به نام خدای بخشاینده مهربان

Fabiotic, the next generation Anti-staphylococcal Antibiotic

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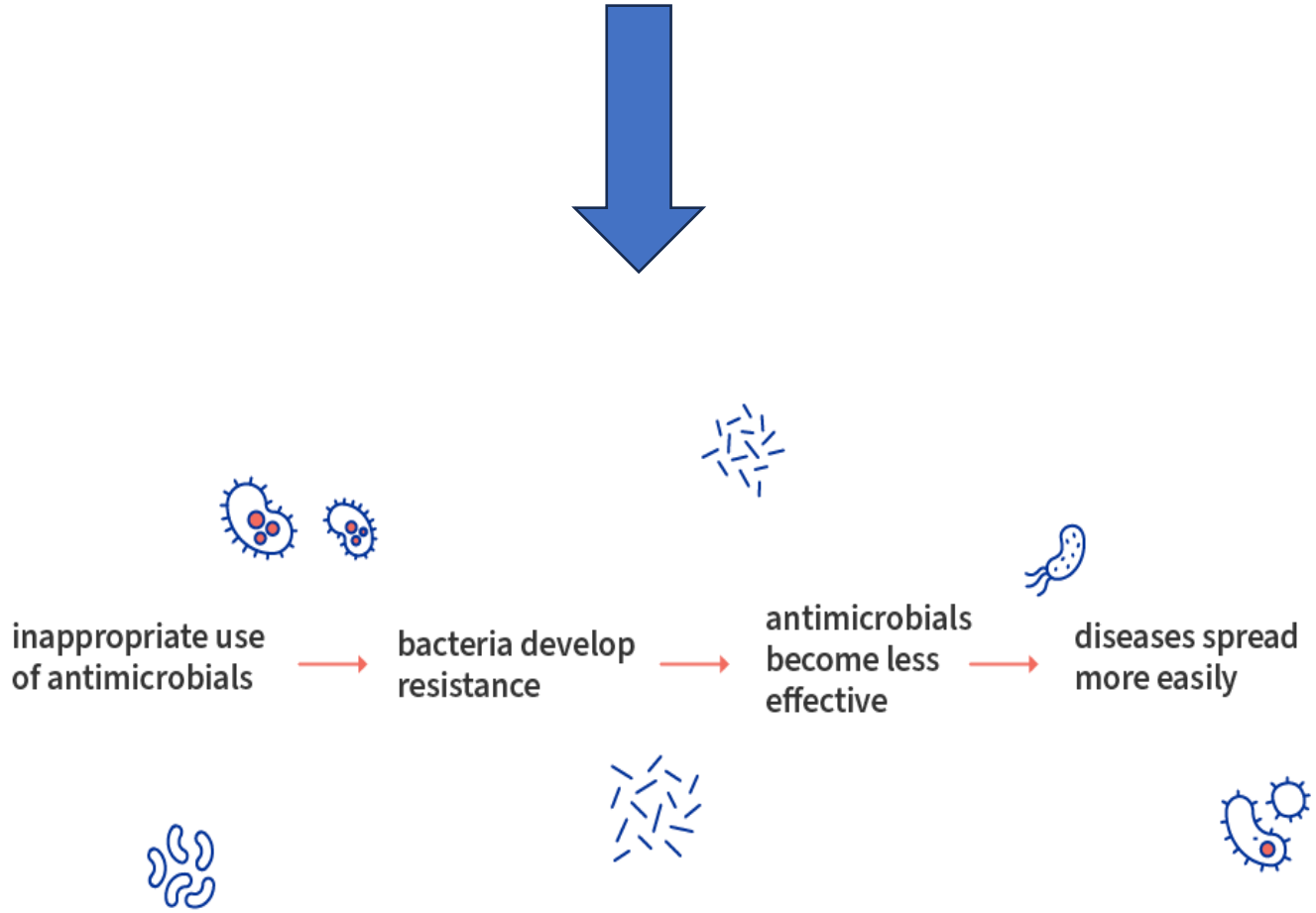
Outline

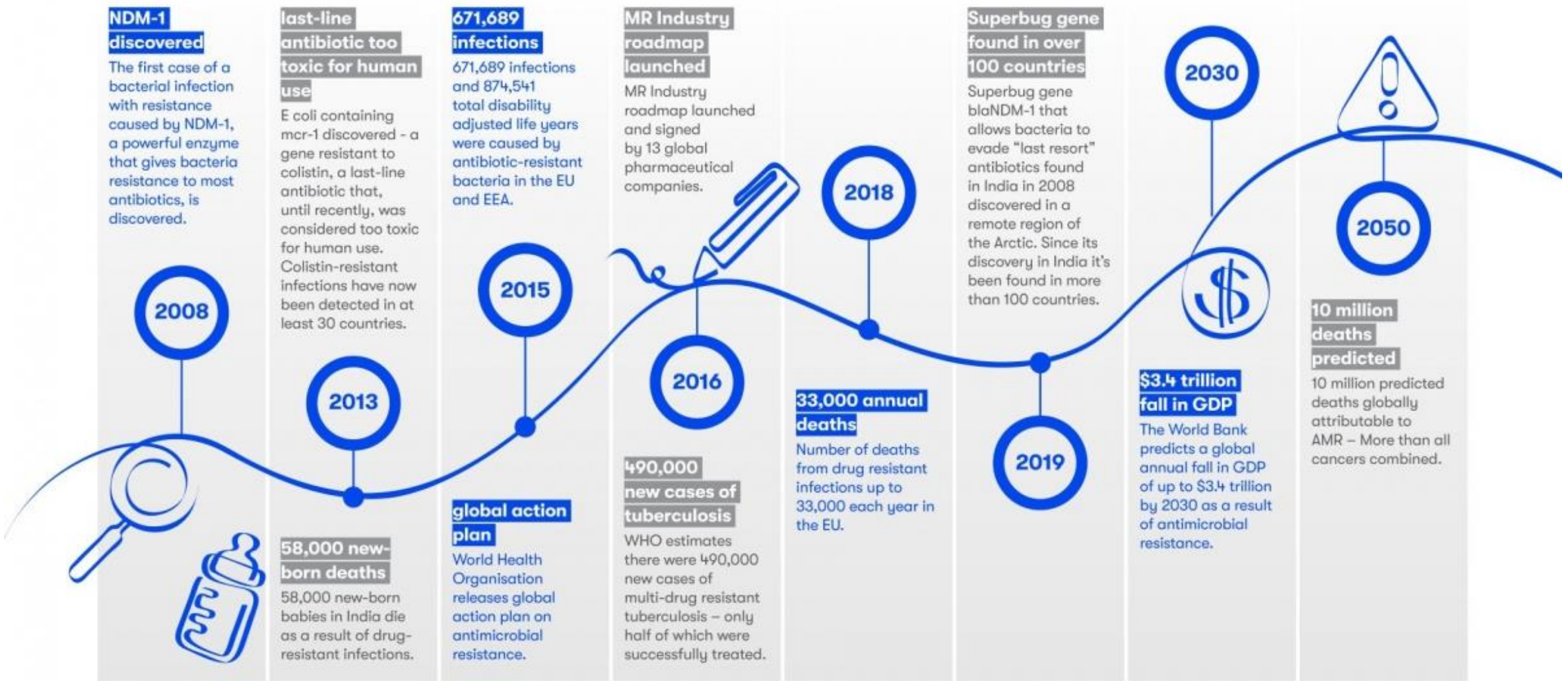
- Introduction
- What is Fabiotic?
- Clinical trials
- Conclusion

Introduction

- Antimicrobial resistance (AMR)



Antimicrobial Resistance
Timeline



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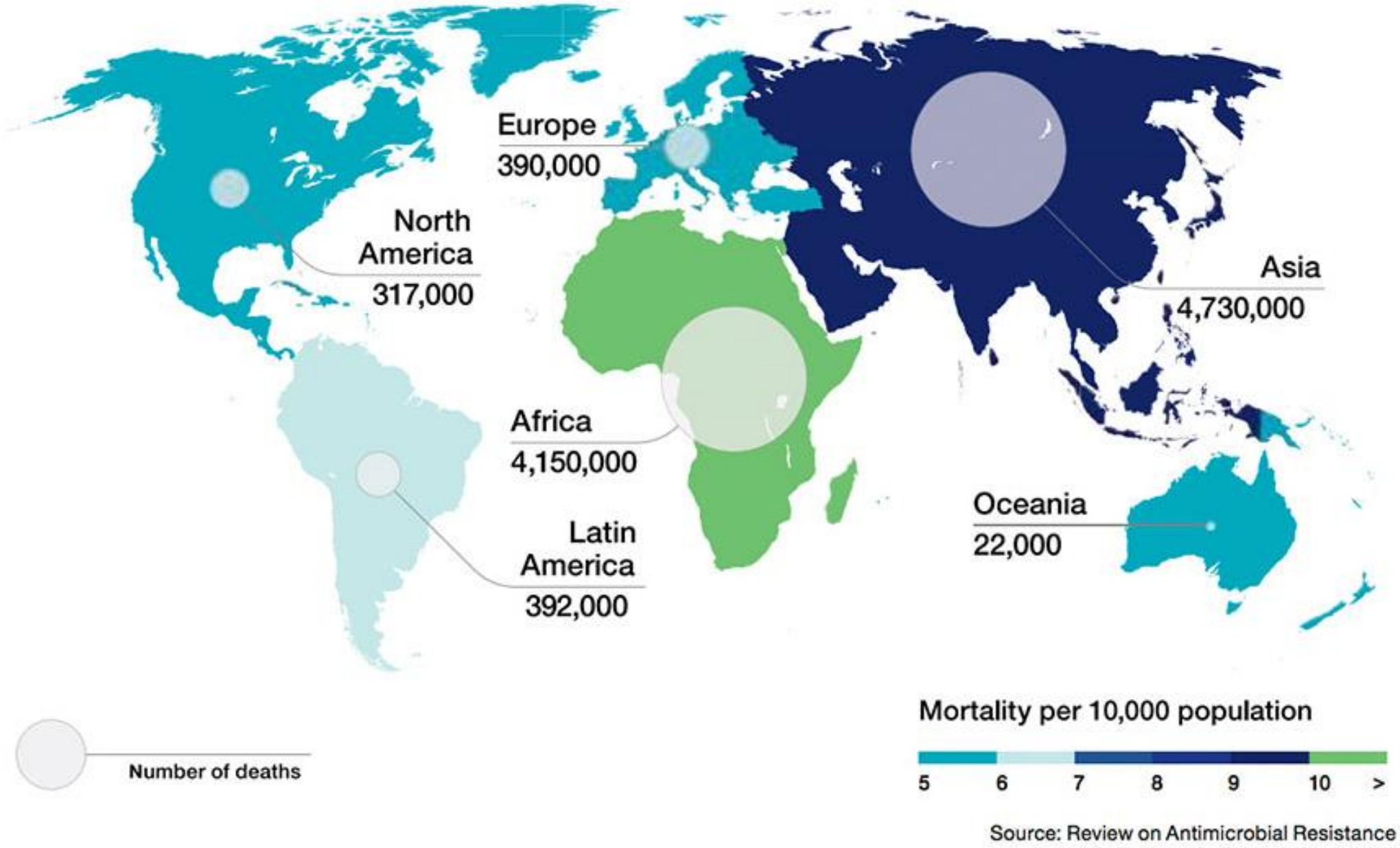

EUROPEAN ANTIBIOTIC AWARENESS DAY

A EUROPEAN HEALTH INITIATIVE

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EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

EU ANTIMICROBIAL RESISTANCE (AMR) TARGETS BY 2030:

Reduce by 20% the total consumption of antibiotics in humans.

At least 65% of the total consumption of antibiotics in humans belongs to the 'Access' group of antibiotics.

Reduce by 15% the total incidence of bloodstream infections with meticillin-resistant MRSA *Staphylococcus aureus*.

Reduce by 10% the total incidence of bloodstream infections with third-generations cephalosporin-resistant *Escherichia coli*.

Reduce by 5% the total incidence of bloodstream infections with carbapenem-resistant *Klebsiella pneumoniae*.

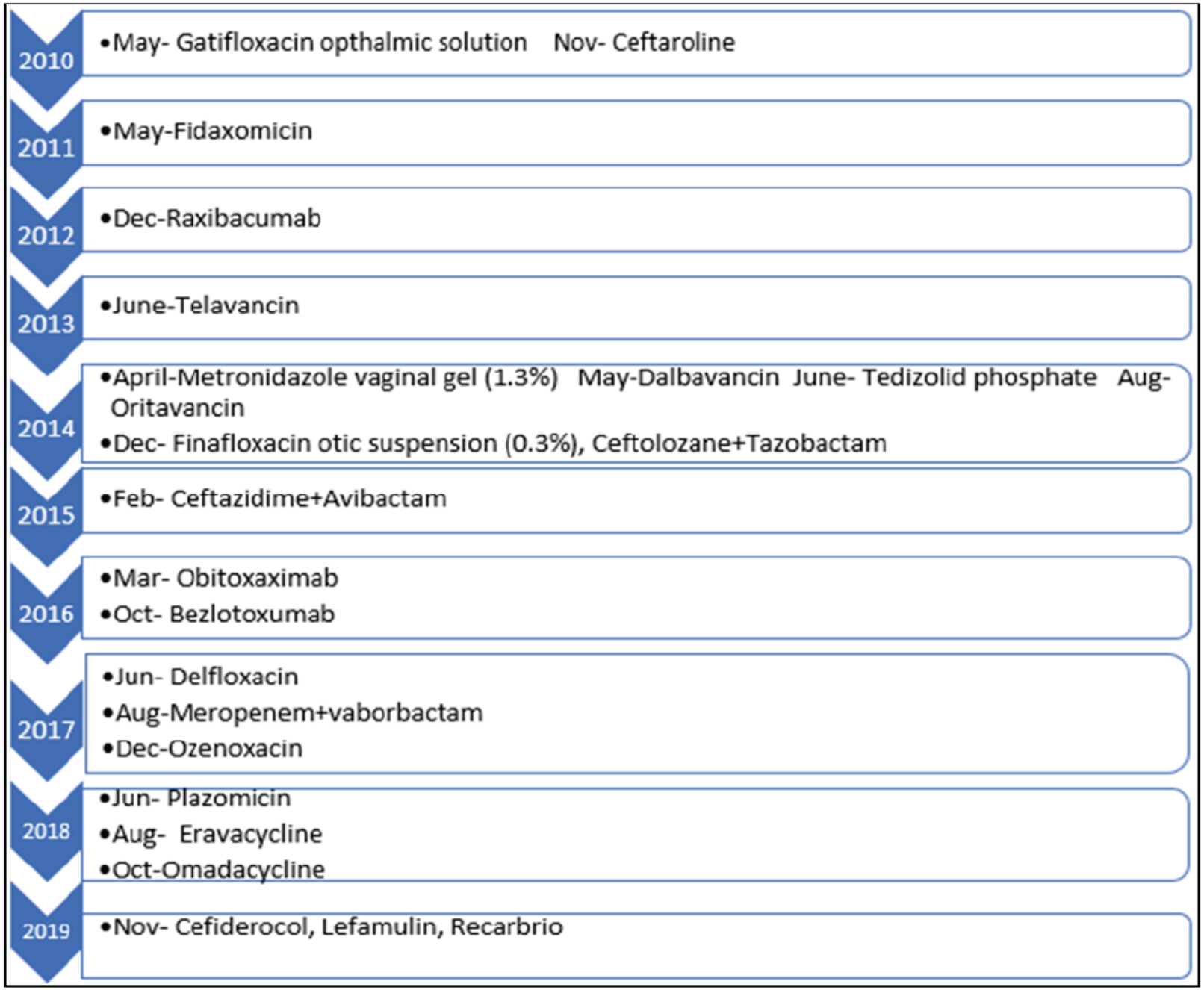
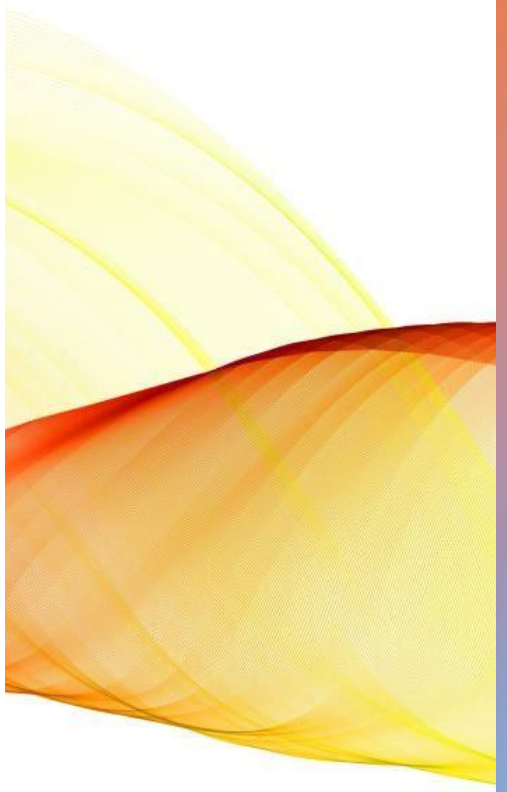


Fig. 1: Timeline of FDA approval of antibiotics in the past 10 years

- In 2017 WHO published a list of 12 families of bacteria for which new antibiotics are needed urgently, a list of “priority pathogens”.

- The list was created to identify, guide, and promote the research and development of newer antibiotics and to address urgent healthcare needs.

- The WHO priority pathogens are classified as critical, high, and medium priority pathogens.



The critical priority pathogens are:

carbapenem-resistant *Acinetobacter baumannii* (CRAB)

carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)

Enterobacteriaceae resistant to 3rd gen cephalosporins and carbapenems (CRE).

In 2019, WHO identified 50 antibiotics and combinations and 10 biologicals in clinical development, of which 26 are active against the WHO list of priority pathogens.

Out of the 26, only seven were considered to be original due to performance of at least one of the novelty criteria.

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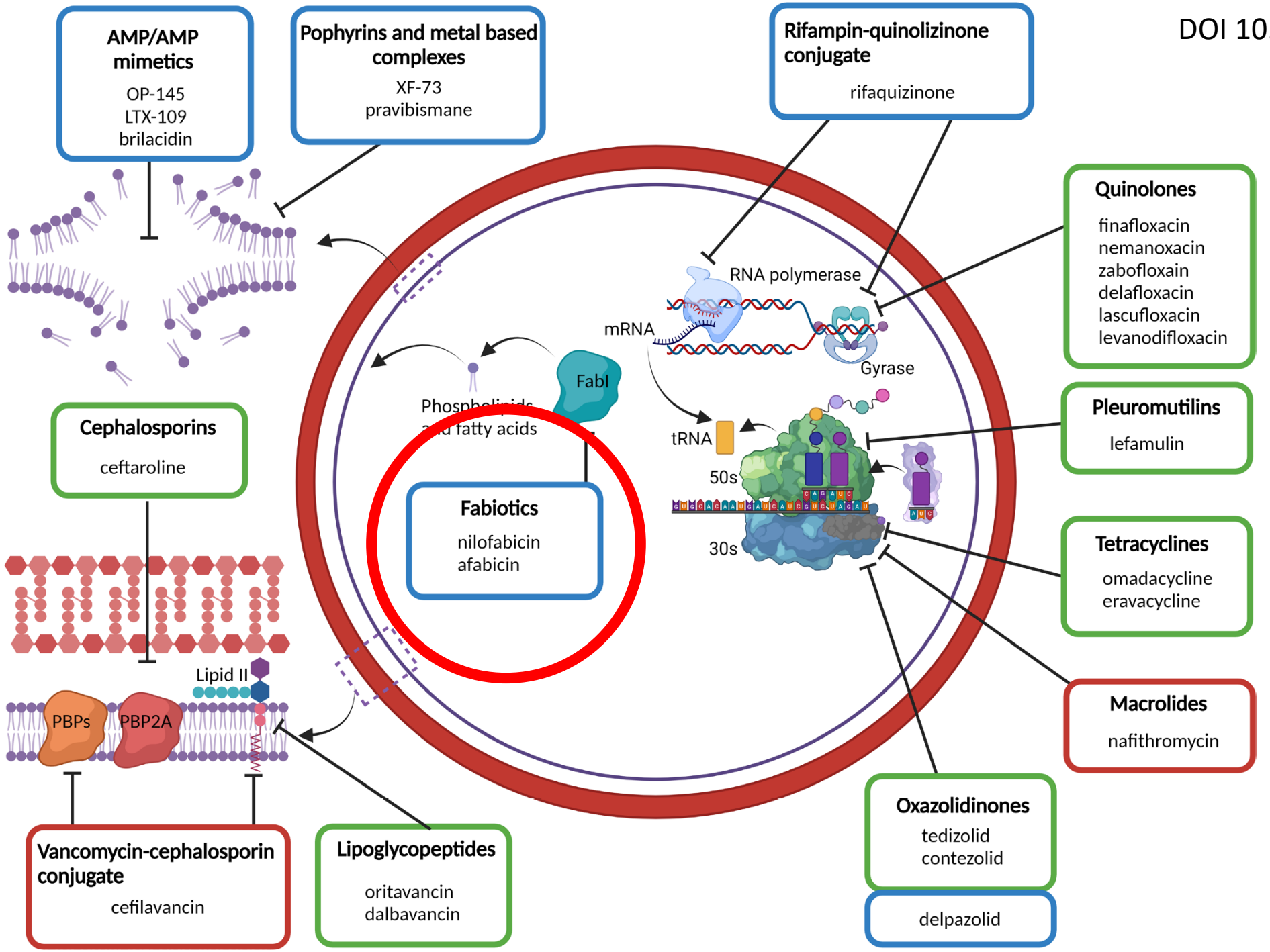


To avoid cross-resistance, new drugs should be directed towards unexploited targets or vital metabolisms, e.g., ATP and fatty acid biosynthesis.

Fatty acid biosynthesis will be explored.

Fatty acids are the main constituents of bacterial and plasmodial membranes and metabolic intermediates.

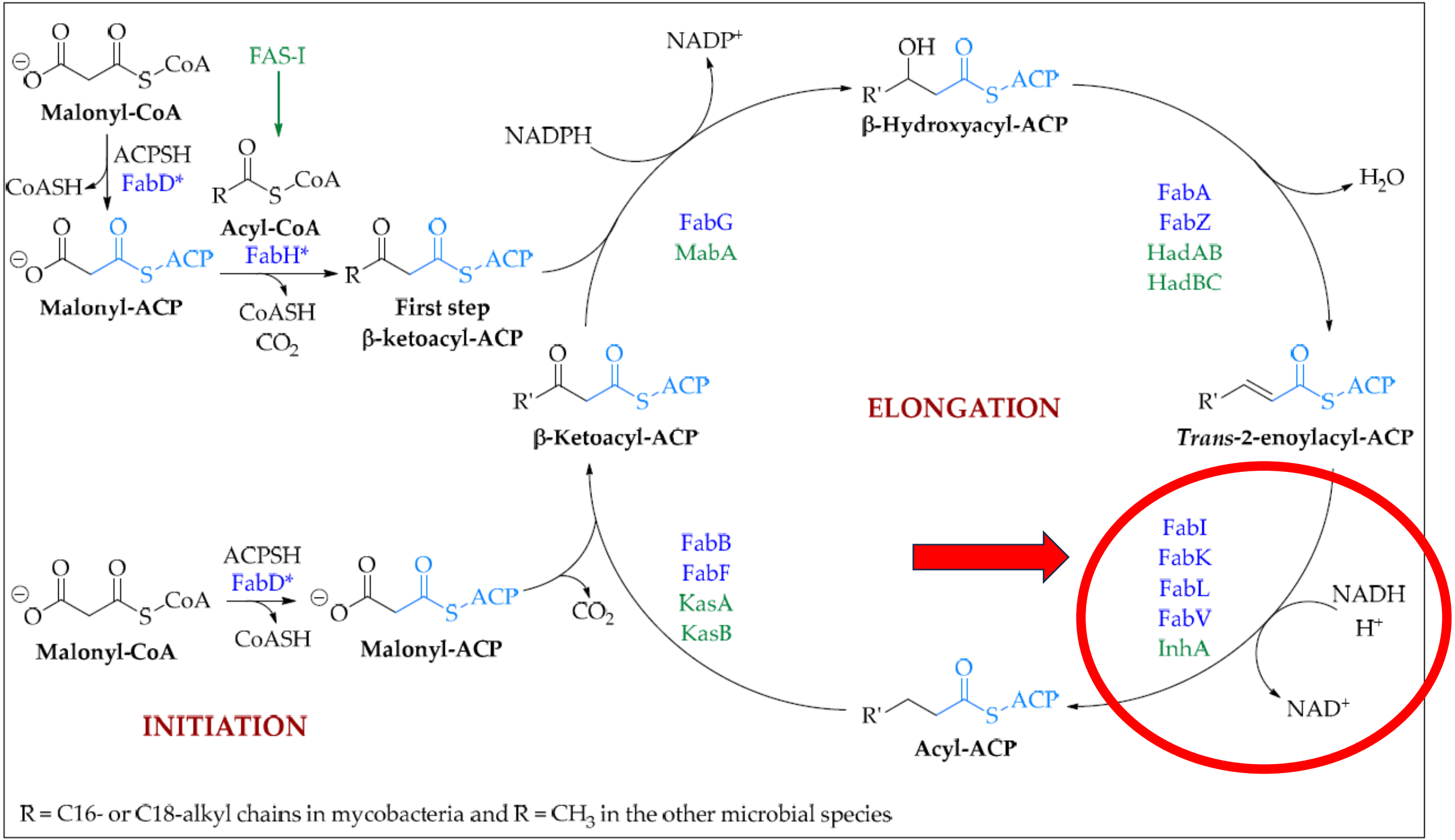
Their biosynthesis involves fatty acid synthase systems which are divided into two distinct molecular forms called types I and II (FAS-I and FAS-II).

FAS-I is constituted of a unique multifunctional protein whereas in FAS-II, several separate enzymes co-exist, and each one catalyzes a sole reaction.

Only FAS-I is present in humans, while FAS-II is found in bacteria, *mycobacteria* and *P. falciparum.*

FAS-II enzymes are attractive targets for drug development because:

I. Fatty acids are essential to maintain the vital integrity of bacterial membrane
II. FAS-II is essential in the late liver stage development of *P. falciparum*
III. The amino acid sequences of the active sites of FAS-II enzymes are well conserved in microbial pathogens, allowing broad-spectrum activity
IV. FAS-II does not exist in humans, limiting side effects
V. The crystal structures of FAS-II enzymes are available in the Protein Data Bank (PDB), allowing rational design of inhibitors.



R = C16- or C18-alkyl chains in mycobacteria and R = CH_3 in the other microbial species

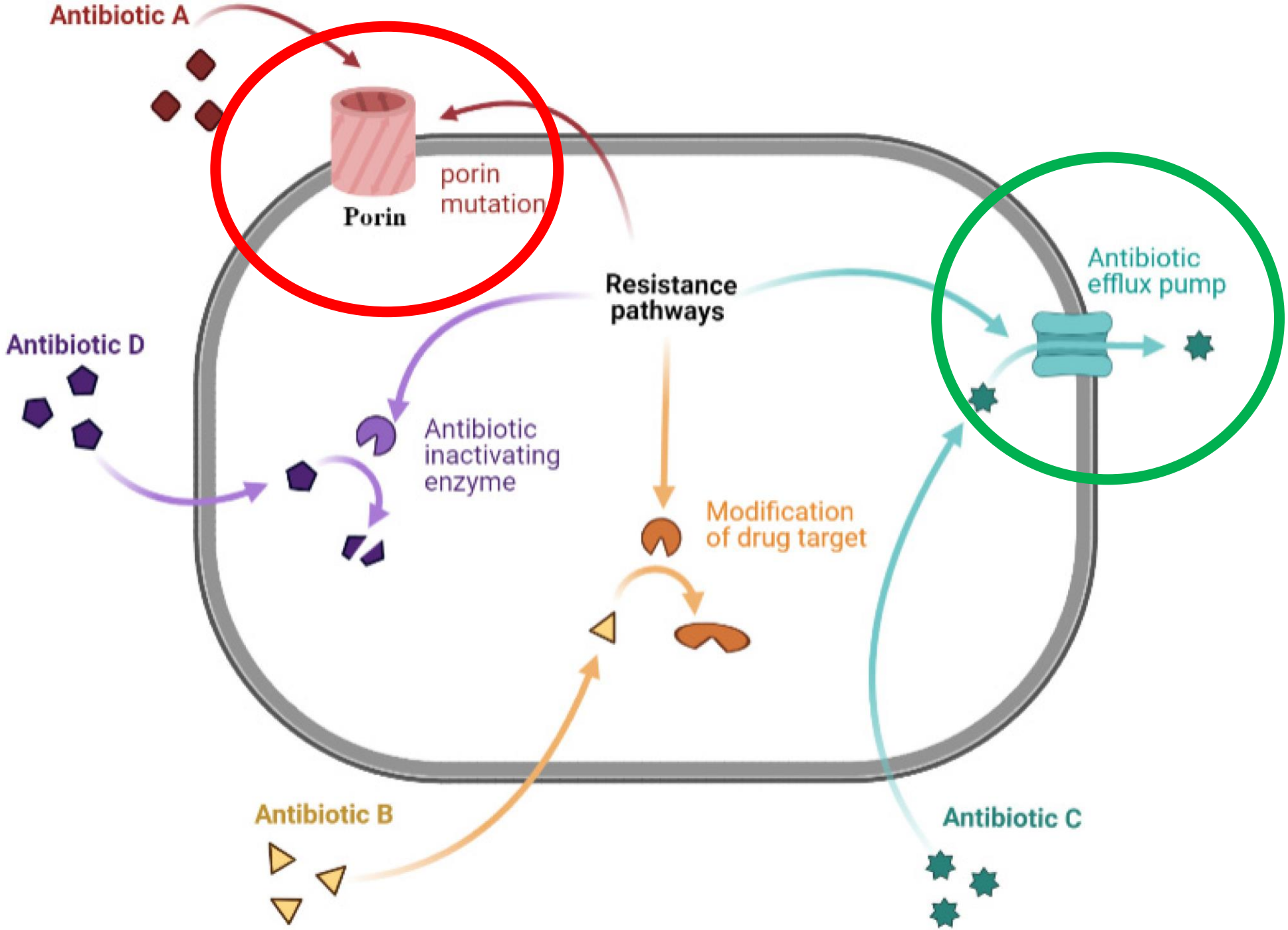
Staphylococcus aureus

Staphylococcus aureus represents a major and recurrent challenge to clinicians due to the combination of bacterial and host

It evades immune defences and against which antibiotic action is severely limited compared with extracellular forms factors

Considered by the WHO to be a high priority pathogen for development of novel therapies.

S. aureus readily adapts to changing environments and acquires antibiotic-resistance genes through several different mechanisms;


Antibiotic A
Porin
porin
mutation
Resistance
pathways
Antibiotic
efflux pump
Antibiotic D
Antibiotic
inactivating
enzyme
Modification
of drug target
Antibiotic B
Antibiotic C

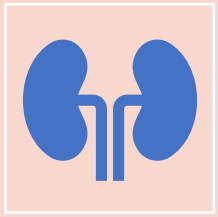
This has led to an almost constant increase of resistance that today affects most (if not all) the major classes of clinically-approved antibiotics, including:

β-lactams, lipopeptides, glycopeptides, and oxazolidinones, are available for the treatment of staphylococcal infections

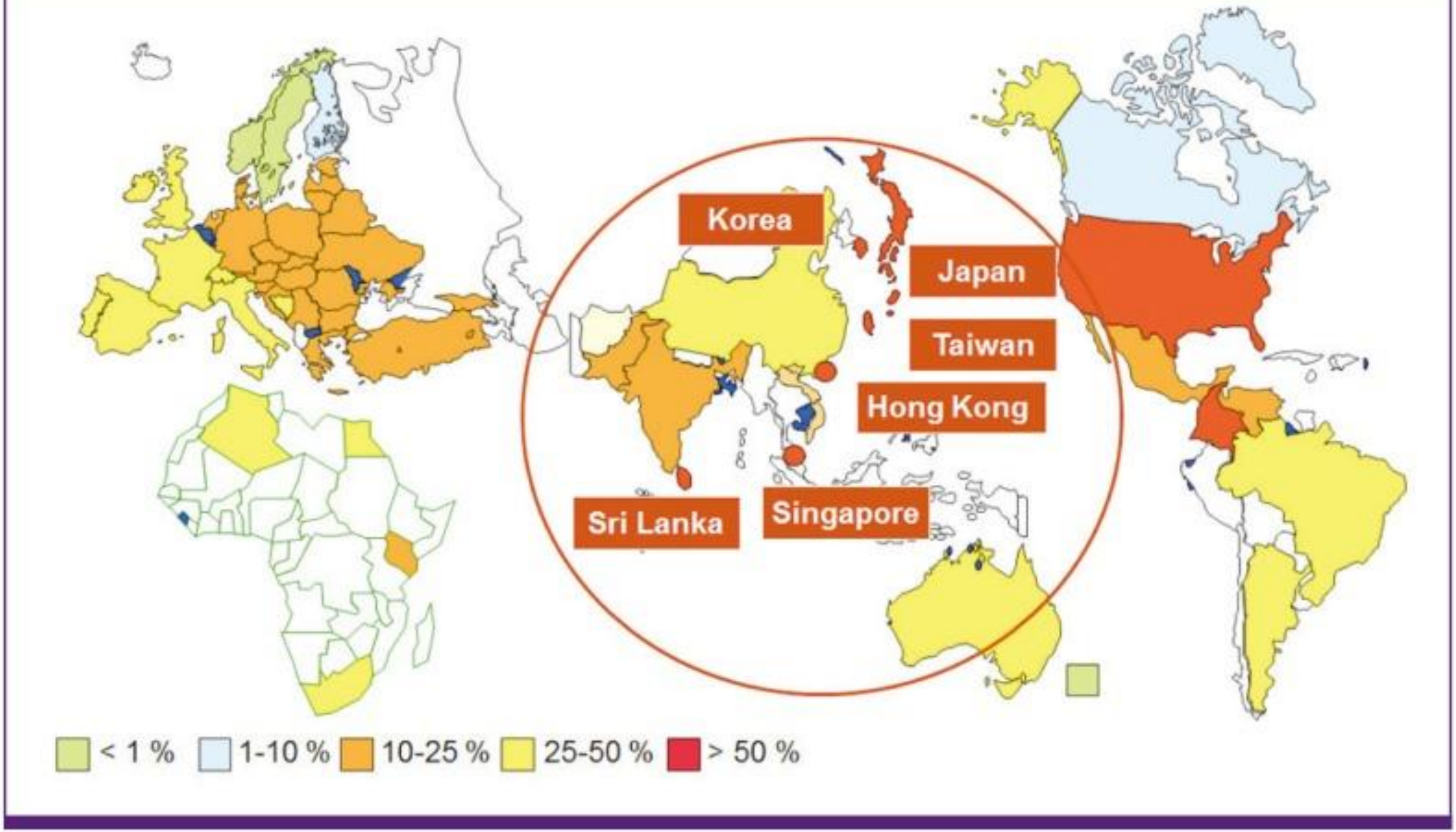
Antibiotic resistance causes 700,000 deaths globally, every year

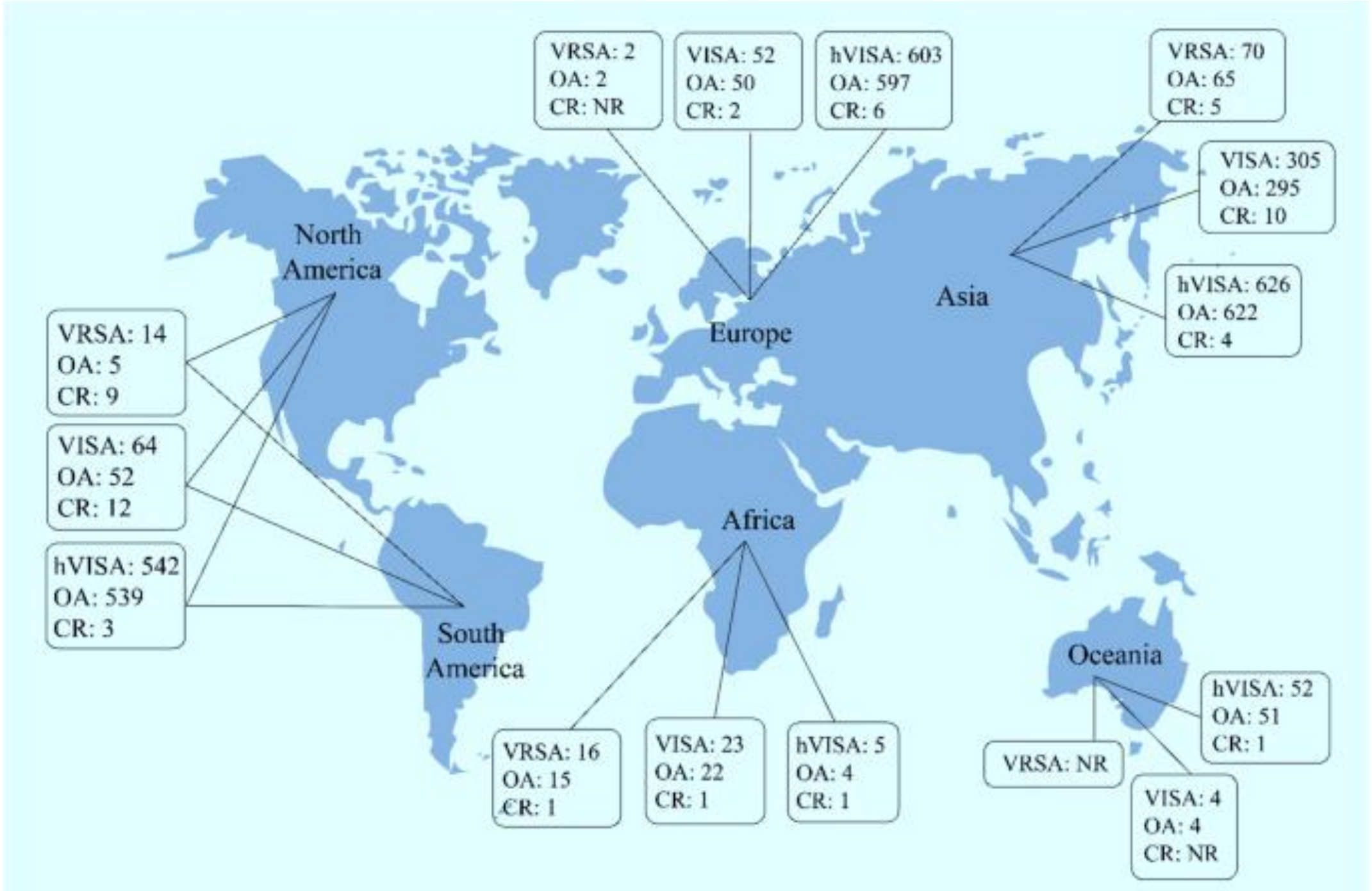
Staphylococcal infections are a significant global concern for multiple reasons:

Methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA)



Infection ranged from 30% to 60% for osteomyelitis cases and 39% to 76% for septic arthritis cases


Korea
Japan
Taiwan
Hong Kong
Sri Lanka
Singapore
< 1 %
1-10 %
10-25 %
25-50 %
> 50 %


VRSA: 2
OA: 2
CR: NR
VISA: 52
OA: 50
CR: 2
hVISA: 603
OA: 597
CR: 6
VRSA: 70
OA: 65
CR: 5
VISA: 305
OA: 295
CR: 10
hVISA: 626
OA: 622
CR: 4
North America
Europe
Asia
VRSA: 14
OA: 5
CR: 9
VISA: 64
OA: 52
CR: 12
hVISA: 542
OA: 539
CR: 3
Africa
South America
Oceania
VRSA: 16
OA: 15
CR: 1
VISA: 23
OA: 22
CR: 1
hVISA: 5
OA: 4
CR: 1
hVISA: 52
OA: 51
CR: 1
VRSA: NR
VISA: 4
OA: 4
CR: NR

- Bone and joint infections (BJIs) are a group of diseases that include osteomyelitis, septic arthritis and prosthetic joint infections affecting over 30,000 people per year within the US, UK, France, Germany, Spain and Italy combined.

- These conditions are associated with significant morbidity and mortality in worldwide.

- BJIs are the most difficult-to-treat bacterial infections and a major public health issue: high rate of treatment failure and recurrence.

- Involving a prolonged course of antibiotics, often with surgical intervention, due to the poor vascularization at the site of infection.

ABSSSI

- Cellulitis, large abscesses, erysipelas, wound infection, and bite infection, which excludes all other indications

Comparison of FDA guidance from 1998[9] and 2013.[8]

	Prior guidance (1998)[9]	New guidance (2013)[8]
Indication/terminology	Complicated skin and skin structure infection (cSSSI)	Acute bacterial skin and skin structure infection (ABSSSI)
Infection type	Varying sized abscesses, wound, cellulitis, DFI, chronic ulcer, burn infections	Large abscesses, wound, cellulitis, erysipelas of at least 75 cm^2 surface area
Infection severity	Intermediate/severe	Intermediate/severe
Primary endpoints	Subjective Defined as: clinicians' assessment at 7–14 days after EOT	Objective Defined as: at least 20% reduction in lesion size at 48–72 h
Secondary endpoints	Varied Low potential for differentiation	Primary endpoint sustained up to EOT Clinician's assessment at EOT Higher potential for differentiation
Etiology	Chronic and acute infection Gram-positive and Gram-negative bacteria	Acute infection Primarily Gram-positive bacteria; less frequently Gram-negative bacteria

DFI, diabetic foot infection; EOT, end of therapy; FDA, US Food and Drug Administration.

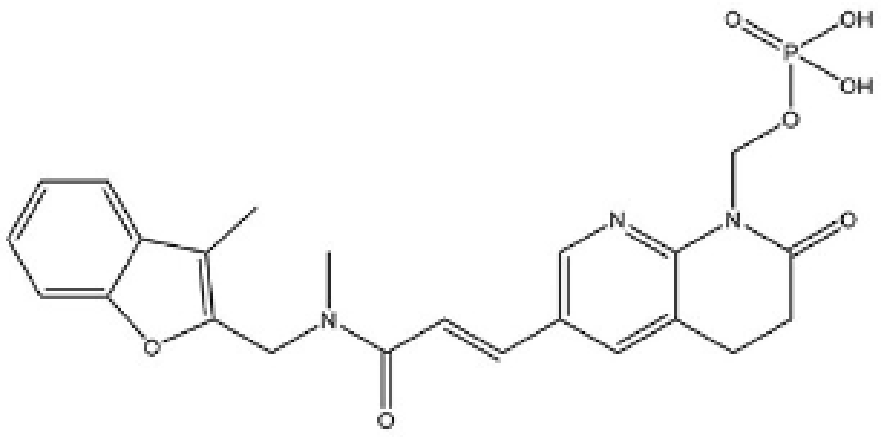
- Use of broad-spectrum antibiotics, surgical intervention for debridement of devitalized bone or removal of an infected prosthetic device for both culture and successful healing.

- The disturbance of the commensal gut microbiota, leading to the spread of antibiotic resistance and increased colonization by various gut pathogens, such as *Clostridioides difficile* and *Salmonella enterica* serovar Typhimurium.

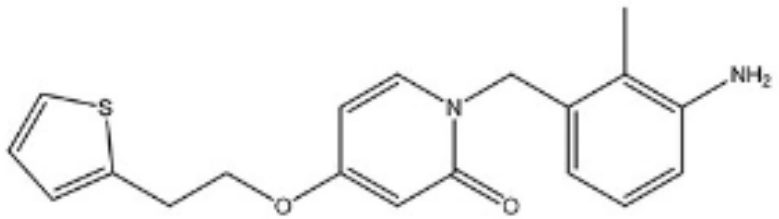
The availability of these broad-spectrum antibiotics and advances in diagnostic and surgical techniques, osteoarticular infections continue to be associated with significant morbidity and mortality.

- ✓ Septic arthritis is considered a medical and surgical emergency, associated with a mortality rate of about 11%.

Ten to 30% of patients with septic arthritis suffer long-term decreased joint function or mobility.



Afabicin



Nilofabicin

Fabiotic

- "**first-in-class antibiotic**"

- Often developed to address unmet medical needs, such as the emergence of antibiotic-resistant bacteria or the lack of effective treatments for certain infections.

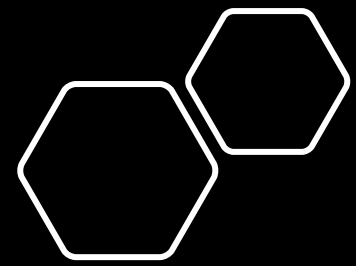
- They offer a new approach to treating bacterial infections and may have advantages over existing antibiotics, such as improved efficacy, reduced toxicity, and lower risk of resistance development.

Afabicin (formerly Debio 1450, AFN-1720) is a first-in-class antibiotic with a novel mode of action that specifically targets fatty acid synthesis in *Staphylococcus* spp.

It is the prodrug of afabicin dephosphono, an enoyl-acyl carrier protein reductase (FabI) inhibitor.

A recent phase 2 trial has shown that afabicin is efficacious and well tolerated for the treatment of ABSSSI and BIJs caused by staphylococci

It displays an excellent penetration potential in mice and human studies



Afabicin dephosphono exhibits selective antibacterial activity against both coagulase-negative and -positive staphylococci, including MRSA, and can be administered intravenously and orally.

The MIC90 against recent MRSA isolates (collected in 2015 and 2018) is 0.008g/ml, with 99.4% of organisms being inhibited at a concentration of 0.06 g/ml.

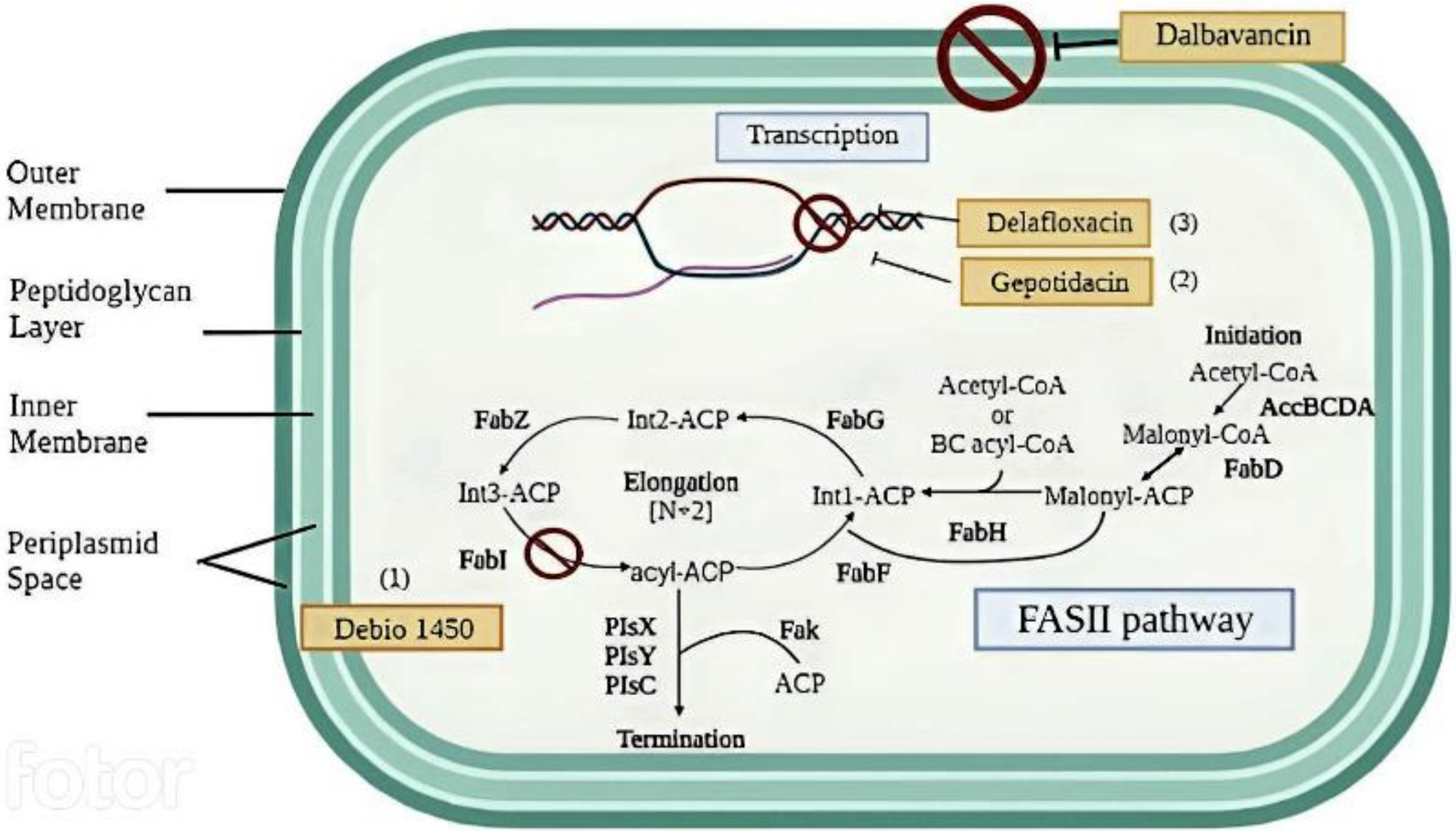
Molecular Formula	Molecular Weight
$C_{23}H_{24}N_3O_7P$	485.4 g/mol

Afabicin dephosphono does not show cross-resistance with other antibacterial classes typically used to treat infections caused by Gram-positive pathogens.

- Very limited water solubility

- High permeability across the mouse intestinal wall and good distribution in skin structures, indicating possible penetration into eukaryotic cells.

Mechanism of action



Clinical trials

Drugs	Status	Mechanism of action	Study design	Outcome
Debio 1450	Under investigation	Inhibit the synthesis of fatty acids (FASII) pathway in staphylococci bacteria by targeting FabI, which is an enoyl-acyl carrier protein (ACP) reductase	*In vitro* (MRSA)	MIC90 = 0.008 μg/ml
			Clinical trial (NCT02726438): A Phase 1 study to assess the effectiveness of oral Debio 1450 in patients who underwent hip replacement surgery (n=17)	Well penetrate bone tissue with a mean ratio of plasma: synovial fluid=2.88
			Clinical trial (NCT02426918): A Phase 2 study to assess the efficacy of Debio 1450 orally and intravenously in comparison with oral linezolid and intravenous vancomycin in ABSSSI patients caused by *Staphylococcus aureus* or MRSA (n=330)	ECRR for Debio 1450 80 mg/120 mg BID = 94.6% ECRR for Debio 1450 160 mg/240 mg BID = 90.1% ECRR for vancomycin/ linezolid BID=91.1%
			Clinical trial (NCT03723551): A Phase 2 study to assess the safety, tolerability, and efficacy of Debio 1450 in the treatment of participants with bone or joint infection due to *S. aureus* and to compare it to the standard of care (n = 96)	NA*

Study to Assess Safety, Tolerability and Efficacy of Afabicin in The Treatment of Participants With Bone or Joint Infection Due to Staphylococcus

You last viewed on Feb 29, 2024

Debiopharm

Status and phase

Enrolling | Phase 2

Conditions

Bone or Joint Infection

Treatments

Drug: Standard of Care | Drug: Afabicin

ClinicalTrials.gov ID NCT03723551

Sponsor Debiopharm International SA

Information provided by Debiopharm International SA (Responsible Party)

Last Update Posted 2023-12-22

Study type

Interventional

Funder types

Industry

Identifiers

NCT03723551

2017-002854-35 (EudraCT Number)

Debio 1450-BJI-205

Details and patient eligibility

About

This is a randomized, active-controlled, open-label study to assess the safety, tolerability and efficacy of Afabicin in the treatment of participants with bone or joint infection due to Staphylococcus aureus [both methicillin-susceptible S. aureus (MSSA) and methicillin-resistant S. aureus (MRSA)] and/or coagulase-negative staphylococci (CoNS) and to compare it to standard of care (SOC).

Enrollment

111 estimated patients

Sex

All

Ages

18+ years old

Volunteers

No Healthy Volunteers

DEBIO: 1450-BJI-205: Randomized Open-label Active-controlled Study to Assess the Safety, Tolerability and Efficacy of Afabicin IV/oral in the Treatment of Patients with Bone or Joint Infection due to Staphylococcus

Study Enrollment

First Name

Last Name

Email Address

Phone Number

Clinical Trial

DEBIO: 1450-BJI-205: Randomized Open-label Active-controlled Study to Assess the Safety, Tolerability and Efficacy of Afabicin IV/oral in the Treatment of Patients with Bone or Joint Infection due to Staphylococcus

This study will see how safe, effective and well-tolerated the study drug Afabicin is when given IV, followed by oral treatment, in patients hospitalized with bone or joint infections from staph aureus.

Phase 1

- In the first part, single doses of 100, 200, 300, or 400 mg of AFN–1252 were administered.
- In the second part, subjects received 100, 200, 300 and 400 mg twice a day.
- This study showed oral doses to be safe and well tolerated and highlighted the potential of the drug for once or twice-a-day dosing to treat staphylococcal infections.
- AFN-1252 was well-absorbed with C-max at 3–4 h when given once per day and 2.5–9 h when administered twice daily.

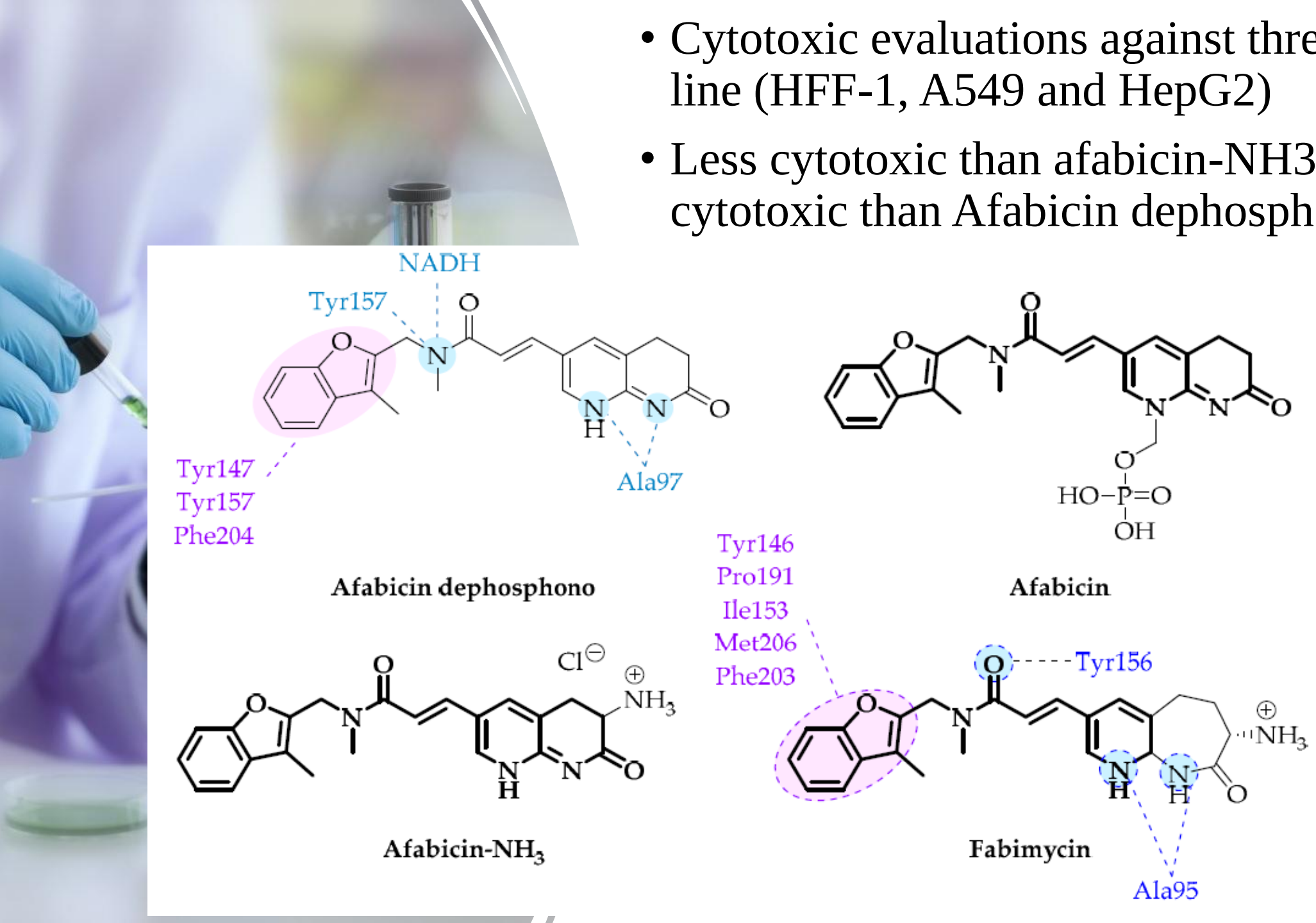
Phase 2

- Evaluate the efficacy and safety of 200 mg, given orally twice-a-day in the treatment of ABSSSI.
- Showed that is well tolerated and highly effective in the treatment of ABSSSI caused by *S. aureus*, including MRSA.
- The overall early response rate at day 3 was 97.3%, where 82.9% of patients had a >20% decrease in the area of erythema, and 77.9% of patients had a >20% decrease in the area of sclerosis.
- Microbiologic eradication rates for MRSA and MSSA were around 90% at short- and long-term follow-ups.
- The main drug-related AEs reported, which were mostly mild or moderate, were headache (26.2%) and nausea (21.4%)

- ✓ Re-design Afabicin, Afabicin-NH3 to inhibit Gram-negative bacteria

- ✓ Parker et al, 2022, developed **fabimycin** based on Afabicin dephosphono and Afabicin-NH3 by extending and reducing the tetrahydronaphthydinaminium to hexahydropyridoazepinaminium.

- Cytotoxic evaluations against three human cell line (HFF-1, A549 and HepG2)
- Less cytotoxic than afabicin-NH3 but more cytotoxic than Afabicin dephosphono

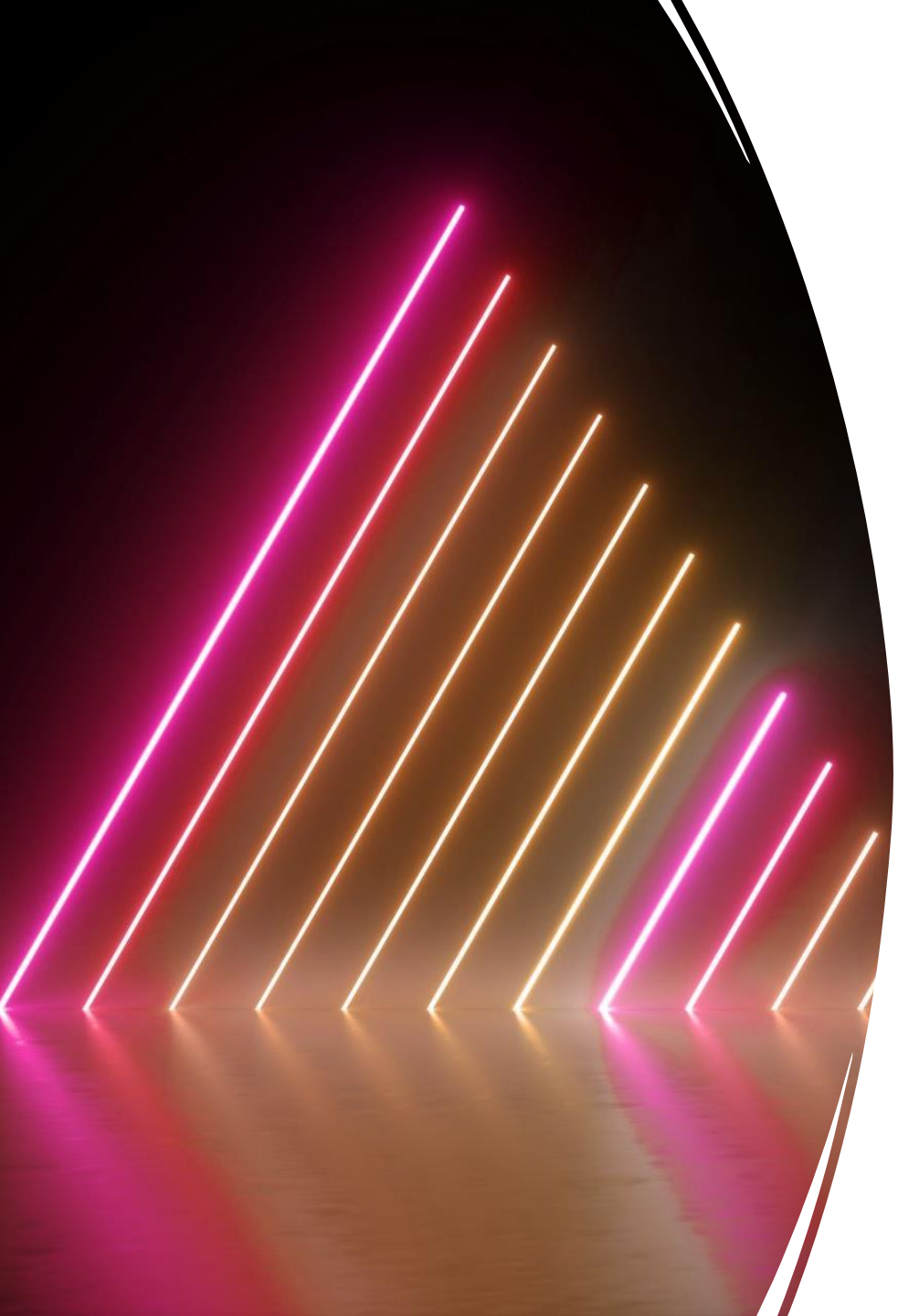


- Nilofabicin (CG400549) is a benzyl-pyridine

- ❑ Exhibits potent activity against MSSA and MRSA isolates

- ❑ Effective in combating systemic *S. aureus* infection in a murine model

- ❑ Overexpression of FabI in *S. aureus* resulted in enhanced resistance to Nilofabicin



Challenges

- As afabicin is a relatively new compound, there remains uncertainty around its long-term effects and optimal dosing regimen.

- Its narrow-spectrum activity means it must be used carefully to prevent the emergence of resistant strains

How does Afabicin compare to other antibiotics in terms of effectiveness

1. Non-interference to Vancomycin/Linezolid

2. Narrow-Spectrum Activity

3. Preservation of Gut Microbiota

4. Ease of Administration

5. Unique Mechanism of Action

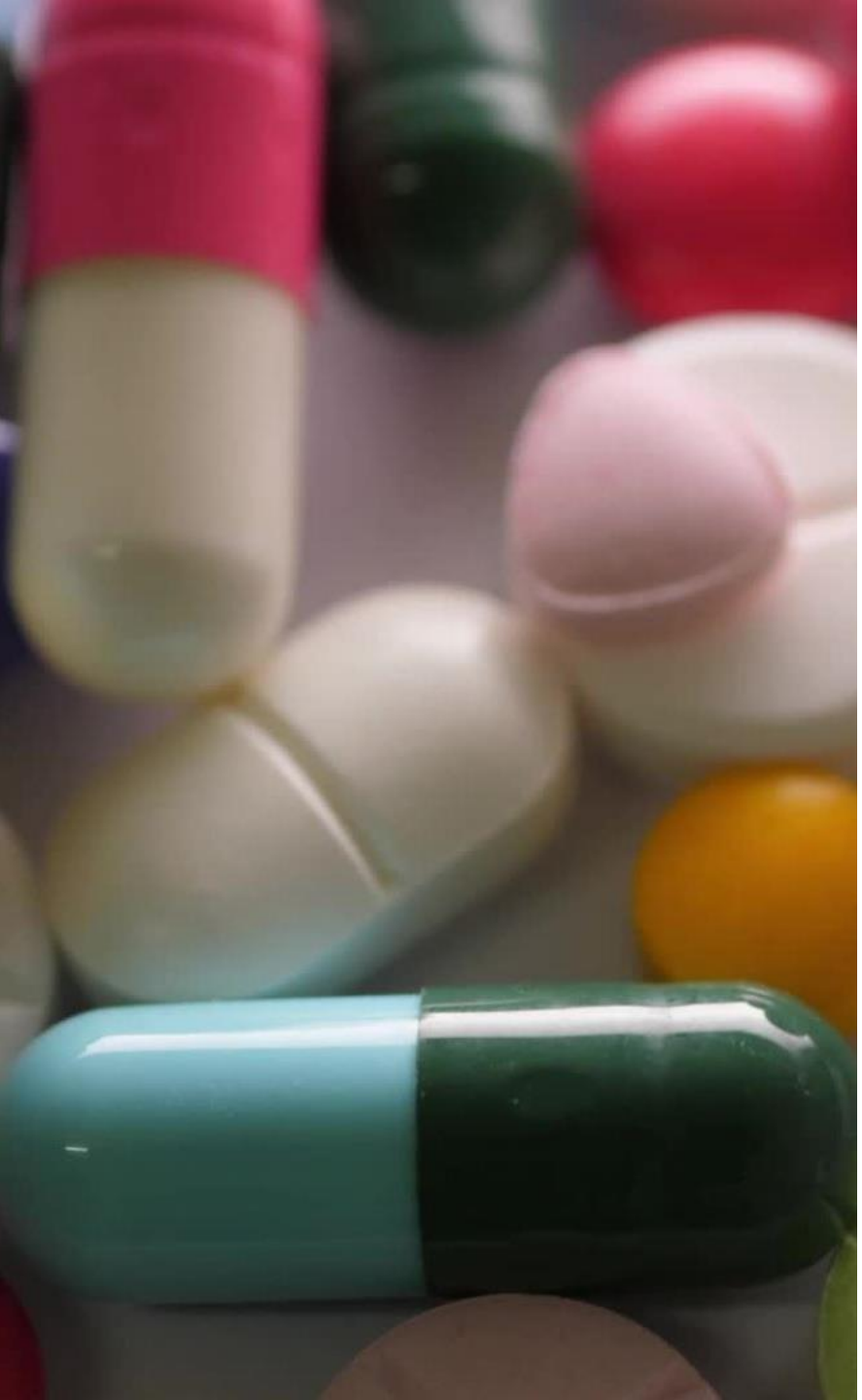
6. Clinical Success Rates

Comparison Between Afabicin and Vancomycin

1. Efficacy

2. Mechanism of Action

3. Spectrum of Activity



4. Safety Profile

Vancomycin

MOST COMMON USE

Gram-Pos. organisms: Includes MRSA,
S. epidermidis, Enterococci, C. difficile.

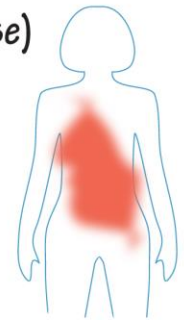
BACTERIAL RESISTANCE

Inhibits peptidoglycan synthesis via binding to D-ala-D-ala in Gram-Pos. bacteria.

Resistance when modified to D-ala-D-Lac.

ADVERSE EFFECTS

Red Man Syndrome (Histamine release)
Neprhotoxicity
Ototoxicity
Thrombophlebitis



The cost of Afabicin compared to other antibiotics is as follows:

- **Afabicin:**
  - **Adooq Bioscience:**
    - **1mg for $320.00**
    - **5mg for $960.00**
    - **10mg for $1,600.00**
  - **MedKoo:**
    - **1mg for $150.00**
    - **5mg for $450.00**
    - **10mg for $750.00**
    - **25mg for $1,450.00**

- **Vancomycin**:
  - The cost of Vancomycin can vary depending on the formulation and supplier but generally ranges from around $4 to $20 per vial or tablet.

Conclusion

AMR has become a public health issue. Consequently, there is an urgent need for treatments with new modes of action.

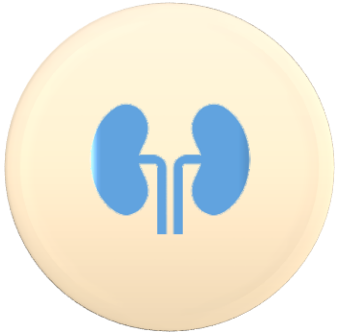
Fatty acid biosynthesis, particularly the FAS-II system, is a prime target to fight AMR.

This systemis constituted of eleven potential targets: one transacylase (FabD), three condensing enzymes (FabB, FabF and FabH), one ketoacyl reductase (FabG), two dehydratases (FabA and FabZ) and four enoyl reductases (FabI, FabK, FabL and FabV).

Despite expanded efforts, only two FAS-II enzyme inhibitors (both of FabI), **afabicin dephosphono** and **CG400549**, are in the clinical pipeline to treat *S. aureus* infections.

For now, FabI inhibitors are selective for bacteria possessing exclusively FabI as enoyl-ACP reductase,which could be interesting to limit side effects, but it also reduces their spectrum of activity

Many inhibitors display broad-spectrum activities, and some of them are active against strains which are resistant to current ATBs with cytotoxicity.



At present, **afabicin** and its derivative **fabimycin** appear to be the most promising AMR candidates

References

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Clin Infect Dis. 2023 Oct 15; 77(8): 1092–1101.
Published online 2023 Jun 13. doi: 10.1093/cid/ciad363
PMCID: PMC10573727
PMID: 37310693

Global Differences in the Management of *Staphylococcus aureus* Bacteremia: No International Standard of Care

Annette C Westgeest, David T P Buis, Kim C E Sigaloff, Felicia Ruffin, Leo G Visser, Yunsong Yu, Emile F Schippers, Merel M C Lambregts, Steven Y C Tong, Mark G J de Boer, and Vance G Fowler, Jr

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Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother 2023; **78**: 1900–1908
https://doi.org/10.1093/jac/dkad181 Advance Access publication 9 June 2023

Evaluation of the microbiota-sparing properties of the anti-staphylococcal antibiotic afabicin

J. Nowakowska[1], D. R. Cameron[1]*, A. De Martino[2], J. Kühn[1], S. Le Fresne-Languille[2], S. Leuillet[2], Y. Amouzou[2], F. Wittke[3], T. Carton[2], F. Le Vacon[2], R. L. Chaves[3], V. Nicolas-Metral[1] and G. Vuagniaux[1]

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Global prevalence and distribution of vancomycin resistant, vancomycin intermediate and heterogeneously vancomycin intermediate *Staphylococcus aureus* clinical isolates: a systematic review and meta-analysis

Aref Shariati, Masoud Dadashi, Majid Taati Moghadam, Alex van Belkum, Somayeh Yaslianifard & Davood Darban-Sarokhalil

ORIGINAL RESEARCH article

Front. Microbiol., 24 July 2023
Sec. Antimicrobials, Resistance and Chemotherapy
Volume 14 - 2023 |
https://doi.org/10.3389/fmicb.2023.1208131

This article is part of the Research Topic
Insights in Antimicrobials, Resistance & Chemotherapy: 2022
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Antimicrobial resistance and clonality of Staphylococcus aureus causing bacteraemia in children admitted to the Manhiça District Hospital, Mozambique, over two decades

Marcelino Garrine[1,2] Sofia Santos Costa[2] Augusto Messa Jr[1]
Sérgio Massora[1] Delfino Vubil[1] Sozinho Ácacio[1,3] Tacilta Nhampossa[1,3]
Quique Bassat[1,4,5,6,7] Inacio Mandomando[1,3,4] Isabel Couto[2]*

FDA NEWS RELEASE

FDA issues final rule on safety and effectiveness of antibacterial soaps

Rule removes triclosan and triclocarban from over-the-counter antibacterial hand and body washes

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The top 10 causes of death

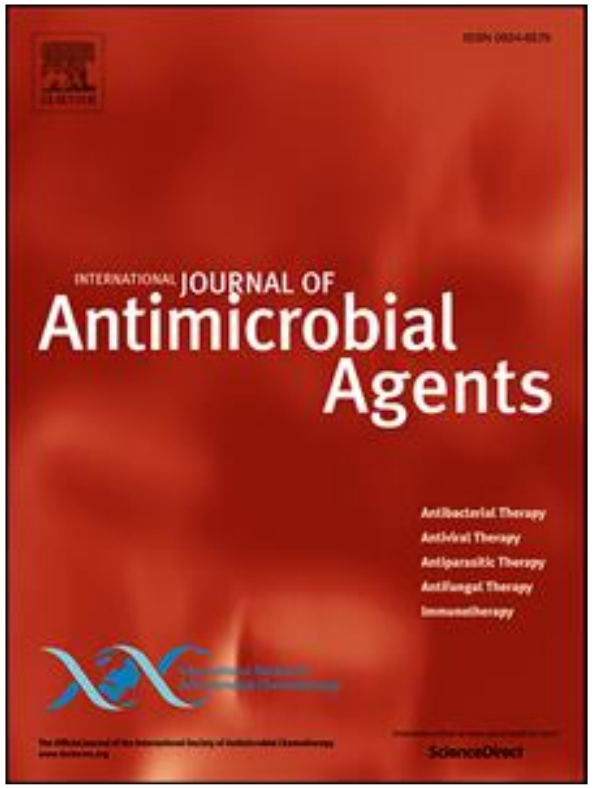
9 December 2020

In 2019, the top 10 causes of death accounted for 55% of the 55.4 million deaths worldwide.

The top global causes of death, in order of total number of lives lost, are associated with three broad topics: cardiovascular (ischaemic heart disease, stroke), respiratory (chronic obstructive pulmonary disease, lower respiratory infections) and neonatal conditions – which include birth asphyxia and birth trauma, neonatal sepsis and infections, and preterm birth complications.

Causes of death can be grouped into three categories: communicable (infectious and parasitic diseases and maternal, perinatal and nutritional conditions), noncommunicable (chronic) and injuries.

Leading causes of death globally



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HAI Data +

Staphylococcus aureus in Healthcare Settings

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Journal Article

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Staphylococcus Great Britain and Ireland 2023 (StaphGBI 2023) Conference Report

James P. O'Gara[1,*] and Merve S. Zeden[1,*]

pharmaceuticals

MDPI

Review

A Review of Fatty Acid Biosynthesis Enzyme Inhibitors as Promising Antimicrobial Drugs

Laurie Bibens, Jean-Paul Becker, Alexandra Dassonville-Klimpt and Pascal Sonnet *

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CLINICAL THERAPEUTICS

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Afabicin, a First-in-Class Antistaphylococcal Antibiotic, in the Treatment of Acute Bacterial Skin and Skin Structure Infections: Clinical Noninferiority to Vancomycin/Linezolid

Frederick Wittke,[a*] Catherine Vincent,[a] James Chen,[b] Barry Heller,[c] Heidi Kabler,[d] J. Scott Overcash,[e] François Leylavergne,[a] Guennaëlle Dieppois[a]

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Review article

Antibiotics with novel mode of action as new weapons to fight antimicrobial resistance

Francesca Ruggieri [1], Nina Compagne [1], Kevin Antraygues [1], Maxime Eveque [1], Marion Flipo, Nicolas Willand [*]

Univ. Lille, Inserm, Institut Pasteur de Lille, U1177—Drugs and Molecules for Living Systems, F-59000, Lille, France

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Bone and Joint Tissue Penetration of the *Staphylococcus*-Selective Antibiotic Afabicin in Patients Undergoing Elective Hip Replacement Surgery

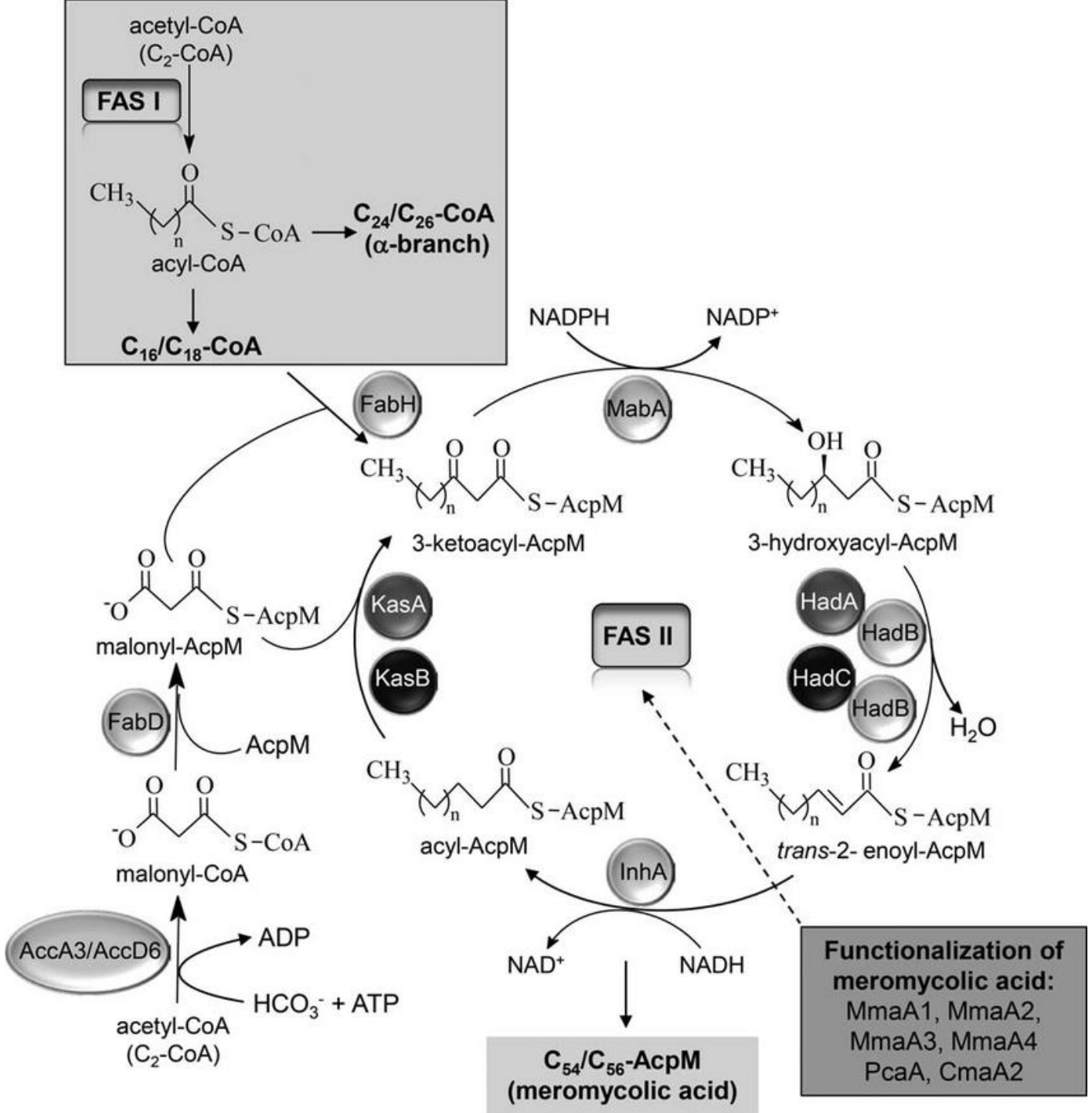
Annick Menetrey,[a] Annick Janin,[a] John Pullman,[b] J. Scott Overcash,[c] Amina Haouala,[a] François Leylavergne,[a] Laurent Turbe,[d] Frederick Wittke,[a*] Valérie Nicolas-Métral[a]

Yours truly, Sina

- There are two principal classes of fatty acid synthases.
- Type I systems utilise a single large, multifunctional polypeptide and are common to both animals and fungi (although the structural arrangement of fungal and animal syntheses differ). A Type I fatty acid synthase system is also found in the CMN group of bacteria (corynebacteria, mycobacteria, and nocardia). In these bacteria, the FAS I system produces palmitic acid, and cooperates with the FAS II system to produce a greater diversity of lipid products.
- Type II is found in archaea, bacteria and plant plastids, and is characterized by the use of separate, monofunctional enzymes for fatty acid synthesis.

- The mechanism of FAS I and FAS II elongation and reduction is the same, as the domains of the FAS II enzymes are largely homologous to their domain counterparts in FAS I multienzyme polypeptides.

- However, the differences in the organization of the enzymes - integrated in FAS I, discrete in FAS II - gives rise to many important biochemical differences.


acetyl-CoA
(C_2-CoA)
FAS I
acyl-CoA
C_{24}/C_{26}-CoA
(α-branch)
C_{16}/C_{18}-CoA
NADPH
NADP+
FabH
MabA
3-ketoacyl-AcpM
3-hydroxyacyl-AcpM
KasA
KasB
malonyl-AcpM
FAS II
HadA
HadB
HadC
HadB
H_2O
FabD
AcpM
malonyl-CoA
acyl-AcpM
trans-2- enoyl-AcpM
InhA
AccA3/AccD6
ADP
HCO_3^- + ATP
acetyl-CoA
(C_2-CoA)
NAD+
NADH
C_{54}/C_{56}-AcpM
(meromycolic acid)
Functionalization of meromycolic acid:
MmaA1, MmaA2,
MmaA3, MmaA4
PcaA, CmaA2