



Výhled na nové možnosti boje s AMR

MUDr. Tomáš Boráň
Ředitel Státního ústavu pro kontrolu léčiv

13.11.2024

Rychlost vývoje nových ATB

- Od roku 2017: Quofenix (delafloxacin), Vaborem (**vaborbactam / meropenem**), Xerava (eravacycline), Nuzyra (omadacycline), Recarbrio (relebactam / imipenem / cilastatin), Xenleta (**lefamulin**), Dovprela (pretomanid) a aztreonam/avibaktam (Emblaveo)

Nové třídy „konvenčních“ ATB ve vývoji

- FabI inhibitory a FtsZ inhibitory (afabycin a TXA-709)
- Nefluorochinolonové inhibitory topoisoméráz (gepotidacin a zoliflodacin)
- Deriváty polymyxinů (eCAP)
- Antituberkulotika: DprE1 inhibitory, LeuRS inhibitory a amidazopyridin amid
- *C. difficile*: ridinilazol, MGB-BP-3 (derivát dystamicinu), CRS3123

Další

- Taniborbactam (plus cefepim)
- **Bakteriofágy**
- Rekombinantní endolysiny
- 514G3, tosatuxumab, DSTA4637S: antivirulenční přístupy
- monoklonální protilátky
- GSK3882347, OligoG
- **FMT**
- Polymery
- In vitro diagnostika

Review | [Open access](#) | Published: 01 November 2024

Current status of bacteriophage therapy for severe bacterial infections

[Teiji Sawa](#) , [Kiyoshi Moriyama](#) & [Mao Kinoshita](#)[Journal of Intensive Care](#) **12**, Article number: 44 (2024) | [Cite this article](#)845 Accesses | [Metrics](#)

Abstract

The increase in the incidence of antibiotic-resistant bacteria poses a global public health threat. According to a 2019 WHO report, approximately 1.27 million deaths were attributed to antibiotic-resistant bacteria, with many cases linked to specific bacterial species, such as drug-resistant *Pseudomonas aeruginosa* and *Staphylococcus aureus*. By 2050, the number of deaths caused by these bacteria is predicted to surpass that caused by cancer. In response to this serious situation, phage therapy, an alternative to antibiotic treatment, has gained attention. Phage therapy involves the use of viruses that target specific bacteria to treat infections. This method has proven effective in multiple clinical cases, particularly for patients with severe infections caused by multidrug-resistant bacteria. For example, there are reports of patients with systemic infections caused by multidrug-resistant *Acinetobacter* who recovered following phage administration and patients infected with panresistant *Pseudomonas aeruginosa* who were cured by phage therapy. A key feature of phage therapy is its high specificity. Phages infect only specific bacteria and eliminate them. However, this specificity can also be a disadvantage, as careful selection of the appropriate phage for the target bacteria is needed. Additionally, bacteria can develop resistance to phages, potentially reducing treatment effectiveness over time. Efforts are underway to select, combine, and improve phages to address these challenges. In Belgium, a national phage bank has been established, and in the United States, the University of California, San Diego, has founded Innovative Phage Applications and Therapeutics (IPATH), marking significant progress toward the clinical application of phage therapy in the country. As a result, phage therapy is emerging as a component of personalized medicine, offering a new treatment option against antibiotic-resistant bacteria. The clinical application of phage therapy is particularly important in life-saving treatments for patients with severe bacterial infections, and its use in conjunction with antibiotics could enhance therapeutic outcomes. Continued research and development of this therapy could provide hope for many more patients in the future.

Randomized Controlled Trial > Sci Transl Med. 2023 Nov;15(720):eabo2750.

doi: 10.1126/scitranslmed.abo2750. Epub 2023 Nov 1.

Fecal microbiota transplantation promotes reduction of antimicrobial resistance by strain replacement

Michael H Woodworth^{1 2}, Roth E Conrad³, Marina Haldopoulos², Stephanie M Pouch^{1 2}, Ahmed Babiker^{1 2 4}, Aneesh K Mehta^{1 5}, Kaitlin L Sitchenko^{1 4}, Charlotte H Wang⁶, Amanda Strudwick¹, Jessica M Ingersoll⁴, Cécile Philippe¹, Sarah Lohsen¹, Kumru Kocaman⁷, Blake G Lindner⁷, Janet K Hatt⁷, Rheinallt M Jones⁸, Candace Miller⁴, Andrew S Neish⁴, Rachel Friedman-Moraco¹, Geeta Karadkhele⁵, Ken H Liu⁹, Dean P Jones⁹, C Christina Mehta¹⁰, Thomas R Ziegler¹¹, David S Weiss^{1 2}, Christian P Larsen⁵, Konstantinos T Konstantinidis⁷, Colleen S Kraft^{1 2 4}

Affiliations + expand

PMID: 37910603 PMCID: PMC10821315 DOI: 10.1126/scitranslmed.abo2750

Abstract

Multidrug-resistant organism (MDRO) colonization is a fundamental challenge in antimicrobial resistance. Limited studies have shown that fecal microbiota transplantation (FMT) can reduce MDRO colonization, but its mechanisms are poorly understood. We conducted a randomized, controlled trial of FMT for MDRO decolonization in renal transplant recipients called PREMIX (NCT02922816). Eleven participants were enrolled and randomized 1:1 to FMT or an observation period followed by delayed FMT if stool cultures were MDRO positive at day 36. Participants who were MDRO positive after one FMT were treated with a second FMT. At last visit, eight of nine patients who completed all treatments were MDRO culture negative. FMT-treated participants had longer time to recurrent MDRO infection versus PREMIX-eligible controls who were not treated with FMT. Key taxa (*Akkermansia muciniphila*, *Alistipes putredinis*, *Phocaeicola dorei*, *Phascolarctobacterium faecium*, *Alistipes* species, *Mesosutterella massiliensis*, *Barnesiella intestinihominis*, and *Faecalibacterium prausnitzii*) from the single feces donor used in the study that engrafted in recipients and metabolites such as short-chain fatty acids and bile acids in FMT-responding participants uncovered leads for rational microbiome therapeutic and diagnostic development. Metagenomic analyses revealed a previously unobserved mechanism of MDRO eradication by conspecific strain competition in an FMT-treated subset. Susceptible *Enterobacteriales* strains that replaced baseline extended-spectrum β -lactamase-producing strains were not detectable in donor microbiota manufactured as FMT doses but in one case were detectable in the recipient before FMT. These data suggest that FMT may provide a path to exploit strain competition to reduce MDRO colonization.

Seznam esenciálních antiinfektiv 2024

| NÁZEV LÉČIVÉ LÁTKY | LÉKOVÉ FORMY | ZDŮVODNĚNÍ |
|------------------------------|--|--|
| <u>imipenem/relebaktam</u> | Prášek pro infuzní roztok: 500mg <u>imipenem</u> (monohydrát) + 500 mg <u>cilastatin</u> (sodná sůl) + 250 mg <u>relebaktam</u> (monohydrát) v lahvičce (J01DH56) | Indikace: Komplikované infekce způsobené rezistentními gramnegativními bakteriemi, není-li jiná volba. |
| <u>ceftolozan/tazobaktam</u> | Prášek pro koncentrát pro infuzní roztok: 1 g <u>ceftolozan</u> (sulfát) + 0,5 g <u>tazobaktam</u> (sodná sůl) (J01DI54) | Indikace: Komplikované infekce způsobené rezistentní <u>Pseudomonas aeruginosa</u> , není-li jiná volba. |
| <u>daptomycin</u> | Prášek pro injekční/infuzní roztok: 350 mg; 500 mg (J01XX09) | Indikace: Komplikované infekce způsobené MRSA, není-li jiná volba. |

Návrh do seznamu esenciálních antiinfektiv 2025

- **aztreonam/avibaktam** - indikace: infekce způsobené producenty karbapenemáz (KPC, OXA-48, NDM), není-li jiná volba

Revize farmaceutické legislativy – revize Nařízení 726/2004 ES

- „převoditelné poukazy na exkluzivitu údajů“
- plán dohledu nad antimikrobiální rezistencí, který bude obsahovat informace o opatřeních ke zmírnění rizik, monitorování a hlášení rezistence vůči danému léčivému přípravku
- osud antimikrobiální látky v životním prostředí

Updated Note on Transferable Exclusivity Extension vouchers & Better Alternatives

November 2022

Medicines for Europe strongly supports the objective to fight antimicrobial resistance (AMR) and to develop medicines to address unmet medical needs, including in the field of orphan and paediatric medicines.

The European Commission has been considering introducing novel rewards to address unmet medical needs, including in the field of antibiotics, orphan and paediatric medicines. Among different options, the EC has been evaluating the introduction of transferable exclusivity extension vouchers, a system that does not exist anywhere else in the world.


As demonstrated in independent studies and stressed below, the introduction of transferable exclusivity extension vouchers in the EU would

- dramatically increase costs for healthcare budgets, with significant risk of overcompensation especially if the development for instance of an antimicrobial would have taken place anyway
- break the founding principle of the relationship between innovation and reward
- extend monopolies on more profitable products that would not otherwise qualify for that extension
- unduly delay access to generic and biosimilar medicines for patients.
- be unfair to those patient categories that would bear the financial burden for an innovation they do not use
- increase legal uncertainty & unnecessary litigation, including for users of SPC manufacturing waiver, which need predictability for their investment plans
- it would particularly hit biosimilar developers due to their very long development time and R&D costs


For these reasons, several countries around the world have adopted alternative novel incentives to stimulate the development of novel antibiotics and the development and production of generic antibiotics.



To tackle AMR and create a **market for reserve antibiotics**, a simple and efficient system could be introduced, including a **(1) fast-track approval process** for novel molecules and for the reintroduction of well-established molecules no longer licenced in Europe, coupled with **(2) a EU fund** to purchase the reserve molecules. With this model, the EU would ensure that physicians everywhere in Europe have access to reserve molecules at all times, which is certainly not guaranteed by the introduction of a transferable exclusivity extension

Intenzivnější opatření EU

Rada přijala 13. června 2023 návrh Evropské komise ohledně [doporučení o posílení opatření EU pro boj proti antimikrobiální rezistenci v rámci přístupu „jedno zdraví“](#) 

- [Infopřehled](#) 
- [Časté otázky](#) 
- [Prohlášení](#) 

Evropský parlament přijal 1. června 2023 [usnesení o opatřeních EU v boji proti rezistenci vůči antimikrobiálním látkám](#) 

Evropská komise přijala 26. dubna 2023 jako součást tzv. [farmaceutického balíčku](#) , [návrh doporučení Rady o posílení opatření EU pro boj proti antimikrobiální rezistenci v rámci přístupu „jedno zdraví“](#) , k němuž je připojen pracovní dokument útvarů Komise.

- [Tisková zpráva](#) 

Tento návrh doporučení Rady rozšiřuje a doplňuje akční plán EU „jedno zdraví“ proti antimikrobiální rezistenci z roku 2017 ve všech aspektech. Jeho cílem je maximalizovat synergie a dosáhnout silné a účinné reakce proti antimikrobiální rezistenci v celé EU.

Cíle návrhu doporučení Rady

- posílit národní akční plány v rámci přístupu „jedno zdraví“ týkající se antimikrobiální rezistence
- zvýšit dohled nad antimikrobní rezistencí a spotřebou antimikrobiálních látek a jejich monitorování
- zlepšit prevenci a kontrolu infekcí
- zvýšit dohled nad antimikrobiálními látkami a jejich obezřetné používání
- doporučit cíle pro boj proti AMR a spotřebu antimikrobiálních látek v oblasti lidského zdraví
- zlepšit informovanost, vzdělávání a odbornou přípravu
- podporovat výzkum a vývoj i pobídky pro inovace a přístup k antimikrobiálním látkám
- zintenzivnit spolupráci
- posílit globální opatření

1 THE AMR CHALLENGE



- ▶ Antimicrobial resistance (AMR) occurs **when microbes change over time and stop responding to medicines** designed to kill them.
 - ▶ infections harder to treat.
 - ▶ higher risk of diseases, severe illnesses, and death.



AMR CAUSES **35 000 DEATHS** EVERY YEAR IN THE EUROPEAN UNION AND LEADS TO HIGH COSTS, INCLUDING **€1.5BN ANNUALLY** FOR OUR HEALTHCARE SYSTEMS.

- ▶ AMR **affects humans, animals, and plants**, as well as the environment, impacting healthcare and food production.
- ▶ It is a **cross-border** issue and is one of the **top 3 health threats** faced by the EU.



2 More prudent use of antimicrobials



Overuse and misuse of antimicrobials such as antibiotics means AMR is increasing.



ONLY HALF OF EU CITIZENS ARE AWARE THAT ANTIBIOTICS ARE INEFFECTIVE AGAINST VIRUSES.



BETWEEN 2016 AND 2020 THE NUMBER OF INFECTIONS AND DEATHS DUE TO AMR IN THE EU/EEA INCREASED SIGNIFICANTLY.

EU Health ministers have agreed

- ▶ **Prudent use measures** (such as prescription status, adequate pack size, appropriate information for patients and healthcare professionals, antimicrobial stewardship plans including risk mitigation measures, monitoring and reporting of resistance to the antimicrobial.
- ▶ Recommended **EU and national targets** to decrease the use of antibiotics in humans and the level of key antibiotic resistant infections by 2030.
 - ▶ **20% less consumption of antibiotics.**
- ▶ Additional surveillance and monitoring of AMR and consumption of antimicrobials, better infection prevention and control, better awareness of the public, education and training of professionals.

3 ENSURING THE AVAILABILITY OF ANTIBIOTICS



Prudent use of antibiotics is essential to tackle AMR, but this also **affects sales volumes and return on investment** for medicine developers.

Therefore, we need to **encourage the development of innovative antimicrobials** and to ensure access to and availability of antimicrobials. The Commission has proposed:

- ▶ a **transferable data exclusivity voucher** giving developers of new antimicrobials an extra year of regulatory data protection, making it more attractive for them to develop innovative antimicrobials without direct financial contributions from Member States.
- ▶ **Procurement mechanisms** to provide access to antimicrobials, including those under development.

4 FIGHTING AMR GLOBALLY



AMR cannot be tackled by one sector, one country or one continent in isolation. This means:

- ▶ Keeping AMR at the centre of the **EU's Global Health Strategy**
- ▶ **Pushing for more** global cooperation and addressing AMR in the **WHO international agreement** on pandemic prevention, preparedness and response currently being negotiated.

5 MORE RESEARCH AND TECHNOLOGICAL INNOVATION INTO AMR



- ▶ **Horizon 2020:** more than **€ 690 million** for research and innovation into AMR.
- ▶ **Horizon Europe:** in first 2 years **€ 32.5 million for 13 research projects** addressing antimicrobial resistance.
- ▶ **EU4Health Programme:** in 2024 launch of a **€ 50 million joint action** with Member States, Norway, Iceland and Ukraine on AMR.

A Swedish pilot study of an alternative reimbursement model

Availability to antibiotics of particular importance

In a pilot project, the Public Health Agency of Sweden has investigated whether a model with guaranteed reimbursement to the pharmaceutical company can improve access to particularly important antibiotics in Sweden. An initial evaluation shows that the studied reimbursement model led to increased access to the antibiotic products in our country, earlier than in other comparable European countries.

Having access to the right kind of antibiotics is crucial for infections with resistant bacteria. But Sweden is a small market with restrictive antibiotic use. New drugs tend to be introduced late or not at all.

In 2018, the Public Health Agency of Sweden (PHAS) was commissioned by the government to test and evaluate a new reimbursement model aiming to ensure that particularly important antibiotics for hospital use are available in Sweden. The overall aim was to propose a model that would strengthen the availability of certain antibiotics in Sweden, so that patients with infections caused by multi-resistant bacteria can receive the best possible treatment. The goal of the assignment was to make a recommendation to the government on whether the activities within the pilot study should be extended, and if so, in what way. Any additional measures required for a long-term solution were also to be presented. The proposal would be analysed for legal aspects and financial consequences, as well as suggest division of responsibilities between the state and the regions.

Methods

The work on this assignment was divided into three phases: preparation, implementation and evaluation. In the preparation phase, the PHAS established all the principles for the reimbursement model to be tested. The preparation phase included several dialogue meetings and exchanges of experience with relevant national and international stakeholders, including pharmaceutical companies.

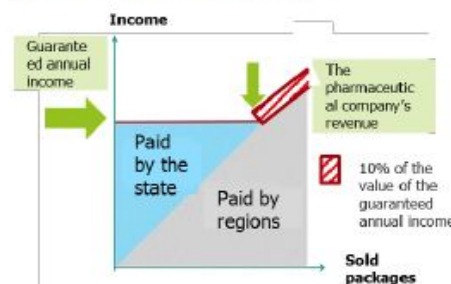
The reimbursement model

The studied reimbursement model is a so-called pull mechanism where the revenue is partially de-linked from the sale. This means that pharmaceutical companies are guaranteed a minimum income (in the pilot study via state funds from the Innovation Agency Vinnova) in return for providing the product on the market.

The guaranteed level was set at: volume of stock set aside for Sweden * template price per pack * 1.5.

The defined stock volume was based on an estimated medical need in a "worst case scenario". The aim was to cope with unpredictable global delivery problems. During the preparation phase, a principle in the reimbursement model called the inventory incentive part was also designed. The incentive share was set at 10 percent of the annual guaranteed minimum revenue. It was set as an extra pull mechanism for all products, even if annual sales exceed the reimbursement level during the contract period. The intention was to cover costs for maintaining availability according to the agreement.

Figure 1. Schematic principles of the model.



Requirements specification

The principles for deciding which antibiotics to include in the pilot study were based on a priority by the PHAS

<https://www.folkhalsomyndigheten.se/contentassets/700919bb88944affbfe814c1b23e53ed/availability-to-antibiotics-of-particular-importance.pdf>

EU multi-country revenue guarantee to improve access to new antimicrobials

- **Cefiderocol (Fetcroja)**
- Meropenem/Vaborbactam (Vaborem)
- Aztreonam/Avibactam (Emblaveo)



Dotazník spokojenosti:



Máte zkušenosti se SÚKL?

Podělte se o ně s námi!

SÚKL se jako každá organizace snaží zlepšovat a rozvíjet poskytované služby.

Budeme proto rádi, když nám dáte zpětnou vazbu vyplněním následujícího dotazníku.

[DOTAZNÍK SPOKOJENOSTI](#)

Předem děkujeme za spolupráci a za čas věnovaný odpovědím.



DĚKUJEME ZA POZORNOST

STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV

Šrobárova 48, 100 41 Praha 10

tel.: +420 272 185 111

e-mail: posta@sukl.cz

www.sukl.cz

UŽ MÁTE NAŠI APLIKACI eRecept?

Aplikace navíc nabízí i benefity pro pacienty, např. možnost přístupu ke všem údajům o své elektronické preskripci, včetně lékového záznamu a nastavení souhlasů k němu.

Upozorňujeme, že při aktivaci aplikace budete vyzváni k ověření vaší identity prostřednictvím identity občana.

Aplikace ke stažení:

