



FARMACEUTICKÁ FAKULTA
V HRADCI KRÁLOVÉ
Univerzita Karlova



Česká platforma antibiotické rezistence, z.s.

Antibiotická rezistence v ČR: jak
společně zastavit nezastavitelné

"Vzkříšení" a modifikace starých antimikrobních léčiv – nový trend?

Martin Krátký

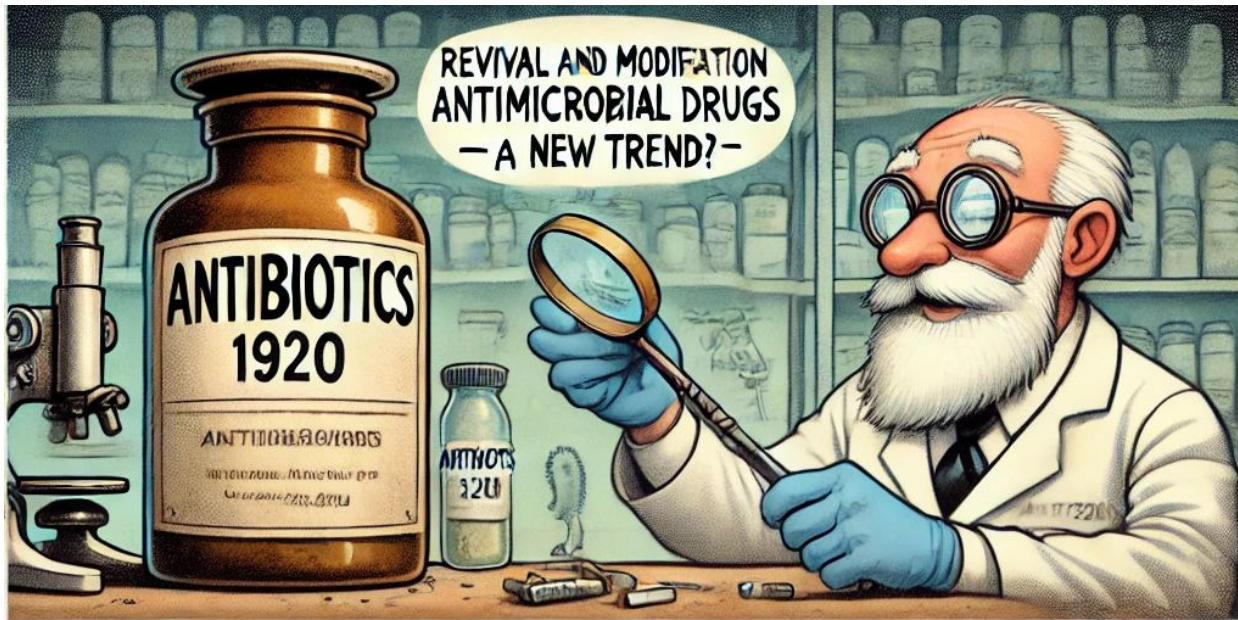
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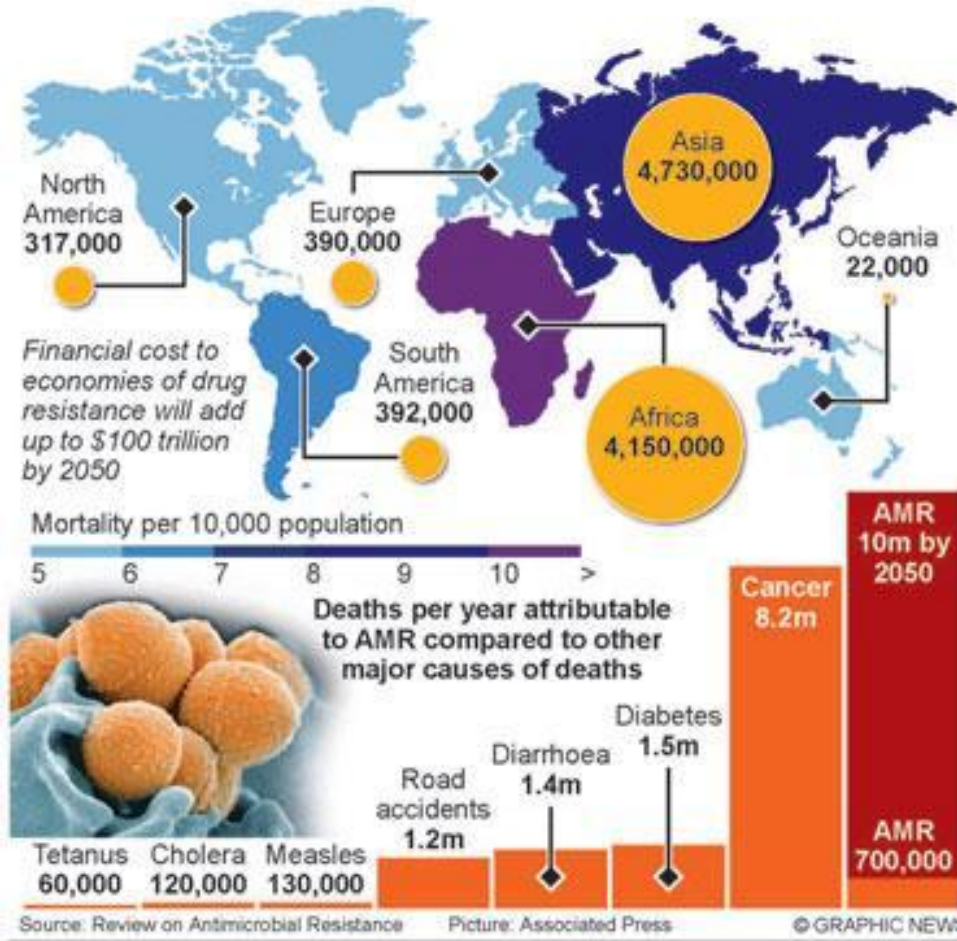
NÁRODNÍ
PLÁN OBNOVY



Superbugs “bigger risk than cancer”

An extra 10 million people could die every year by 2050 unless sweeping global changes are agreed to tackle increasing resistance to antibiotics

Deaths per year attributable to Antimicrobial Resistance (AMR) by 2050



Aktivity proti rezistenci

- ▶ organizační
 - ▶ rovný přístup k dg. a léčbě - dostupnost léčiv
 - ▶ monitoring trendů, mezinárodní dohled a spolupráce
 - ▶ antibiotický stewardship
 - ▶ omezení „over-preskripce“, regulace ve veterinárním lékařství a zemědělství
 - ▶ edukace
- ▶ preventivní
 - ▶ lepší diagnostika
 - ▶ zlepšení zdravotního stavu (výživa, pitná voda)
 - ▶ hygiena osob i prostředí, desinfekce
 - ▶ izolace
 - ▶ vakcinace
- ▶ terapeutické

Aktivity proti rezistenci

- ▶ terapeutické
 - ▶ vývoj a výzkum nových antimikrobních léčiv
 - ▶ repurposing (vč. ne-ATB)
 - ▶ kombinační léčba
 - ▶ drug delivery systémy
 - ▶ alternativní strategie
 - ▶ fagy
 - ▶ imunoterapie...

Vzkříšení starých léčiv a jejich modifikace

- kombinace dvou přístupů
 - „hledání ztraceného“
 - důvody vyřazení - vedlejší účinky, rezistence, nižší účinnost, cesta podání, dávkování...
 - +: ↓ rezistence, klinické zkušenosti, schválené, levné, ↓ selekční tlak na nová ATB
 - „me-too drugs“

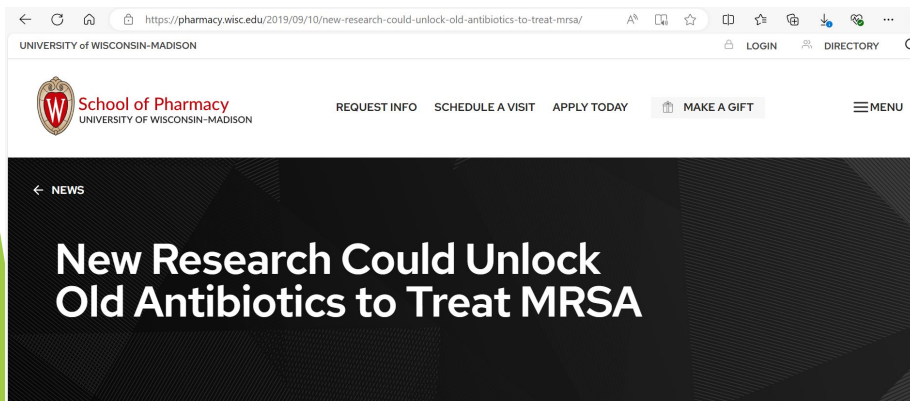


Vzkříšení starých léčiv

- ▶ prioritizace - MDR a XDR kmeny
 - ▶ ESBL *Enterobacteriaceae*
 - ▶ nitrofurantoin (1954), (piv)mecilinam (1975), fosfomycin (1969)
 - ▶ karbapenem-rezistentní G- bakterie
 - ▶ kolistin (1947), polymyxin B (1964), fosfomycin
 - ▶ MRSA
 - ▶ kotrimoxazol (1974), minocyklin (1960), fosfomycin

Conserving antibiotics for the future: New ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective

Johan W. Mouton^{a, b, c}, Paul G. Ambrose^d, Rafael Canton^e, George L. Drusano^f,
Stephan Harbarth^g, Alasdair MacGowan^h, Ursula Theuretzbacherⁱ, John Turnidge^j



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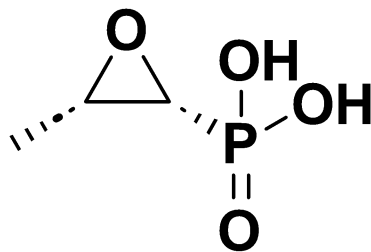
Reviving old antibiotics

Ursula Theuretzbacher^{1*}, Françoise Van Bambeke², Rafael Cantón³, Christian G. Giske^{4,5}, Johan W. Mouton^{6,7},
Roger L. Nation⁸, Mical Paul⁹, John D. Turnidge¹⁰ and Gunnar Kahlmeter^{11,12}

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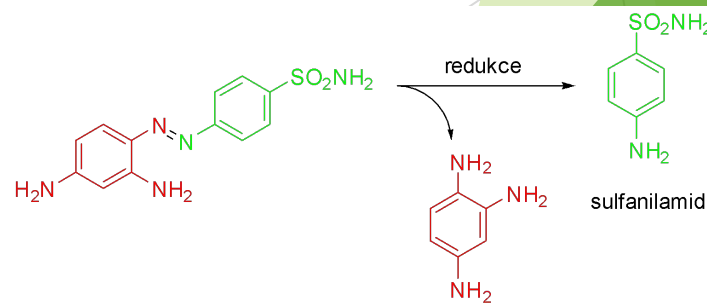
Příklad 1: Fosfomycin

- ▶ *Streptomyces fradiae* (Španělsko; Merck)
- ▶ 1969
- ▶ unikátní MoA
- ▶ × nízká mg účinnost
- ▶ zájem po r. 2010
- ▶ uroinfekce (p. o.) → systémové infekce (i. v.; MRSA, ESBL G⁻)



Příklad 2: sulfonamidy

- ▶ 1932
 - ▶ syntéza - Prontosil rubrum (Bayer/IG Farben)
 - ▶ zahájení testování (i klinické)
- ▶ 1935
 - ▶ publikace výsledků (*Deutsche Medizinische Wochenschrift*)
 - ▶ aktivita *in vivo* (myš), zejm. G^+ koky (G. Domagk)
 - ▶ mírně skeptické přijetí × 1939 - PN
 - ▶ zjištění, že jde o prodrug → bezbarvý sulfanilamid (1906)
- ▶ levné, snadno připravitelné
- ▶ boom - 2. světová válka
- ▶ do konce 50. let - tisíce sulfonamidů



Příklad 2: sulfonamidy

- ▶ nevýhody
 - ▶ prvotní - nízká rozpustnost, nežádoucí účinky, krátký biologický poločas, vysoké dávkování, statické
 - ▶ část lze překonat
 - ▶ sekundární
 - ▶ vznik rezistence
 - ▶ vývoj PNC
- ▶ → pokles využití

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 - ▶ vývoj PNC
- ▶ → pokles využití
- ▶ kombinace s trimethoprimem
 - ▶ *in vitro* popsána na konci 60. let
 - ▶ FDA approval 1974 (kotrimoxazol)
 - ▶ cidní
 - ▶ postupně pokles využití, „okrajové“ indikace

Příklad 2: sulfonamidy

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Tuberculosis and Trimethoprim-Sulfamethoxazole[†]

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Mark L. Silverman,⁴ and Glenn D. Roberts²

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The sulfonamides were the first drugs with antituberculous effects. Their use was abandoned and basically forgotten with the advent of streptomycin and isoniazid combination treatment. There is a widespread belief, apparently based on testing a single isolate on questionable media, that *Mycobacterium tuberculosis* is resistant to trimethoprim-sulfamethoxazole (TMP-SMX). We saw a complex immunocompromised patient with tuberculosis who was initially treated with TMP-SMX without antituberculous drugs and defervescenced on this treatment. An isolate of *M. tuberculosis* from this patient was found to be sensitive to TMP-SMX. We examined how frequently *M. tuberculosis* is sensitive to TMP-SMX. Isolates were tested for susceptibility to TMP-SMX on supplemented Middlebrook 7H10 plates. We found that 43 of 44 (98%) isolates of *M. tuberculosis* were susceptible to the combination of ≤ 1 μ g/ml of TMP and 19 μ g/ml of SMX ($\leq 1/19$ μ g/ml). Thus, the vast majority of our *M. tuberculosis* isolates were susceptible to TMP-SMX at an MIC similar to that for *Mycobacterium kansasii*, *Mycobacterium marinum*, and sensitive rapidly growing mycobacteria, organisms successfully treated with TMP-SMX as part of the treatment regimen. It is possible that TMP-SMX may be useful in treating patients with multiple-drug-resistant and extended drug-resistant tuberculosis. We feel that a clinical trial looking at the effectiveness of TMP-SMX as an antituberculous drug is worthwhile.

Susceptibility of *Mycobacterium tuberculosis* to sulfamethoxazole, trimethoprim and their combination over a 12 year period in Taiwan

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Objectives: This study was designed to determine the susceptibility of clinical isolates of multidrug-resistant (MDR) and non-MDR *Mycobacterium tuberculosis* to sulfamethoxazole, trimethoprim and trimethoprim/sulfamethoxazole over a 12 year period in Taiwan.

Patients and methods: We examined a total of 117 clinical isolates of *M. tuberculosis* collected from Southern Taiwan, 116 from 1995 to 2006 and an extensively drug-resistant (XDR) isolate in 2009. These included 28 isolates susceptible to all four first-line agents, 52 MDR isolates and 36 isolates with a mixed combination of drug resistance patterns other than MDR and 1 XDR isolate.

Results: Sulfamethoxazole inhibited 80% growth of all 117 isolates regardless of their susceptibility to the first-line agents at an MIC₅₀ of 9.5 mg/L. The concentration required to inhibit 99% growth was 38 mg/L. There were no significant changes in the MIC₅₀ or MIC₉₀ of sulfamethoxazole over a 12 year period. All 117 isolates were resistant to trimethoprim at >8 mg/L. The combination of trimethoprim/sulfamethoxazole at a ratio of 1:19 had no additive or synergistic effects.

Conclusions: Sulfamethoxazole inhibited the growth of clinical isolates of *M. tuberculosis* at achievable concentrations in plasma after oral administration. Susceptibility to sulfamethoxazole remained constant over a 12 year period. Trimethoprim was inactive against *M. tuberculosis* and trimethoprim/sulfamethoxazole provided no additional activity. Although the current and prior studies demonstrate that sulfamethoxazole is active against *M. tuberculosis* the search needs to continue for more active, lipid-soluble sulphonamides that are better absorbed into tissues and have improved therapeutic efficacy.

The potential role of trimethoprim-sulfamethoxazole in the treatment of drug-resistant tuberculosis

By Palomino, JC (Palomino, Juan Carlos) [1]; Martin, A (Martin, Anandi) [1]

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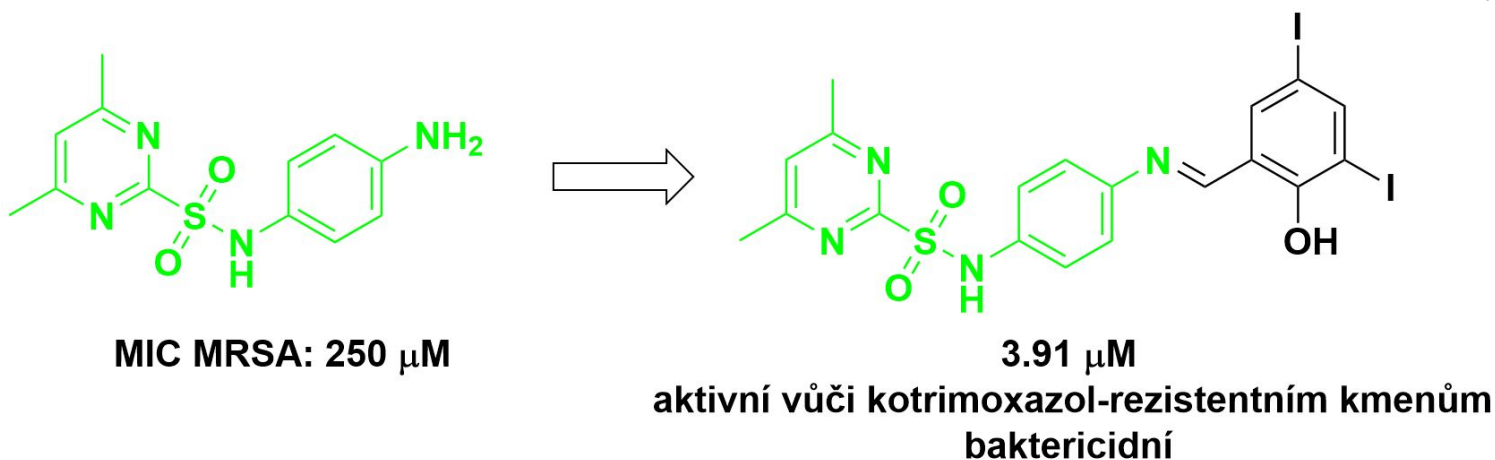
Document Type Review

Abstract

Tuberculosis (TB) remains a serious public health threat worsened by emerging drug resistance. *Mycobacterium tuberculosis* has become resistant not only to front-line drugs but also to second-line antimicrobials directed at drug-resistant TB. Renewed efforts are devoted for the development of new antibiotics active against TB. Also, repurposing of other antibiotics is being explored to shorten the time to develop new drugs against *M. tuberculosis*. As a result, trimethoprim-sulfamethoxazole (SXT) has emerged as a potential new option to treat drug-resistant TB. SXT has been found to be surprisingly active against drug-resistant *M. tuberculosis*, not only in vitro but also in vivo. The potential role of SXT for the treatment of multidrug resistant/extensively drug resistant TB might be explored in further clinical evaluations.

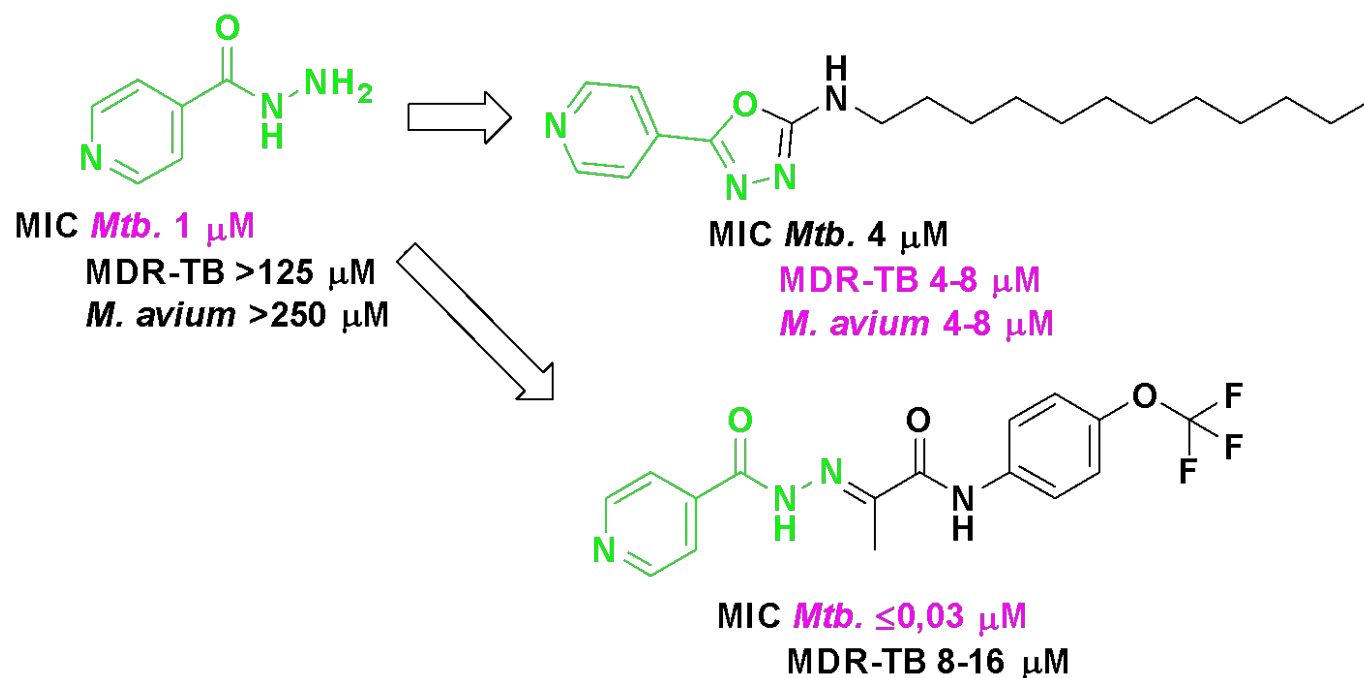
Příklad 2: Sulfonamidy - modifikace

- ▶ me-too approach
 - ▶ riziko zkřížené rezistence
 - ▶ nutné kompletní preklinické a klinické hodnocení



Příklad 3: Isoniazid - modifikace

- me-too approach



Perspektivy boje proti AMR

- ▶ „revival“ starých AM léčiv
 - ▶ viabilní koncept
 - ▶ výzvy
 - ▶ bezpečnost
 - ▶ EBM
 - ▶ PK/PD charakterizace (+ bioanalytika), dávkování
 - ▶ zachování účinnosti
 - ▶ financování a ne-patentovatelnost
 - ▶ edukace
 - ▶ organizační - harmonizace, dostupnost...
- ▶ modifikace léčiv
 - ▶ může překonat rezistenci
 - ▶ × celé farmakologické hodnocení
- ▶ repurposing a kombinální léčba



Děkuji za pozornost.



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