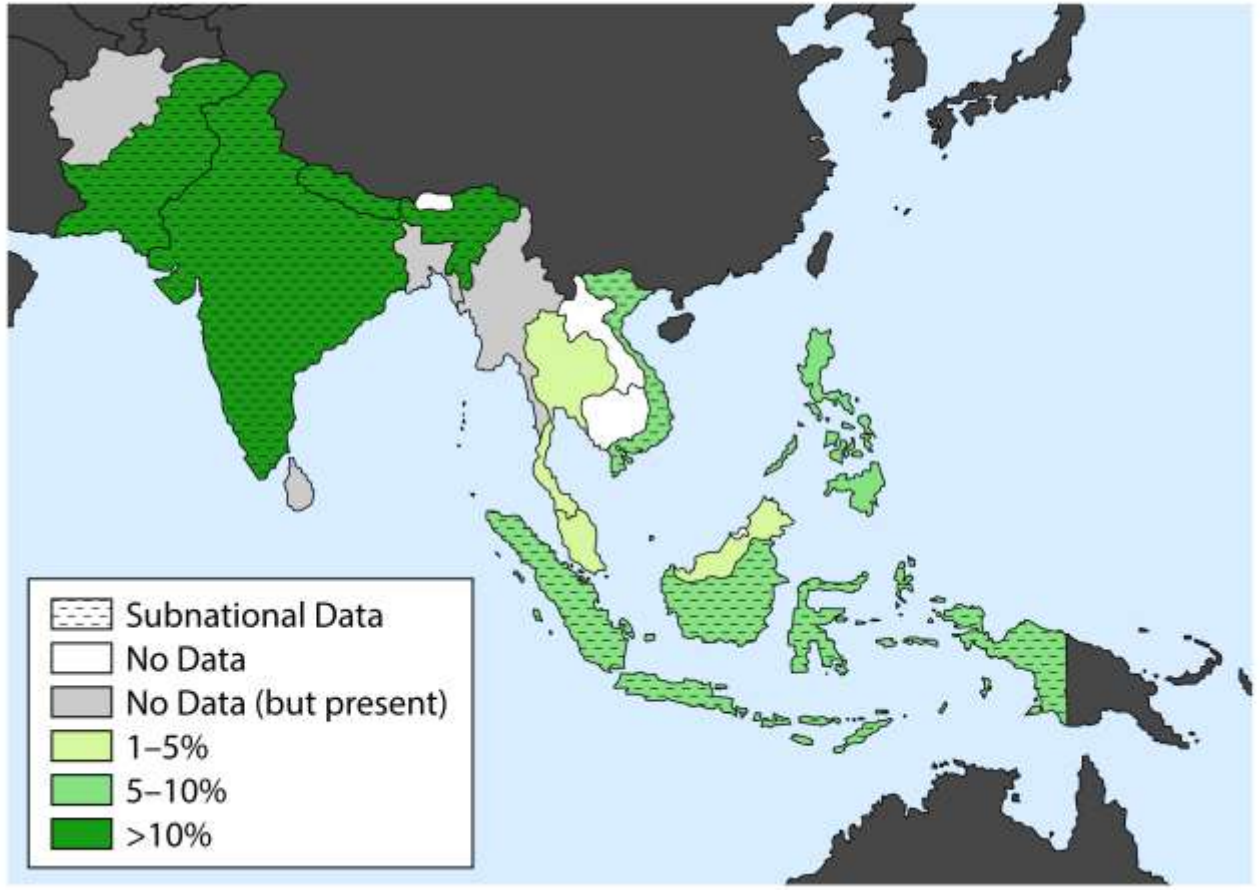
- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

Carbapenem-Resistant Gram-Negative Infections Top the List of AMR Threats

Carbapenem-Resistant *Acinetobacter baumannii*



Carbapenem-Resistant Enterobacterales



Clin Microbiol Rev. 2017. Enhanced by ScEYEnce Studios.

Mechanisms of Carbapenem Resistance

Acinetobacter baumannii

- Multiple carbapenemases (mainly OXA-23)
- Drug efflux pumps (minor)
- Altered membrane proteins (minor)

Enterobacterales

- ESBL/ampC + porin loss:
  - Generally low-level carbapenem resistance.
  - Poorly transmissible – primarily clonal spread.
- Plasmid-borne carbapenemases:
  - Variable (low- to high-level) carbapenem resistance.
  - Highly transmissible via plasmid transfer or clonal spread.
  - KPC, OXA, NDM, IMP, others

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0

Published by IDSA, 3/7/2022

A Focus on Extended-Spectrum β-lactamase Producing Enterobacterales, Carbapenem-Resistant Enterobacterales, and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance

Carbapenem-Resistant Enterobacterales

Carbapenemase absent	High-dose meropenem (if susceptible)
	Otherwise see below
Carbapenemase present	Meropenem-vaborbactam
	Ceftazidime-avibactam (+/- Aztreonam)
	Imipenem-relebactam
	Cefiderocol
	*Tigecycline or Eravacycline
	**Polymyxins

*Used if resistant to beta-lactams or patient allergic. Not recommended for urinary tract or bloodstream infections
**Not recommended alone or in combination

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

Published by IDSA, 3/31/2022

A focus on AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Carbapenem-Resistant *A. baumannii*

Mild infections	Ampicillin/sulbactam (if susceptible)
	Otherwise other single agents as susceptible
Severe infections	*Combination therapy preferred until clinical response seen
	High-dose ampicillin/sulbactam AND/OR
	Polymyxin B AND/OR
	Tigecycline AND/OR
	Minocycline
	**Colistin

*However, lack of reliable clinical trial data

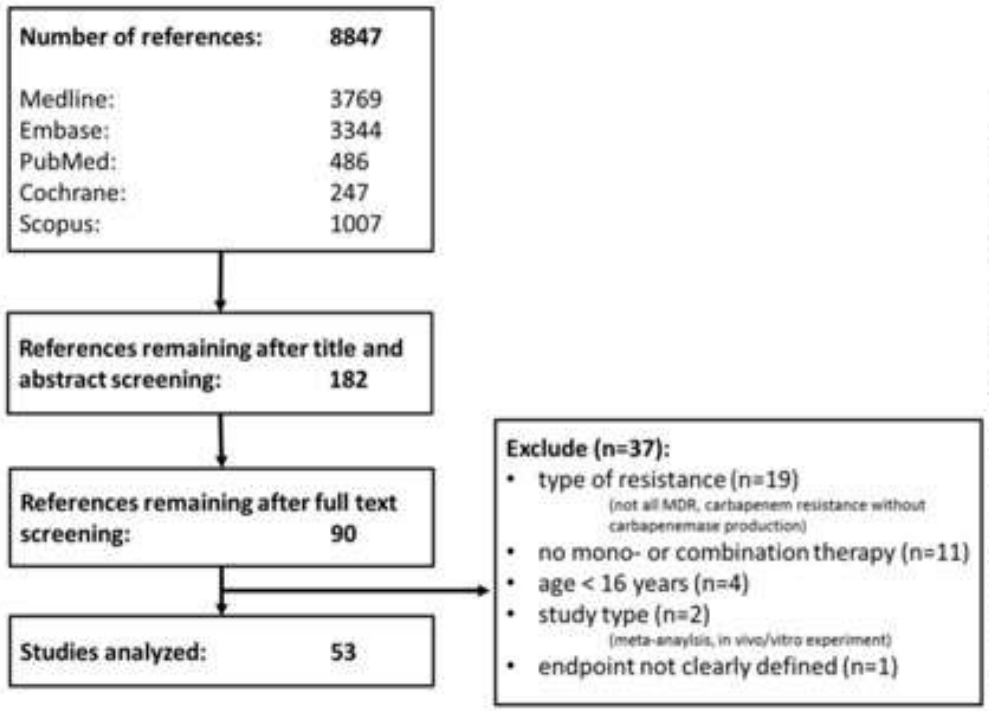
**Less preferred compared to Polymyxin B (less favorable pharmacokinetic profile)

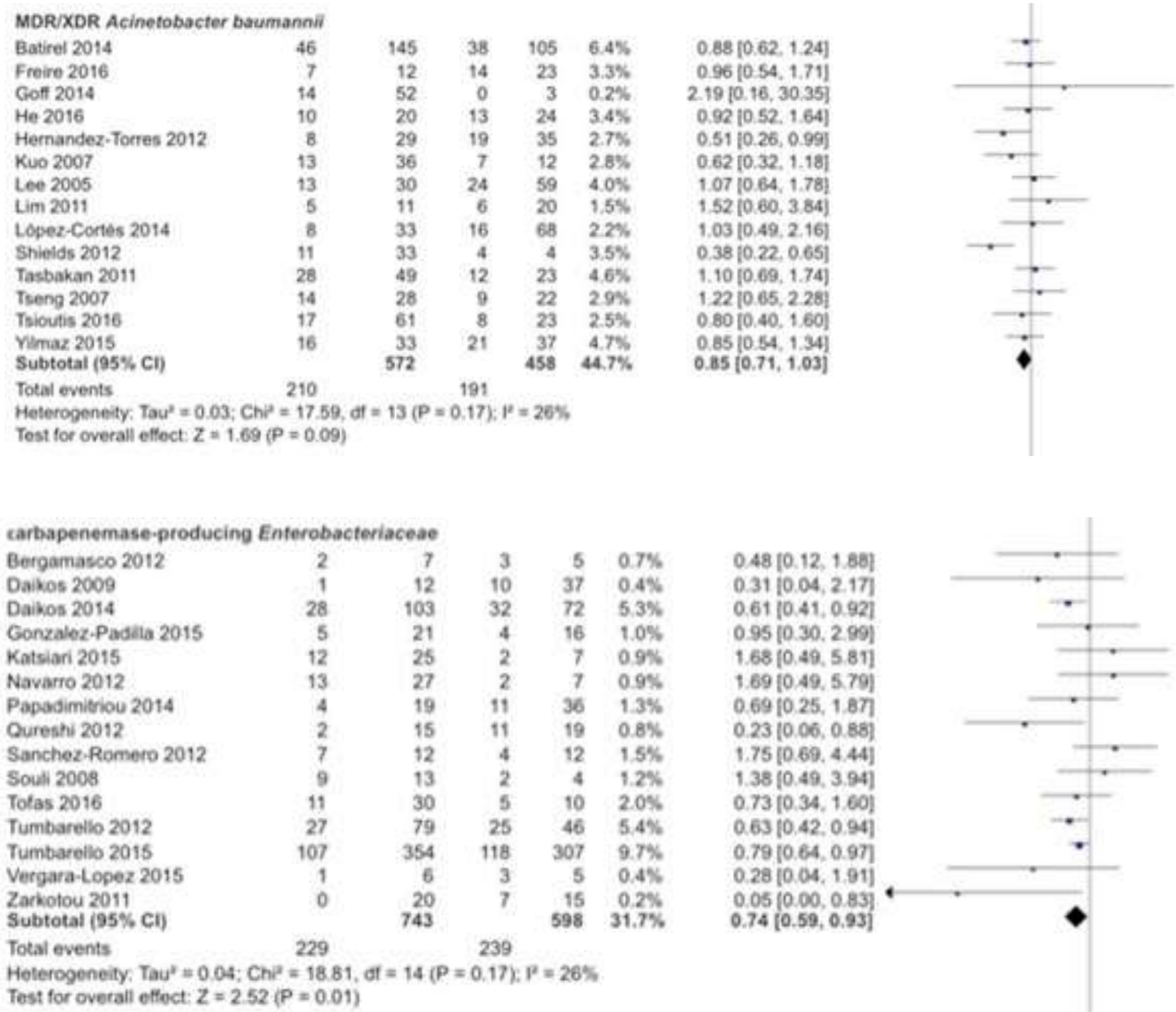
SCIENTIFIC REPORTS
nature research

OPEN

Monotherapy versus combination therapy for multidrug-resistant Gram-negative infections: Systematic Review and Meta-Analysis

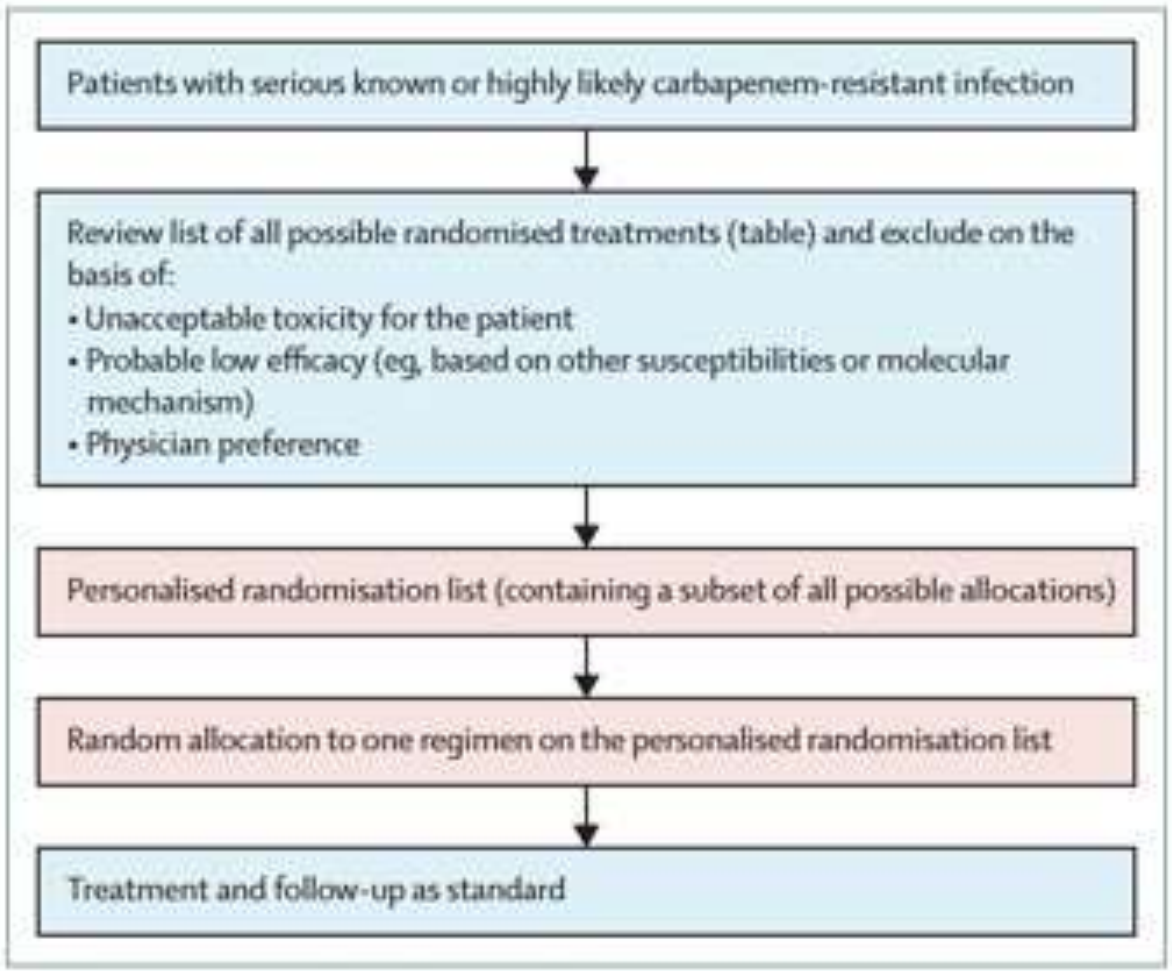
Adrian Schmid, Aline Wolfensberger, Johannes Nemeth, Peter W. Schreiber, Hugo Sax & Stefan P. Kuster*

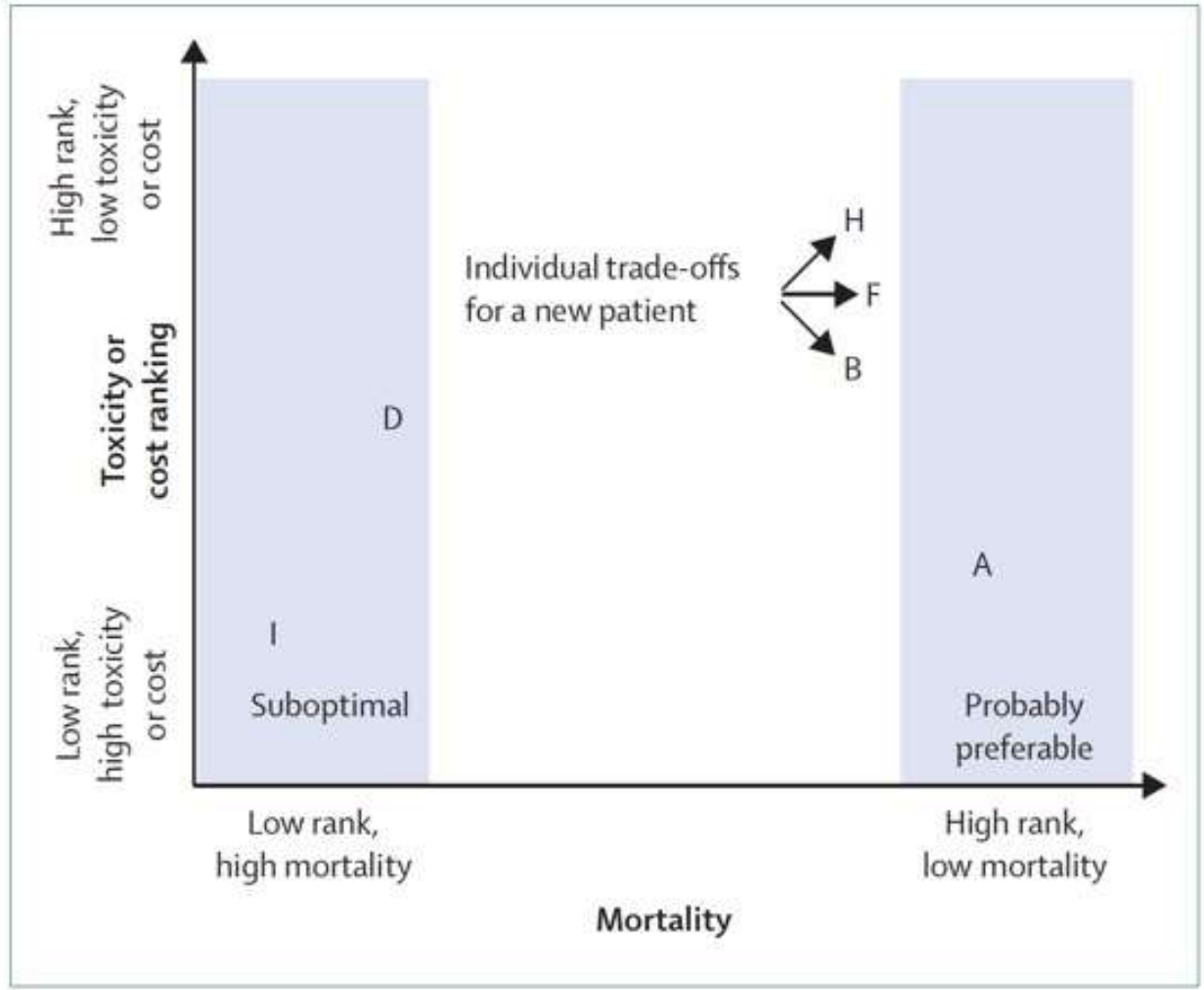




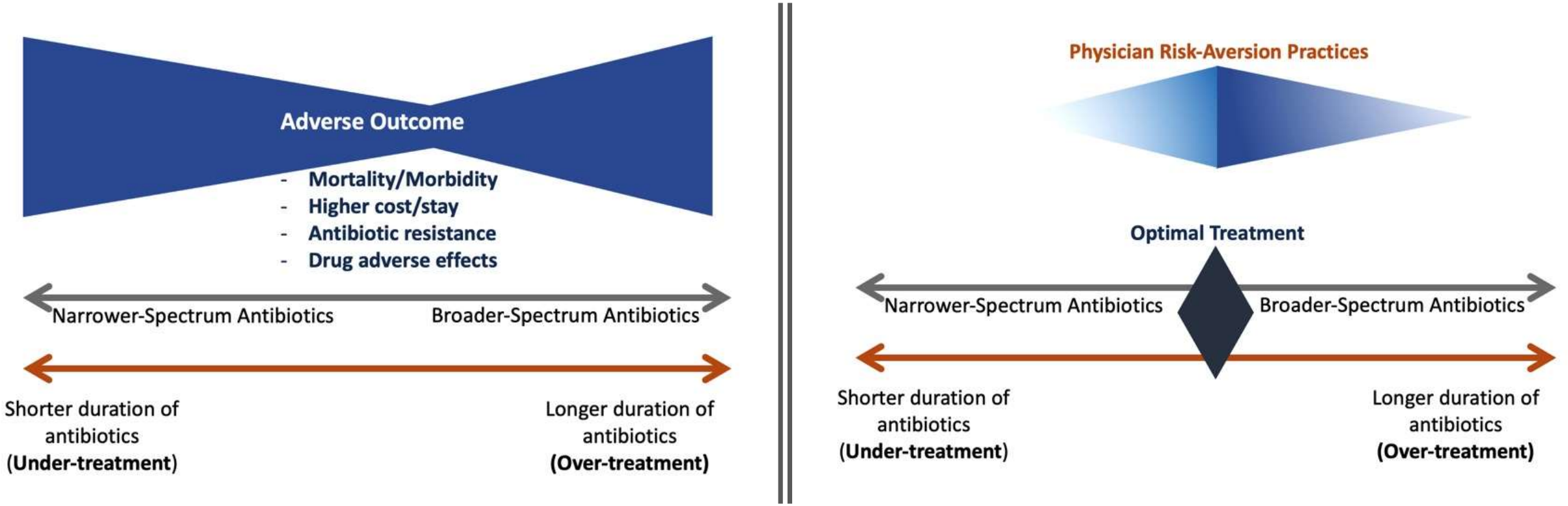
Personalised randomised controlled trial designs—a new paradigm to define optimal treatments for carbapenem-resistant infections

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





Antibiotic Prescription Spectrum

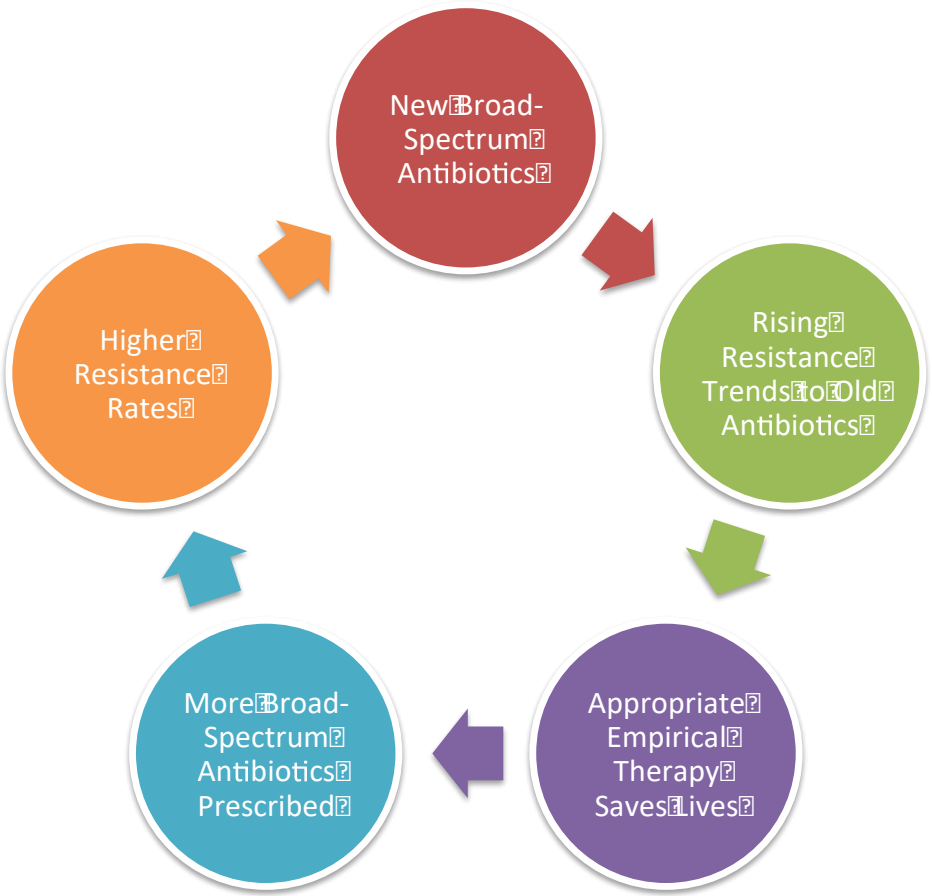


On average, 30% of antimicrobial prescriptions are inappropriate.

Decision to have antimicrobial stewardship – given sufficient resources – is completely logical.

“The Culture of Antibiotic Prescription”

- “Broader is better”
- “Failure to respond is failure to cover”
- “When in doubt, change drugs or add another”
- “More diseases = more drugs”
- “Antibiotics are nontoxic”



Kim JH, et al. Am J Med. 1989;87:201-6.

Control of AMR – “30,000 feet view”

- Recommendations by the Interagency Coordination Group on Antimicrobial Resistance (IACG)
  - Accelerate progress in countries
    - Equitable and affordable access to existing and new antimicrobials, vaccines and diagnostics
    - Prudent use of the above by licensed professionals in human, animal and plant health.
    - Phase out use of antimicrobials for growth promotion.
    - Accelerate development and implementation of national AMR plans.

  - Innovate to secure the future
    - Increase investment and innovation in new antimicrobials, diagnostics, vaccines, waste management, and alternatives to antimicrobials.
    - Strengthen implementation and operational research and research coordination and collaboration in a One Health context.

IACG Final Report. https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf?ua=1

Conclusion

Carbapenem- and multidrug-resistant Gram-negative bacteria are a global health threat.

Current evidence for optimal treatment of these bacteria is not robust.

An approach to reduce the impact of AMR must be balanced between reducing selection pressure of antibiotics as well as strengthening the antibiotic pipeline.


THE COSTS AND DIFFICULTY OF DEVELOPING NEW TREATMENTS TO FIGHT BACTERIA ALSO KEEPS GOING UP...
WHICH MEANS THE TREATMENTS BECOME MORE EXPENSIVE AND LESS ACCESSIBLE...
AND THIS HAS A REAL IMPACT ON THOSE WHO ARE LESS WELL-OFF, ESPECIALLY IN LOWER INCOME COUNTRIES.
TODAY, AN ESTIMATED 700,000 PEOPLE DIE EACH YEAR FROM DRUG-RESISTANT INFECTIONS...
AND SOME EXPERTS PREDICT THAT IF WE DON'T CHANGE OUR WAYS, THAT NUMBER COULD RISE TO TEN MILLION BY 2050.
SO...

The End