

**FOCUS**

# **LOTTA ALLE INFEZIONI CORRELATE ALL'ASSISTENZA**

**MOTORE  
SANITÀ**  
Innovazione Sostenibile

## **La Microbiologia dalla diagnostica alla ricerca**

Anna Teresa Palamara



**ROMA, 23 GENNAIO 2020**

# First report on antibiotic-resistance

No. 3713, DEC. 28, 1940

NATURE

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## LETTERS TO THE EDITORS

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IN THE PRESENT CIRCUMSTANCES, PROOFS OF "LETTERS" WILL NOT BE SUBMITTED TO CORRESPONDENTS OUTSIDE GREAT BRITAIN.

### An Enzyme from Bacteria able to Destroy Penicillin

*B. coli*, it was not necessary to crush the organism in the bacterial mill in order to obtain the enzyme from it; the latter appeared in the culture fluid.

E. P. ABRAHAM.

E. CHAIN.

*"There is probably no chemotherapeutic drug to which in suitable circumstances the bacteria cannot react by in some way acquiring 'fastness' [resistance]."*

—Alexander Fleming, 1946







# Consumo di antibiotici

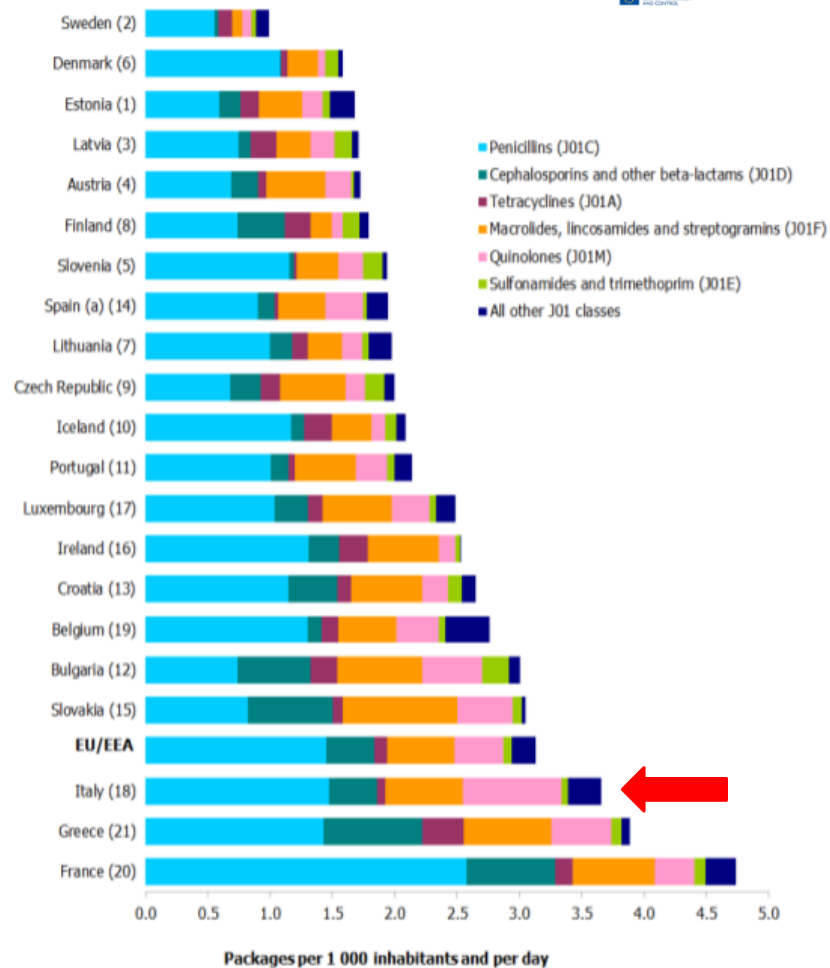
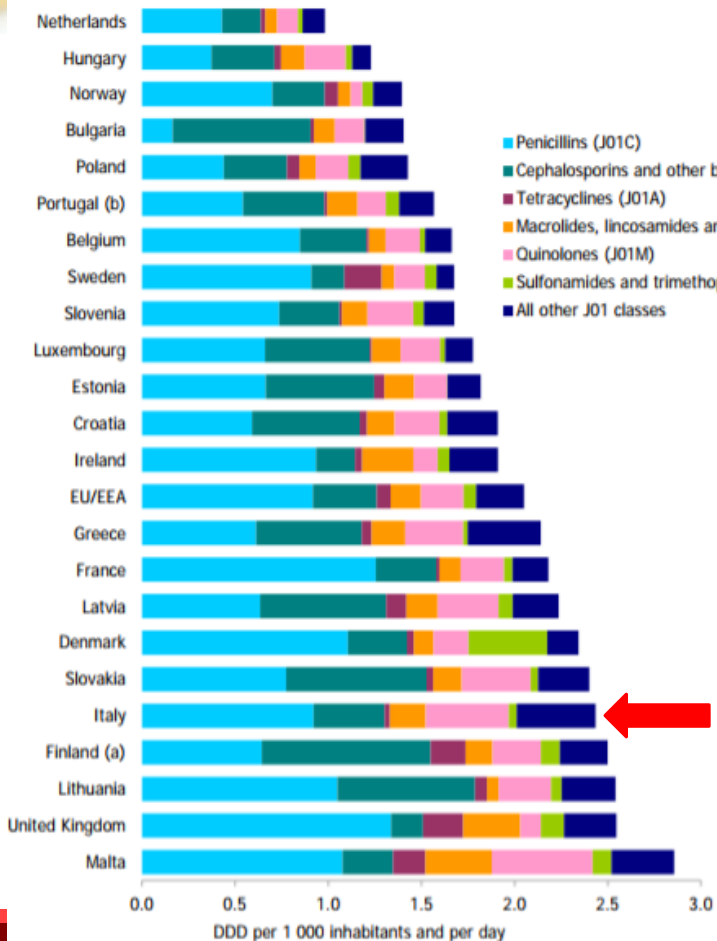
## Ambiente nosocomiale



## Tra la popolazione



## In agricoltura





## Incidence and antimicrobial resistance trends in bloodstream infections caused by ESKAPE and *Escherichia coli* at a large teaching hospital in Rome, a 9-year analysis (2007–2015)

Giulia De Angelis<sup>1</sup> · Barbara Fiori<sup>1</sup> · Giulia Menchinelli<sup>1</sup> · Tiziana D’Inzeo<sup>1</sup> · Flora Marzia Liotti<sup>1</sup> · Grazia Angela Morandotti<sup>1</sup> · Maurizio Sanguinetti<sup>1</sup> · Brunella Posteraro<sup>2</sup> · Teresa Spanu<sup>1</sup>

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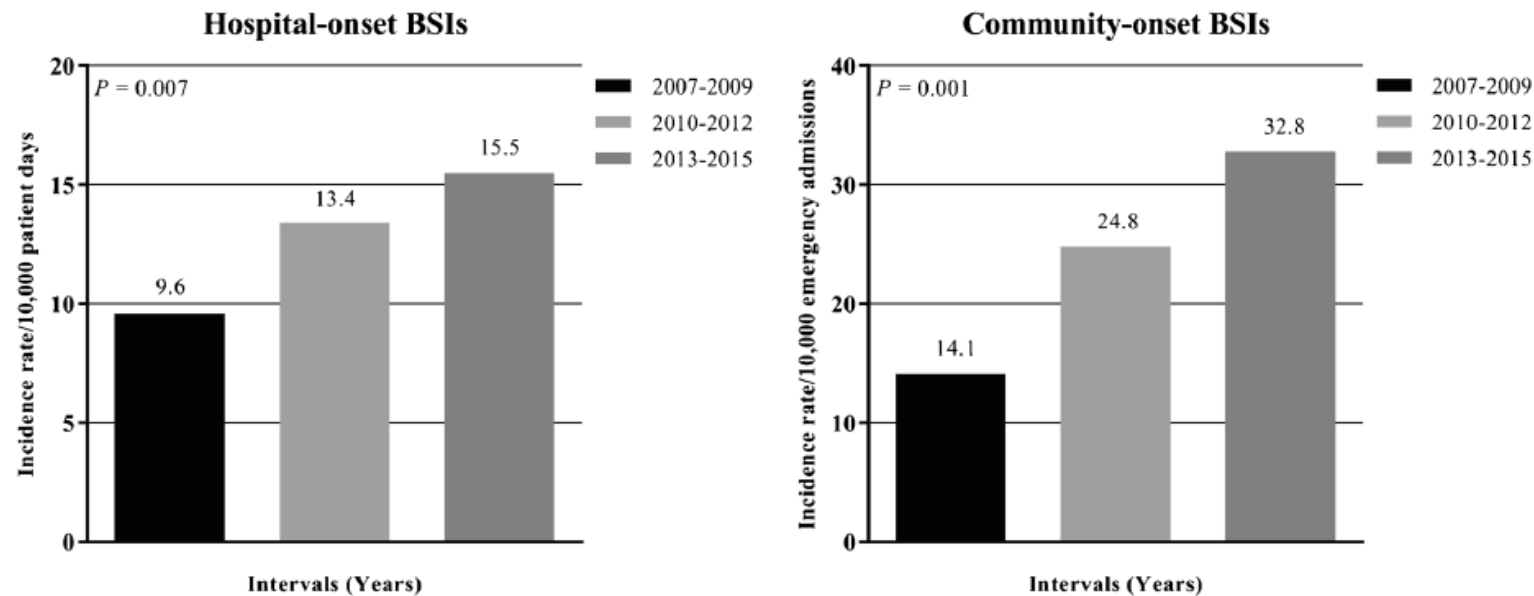
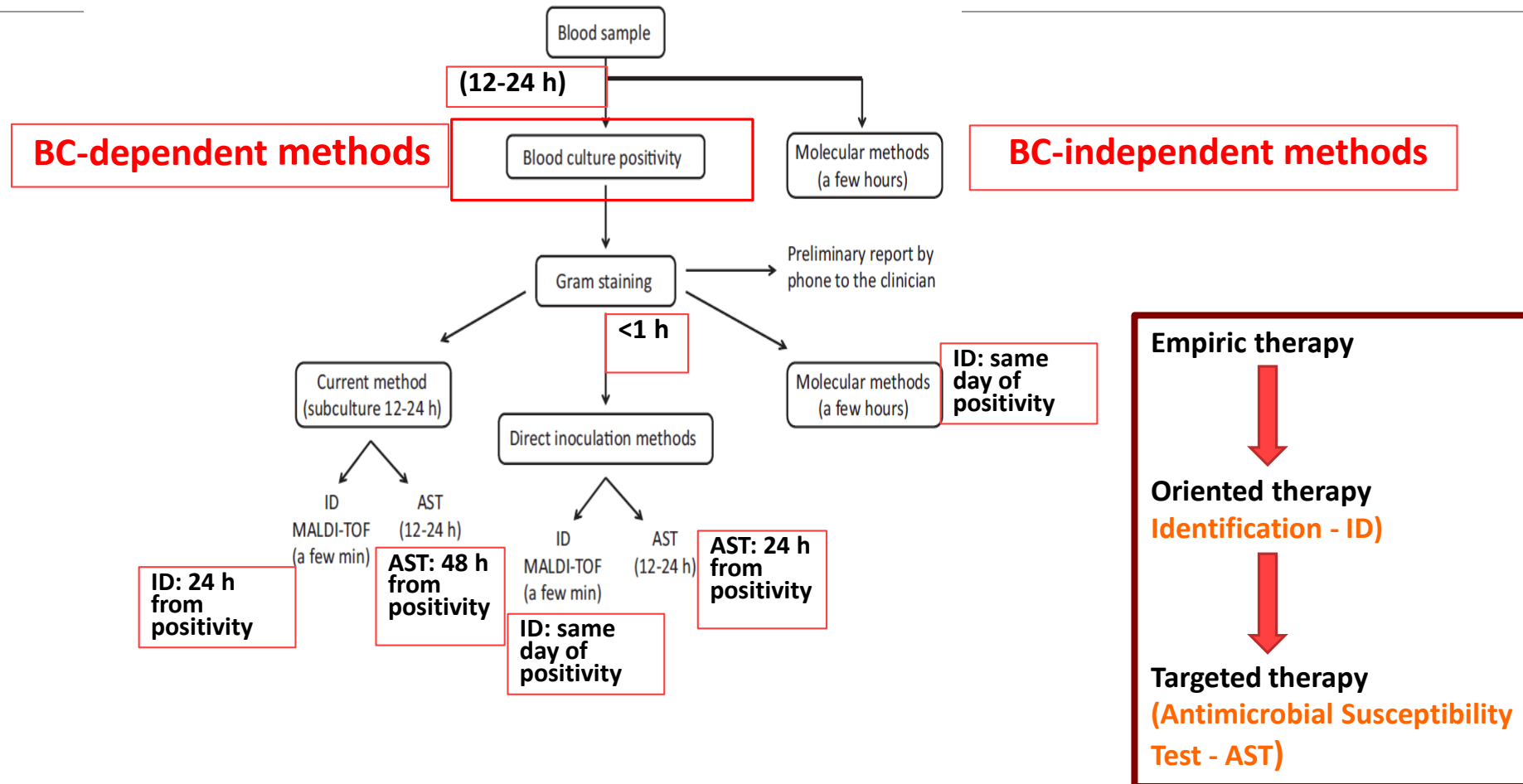


Fig. 1 Incidence rates of bloodstream infections (BSIs) in three 3-year intervals (2007 to 2015), according to the onset (hospital or community) of BSI

# Standard methods and Rapid Diagnostic Tests in Sepsis



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## L'innovazione tecnologica può essere efficace solo se inserita nel giusto modello organizzativo

L'accorciamento dei tempi di diagnosi, deve tener conto delle numerose variabili che rendono ogni laboratorio diverso dall'altro:

- Personale
- Turni di apertura
- Parco tecnologico e reali possibilità applicative
- Sensibilità e disponibilità del management sanitario
- Sensibilità e disponibilità del personale sanitario
- .....

*Le tecniche di diagnostica rapida  
sono potenzialmente in grado di  
rivoluzionare il percorso clinico-  
microbiologico del paziente settico  
e di offrire un contributo  
determinante ai programmi di  
stewardship antimicrobica*

*Dal momento che si tratta di  
tecnologie ad alto costo, è  
essenziale prevedere una  
implementazione selezionata e  
razionale al fine di garantire un  
utilizzo sostenibile e direi equo*

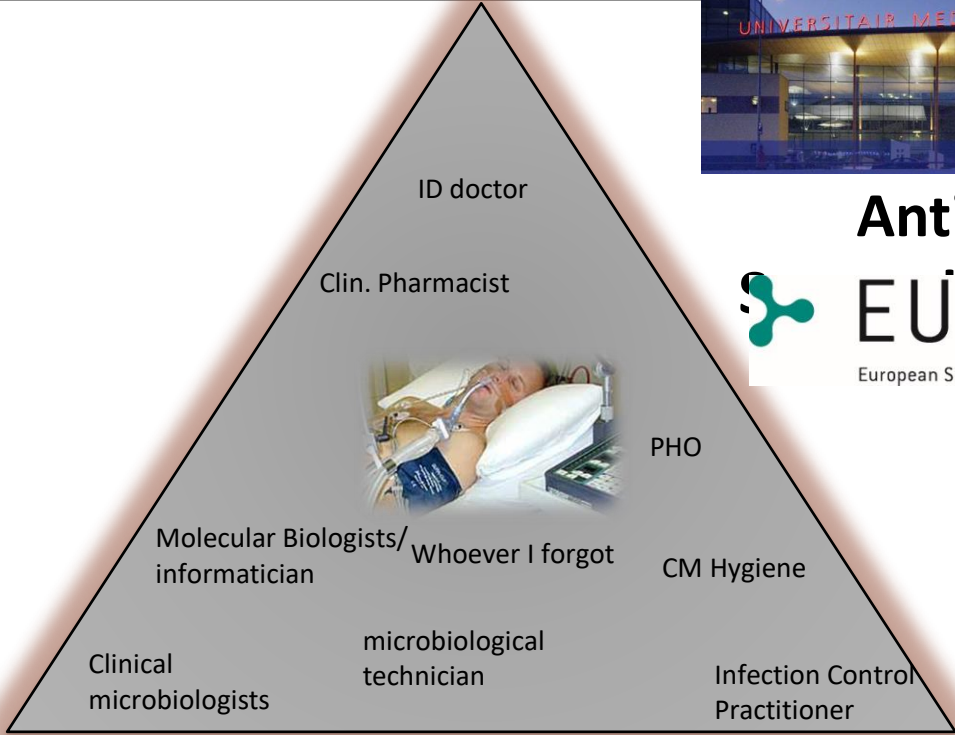
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# Il modello olandese



Medical Microbiology and Infection Prevention  
 University Medical Center Groningen  
 Netherlands



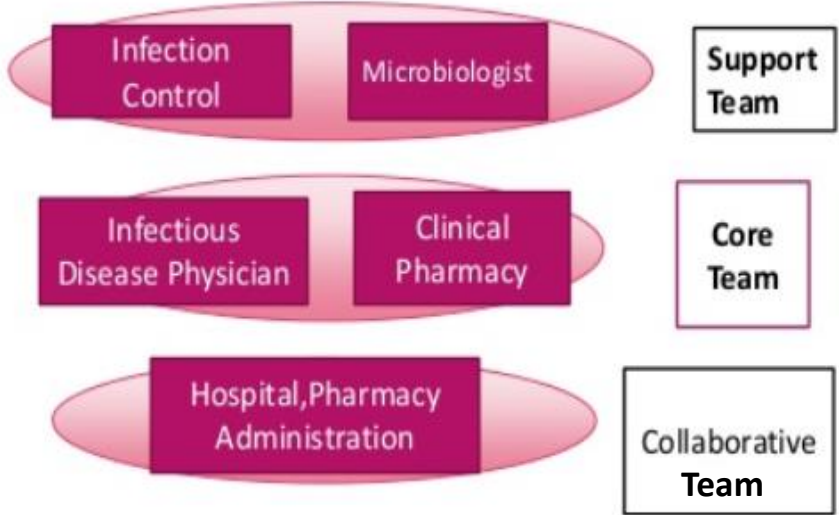
## Antimicrobial



## Diagnostic Stewardship

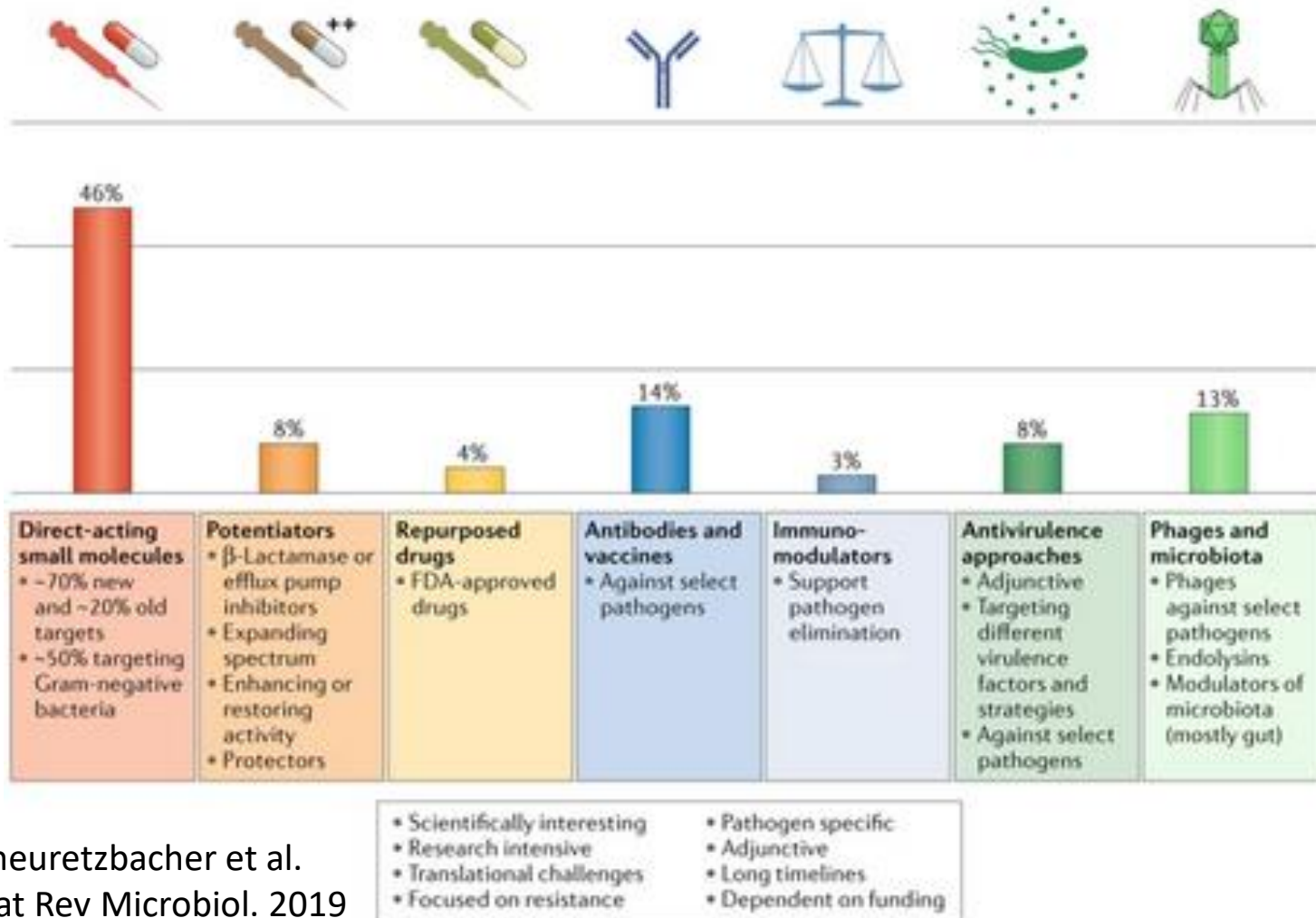
Dik et al. 2015 Future Microbiology  
 Zingg et al. 2015 CMI

## Infection Prevention Stewardship



# The global preclinical antibacterial pipeline

407 preclinical antibiotic projects from 314 institutions (81% small and medium-sized enterprises)



## ANTIMICROBIALS

### New drugs for the antibacterial pipeline?

“these studies highlight the importance of investing in discovery platforms”

Over the past 50 years, the rate of antibiotic discovery has plummeted while the incidence of resistance has soared. The decreasing effectiveness of antibiotics is one of the greatest health threats of our time and in response, the WHO has published a list of bacteria for which new antibiotics are urgently needed. Now, two recent studies report new compounds that could be useful in combating antibiotic resistance.

First, Meyer et al. discovered a new antibiotic that selectively kills Gram-negative pathogens. In their search, the authors reasoned that useful compounds might be found in symbionts that have a need to produce antibiotics (for example, to fend off invasive species) that are non-toxic to their host. The authors focused on symbionts of entomopathogenic nematodes and screened a library of *Fluorohabibus* and *Xenorhabdus* strains for the ability to inhibit *Escherichia coli* growth in vitro. A concentrated extract of *Fluorohabibus iblandi* produced a zone of inhibition, and using high performance liquid chromatography, the active fraction

of the extract was identified. Subsequent mass spectrometric fragmentation and NMR elucidated the structure of the active compound,

### DAROBACTIN

crossed by a novel, non-enzymatic, cyclic diester (air operon) and is ribosomally synthesized. Darobactin was found to have activity against a range of Gram-negative pathogens (for example, *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*), including polymyxin-resistant, extended spectrum  $\beta$ -lactamase-producing or carbapenem-resistant clinical isolates, in vitro and in a mouse model. By contrast, low activity was detected against Gram-positive bacteria.

To identify the target of darobactin, the authors performed evolution experiments with *E. coli*, which led to the isolation of darobactin-resistant mutants. All mutations mapped to BamA, an essential component of the  $\beta$ -barrel assembly machinery (BAM) complex, which catalyses the folding and insertion of  $\beta$ -barrel outer membrane proteins. Darobactin was found to interact directly with BamA and inhibit BAM activity, and NMR studies suggest that darobactin stabilises the BAM complex in a gate-closed conformation, preventing the assembly of a functional outer membrane.

In a different study, El-Halloufy et al. discovered an antivirulence compound that reverses  $\beta$ -lactam resistance in methicillin-resistant *Staphylococcus aureus* (MRSA). Antivirulence compounds are a promising alternative or adjunct to antibiotics as they do not impose strong selective pressures

of the extract was identified. Subsequent mass spectrometric fragmentation and NMR elucidated the structure of the active compound, that lead to the evolution of resistance. The authors performed a high-throughput cell-based screen of ~45,000 compounds in test, with the aim of identifying molecules that both attenuate and reverse antibiotic resistance; the screen was designed to identify compounds that target cell envelope virulence factors and synergise with the  $\beta$ -lactam carbapenem. The authors identified a potent compound (MAC-545496) that reversed resistance in various  $\beta$ -lactam antibiotics (that is, decreased the minimum inhibitory concentration), including penicillins, cephalosporins and the carbapenems. [Meyer et al. 2019](#)

### MAC-545496

resistance. MAC-545496 could inhibit virulence alone in *Galleria mellonella* larvae infected with *S. aureus* and was found to inhibit biofilm formation and reduce survival of *S. aureus* within macrophages, suggesting that it could be useful in treating MRSA infections.

Together, these studies highlight the importance of investing in discovery platforms, as they can uncover new sources of urgently needed antibacterial drugs. [Astley Turk](#)



# Education

Educate the clinicians for appropriate antibiotic prescribing



About 50% of the antibiotic prescriptions, both in the community and in hospitals, can be considered inappropriate (inadequate dosing and wrong duration)

Educate patients, children (e.g., through schools and day care), the public, and other relevant healthcare professionals (e.g., primary-care staff, pharmacists, dentists and medical students) regarding prudent antibiotic prescribing and personal hygiene (e.g., handwashing)



Lee et al. Int J Environ Res Public Health. 2013



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ANNA TERESA PSLSMARA  
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DANIELA SCRIBANO



**SUPERBATTERI:**  
Quel che non uccide  
rende resistenti