



# Má smysl bojovat s antibiotickou rezistencí?

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# Antimikrobiální terapie - historie

## Prevence infekčních komplikací:

- 1846 Semmelweis (desinfekce rukou)
- 1865 Lister (fenol – operační rány)

## Chemoterapie:

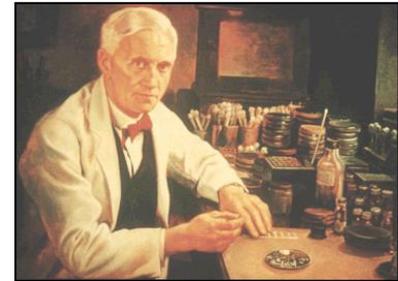
- 1899 Honl, Bukowsky - pyocyanáza – antibakteriální extrakt z *P. aeruginosa*
- 1932 Klarer and Mietzsch – sulfonamidy

## Objev penicilinu

- 1928 Fleming (*Penicillium chrysogenum (notatum)* )
- 1941 – 1945 Florey, Chain (purifikace)



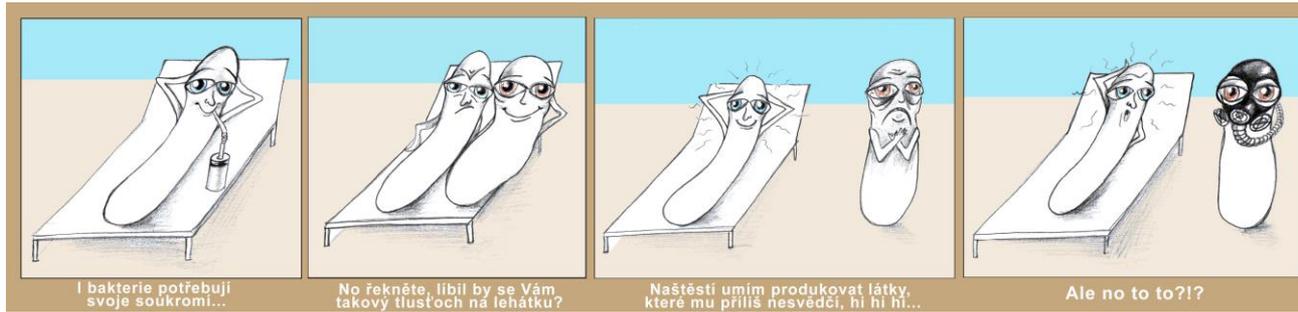
Prof. Ivan Honl



Sir Alexander Fleming



# Vznik antibiotické rezistence



## Antibiotic resistance is ancient

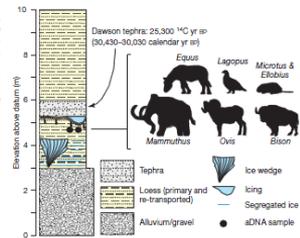
Vanessa M. D'Costa<sup>1,2\*</sup>, Christine E. King<sup>1,4\*</sup>, Lindsay Kaban<sup>1,2</sup>, Mariya Morar<sup>1,2</sup>, Wilson W. L. Sung<sup>4</sup>, Carsten Schwarz<sup>5</sup>, Duane Froese<sup>6</sup>, Grant Zazula<sup>6</sup>, Fabrice Calmeck<sup>6</sup>, Regis Debruyne<sup>6</sup>, G. Brian Golding<sup>4</sup>, Hendrik N. Poinar<sup>1,3,4</sup> & Gerard D. Wright<sup>1,2</sup>

The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes<sup>1,2</sup>. This history has been interpreted to mean that antibiotic resistance in pathogenic bacteria is a modern phenomenon; this view is reinforced by the fact that collections of microbes that predate the antibiotic era are highly susceptible to antibiotics<sup>3</sup>. Here we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments and the identification of a highly diverse collection of genes encoding resistance to  $\beta$ -lactam, tetracycline and glycopeptide antibiotics. Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants. These results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

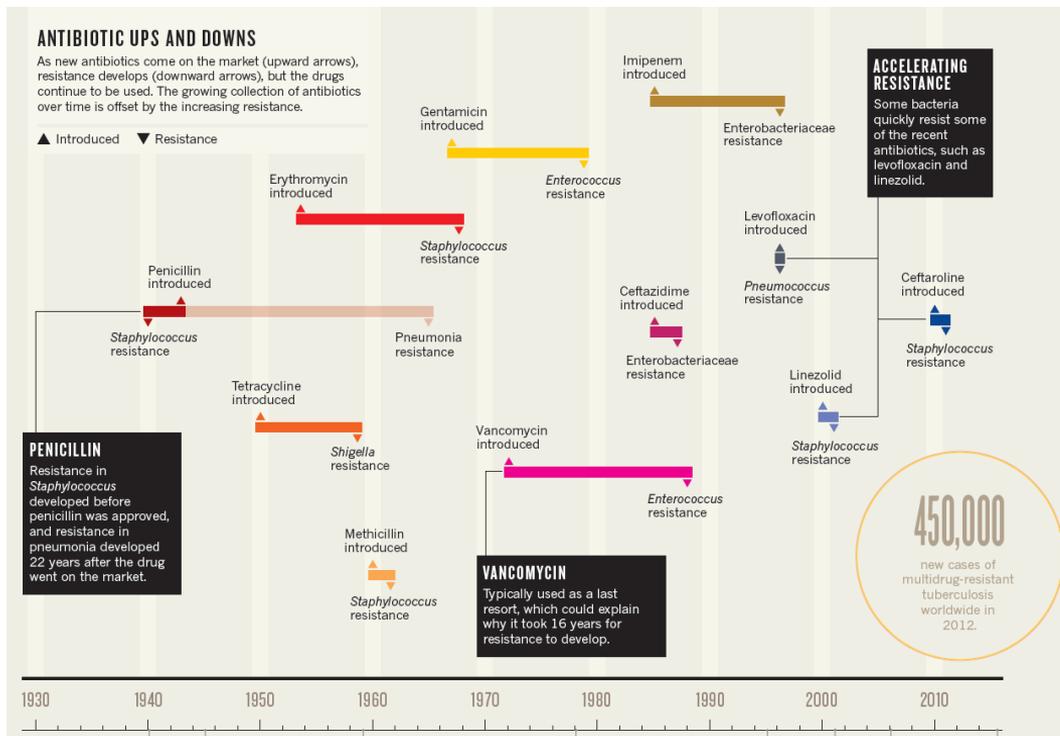


with high concentrations of *Escherichia coli* harbouring the *gfp* (green fluorescent protein) gene from *Aequorea victoria* (Supplementary Information).

After fracturing of the samples (Supplementary Fig. 3), total DNA was extracted from a series of five subsamples taken along the radius of each core (Supplementary Information). Quantitative polymerase



# “Životnost” antibiotik



## RAPID COMMUNICATIONS

### Nosocomial outbreak by NDM-1-producing *Klebsiella pneumoniae* highly resistant to ceftiderocol, Florence, Italy, August 2021 to June 2022

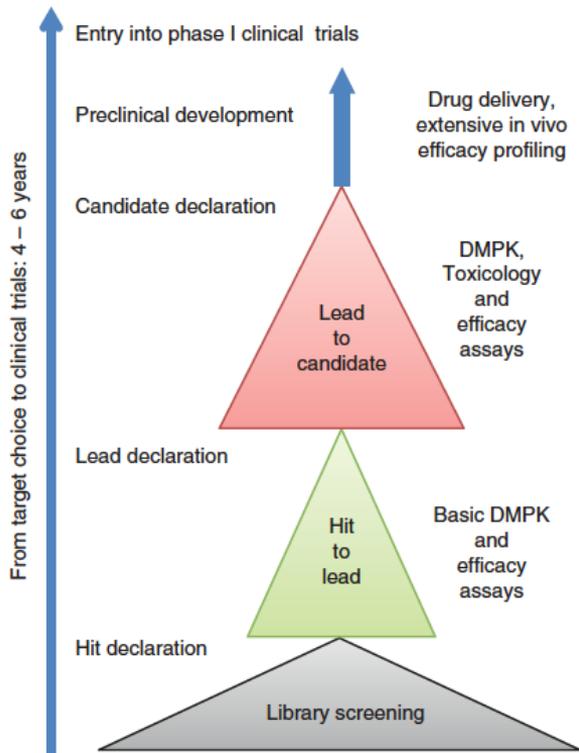
Marco Coppi<sup>1,2</sup>, Alberto Antonelli<sup>1,2</sup>, Claudia Nicolai<sup>1,2</sup>, Andrea Bartolini<sup>1</sup>, Laura Bartolini<sup>1</sup>, Maddalena Grazzini<sup>1</sup>, Elisabetta Mantengoli<sup>3,4</sup>, Alberto Farese<sup>4</sup>, Filippo Pieralli<sup>5</sup>, Maria Teresa Mech<sup>1</sup>, Vincenzo Di Pilato<sup>6</sup>, Tommaso Gian<sup>1,2</sup>, Gian Maria Rossolini<sup>1,2</sup>

1. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
2. Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy
3. Hospital Infection Prevention and Control Unit, Florence Careggi University Hospital, Florence, Italy
4. Infectious and Tropical Diseases Unit, Florence Careggi University Hospital, Florence, Italy
5. Subintensive Care Unit, Florence Careggi University Hospital, Florence, Italy
6. Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy

Correspondence: Gian Maria Rossolini (gianmaria.rossolini@unifi.it)

A nosocomial outbreak by ceftiderocol (FDC)-resistant NDM-1-producing *Klebsiella pneumoniae* (NDM-Kp) occurred in a large tertiary care hospital from August 2021–June 2022 in Florence, Italy, an area where NDM-Kp strains have become endemic. Retrospective analysis of NDM-Kp from cases observed in January 2021–June 2022 revealed that 21/52 were FDC-resistant. The outbreak was mostly sustained by clonal expansion of a mutant with inactivated *cirA* siderophore receptor gene, which exhibited high-level resistance to FDC (MIC<sub>50</sub> ≥ 32 mg/L) and spread independently of FDC exposure.

# Vývoj nových antibiotik



**Table 1**  
Global cost of R&D for a new antibiotic and effect of incentives on R&D and eNPV.

	PCR	Phase I	Phase II	Phase III	Registration	Post-launch study	Total
Base case without incentives							
Global cost (million) <sup>a</sup>	\$19	\$16	\$54	\$196	\$29	\$48	\$462
Progression rate <sup>b</sup>	0.35	0.67	0.46	0.70	0.87	0.87	0.87
Duration	5 years 0 months	1 year 4 months	2 years 2 months	2 years 5 months	0 years 0 months	0 years 0 months	11 years 8 months
Total programs <sup>c</sup>	15.22	5.33	3.57	1.64	0.87	0.87	15.22
Global capitalised cost (million) <sup>d</sup>	\$708	\$153	\$292	\$393	\$20	\$20	\$1581
eNPV (\$m)							-\$1510
With matched (50%) co-funding as part of Public Health Innovation Challenge							
Global capitalised cost (million)	\$354	\$76	\$146	\$196	\$20	\$20	\$791
eNPV (\$m)							-\$701
Implementation of the Tier B framework for registration							
Global cost (millions)	\$19	\$16	\$54	\$98	\$29	\$40	\$366
Global capitalised cost (\$m)	\$708	\$153	\$292	\$197	\$35	\$40	\$1385
eNPV (\$m)							-\$1313
Implementation of PPP for R&D and implementation of the Tier B framework for registration							
Global capitalised cost (\$m)	\$354	\$76	\$146	\$99	\$17	\$20	\$692
eNPV (\$m)							-\$603

Nejdelší možnost trvání patentové ochrany – 20 let

*Upsala Journal of Medical Sciences*, 2014; 119: 162-169

informa  
healthcare

REVIEW ARTICLE

Discovery and preclinical development of new antibiotics

DIARMAID HUGHES<sup>1</sup> & ANDERS KARLÉN<sup>2</sup>

Health Policy 121 (2017) 1025-1030

Contents lists available at ScienceDirect

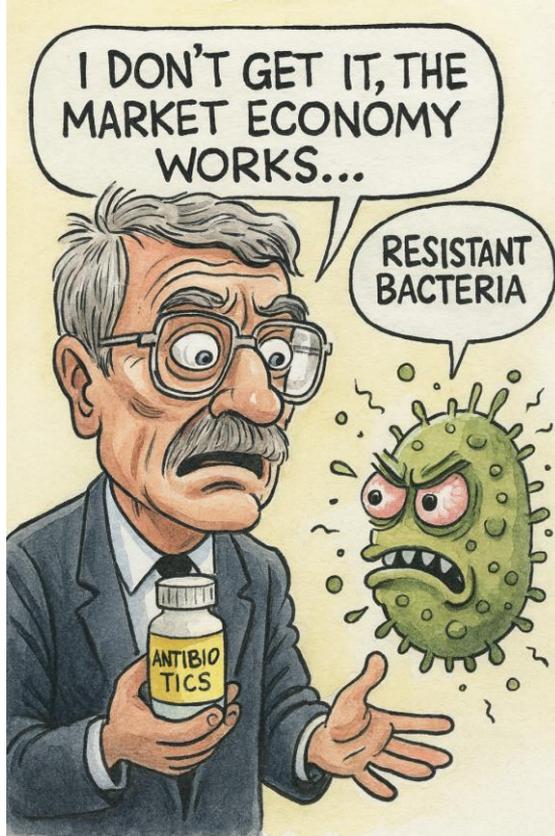
Health Policy

Journal homepage: [www.elsevier.com/locate/healthpol](http://www.elsevier.com/locate/healthpol)

Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation

Adrian Towse<sup>a,\*</sup>, Christopher K. Hoyle<sup>b</sup>, Jonathan Goodall<sup>b</sup>, Mark Hirsch<sup>b</sup>, Jorge Mestre-Ferrandiz<sup>c,1</sup>, John H. Rex<sup>c,1,2</sup>

# Vývoj nových antibiotik a tržní ekonomika (závěr I)

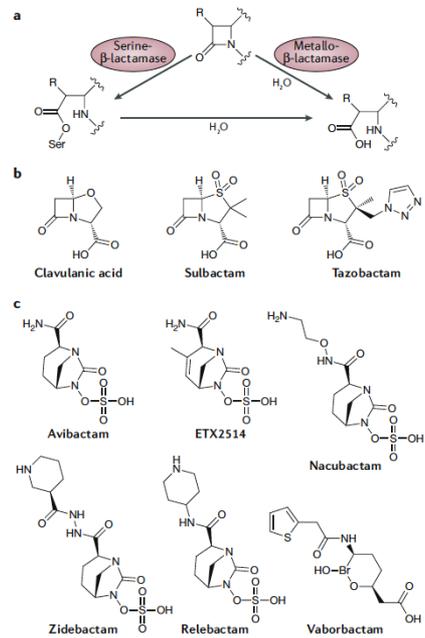
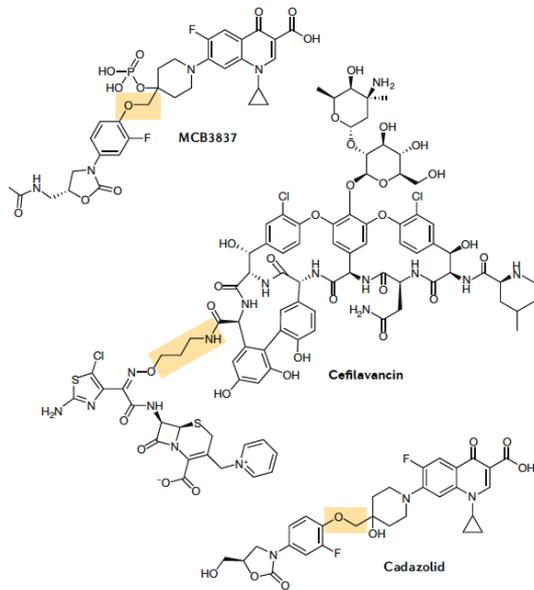
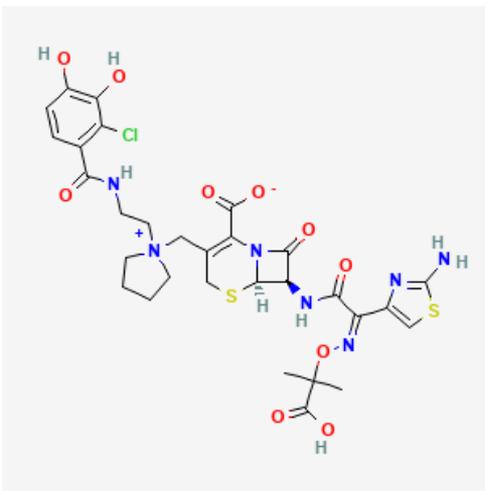


# Jaké jsou alternativy?



# Nová antibiotika v klinické praxi a výzkumu

- Inhibitory enzymů (např. karbapenemáz)
- Synergické molekuly
- Hybridní antibiotika



**REVIEWS**

ANTIMICROBIAL RESISTANCE

Drug combinations: a strategy to extend the life of antibiotics in the 21st century

Mike Tijers<sup>1</sup> and Gerard D. Wright<sup>2</sup>\*

# Další alternativy

Strategy	Advantages over conventional antibiotics	Possible disadvantages
Phage therapy	<ul style="list-style-type: none"><li>• Self-replicating pharmaceuticals</li><li>• Selective towards specific strains of bacteria</li><li>• Amenable to genetic engineering</li></ul>	<ul style="list-style-type: none"><li>• Immunogenicity</li><li>• Pharmacokinetics</li><li>• Release of bacterial endotoxins</li><li>• Inadequate preparations – failure to remove endotoxins and pyrogenic substances</li><li>• Resistance development</li></ul>
Lysins	<ul style="list-style-type: none"><li>• Amenable to genetic engineering</li><li>• Selective towards specific strains of bacteria</li><li>• Not prone to resistance development</li></ul>	<ul style="list-style-type: none"><li>• Production</li><li>• Lack of sufficient knowledge</li></ul>
CRISPR/Cas9	<ul style="list-style-type: none"><li>• Can be tuned for a variety of antimicrobial applications</li><li>• Reversal of antibiotic usage</li><li>• Specificity towards pathogenic strains</li></ul>	<ul style="list-style-type: none"><li>• Expensive large-scale production</li><li>• Toxicity</li></ul>
Antimicrobial peptides	<ul style="list-style-type: none"><li>• Not prone to resistance development</li><li>• Broad-spectrum activity is an advantage, depending upon application</li></ul>	<ul style="list-style-type: none"><li>• Expensive large-scale production</li><li>• Susceptible to proteolysis</li><li>• Toxicity</li></ul>



# Další alternativy

Bacteriocins	<ul style="list-style-type: none"><li>• Specificity towards pathogenic strains of bacteria</li><li>• Resistance to heat and UV</li></ul>	<ul style="list-style-type: none"><li>• Expensive large-scale production</li><li>• Susceptible to proteolysis</li></ul>
SMAMPs <sup>a</sup>	<ul style="list-style-type: none"><li>• Ease of synthesis</li><li>• Not prone to resistance development</li><li>• Broad-spectrum activity is an advantage, depending upon application</li></ul>	<ul style="list-style-type: none"><li>• Toxicity</li><li>• Route of administration</li></ul>
IDR peptides <sup>b</sup>	<ul style="list-style-type: none"><li>• Work by modulating the immune system</li><li>• No resistance development as no direct antimicrobial activity</li></ul>	<ul style="list-style-type: none"><li>• Expensive large-scale production</li><li>• Susceptible to proteolysis</li></ul>
Probiotics	<ul style="list-style-type: none"><li>• Easy availability</li></ul>	<ul style="list-style-type: none"><li>• Used mostly for intestinal infections</li></ul>
Antibodies	<ul style="list-style-type: none"><li>• Selective towards specific strains of bacteria</li><li>• Do not damage the microflora</li></ul>	<ul style="list-style-type: none"><li>• High cost of production</li><li>• Poor shelf life</li></ul>

Synthetic Mimics of Antimicrobial Peptides (SMAMPs)

Innate Defence Regulatory Peptides

Trends in Microbiology

CellPress  
REVIEWS

Review

Alternatives to Conventional Antibiotics in the Era of Antimicrobial Resistance

Chandradrieh Ghosh,<sup>1</sup> Paramita Sarkar,<sup>2</sup> Rahaf Issa,<sup>2</sup> and Jayanta Halder<sup>1\*</sup>

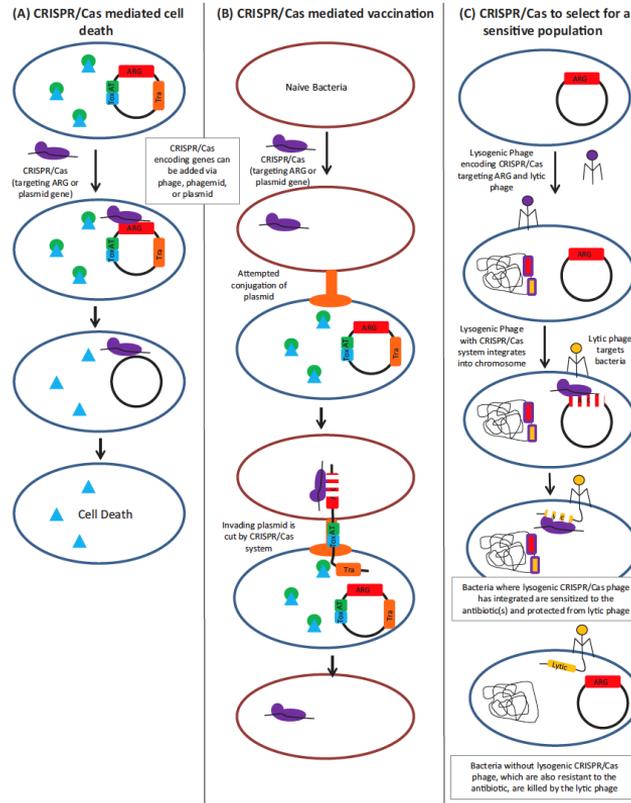


National Institute  
of Virology and Bacteriology



FACULTY OF MEDICINE  
IN PLZEŇ  
Charles University

# Jiné přístupy kromě fagoterapie (např. Plasmid curing)

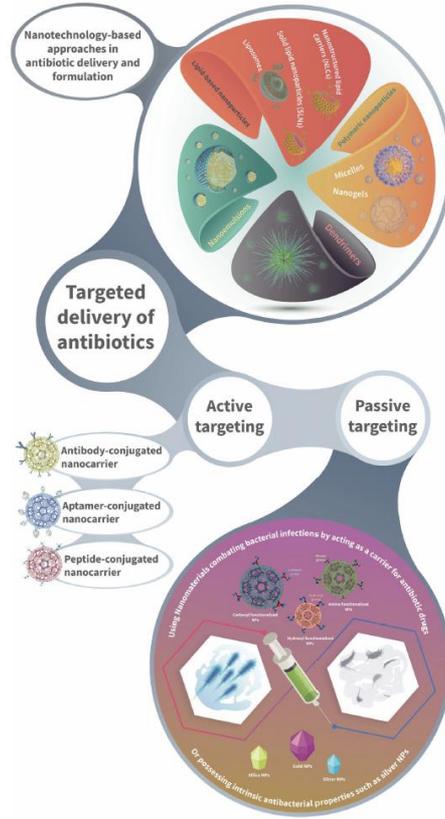


REVIEW ARTICLE

Strategies to combat antimicrobial resistance: anti-plasmid and plasmid curing

Michelle M. C. Buckner<sup>†</sup>, Maria Laura Ciusa and Laura J. V. Piddock<sup>\*,†</sup>

# Lepší zacílení antibiotické terapie



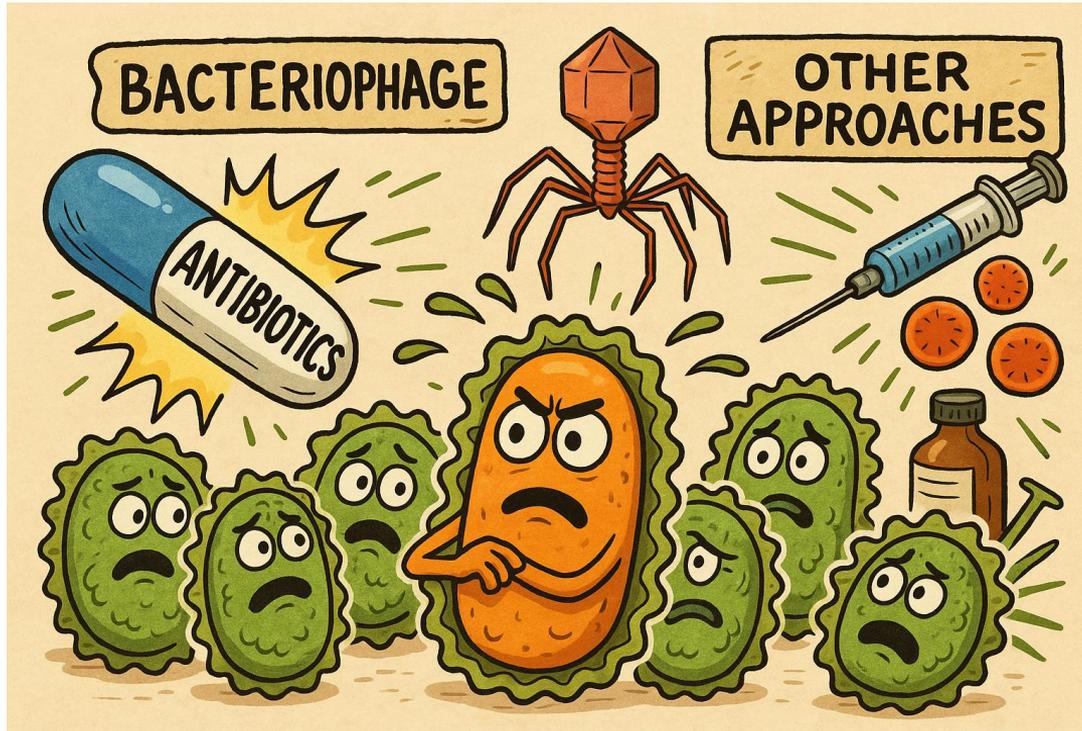
Pharmaceutical Research (2025) 4:2859–2889  
<https://doi.org/10.1007/s11095-025-03871-x>

REVIEW ARTICLE

**The Next Frontier: Unveiling Novel Approaches for Combating Multidrug-Resistant Bacteria**

Praveen Mallan<sup>1</sup> · Lella D. Rostami<sup>2</sup> · Ida Alanko<sup>3,4</sup> · Fadak Howali<sup>5</sup> · Meixin Ran<sup>3,4</sup> · Kuldeep K. Bansal<sup>6</sup> · Jessica M. Rosenholm<sup>7</sup> · Ossi M. H. Salo-Ahene<sup>8</sup>

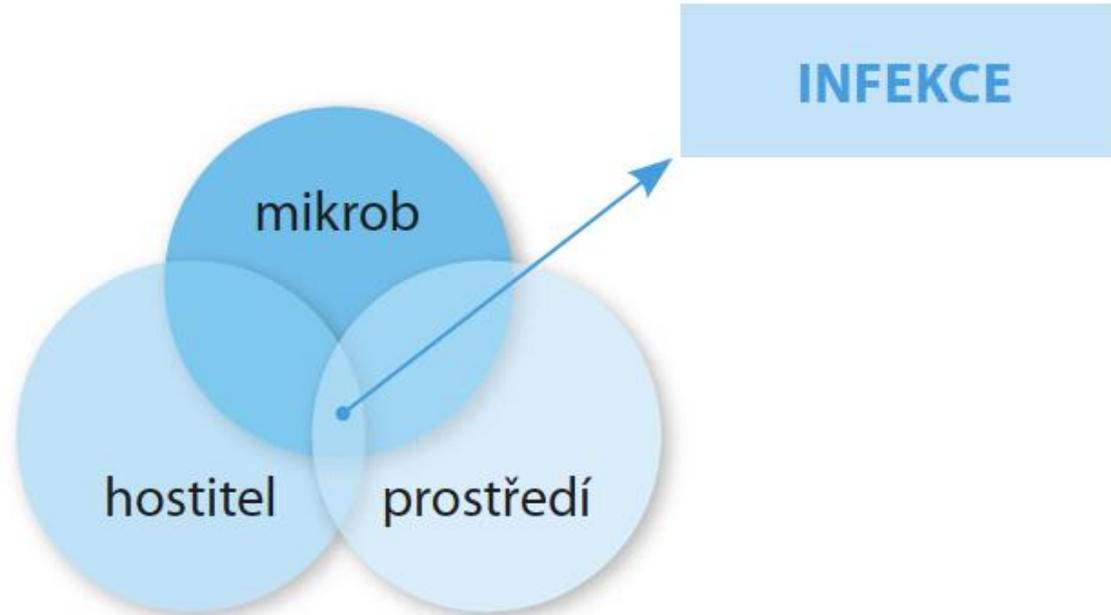
# Stále se potýkáme se selekčním tlakem – bakterie chtějí přežít... (závěr II)



# Existuje další možný přístup?

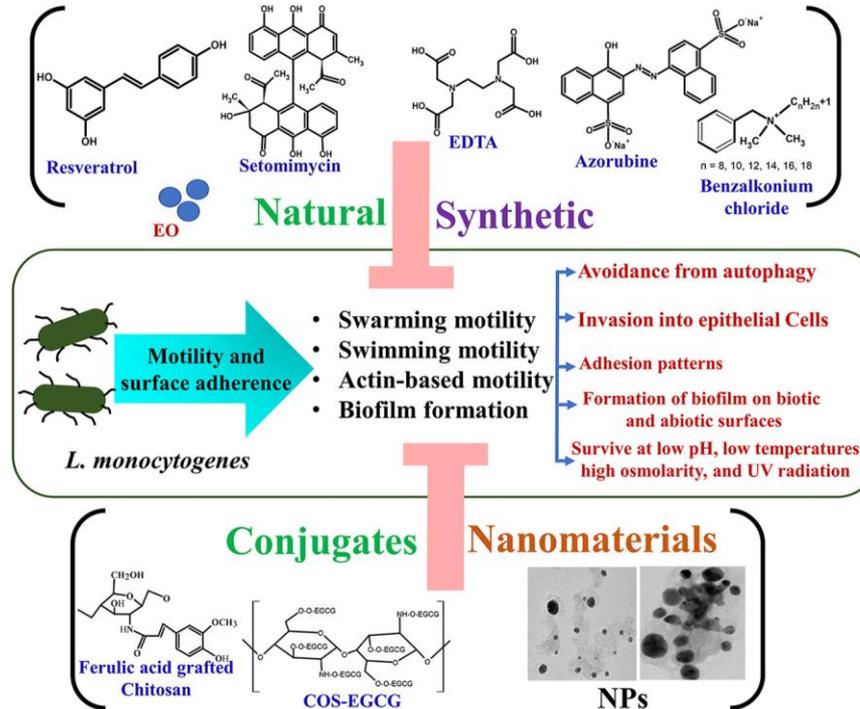


# Vznik infekce



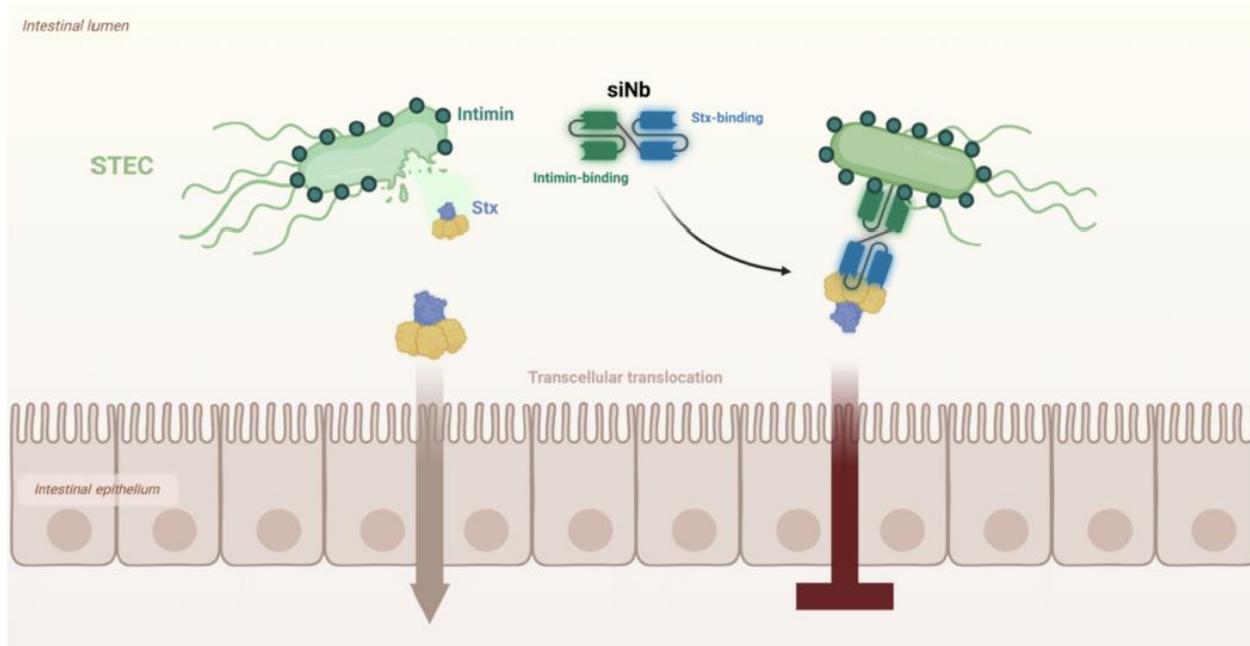
# Antivirulenční strategie

- Např. pohyblivost u *Listeria monocytogenes*



# Antivirulenční strategie

- Např. inhibice toxinů



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**Cellular Signalling**

journal homepage: [www.elsevier.com/locate/celsig](http://www.elsevier.com/locate/celsig)

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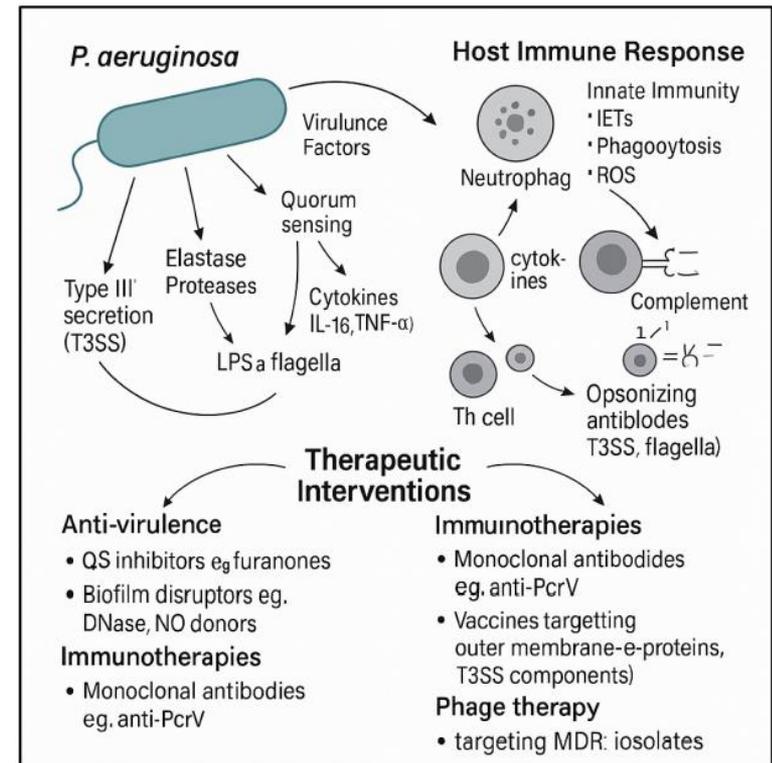
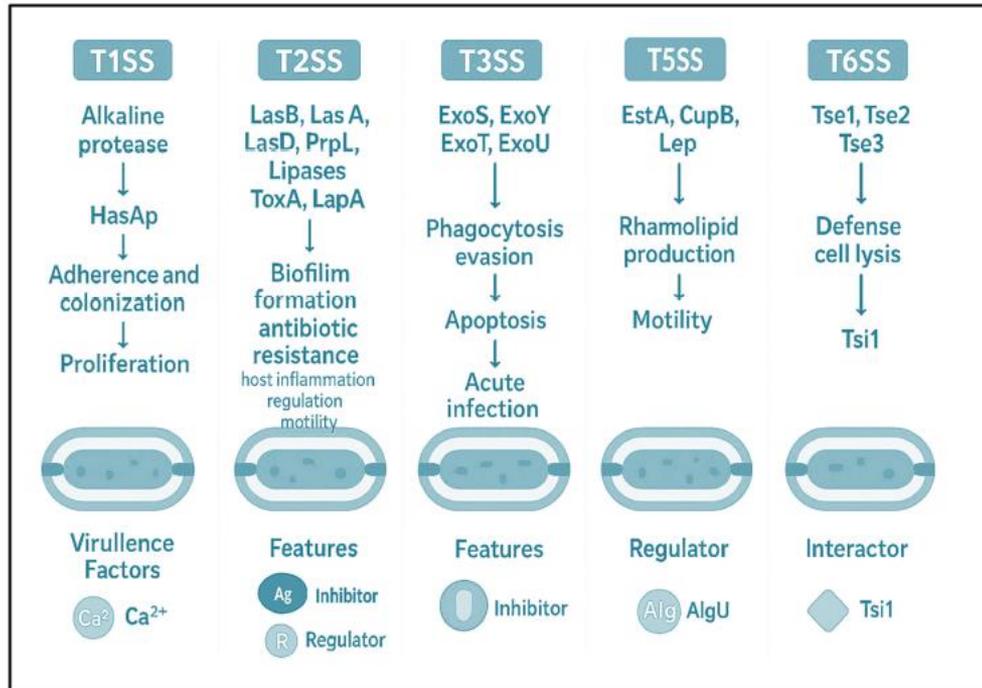
One problem, multiple potential targets: Where are we now in the development of small molecule inhibitors against Shiga toxin?

Samantha K. Tucker, Rebecca E. McHugh, Andrew J. Roe<sup>\*</sup>

School of Infection and Immunity, University of Glasgow, Glasgow G12 8TA, United Kingdom

# Antivirulenční strategie

- Komplexní přístup



**Virulence** 2025, Vol. 16, No. 1, 2580160  
<https://doi.org/10.1080/21505594.2025.2580160>

**BACTERIAL PATHOGENESIS** Taylor & Francis  
Taylor & Francis Group

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**Multidrug-resistant *Pseudomonas aeruginosa*: Pathogenesis, resistance mechanisms, and novel therapeutic strategies**

Mohammed Salem Alharbi , Soha Abdallah Moursi , Ahmed Alshammari<sup>†</sup>, Rana Aboras<sup>†</sup>, Ehab Rakha<sup>†\*</sup>, Ashfaque Hossain<sup>†</sup>, Sami Alshubrumi<sup>†</sup>, Khaled Alnazha<sup>†</sup>, Azharuddin Sajid Syed Khaja<sup>†</sup>, and Mohd Saleem<sup>†</sup>

# Antivirulenční strategie

- Praktické aplikace

Online Laboratory Investigations

OPEN

## Vagus Nerve Stimulation Attenuates Multiple Organ Dysfunction in Resuscitated Porcine Progressive Sepsis

Michaela Kohoutova, MSc<sup>1,2</sup>; Jan Horak, MD<sup>2,3</sup>; Dagmar Jarkovska, Ing, PhD<sup>1,2</sup>;  
Vendula Martinkova, MD<sup>2,4</sup>; Vaclav Tegl, MD<sup>2,5</sup>; Lukas Nalos, MD, PhD<sup>1,2</sup>; Lucie Vistejnova, Ing, PhD<sup>2</sup>;  
Jan Benes, MD, PhD<sup>2,5</sup>; Jitka Sviglerova, MD, PhD<sup>1,2</sup>; Jitka Kuncova, MD, PhD<sup>1,2</sup>;  
Martin Matejovic, MD, PhD<sup>2,3</sup>; Milan Stengl, MD, PhD<sup>1,2</sup>

Blood Purification

Clinical Engineering

Blood Purif  
DOI: 10.1159/000547419

Received: January 24, 2025  
Accepted: June 23, 2025  
Published online: July 14, 2025

## Endotoxin and Cytokine Removal with a New (CA) Sorbent Cartridge

Anna Lorenzin<sup>a,b</sup> Natascha Perin<sup>a,b</sup> Massimo de Cal<sup>a,b</sup> Monica Zanella<sup>a</sup>  
Claudio Ronco<sup>b</sup>

<sup>a</sup>Department of Nephrology Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy; <sup>b</sup>International Renal Research Institute of Vicenza (IRRV), San Bortolo Hospital, Vicenza, Italy

Blood Purification

Critical Care Nephrology

Blood Purif  
DOI: 10.1159/000546923

Received: January 16, 2025  
Accepted: May 9, 2025  
Published online: June 18, 2025

## Endotoxin, Virus, and Bacterial Removal: Why, When, and How?

Lui G. Forni<sup>a,b</sup> Vedran Premuzic<sup>c,d</sup>

<sup>a</sup>Intensive Care Unit, Royal Surrey Hospital Foundation Trust, Guildford, UK; <sup>b</sup>School of Medicine, Kate Granger Building, University of Surrey, Guildford, UK; <sup>c</sup>School of Medicine, University of Zagreb, Zagreb, Croatia; <sup>d</sup>Department for Nephrology, Hypertension, Dialysis and Transplantation, University Hospital Center Zagreb, Zagreb, Croatia

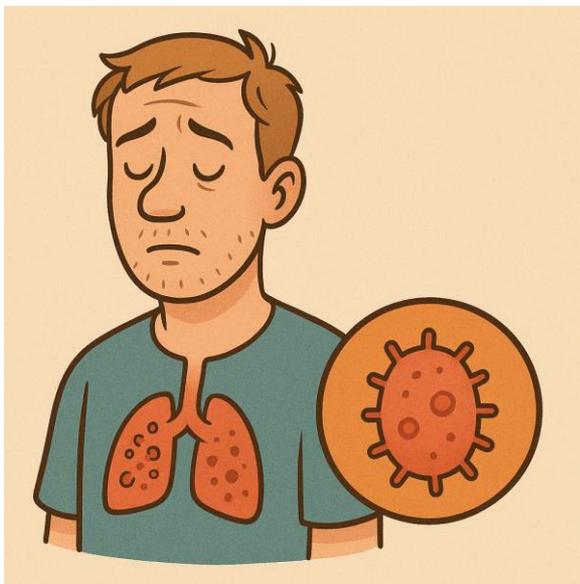


# Závěry



# Jaké přístupy zvolit?

- Nutný individuální přístup s ohledem na **stav** pacienta a jeho **imunitní systém**



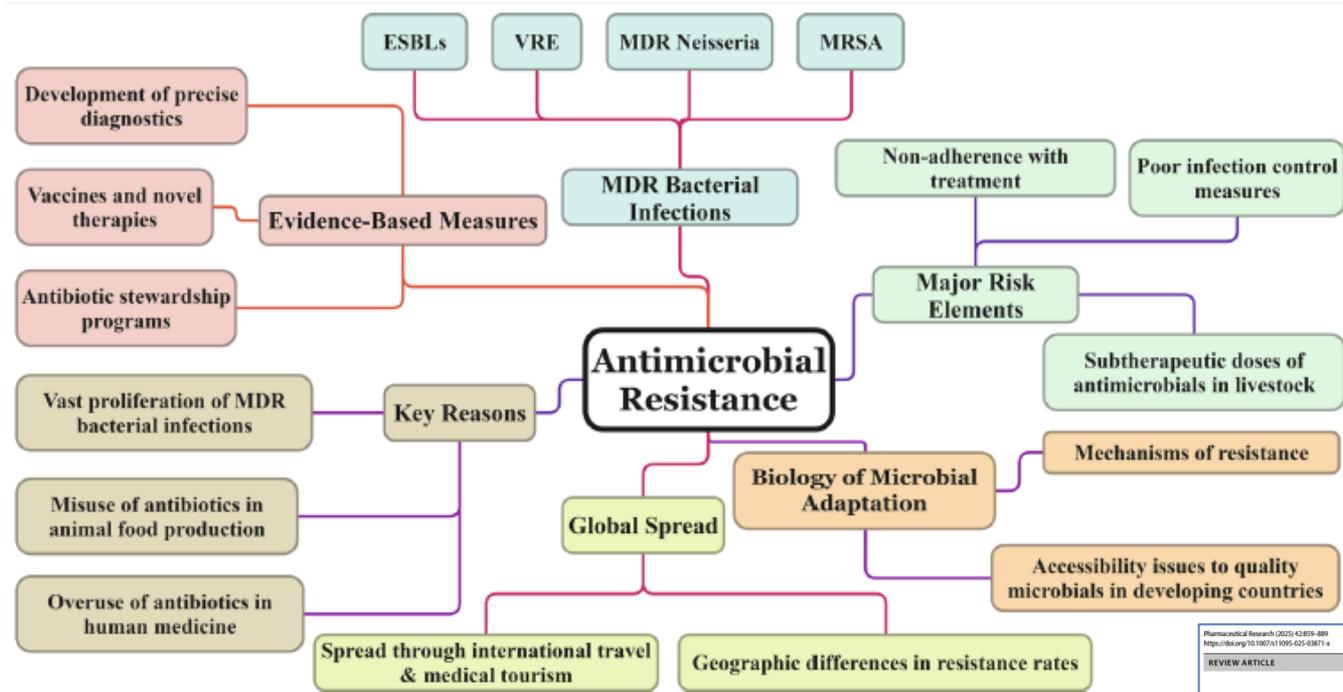
Antivirulenční strategie



Klasický „antibiotický“ přístup  
s moderními postupy



# Jak předcházet vzniku antibiotické rezistence



Pharmaceutical Research (2025) 4:2819–2899  
<https://doi.org/10.1007/s11096-025-08871-x>

REVIEW ARTICLE

The Next Frontier: Unveiling Novel Approaches for Combating Multidrug-Resistant Bacteria

Praveen Mallari<sup>1</sup> · Leila D. Rontani<sup>2</sup> · Ida Alanko<sup>3,4</sup> · Fadak Howaili<sup>5</sup> · Meixin Ran<sup>6,4</sup> · Kuldeep K. Bansal<sup>7</sup> · Jessica M. Rosenholm<sup>8</sup> · Outh M. H. Salo-Ahven<sup>9,10</sup>





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