The Riddle of TB Drug Resistance

The 2025 George W. Comstock Lecture

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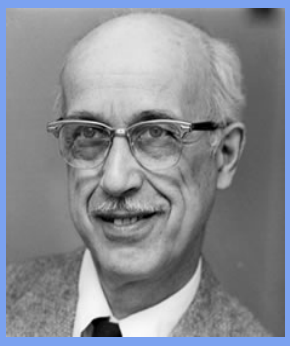
Disclosure

- Dr. Horsburgh has no conflicts of interest to disclose

George Wills Comstock, MD, 1915-2007

- Captain, US Public Health Service
- Professor, Johns Hopkins School of Public Health;
- Founder and Director, Training Center for Public Health Research and Prevention
- Accomplished Bassoonist



Objectives

- How did we get here?
- What do we know now that we didn't appreciate then?
- What are our options going forward?
- What might be the answer to this riddle?

BRITISH MEDICAL JOURNAL

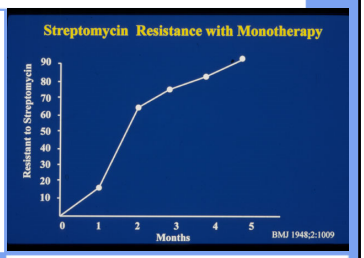
LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

TABLE II.—*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement	28	51%	4	8%
Moderate or slight improvement	10	18%	13	25%
No material change	2	4%	3	6%
Moderate or slight deterioration	5	9%	12	23%
Considerable deterioration	6	11%	6	11%
Deaths	4	7%	14	27%
Total	55	100%	52	100%



"streptomycin-resistant bacilli, if transmitted to another individual. would produce disease resistant to streptomycin from the start…***this is a very grave danger for the future***"

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY DECEMBER 11 1948

STREPTOMYCIN RESISTANCE IN TUBERCULOSIS

The Achilles heel of streptomycin is acquired bacterial resistance. All species are liable to develop this to a degree which renders further treatment quite fruitless, and the rapidity with which it occurs varies with their rate of

The Advent of Combination Chemotherapy

THE PREVENTION OF STREPTOMYCIN RESISTANCE BY COMBINED CHEMOTHERAPY

A MEDICAL RESEARCH COUNCIL INVESTIGATION

THE AMERICAN REVIEW OF TUBERCULOSIS

VOLUME 67 May, 1953 NUMBER 5

THE EFFECT OF STREPTOMYCIN ON THE EMERGENCE OF BACTERIAL RESISTANCE TO ISONIAZID

A United States Public Health Service Cooperative Investigation

- BMRC and USPHS Trials:
  INH+SM+PAS (1953)
  SM+PAS (1952)
- Expected likelihood of developing resistance to all three agents, only 1 in 10^{15} bacilli
- TB burden in cases of severe, cavitary disease estimated to be 10^{8} to 10^{10} bacilli

Br Med J 1952;1:1157–1162
Am Rev Tuberc 1953;67:553-67
Proc Staff Meet Mayo Clin 1947;22:465-473

Drug-resistant Bacilli are Less Fit

THE ALTERED GROWTH CHARACTERISTICS OF ISONIAZID-RESISTANT TUBERCLE BACILLI

- 1952 – "H37Rv…made resistant to isoniazid has lost its ability to grow in synthetic media" (MW Fisher et al Am Rev Tuberc 1952;66:626-8)

TUBERCLE BACILLI RESISTANT TO ISONIAZID

VIRULENCE AND RESPONSE TO TREATMENT WITH ISONIAZID IN GUINEA-PIGS

BY

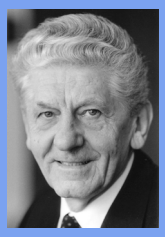
D. A. MITCHISON, M.B.*

Lecturer in Bacteriology, Postgraduate Medical School of London

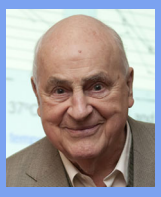
- 1954 - "INH resistant strains were less virulent for guinea pigs" (Mitchison, BMJ 1954;1(4854):128-30

The Conclusions..

- "At the start of the study the prevalence of persons harbouring tubercle bacilli resistant to at least one drug was accounted for mainly by secondary resistance…the results reveal that *with adequate, timely treatment drug-resistance ceases to be a serious problem*."



- "The mutation rate is balanced by a tendency of strains to revert to sensitivity or by a failure of the resistant strains to grow as successfully as the sensitive organisms…the balance between creation of resistance and reversion to sensitivity *tends towards the slow elimination of resistance*."



Bull WHO 1967;37:819-74
Br Med Bull 1984;49:84-90

Does Drug Resistance Even Matter?

- "Bacteriologial relapses…occur almost invariably with strains of tubercule bacilli fully sensitive to the drugs" (Lancet 1976;1:162-3)
- Response to retreatment with standard regimen: 68/73 (93%) were cured. (Lancet 1976;1:162-3)
- "When results in the presence of initial resistance are virtually as good as those in patients with initially sensitive bacilli, … there seems to be no point in changing a regimen if initial resistance to isoniazid or streptomycin is found and therefore no point in looking for it." (Am Rev Respir Dis 1986;133:423-30)

But on the other hand…

- 1981 – Four contacts of a patient with INH, SM and PAS resistance develop DR disease; "the potential of DR strains for causing disease in humans should not be underestimated"
- 1985 – In Peru, the standard WHO recommended 8-month regimen 70% had a favorable outcome and 14% "abandoned"; 25% of previously treated patients had drug-resistant organisms.

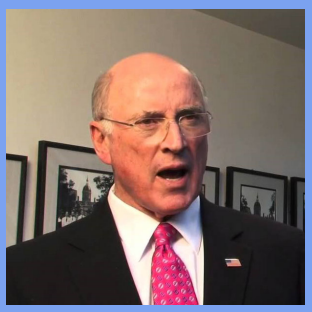
Am J Epidemiol 1981;113:423-35
ARRD 1984;129:439-43
ARRD 1985;132:737-41

Not to say we weren't warned

Editorial

Tailoring a Time-Bomb

Inadvertent Genetic Engineering[1]



- "We are unwittingly transforming an eminently treatable infection into a life-threatening disease that is exorbitantly expensive to treat."

ARRD 1985;132:735

The Rifampicin Era

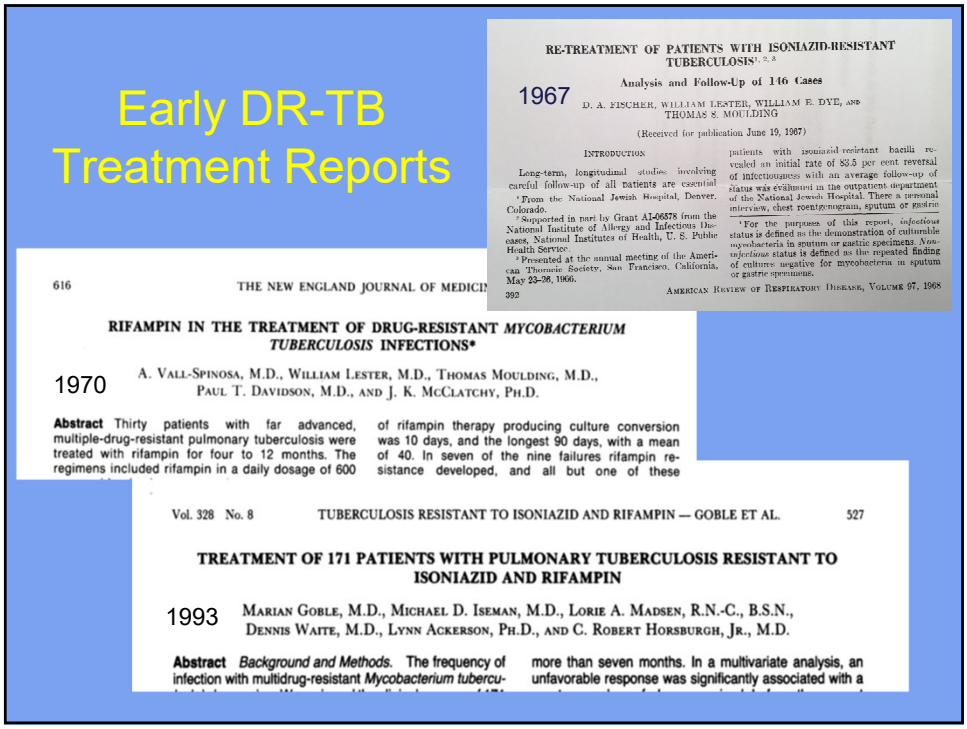
- 1966 – First used for salvage therapy
- 1971 – First studied for newly-diagnosed TB
- "A new drug, rifampin, still very expensive, is just now being released for general use. It appears to be virtually as effective as INH and even more promising…. It is thought that it may replace streptomycin in primary treatment before long. (NEJM 1971;284:1381).
- 1976 – First report of clinical RIF resistance (JID 1976; 133:88-90)

Table 1. Increasing frequency of isolation of rifampin-resistant strains of *Mycobacterium tuberculosis* in Massachusetts, 1971–1974.

Year	No. of strains resistant/ no. of strains tested (%)
1971	0/328 (0)
1972	2/435 (0.46)
1973	9/657 (1.37)
1974	16/814 (1.96)

NOTE. Strains were resistant to 1 μg of rifampin/ml.

Early DR-TB Treatment Reports



RE-TREATMENT OF PATIENTS WITH ISONIAZID-RESISTANT TUBERCULOSIS[1, 2, 3]

1967

Analysis and Follow-Up of 146 Cases

D. A. FISCHER, WILLIAM LESTER, WILLIAM E. DYE, AND THOMAS S. MOULDING

(Received for publication June 19, 1967)

INTRODUCTION

Long-term, longitudinal studies involving careful follow-up of all patients are essential

[1] From the National Jewish Hospital, Denver, Colorado.

[2] Supported in part by Grant AI-06578 from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, U. S. Public Health Service.

[3] Presented at the annual meeting of the American Thoracic Society, San Francisco, California, May 23–26, 1966.

patients with isoniazid-resistant bacilli revealed an initial rate of 83.5 per cent reversal of infectiousness with an average follow-up of status was evaluated in the outpatient department of the National Jewish Hospital. There a personal interview, chest roentgenogram, sputum or gastric

[1] For the purposes of this report, *infectious* status is defined as the demonstration of culturable mycobacteria in sputum or gastric specimens. *Non-infectious* status is defined as the repeated finding of cultures negative for mycobacteria in sputum or gastric specimens.

392 AMERICAN REVIEW OF RESPIRATORY DISEASE, VOLUME 97, 1968

616 THE NEW ENGLAND JOURNAL OF MEDICI

RIFAMPIN IN THE TREATMENT OF DRUG-RESISTANT *MYCOBACTERIUM TUBERCULOSIS* INFECTIONS*

1970

A. VALL-SPINOSA, M.D., WILLIAM LESTER, M.D., THOMAS MOULDING, M.D., PAUL T. DAVIDSON, M.D., AND J. K. MCCLATCHY, PH.D.

Abstract Thirty patients with far advanced, multiple-drug-resistant pulmonary tuberculosis were treated with rifampin for four to 12 months. The regimens included rifampin in a daily dosage of 600

of rifampin therapy producing culture conversion was 10 days, and the longest 90 days, with a mean of 40. In seven of the nine failures rifampin resistance developed, and all but one of these

Vol. 328 No. 8 TUBERCULOSIS RESISTANT TO ISONIAZID AND RIFAMPIN — GOBLE ET AL. 527

TREATMENT OF 171 PATIENTS WITH PULMONARY TUBERCULOSIS RESISTANT TO ISONIAZID AND RIFAMPIN

1993

MARIAN GOBLE, M.D., MICHAEL D. ISEMAN, M.D., LORIE A. MADSEN, R.N.-C., B.S.N., DENNIS WAITE, M.D., LYNN ACKERSON, PH.D., AND C. ROBERT HORSBURGH, JR., M.D.

Abstract *Background and Methods.* The frequency of infection with multidrug-resistant *Mycobacterium tubercu-*

more than seven months. In a multivariate analysis, an unfavorable response was significantly associated with a

The Global impact of Rifampicin

- A 6-month rifampicin-based regimen (“Short-Course”) became the standard in developed countries after 1976
- Rifampicin-based treatment was prioritized in the U.S. by ATS/CDC in 1978
- Developing countries continued to use INH- and Strep-based regimens because rifampicin was felt to be too expensive
- “In developing countries, a standardized regimen of chemotherapy, ignoring the results of pre-treatment sensitivity tests is recommended, while in technically advanced countries, resistant drugs should be changed to sensitive ones.” (Tubercle 1987;68:S5-15)

The Wake-up Call

1514 THE NEW ENGLAND JOURNAL OF MEDICINE June 4, 1992

AN OUTBREAK OF MULTIDRUG-RESISTANT TUBERCULOSIS AMONG HOSPITALIZED PATIENTS WITH THE ACQUIRED IMMUNODEFICIENCY SYNDROME

BRIAN R. EDLIN, M.D., JEROME I. TOKARS, M.D., M.P.H., MICHAEL H. GRIECO, M.D., J.D., JACK T. CRAWFORD, PH.D., JULIE WILLIAMS, R.N., M.S.N., EMELIA M. SORDILLO, M.D., PH.D., KENNETH R. ONG, M.D., JAMES O. KILBURN, PH.D., SAMUEL W. DOOLEY, M.D., KENNETH G. CASTRO, M.D., WILLIAM R. JARVIS, M.D., AND SCOTT D. HOLMBERG, M.D., M.P.H.

- Increased susceptibility of HIV+ persons to TB was noted early in the AIDS epidemic
- Deterioration in the NYC TB Control program had led to many TB patients not completing treatment
- Failure to complete treatment led to unrecognized MDR
- Poor hospital infection control led to this outbreak

NEJM 1992;326:1514-21

Next Steps

- 1989 – WHO TB Program consists of 2 people
- 1992 - the U.S. recommends drug-susceptibility testing be performed on all initial and final isolates.
- 1993 - TB Global Emergency declared
- 1993 - WHO endorses RIF-based treatment for everyone!
- 1993 – WHO rolls out DOTS to prevent DR
- 1994 - WHO and IUATLD initiate Global TB Drug Resistance Surveillance

WHO Calls Tuberculosis a Global Emergency

April 24, 1993 | Reuters

Email Share Tweet Recommend 0

LONDON -- The World Health Organization on Friday declared tuberculosis a global emergency, saying the disease will claim more than 30 million lives in the next decade unless action is taken now.

The bugs are staying ahead of us…

- 1998 - Surveillance for drug resistance in 35 countries shows 9.9% of patients with no prior treatment had DR and MDR was found in 13% of previously treated patients
- 1998 - DOTS-Plus initiated
- 2006 - XDR-TB in HIV+ in South Africa

Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Ned R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Lalloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

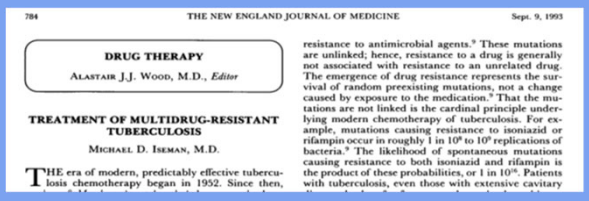
BMJ 1998;317:6714, NEJM 1998;338:1641-9
Lancet 2006;368:1575-80; JAMA 2000;283-2537-45

MDR-TB Treatment Recommendations - 1993

"Second-line" drugs; 4-6 drugs for 20-24 months

- Based on "Expert Opinion"

- Ciprofloxacin/Ofloxacin
- Kanamycin/Amikacin
- Ethionamide
- Cycloserine
- Thiacetazone
- PAS
- Capreomycin



784 THE NEW ENGLAND JOURNAL OF MEDICINE Sept. 9, 1993

DRUG THERAPY
ALASTAIR J.J. WOOD, M.D., *Editor*

TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS

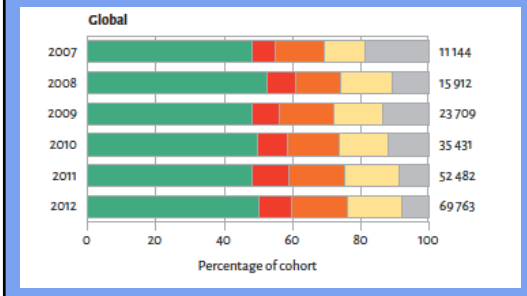
MICHAEL D. ISEMAN, M.D.

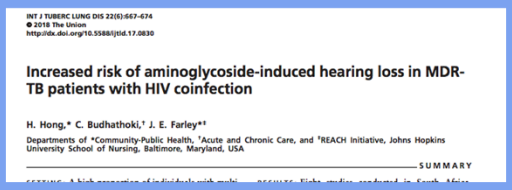
THE era of modern, predictably effective tuberculosis chemotherapy began in 1952. Since then, resistance to antimicrobial agents.[9] These mutations are unlinked; hence, resistance to a drug is generally not associated with resistance to an unrelated drug. The emergence of drug resistance represents the survival of random preexisting mutations, not a change caused by exposure to the medication.[9] That the mutations are not linked is the cardinal principle underlying modern chemotherapy of tuberculosis. For example, mutations causing resistance to isoniazid or rifampin occur in roughly 1 in 10^8 to 10^9 replications of bacteria.[9] The likelihood of spontaneous mutations causing resistance to both isoniazid and rifampin is the product of these probabilities, or 1 in 10^{16}. Patients with tuberculosis, even those with extensive cavitary

NEJM 1993;329:784-91

Results with Early MDR-TB Regimens

- 50-60% cures
- 10-20% mortality
- High rates of LTFU
- Substantial ototoxicity




INT J TUBERC LUNG DIS 22(6):667–674
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http://dx.doi.org/10.5588/ijtld.17.0830

Increased risk of aminoglycoside-induced hearing loss in MDR-TB patients with HIV coinfection

H. Hong,* C. Budhathoki,† J. E. Farley*†

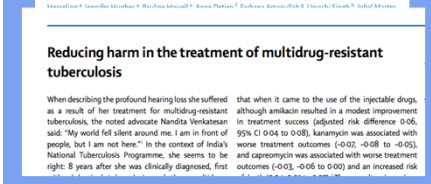
Departments of *Community-Public Health, †Acute and Chronic Care, and ‡REACH Initiative, Johns Hopkins University School of Nursing, Baltimore, Maryland, USA

SUMMARY


THE LANCET
Respiratory Medicine
Volume 6, Issue 9, September 2018, Pages 662-664

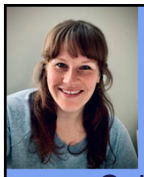
Comment

Time to act on injectable-free regimens for children with multidrug-resistant tuberculosis


Reducing harm in the treatment of multidrug-resistant tuberculosis

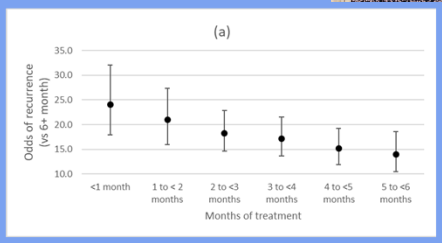
When describing the profound hearing loss she suffered as a result of her treatment for multidrug-resistant tuberculosis, the noted advocate Nandita Venkatesan said: "My world fell silent around me. I am in front of people, but I am not here."[1] In the context of India's National Tuberculosis Programme, she seems to be right: 8 years after she was clinically diagnosed, first

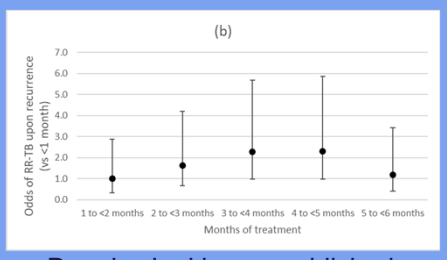
that when it came to the use of the injectable drugs, although amikacin resulted in a modest improvement in treatment success (adjusted risk difference 0·06, 95% CI 0·04 to 0·08), kanamycin was associated with worse treatment outcomes (−0·07, −0·08 to −0·05), and capreomycin was associated with worse treatment outcomes (−0·03, −0·06 to 0·00) and an increased risk



Does HRZE Prevent DR?

- Cohort study in Ukraine, 2015-18
- 29,363 people with RS-TB at baseline, 1,165 people (4.0%) experienced recurrence within 18 months of discontinuing treatment
- Of those, 254 (21.8%, or 0.84% of all persons with RS-TB) had developed RR-TB





Dupuis, Jenkins, unpublished

Why Isn't Adherence Better?

- TB drugs are not well tolerated
- Adverse Events (AE) occur in 25–75% of people receiving treatment for TB
- AE to TB drugs are associated with poor treatment adherence, treatment interruption and treatment failure
- In a recent study, DR-TB treatment-related AE were associated with concomitant medications, HbA1c, alcohol, HIV, older age and lower BMI

PLoS Med 2024;21(7):e1004438
JID 2024;229:813-23

Are DR Strains Really Less Fit?

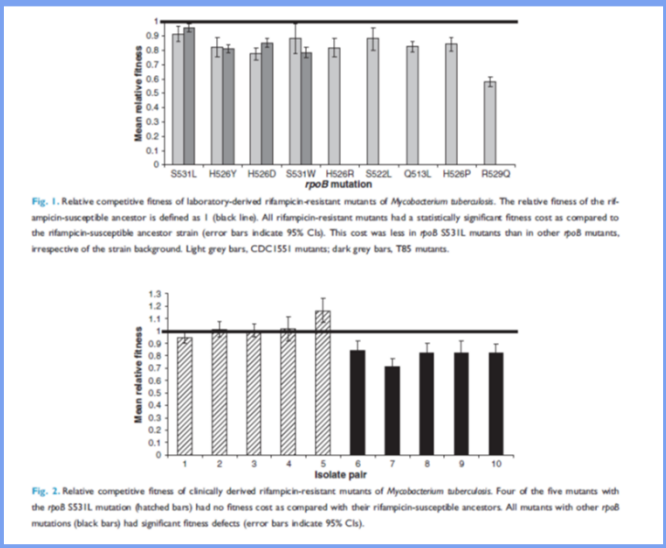


Fig. 1. Relative competitive fitness of laboratory-derived rifampicin-resistant mutants of *Mycobacterium tuberculosis*. The relative fitness of the rifampicin-susceptible ancestor is defined as 1 (black line). All rifampicin-resistant mutants had a statistically significant fitness cost as compared to the rifampicin-susceptible ancestor strain (error bars indicate 95% CIs). This cost was less in *rpoB* S531L mutants than in other *rpoB* mutants, irrespective of the strain background. Light grey bars, CDC1551 mutants; dark grey bars, T85 mutants.

Fig. 2. Relative competitive fitness of clinically derived rifampicin-resistant mutants of *Mycobacterium tuberculosis*. Four of the five mutants with the *rpoB* S531L mutation (hatched bars) had no fitness cost as compared with their rifampicin-susceptible ancestors. All mutants with other *rpoB* mutations (black bars) had significant fitness defects (error bars indicate 95% CIs).

Clin Micro Infect 2009;15:S66-S68

Why Doesn't Combination Therapy Prevent Emergence of DR?

- "Unlikelihood of developing resistance to all three agents, an event that would occur in only 1 in 10^{15} bacilli" (ARRD, 1953)
- Based on *in vitro* mutation rates
- 2010: E. coli, under sublethal antibiotic pressure, develops resistance to antibiotics – even ones that were not administered!
- Increased DNA mutation, mediated by reactive oxygen species

Mol Cell 2010;37:311-20

A Closer Look at Acquisition of DR

- The INH-R *katG* mutation arises before RIF-R mutations in MDR isolates
- INH kills M. tb the most rapidly
- Homozygous fast acetylation (FF) shortens effective INH exposures
- Sublethal antibiotic exposures drive emergence of resistance
- Acquired rifamycin resistance has been clinically associated with low INH AUC

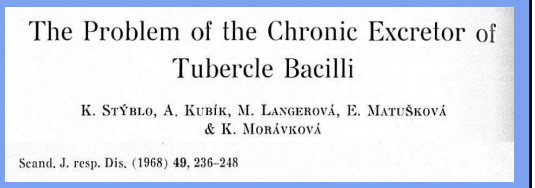
Eur J Clin Pharm 2007;63:633-9 ; Nat Genet 2017;49:395-404
CID 2005;40:1481-91 ; Lancet RM 2018;6:265-75

Other Reasons for PK Mismatch

- Poor absorption of one drug and not others
  - H,R,Z,E better absorbed on an empty stomach
  - Rifapentine exposures increased with fatty meal
- Differing penetration into caseum or cavities
  - Penetrate well: Rifamycins, Fluoroquinolones
  - Intermediate: BDQ, LZD, PZA, EMB
  - Poor: INH, PAS, KM, CF
- Differing activity vs. nonreplicating organisms
  - Active: Rifamycins, BDQ
  - Inactive: INH, Fluoroquinolones, PZA, PAS, CS

Why is MDR continuing to spead?

- 1990: “90% of patients with smear-positive pulmonary tuberculosis have objective symptoms”
- 2022: Less than half of persons with TB have symptoms
- Asymptomatic persons account for 35-51% of M.tb transmission


The Problem of the Chronic Excretor of Tubercle Bacilli

K. Stýblo, A. Kubík, M. Langerová, E. Matušková & K. Morávková

Scand. J. resp. Dis. (1968) 49, 236–248

Bull IUAT 1990;65:6-24, Lancet ID 2024;24:726-36, PNAS 2022;119:e2211045119

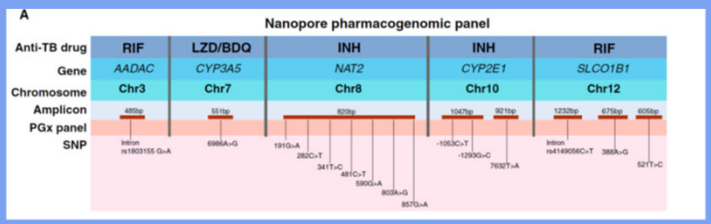
Coming to your clinic soon: Bedaquiline Resistance

- In South Africa between 2015-2019, 8041 patients received BDQ in combination regimens
- 3.8% had baseline BDQ resistance
- Baseline BDQ resistance was associated with previous exposure to BDQ or CF
- Baseline BDQ resistance was also seen among persons exposed to patents with BDQ-R
- Resistance to BDQ developed during treatment in 3.5% of patients

Lancet ID 2022;22:496-505, BMC ID 2022;22:870

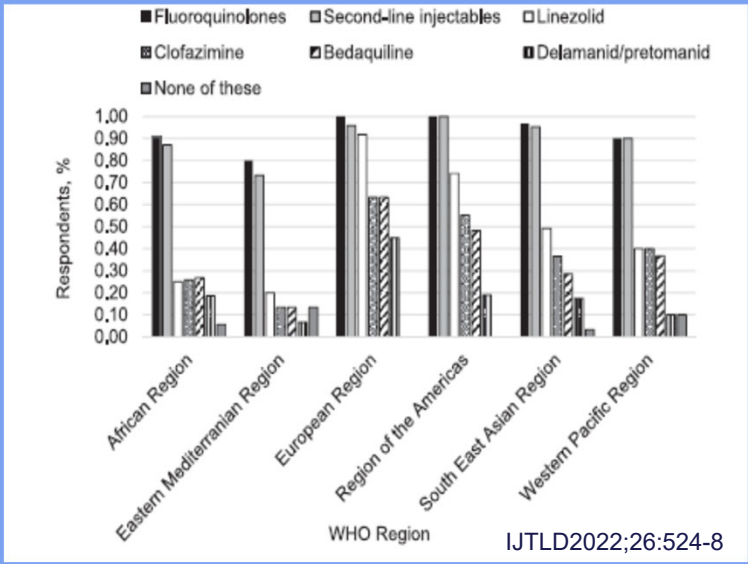
What Can be Done to Prevent DR?

- Initial DR testing, including INH
- NAT2 testing to optimize dosing
- Discard standardized MDR treatment regimens



AJRCCM 2024;209:1486-96

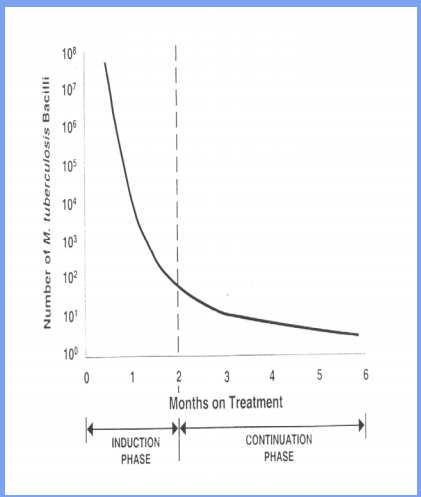
Don't Fly Blind!



IJTLD2022;26:524-8

But TB is not like HIV…

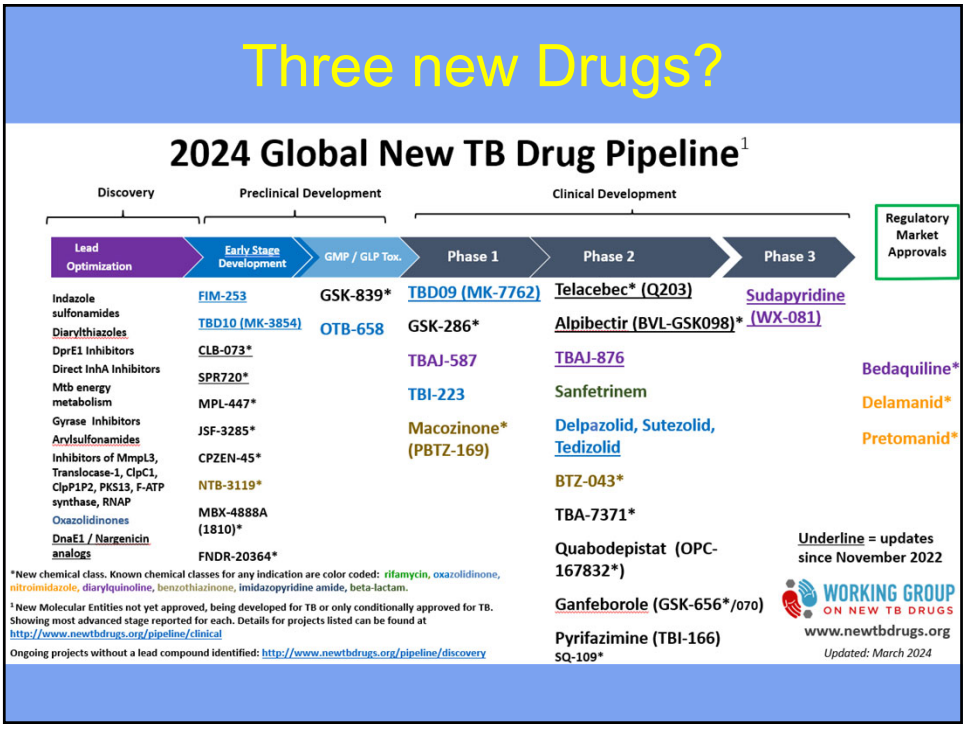
- Two phases of growth:
  - rapid multiplication
  - nonreplicating persistence
- Sequestration of bacteria in caseum and cavities



What Can be Done to Prevent DR?

- Develop regimens of 3+ all-new drugs
  - That have similar PK
  - That have good penetration into caseum
  - That kill nonreplicating organisms
  - That are well tolerated!

Three new Drugs?



TB Drugs in Phase 1 & 2 Trials

Target	Class	Mode of Action	Candidates	Half-life	Penetrates Caseum?
ATP synthase	Diarylquinolone	Inhibits electron chain transport	Sudapyrine TBAJ-876 TBAJ-587 Telacebac	3-12 hrs	+
rRNA	Oxazolidinone	Inhibits protein synthesis	Delpazolid Sutezolid TBI-223 TBA-7371	2-26 hrs	+
Leucyl-tRNA synthetase (LeuRS)	Oxaborole	Inhibits protein synthesis	Ganfeborole	40 hrs	+
Decaprenylphosphoryl -β-D-ribose oxidase (DprE1)	Benzathiazinone	Inhibits cell wall formation	BTZ-043 Quabodepostat Macozinone	3-30 hrs	–
Transpeptidase	Beta-Lactam	Inhibits cell wall formation	Sanfetrinum	0.5 hrs	–
EthA monooxygenase	Mycolic Acid Synthesis inhibitor	Inhibits cell wall formation	Alpibectir/ETA	20 hrs	–
DNA Gyrase B	Aminobenzimidazole	Inhibits DNA replication	Fobrepodacin	?	?
cAMP	Cholesterol synthesis inhibitor	Inhibits cholesterol synthesis	GSK 286	>24 hrs	?
?	Rimophenazine	?	Pyrifazimine	45 hrs	?

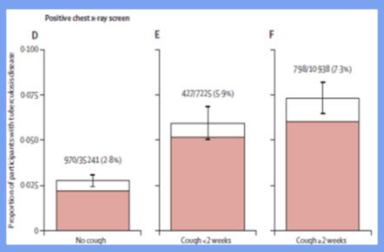
Optimizing Adherence to Reduce Generation of DR

- Linezolid, Moxifloxacin poorly tolerated (especially by older patients)
- Bedaquiline prolongs QT and may raise the risk of Torsade de Pointes
- Future clinical trials need to focus on improved tolerability
- <u>This is even more important than treatment shortening!</u>

PLoS Med 2024;21(7):e1004438

Reducing Transmission of MDR

- 25% of those with CXR+ for TB had a positive smear
- As much as half of transmitted TB can be attributed to such people
- Finding and treating MDR sooner will be important for decreasing transmission



Lancet ID 2024;24:726-36
PNAS 2022;119:e2211045119
eLife 2023;12:e82469

Conclusions

- New information requires rethinking theories
- Finding and treating Chronic Excretors is still the essential DR prevention strategy
- Rolling out one new drug at a time will always result in its becoming resistant
- We may now have the opportunity to escape this trap
- Continued new drug development will be essential

"…The art of epidemiologic reasoning is to draw sensible conclusions from imperfect data…"

Comstock GW. Am J Epidemiol 1990;131:206