Tuberculosis
The Great White Plague Keeps Coming Back
Demystifying Medicine

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Case Scenario 1

35 year old homeless male presents with cough x2 months that has gradually gotten worse. Patient’s cough is productive of yellow phlegm and has persisted despite OTC cough remedies. His phlegm has occasionally been blood-tinged recently. He also reports intermittent fevers and sweats and feeling poorly overall. He says this cold is worse than his usual colds and he hasn’t been able to get over it. He has lost weight over the last few months but says this is due to not having consistent meals. He does not feel short of breath and is able to continue working during the day selling newspapers. He has otherwise been relatively healthy and does not take any regular medicines. He has smoked for 20 years but does not drink or do drugs. No one else around him at the shelter has been sick, that he knows of. He reports testing PPD+ last year but said the reaction was because he kept scratching at the site so declined further treatment.
Case Scenario 1

Physical exam:
- Thin AAM in no distress but with occasional cough
- Temp: 99.9°F; BP 140/72; HR 104; RR 20
- Physical exam is normal, including the lung exam.

He does not look acutely ill and chronic coughs are common, especially in smokers. What do you do next?

A. This is probably a smoker’s cough. Give him Robitussin and have him follow-up in 1-2 weeks for further evaluation if not better.

B. This is more likely a viral or bacterial upper respiratory infection. Give him a Z-pack and have him follow-up in 1-2 weeks for further evaluation if not better.

C. This is concerning for TB or other more serious diseases. Order a CXR now.
Case Scenario 1

This CXR is very concerning for active TB. You send a sputum sample to the lab for AFB smear and culture. What do you do next?

A. Since he is not acutely ill, start empiric TB therapy as an outpatient.
B. Admit him to the hospital for evaluation and empiric TB therapy.
Case Scenario 2

33 year old Asian female is a researcher who came to the US two years ago for a post-doctoral research program. Her mother was treated for TB when she was very young. The patient was also treated for TB about 10 years ago for about 9 months. She has been well since. Over the past few months, she developed a cough with bloody phlegm, low grade fevers, shortness of breath, and fatigue. She was initially admitted to an outside hospital, where she was diagnosed with TB and discharged on standard therapy with isoniazid, rifampin, pyrazinamide, and ethambutol. One month later, drug sensitivity testing results show resistance to isoniazid and rifampin, as well as the fluoroquinolones and aminoglycosides. What are your treatment options now?
Overview

• Global and US TB epidemiology
• Latent TB
• Active TB and drug resistance
• Recent studies advancing our understanding of TB treatment
• New drugs and how to apply them
• Conclusions
Tuberculosis – Why should we care in 2019?

• 10th leading cause of death globally

• Leading cause of death from a single infectious agent, surpassing HIV

FIG. 3.11
Top causes of death worldwide in 2016. Deaths from TB among HIV-positive people are shown in grey.

FIG. 3.13

Global TB Incidence and Mortality Rates

FIG. 3.4
Estimated TB incidence rates, 2017

FIG. 3.14
Estimated TB mortality rates excluding TB deaths among HIV-positive people, 2017

Global TB Incidence and Mortality

FIG. 3.7
Reported Tuberculosis (TB) Cases and Rates United States, 1993–2017

![Graph showing the number of TB cases and incidence rate from 1993 to 2017.]

### Countries with Highest Incidence Rates

<table>
<thead>
<tr>
<th>Country</th>
<th>2017 Incidence (/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>5.5</td>
</tr>
<tr>
<td>UK</td>
<td>8.9</td>
</tr>
<tr>
<td>Mexico</td>
<td>22</td>
</tr>
<tr>
<td>Brazil</td>
<td>44</td>
</tr>
<tr>
<td>Russia</td>
<td>60</td>
</tr>
<tr>
<td>China</td>
<td>63</td>
</tr>
<tr>
<td>Global average</td>
<td>133</td>
</tr>
<tr>
<td>India</td>
<td>204</td>
</tr>
<tr>
<td>Indonesia</td>
<td>319</td>
</tr>
<tr>
<td>Kenya</td>
<td>319</td>
</tr>
<tr>
<td>Philippines</td>
<td>554</td>
</tr>
<tr>
<td>South Africa</td>
<td>567</td>
</tr>
</tbody>
</table>
TB Cases and Rates Among U.S.-Born versus Non-U.S.–Born Persons, United States, 1993–2017
Active TB disease: 8 million new cases per year

TB DISEASE

LATENT TB INFECTION
- the "hidden epidemic"
- 2 billion people infected
Diagnosis: Purified Protein Derivative (PPD)

- Mantoux tuberculin skin test
  - 5 tuberculin units (0.1 ml) of PPD injected intradermally
  - Test is not specific for *M. tb*
Annu. Rev. Public Health. 34:271–86
Figure 1. Reservoir of TB—we currently have estimates for proportion of population that are immune sensitized (large circle) and number of cases of active TB annually (small filled circle). As TST and IGRA reversion can occur, total number of exposed persons may be greater than this (larger dashed circle), in addition TST and IGRA are only moderately sensitive for active TB. A much smaller pool of people may be at much higher risk of TB (bottom small dashed circle) and also a proportion of people may receive considerable protection against reinfection (top small dashed circle). Identifying these additional populations may be very valuable. (Online version in colour.)

Review article: The ongoing challenge of latent tuberculosis

H. Esmail, C. E. Barry, D. B. Young, R. J. Wilkinson

Pathogenesis

• Infection via droplet nuclei, causes granulomatous inflammatory process due to macrophages, lymphocytes, and fibroblasts recruited to site of infection
  • Bacteria in granuloma may become dormant (latent)
  • Granuloma may have caseous necrotic center

• If latently infected, about 10% lifetime risk of developing active TB
  • About 5% over initial 2 years post infection
  • About 5% over remaining lifetime

• If co-infected with untreated HIV, roughly 10% risk of TB activation/year

• Active infection may spread via bloodstream (miliary); more common in young children and immunocompromised

“1/3 of the world’s population is infected with latent TB”
The “Lübeck Disaster”

The Lübeck disaster, 1930 "Between 10 December 1929 and 30 April 1930, 251 of 412 infants born in the old Hanseatic town of Lübeck received three doses of BCG vaccine by the mouth during the first ten days of life. Of these 251, 72 died of tuberculosis, most of them in two to five months and all but one before the end of the first year. In addition, 135 suffered from clinical tuberculosis but eventually recovered; and 44 became tuberculin-positive but remained well. "---Sir Graham Wilson (Hazards of Immunisation p66)

29% Death rate
82% Disease rate
100% Infection rate

at a high enough dose disease outcomes are severe
Over a year earlier, in May, 1965, aboard the U.S.S. Richard E. Byrd, a Navy ship with over 350 enlisted members and officers, a seaman had converted his five tuberculin unit (TU) tuberculin skin test from negative to positive. At that time, the seaman's chest roentgenogram was normal and his medical officer elected not to place him on isoniazid chemoprophylaxis.

Ten months later, in March, 1966, the seaman began to exhibit significant symptoms. Though he attended sick call on three occasions, the illness was diagnosed as a virus infection. A chest roentgenogram was not done until late August, 1966, about six months after the appearance of the significant symptoms. At that point, a diagnosis of tuberculosis was made, and the seaman was transferred from the ship to the U.S. Naval Hospital at St. Albans, New York.
Over that six month period of exposure...
• 140 (46%) converted from known negative to positive PPD
• 7 cases of active disease developed

1. Compartment that bore 6 of the 7 individuals with active disease.
**COMPARTMENT DIAGRAM 2**

Figure 2. Another highly infected compartment. Ventilation comes from the same system as for Compartment One.

**COMPARTMENT DIAGRAM 5**

Figure 5. Crew's quarters for enlisted personnel in the supply division, including cooks.
What is the point of transition?

- Animal studies suggest development of TB pneumonia when proliferation exceeds "carrying capacity" of granuoma\(^1\)

- Histo-pathological studies support development of TB pneumonia as the earliest event in active pulmonary TB\(^2\)

\(^1\)Lin et al, Nature Medicine 2014. \(^2\)Hunter, Tuberculosis 2011
PET/CT Study UCT

• Use FDG-PET/CT to identify pathology consistent with Subclinical disease in asymptomatic HIV infected persons (CD4>350, ART naïve) with evidence of Latent TB infection (QFN-GIT)

• Derive transcriptional signature and serum biomarkers for Subclinical TB disease
35 HIV+VE, ART naïve, CD4>350, No Previous TB Resident in Khayelitsha (ZA), Latent TB only

Asymptomatic | QFN-GIT– POS | CXR – No active TB | Sputum Cult -ve

**OBSERVATION**
- 2x Sputum Culture
  -6 Week

**IMAGING**
- PET/CT
- Sputum Cult
  0 Week

**TREATMENT**
- 6 months tx
- IPT/Standard
  1 Week
  4 Week
  12 Week

**IMAGING**
- PET/CT
- Sputum Cult
  24 Week

**SAMPLING**
- PBMC
- RNA
- QFN-GIT
- SERUM
- URINE

**CONTROLS** – Age/Sex/CD4 Matched ACTIVE TB + HIV negative
2 patterns of subclinical TB on PET/CT

- **INFLTRATES + SCARS**: Consistent with bronchogenic spread
- **ACTIVE NODULES**: Consistent with haemotogenous spread
Infiltrate and Fibrotic scars

Overview 9 participants

Proportion of participants with infiltrates:

- Score
- No score

p < 0.05
Upper Lobe Reactivation

Infiltrates/Scars

Milliary Pattern

Active Nodules

? Ghon focus

Discrete Nodules Only

Normal Lungs

10
Subclinical

25
Latent
Response to treatment

PRE  POST

6H  6H

2RHZE/4RH  2RHZE
Subclinical TB

Increased FDG uptake in mediastinal LN

\[ p=0.022 \]

Microbiological/clinical evidence of active TB during follow-up

\[ p=0.004 \]

Improvement in baseline PET/CT abnormalities after 6/12 treatment

\[ p=0.005 \]

n=27
• Treatment Efficacy [Time Frame: 15 months] Treatment efficacy (TE) will be evaluated by comparing the incidence of endpoint-defined TB disease over 15 months in treated COR+ versus untreated COR+ participants.

• Performance of COR [Time Frame: 15 months] The performance of the COR will be evaluated by comparing the cumulative incidence of endpoint-defined TB disease over 15 months in untreated COR+ versus untreated COR- participants.
◆ Treating LTBI currently is infeasible (need to treat >10 healthy people to prevent 1 cases)
◆ Diagnostics are within reach that will rapidly identify those at highest risk for disease development
◆ Even 2 months of treatment in otherwise healthy people is operationally difficult and unscalable
◆ “test and treat” would enable TB eradication strategies based on campaigns in hot-spots globally
# CDC Latent TB Treatment Regimens

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum-doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly*</td>
<td>76</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly*</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>3 months</td>
<td>Once weekly*</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

*Use Directly Observed Therapy (DOT)
## CDC Active TB Treatment Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH, RIF, PZA, EMB</td>
<td>7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)</td>
<td>INH, RIF</td>
<td>182 to 130</td>
</tr>
<tr>
<td>2</td>
<td>INH, RIF, PZA, EMB</td>
<td>7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)</td>
<td>INH, RIF</td>
<td>110 to 94</td>
</tr>
<tr>
<td>3</td>
<td>INH, RIF, PZA, EMB</td>
<td>3 times weekly for 24 doses (8 weeks)</td>
<td>INH, RIF</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>INH, RIF, PZA, EMB</td>
<td>7 days/week for 14 doses then twice weekly for 12 doses</td>
<td>INH, RIF</td>
<td>62</td>
</tr>
</tbody>
</table>

Drug Resistance

<table>
<thead>
<tr>
<th>Resistance Pattern</th>
<th>Drugs Resistant To</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug sensitive (DS)</td>
<td>None</td>
<td>6 months</td>
</tr>
<tr>
<td>Multi-drug resistant (MDR)</td>
<td>Isoniazid, Rifampin</td>
<td>9-12 months (no additional resistance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18-20 months</td>
</tr>
<tr>
<td>Extensively-drug resistant (XDR)</td>
<td>Isoniazid, Rifampin, Fluoroquinolones, 2\textsuperscript{nd} line injectable agents</td>
<td>20+ months</td>
</tr>
</tbody>
</table>

- Drug resistance can develop due to:
  - Poor drug adherence causing inadequate drug concentration levels which allows overgrowth of resistant bacterial mutants
  - Primary transmission of a drug resistant TB strain
- 2017: estimated 3.5% of new cases and 18% previously treated cases were MDR-TB
Primary Anti-TB Drug Resistance, United States, 1993–2017*

* Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.
Primary MDR-TB, United States, 1993–2017*

* Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.
XDR TB* Case Count, Defined on Initial DST,† by Year, 1993–2017§

* XDR TB, extensively drug-resistant TB.
† DST, drug susceptibility test.
§ XDR TB is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.
Global MDR-TB Rates

WHO MDR-TB Treatment Guidelines

- Treat for 18-20 months
- Include ≥5 drugs considered to be effective

### Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEDICINE</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A:</strong> Include all three medicines (unless they cannot be used)</td>
<td>Levofloxacin OR Moxifloxacin</td>
<td>Lfx OR Mfx</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline(^1,4)</td>
<td>Bdq</td>
</tr>
<tr>
<td></td>
<td>Linezolid(^2)</td>
<td>Lzd</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>Cfz</td>
</tr>
<tr>
<td></td>
<td>Cycloserine OR Terizidone</td>
<td>Cs OR Trd</td>
</tr>
<tr>
<td><strong>Group B:</strong> Add both medicines (unless they cannot be used)</td>
<td>Ethambutol</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Delamanid(^3,4)</td>
<td>Dlm</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide(^5)</td>
<td>Z</td>
</tr>
<tr>
<td></td>
<td>Imipenem-clavulanic acid OR Meropenem(^6)</td>
<td>Ipm-Cln OR Mpm</td>
</tr>
<tr>
<td></td>
<td>Amikacin (OR Streptomycin)(^7)</td>
<td>Am OR S</td>
</tr>
<tr>
<td></td>
<td>Ethionamide OR Prothionamide</td>
<td>Eto OR Pto</td>
</tr>
<tr>
<td></td>
<td>p-aminosalicylic acid</td>
<td>PAS</td>
</tr>
</tbody>
</table>

WHO. Rapid communication: key changes to treatment of MDR- and RR-TB. August 2018.
WHO MDR-TB Treatment

- Treatment principles:
  - Intensive phase should contain at least four 2nd-line drugs likely to be effective and PZA
  - Generally should include ≥1 drug from each class
  - Intensive phase should last ≥8 mo or ≥4 mo past cx conversion
  - Total treatment duration ≥20 mo or ≥12 mo past cx conversion

TABLE 5.1 WHO recommended grouping of anti-TB drugs

<table>
<thead>
<tr>
<th>GROUP NAME</th>
<th>ANTI-TB AGENT</th>
<th>ABBREVIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1. First-line oral agents</td>
<td>Isoniazid</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>Z</td>
</tr>
<tr>
<td></td>
<td>Rifabutin(a)</td>
<td>Rfb</td>
</tr>
<tr>
<td></td>
<td>Rifapentine(a)</td>
<td>Rpt</td>
</tr>
<tr>
<td>Group 2. Injectable anti-TB drugs (injectable agents or parental agents)</td>
<td>Streptomycin(b)</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
<td>Km</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>Am</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td>Cm</td>
</tr>
<tr>
<td>Group 3. Fluoroquinolones (FQs)(d)</td>
<td>Levofloxacin</td>
<td>Lfx</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>Mfx</td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin(c)</td>
<td>Gfx</td>
</tr>
<tr>
<td>Group 4. Oral bacteriostatic second-line anti-TB drugs</td>
<td>Ethionamide</td>
<td>Eto</td>
</tr>
<tr>
<td></td>
<td>Prothionamide</td>
<td>Pto</td>
</tr>
<tr>
<td></td>
<td>Cycloserine</td>
<td>Cs</td>
</tr>
<tr>
<td></td>
<td>Terizidone(e)</td>
<td>Trd</td>
</tr>
<tr>
<td></td>
<td>Para-aminosalicylic acid</td>
<td>PAS</td>
</tr>
<tr>
<td></td>
<td>Para-aminosalicylate sodium</td>
<td>PAS-Na</td>
</tr>
<tr>
<td>Group 5. Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)</td>
<td>Bedaquiline</td>
<td>Bdq</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
<td>Dlm</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Lzd</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>Cff</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin/ clavulanate</td>
<td>Amx/Clv</td>
</tr>
<tr>
<td></td>
<td>Imipenem/clastatin(f)</td>
<td>Ipm/Cln</td>
</tr>
<tr>
<td></td>
<td>Meropenem(f)</td>
<td>Mpm</td>
</tr>
<tr>
<td></td>
<td>High-dose isoniazid</td>
<td>High dose H</td>
</tr>
<tr>
<td></td>
<td>Thiocetazone(d)</td>
<td>T</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin(e)</td>
<td>Clr</td>
</tr>
</tbody>
</table>

WHO. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. 2014.
Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis


- 41 chronic pulmonary XDR-TB pts no response to background regimen x6 mo randomized add LZD immediately or after 2 mo
- 4 mo: 15/19 (79%) immediate, 7/20 (35%) delayed cx converted (P=0.001)
- 34/39 (87%) converted by 6 mo

Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin P. Grobusch, M.D., Ph.D., Jorge M. de los Rios, M.D., Eduardo Gotuzzo, M.D., Irina Vasilyeva, M.D., Ph.D., Vaira Leimane, M.D., Koen Andries, D.V.M., Ph.D., Nyasha Bakare, M.D., M.P.H., Tine De Marez, Ph.D., Myriam Haxaire-Theeuwes, D.D.S., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Els De Paeppe, M.Sc., Rolf P. van Heeswijk, Pharm.D., Ph.D., and Brian Dannemann, M.D., for the TMC207-C208 Study Group

- 160 patients with smear+ MDR-TB randomized to preferred background regimen (96 wks) plus BDQ vs placebo during initial 24 wks
- Week 24 culture conversion: 79% vs 58%, P=0.008
- Wk 120 cure rates: 58% vs 32%, P=0.003

Figure 3. Time to Sputum-Culture Conversion in the Modified Intention-to-Treat Population.

Shown is the proportion of patients in each study group who had positive results on Mycobacterium tuberculosis culture during the 24-week investigational treatment phase of the study. Patients who withdrew from the study, who died, or who had sputum culture conversion by week 24 were considered to have had treatment failure in the primary analysis, regardless of their culture status at the time of dropout or death. For these patients, data were censored at their last assessment, so the proportion of patients who had culture conversion cannot be derived from the data in the figure. Analysis based on a Cox proportional-hazards model with adjustment for study center and degree of radiographic lung cavitation showed significantly faster conversion in the bedaquiline group than in the placebo group at 24 weeks (P<0.001). The number of patients at risk at each time point is the number of patients who did not have culture conversion and who were still participating in the study.
**TABLE 5.1 WHO recommended grouping of anti-TB drugs (2014)**

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<td></td>
<td>Capreomycin</td>
<td>Cm</td>
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<td>Levofloxacin</td>
<td>Lfx</td>
</tr>
<tr>
<td></td>
<td>莫西沙星</td>
<td>Mfx</td>
</tr>
<tr>
<td></td>
<td>吉法酯</td>
<td>Gfx</td>
</tr>
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<td><strong>Group 4. Oral bacteriostatic second-line anti-TB drugs</strong></td>
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<td></td>
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<td>Para-aminosalicylic acid</td>
<td>PAS</td>
</tr>
<tr>
<td></td>
<td>Para-aminosalicylate sodium</td>
<td>PAS-Na</td>
</tr>
<tr>
<td><strong>Group 5. Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB</strong> (This group includes new anti-TB agents)</td>
<td>Bedaquiline</td>
<td>Bdq</td>
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<tr>
<td></td>
<td>Delamanid</td>
<td>Dlm</td>
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<tr>
<td></td>
<td>Linezolid</td>
<td>Lzd</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>Cff</td>
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<tr>
<td></td>
<td>Amoxicillin-clavulanate</td>
<td>Amx/Cvv</td>
</tr>
<tr>
<td></td>
<td>Imipenem-clavulinate</td>
<td>Ipm/Cln</td>
</tr>
<tr>
<td></td>
<td>Meropenem*</td>
<td>Mpm</td>
</tr>
<tr>
<td></td>
<td>High-dose isoniazid</td>
<td>High dose H</td>
</tr>
<tr>
<td></td>
<td>Thioacetazone*</td>
<td>T</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin*</td>
<td>Clr</td>
</tr>
</tbody>
</table>

- Choose ≥5 active drugs including PZA
- Intensive phase ≥8 months
- Total treatment duration ≥20 months

2016:
- Groups reorganized
- Now allows for 9-12 mo regimen for MDR-TB with no additional resistance and no prior 2nd line treatment

2018:
Groups reorganized again now allowing for all oral regimen
Global TB Treatment Outcomes

XDR-TB treatment outcomes:
- 34% treatment success
- 19% treatment failure
- 26% died
- 21% lost to follow-up or not evaluated
Global Treatment Coverage Rates

FIG. 4.16
Estimated TB treatment coverage (new and relapse patients as a percentage of estimated TB incidence) in 2017. 30 high TB burden countries, WHO regions and globally

FIG. 4.20
Estimated treatment coverage for MDR/RR-TB (patients started on treatment for MDR-TB as a percentage of the estimated incidence of MDR/RR-TB) in 2017. 30 high MDR-TB burden countries, WHO regions and globally

Cost of TB Treatment
Host Factor Affecting Cure

Cure: resolved
14/99 (14%)

Cure: improved (persistent uptake)
51/99 (52%)

Cure: mixed response (new/increased intensity)
34/99 (34%)

3 patients missing treatment outcome

Host Factor Affecting Cure

Cure: new M6 lesion, improved 1y later

Cure: M6 residual nodules, no PET uptake; 1y later with cavitation and increased uptake

Residual uptake at 6M; new consolidation 1y later but cx-; cx+ 6 mo later

Host Factor Affecting Cure

Figure 5

M6 sputum with detectable Mtbf mRNA:
• 22/60 (37%) cured
• 4/4 failed
• 2/9 (22%) recurrent TB
• 0/5 other lung diseases
• 2/20 (10%) healthy controls

EOT BAL with detectable Mtbf mRNA:
• 14/14 cured
• 1/1 failed
• 1/1 newly diagnosed TB
• 1/1 recurrent TB
• 2/10 controls (1 subsequently dxed with TB)

Bacterial Factor Affecting Cure: MIC

• Minimum inhibitory concentration (MIC): the lowest concentration of an antibiotic that prevents >99% growth in solid or liquid medium

• Resistance breakpoint: a chosen concentration of antibiotic which defines whether a bacteria is susceptible or resistant
  • MIC < breakpoint = susceptible
  • MIC = breakpoint = intermediate
  • MIC > breakpoint = resistant
  • INH = 0.1 µg/ml; RIF = 1.0 µg/ml
Bacterial factors (INH/RIF sub-breakpoint MICs) predicted relapse just as well as all other significant host factors (cavity on CXR, underweight, wk 8 sputum cx+)

A subpopulation of “drug-sensitive” *Mtb* may require a higher concentration of antibiotics for better treatment outcomes

Combining host and bacterial factors are highly predictive of relapse and may be used to predict patients cured before 6 months of treatment

Additional prospective studies are needed in larger cohorts

---

<table>
<thead>
<tr>
<th>MIC</th>
<th>Ratio (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Relapse</td>
<td>1.17</td>
<td>0.02</td>
</tr>
<tr>
<td>Cure</td>
<td>1.33</td>
<td></td>
</tr>
</tbody>
</table>

• LR >1 Test result associated with disease
• LR =1 Test result not helpful
• LR <1 Test result associated with absence of disease

---

**Figure 2. Receiver-Operating-Characteristic (ROC) Curves for Relapse after Tuberculosis Treatment.** Shown are ROC curves in the development cohort (Panel A) and the validation cohort (Panel B). Curves are displayed for MIC values of isoniazid (INH) and rifampin (RIF) alone, for MIC values of isoniazid plus rifampin, and for the other models discussed below, as indicated. ROC curves are graphical plots that illustrate the performance of a binary classifier system as its discrimination threshold is varied. The curves were created by plotting the true positive rate against the false positive rate at various threshold settings. The area under the curve (AUC) that is shown in each plot summarizes the overall biomarker performance in a single number, with 0.5 indicating no difference from chance and 1.0 indicating a perfect biomarker with sensitivity and specificity both equal to 100%. The full model includes the following factors: MIC values of isoniazid and rifampin, cavity disease on radiography, being underweight, and a positive 8-week sputum culture. The full model without culture results includes the same covariates as the full model with the exclusion of a positive 8-week sputum culture. The composite model includes the same covariates as the full model with the exclusion of the MIC values of isoniazid and rifampin.
TB Treatment Shortening

• British Medical Research Council (BMRC) conducted multiple trials in 1970s and 1980s to reduce treatment duration from 18 to 9 to 6 months, maintaining relapse rates 1-2%

• Attempts to shorten treatment below 6 months resulted in increased relapse rates so 6 months became established as the standard of care

<table>
<thead>
<tr>
<th>Duration of chemotherapy (months)</th>
<th>Patients assessed*</th>
<th>Bacteriological relapses</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>298</td>
<td>3 (1%)</td>
<td>0.2–2.9</td>
</tr>
<tr>
<td>6</td>
<td>422</td>
<td>4 (1%)</td>
<td>0.3–2.4</td>
</tr>
<tr>
<td>4½–5</td>
<td>465</td>
<td>16 (3%)</td>
<td>2–6</td>
</tr>
<tr>
<td>4</td>
<td>364</td>
<td>43 (12%)</td>
<td>9–16</td>
</tr>
<tr>
<td>3</td>
<td>307</td>
<td>41 (13%)</td>
<td>10–18</td>
</tr>
</tbody>
</table>

* The regimens and duration of follow-up are given in Tables II, III and IV. (The six-month and shorter durations all contain streptomycin, isoniazid, rifampicin and pyrazinamide.)

However, in view of the evidence that a very substantial majority, at least 80%, of patients with drug-sensitive infections are cured by three months of intensive four-drug chemotherapy, it is clear that even six-month regimens based on isoniazid, rifampicin and pyrazinamide are already unnecessarily long for most patients and a nine-month regimen even more so.
TB Treatment Shortening

• DMID 01-009 trial only shortened treatment to 4 mo among those with less severe disease:
  • No cavity on baseline CXR
  • Sputum culture converted to negative by 2 months of treatment

• Trial stopped early due to higher relapse rate in 4-mo arm compared to 6-mo arm (7.0% vs 1.6%, p<0.01)

• Despite study failure, 4-mo arm treatment success rate increased from about 80-85% to 93%

Figure 2. Kaplan Meier curve showing the cumulative percentage of patients who relapsed after completing anti-tuberculosis (TB) treatment. The chi-square test for a difference in the percentage of patients who relapsed by treatment arm was significant (P < 0.01). Error bars represent the standard error of the mean percentage of patients who relapsed at 6, 12, and 24 months of follow-up after completing treatment.
Sensitivity of CXR for Cavities

CLINICAL INDICATION: Active pulmonary tuberculosis infection causing shortness of breath. Clinical Evaluation: pulmonary TB.

TECHNIQUE: Chest AP one view

COMPARISON: No prior chest radiograph available for comparison

FINDINGS:
- Nodular opacities in the upper lungs consistent with history of tuberculosis.
- Linear scarring ill-defined opacity in both mid and lower lungs, with architectural distortion in the right perihilar region, also due to tuberculosis infection.
- Nodularity in the left mid and lower lung.
- Cardiac silhouette within normal radiographic limits.
- Probable mediastinal paratracheal mediastinal soft tissue thickening.
- Skeletal structures intact without focal destructive osseous disease.

IMPRESSION:
- Nodular densities in the upper lungs and left perihilar region with extensive linear scarring and architectural distortion in the perihilar regions, consistent with history of tuberculosis.
CT Scan
Predict TB

DMID 01-009
• Baseline: no cavity on CXR
• Treatment response:
  • Month 2 sputum culture negative

Predict TB
• Baseline: PET/CT burden of disease
• Treatment response:
  • Month 1 PET/CT burden of disease
  • Month 4 Xpert MTB/RIF cycle threshold

<table>
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<tr>
<th>Study</th>
<th>4-month Treatment Success Rate</th>
</tr>
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<tbody>
<tr>
<td>Prior studies (no stratification)</td>
<td>80-85%</td>
</tr>
<tr>
<td>DMID 01-009</td>
<td>93%</td>
</tr>
<tr>
<td>Predict TB</td>
<td>?</td>
</tr>
</tbody>
</table>
Predict TB Study Overview

- Partially randomized phase 2 study;
- Sample size: 310 in Arms B and C combined
- Inclusion criteria: adults; HIV-; diabetes negative
- Locations:
  - Cape Town, South Africa;
  - Henan, China

Legend:
- PET/CT
- W4 PET/CT will be done in Arm A if resources allow
- PET/CT for Arm A at either Week 16 OR Week 24
Predict TB Acknowledgements

**China**
- Henan BOH 河南省卫健委
  - Li Guangsheng 李广胜
- Henan CDC 河南省疾控中心
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  - WANG Zhe 王哲
  - ZHANG Guolong 张国龙
  - MA Liping 马丽萍
  - LI Hui 李辉
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  - YUAN Xing 英
  - ZHU Rujun 朱汝军
  - LIU Xin 刘新
- Kaifeng TB Institute 开封市结核病防治所
  - MA Zhengya 马振亚
- Zhongmu CDC 中牟县卫生防疫站
  - PAN Shouguo 潘守国
- Xinmi CDC 新密市结核病防治所
  - JIN Xiaowei 靳晓伟
- Xinxiang CDC 新乡市结核病防治所
  - ZHANG Ruanqing 张软青
- Fudan University 复旦大学
  - GAO Qian 高谦
- Sino-US Henan Project Office 中美研究办公室
  - ZHU Hong 朱红
  - GAO Jingcai 高静彩
  - LI Baobao 李宝宝
  - CHEN Xipu 陈锡浦
  - XU Binyang 徐斌扬

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  - Fanie Malherbe
  - Bronwyn Smith
- TASK Applied Sciences
  - Andreas Diacon
  - Madeleine Hanekom
- UCT Lung Institute
  - Rod Dawson
  - Kim Narunsky
- UCT Khayelitsha
  - Robert Wilkinson
  - Sandra Mukasa
- UCT SATVI
  - Michele Tameris
  - Mark Hatherill
- UCT Barry Lab
  - Taeksun Song

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  - Paul Corstjens
  - Annemieke Geluk
- University of Zurich
  - Friederich Thienemann
- LINQ Management
  - Claudia Schacht
  - Julia Buech

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- China: LIANG Lili 梁丽丽; DUAN Hongfei 邓辉
- Switzerland: Friedrich Thienemann
- France: Aurelie Gouel
- USA: Ray Chen

**United States**
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  - Laura Via
  - Lisa Goldfeder
  - Chrissie Cai
  - Kriti Arora
  - Derek Armstrong
  - Ray Chen
- NIH/NIAID Statistical Research Branch
  - Lori Dodd
  - Jing Wang
- NIH/NIAID Office of CyberInfrastructure and Computational Biology
  - Michael Duvenhage
  - Chris Whalen
  - Kathy Pomeroy
  - An-Ting Romano
  - Matthew Eisenberg
  - Sergey Grinkrug
  - Vadim Provotorov
  - Terry Nugent
- Rutgers New Jersey Medical School
  - David Alland
- Colorado State University
  - John Belisle
- Catalysis Foundation for Health
  - Jill Winter
The TB Drug Accelerator (TBDA)

The TBDA is a groundbreaking partnership between eight pharmaceutical companies, seven research institutions, and a product development partnership that seeks to develop a new TB drug regimen through collaboration in early-stage drug discovery research.
An exemplar TBDA project: TB oxazolidinone optimization

- Improve Mtb potency by >10x → lower dose
- Limited cross-antibacterial activity
- ↑ MPS & MAO selectivity → improve safety index
- High caseum free fraction & good penetration (low clogP)
  - Profile compounds with various degree of physiochemical properties
- Predicted human PK similar or better than that of linezolid
**SCREENING (Hit Package Delivery)**

<table>
<thead>
<tr>
<th>uHTS</th>
<th>ALIS</th>
<th>FRAG</th>
<th>PHENO</th>
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<td>7/30/15</td>
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**Max Cmpd Flow/Stage**

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</tr>
<tr>
<td>2</td>
<td>15</td>
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<td>6</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
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</tbody>
</table>

**Total Wk** 31

---

**LO ROP:** Oxazolidinones (TBDA)

### Med Chem Oxazolidinone Analogs

- **Mtb H37Rv pMSP12::GFP**
  - MIC < 4 μg/mL
- **B. subtilis ATCC23857**
  - MIC > 200 μM

### In silico modeling

### ADHOC Assays

- **Cross-resistance with Lzd-R strains**
  - CS
- **Kill curves with Mtb**
  - CS
- **FOR/Resistance selection (Mtb; Srif FOR)**
  - CS
- **Analog mutants: Target specific sequencing**
  - CS
- **Analog mutants: Whole genome sequencing**
  - CS
- **Mtb/Macrophage activity**
  - LC
- **Epithelial lung fluid MIC reversal**
  - CS
- **Compound tissue distribution**
  - LC
- **Mouse model**
  - LC
- **MML**
  - CS
- **Click-iT Edu cytotoxicity**
  - CS
- **HepG2 cytotoxicity**
  - CS

**CS:** Compound specific (<10%)

**MO:** Monthly (>10%)

**LC:** Lead candidates only

---

**PCC:**

- **PCC enabling SA studies**
- **PCC enabling SA studies**
- **API scale-up**
- **PCC enabling DMPK/DPS studies**
- **Rat toxicity study (~10 or other and DILI evaluation)**
- **Clinical strains extended panel**
- **Prelim human dose prediction v2**
- **Rodent CV**
- **Marmoset model**
  - 2 log reduction
- **3 strain AMES**
  - In vitro MN
- **Bacterial strains mini-panel**
  - MIC < 4 μg/mL

**RPM:**

- **RPM enabling SA studies**
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**ROP Refresh:** October 2015v2

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**PCC:**

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- **PCC enabling SA studies**

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Ca 1000 molecules designed, made and tested
High FOR was associated with C-5 amines and mutation in Rv0133

- 9/14 TB “Oxa-amine” resistant mutants mapped to Rv0133

**FOR is ~ 10^{-6}**

**FOR is ~ 10^{-9}**

<table>
<thead>
<tr>
<th>Acetamide</th>
<th>Amine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetamide-R</td>
<td>R</td>
</tr>
<tr>
<td>Amine-R</td>
<td>S</td>
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</tbody>
</table>

Same MOA?
662 rapidly sterilizes lesions in marmosets
How to reliably triage which drugs/regimens proceed to resource-intensive Phase III trials?

Early Bactericidal Activity (EBA)
Daily decline in sputum CFU associated with an investigative drug or regimen given for up to **14 days**

Davies, Geraint. Tuberculosis 90 (2010) 171-176
8 treatment arms; 20 patients per arm

1. INH
2. RIF
3. PZA
4. MXF
5. RIF + PZA
6. INH + PZA
7. INH + RIF + PZA + EMB
8. MXF + RIF + PZA + EMB

“INH” – isoniazid; “RIF”-rifampin; “PZA”-pyrazinamide, “EMB”-ethambutol, “MXF”-moxifloxacin

Screen/Enroll

1-2 Baseline
14 days of study treatment (8 arms)
Inpatient monitoring

Daily overnight sputum collection
(CFU count and Time to Positivity)

Baseline
Baseline
Baseline
Baseline

PET/CT
PET/CT
PET/CT
PET/CT

NIAID/NIH
NIAID/NIH
NIAID/NIH
NIAID/NIH

Gerhard Walzl
(Stellenbosch University)
Gerhard Walzl
(Stellenbosch University)
Gerhard Walzl
(Stellenbosch University)
Gerhard Walzl
(Stellenbosch University)

Discharge

14 day
14 day
14 day
14 day

Blood
Blood
Blood
Blood

NexGen EBA Trial in Cape Town, South Africa
Enrollment of 160 drug-naïve, HIV-negative adults with smear-positive tuberculosis from Cape Town, South Africa.

Goal: Improve the ability to predict non-relapsing cure in TB patients in a short-duration trial amenable to combination chemotherapy.
Enrollment: December 2015 to September 2017

EBA (mean daily log_{10} decline of CFU/mL sputum/day over 13 days of treatment) for the 8 blinded treatment arms, arbitrary arm designation.
NG029: Improvement in all lesions

NG041: Heterogenous changes
NexGen EBA Analysis

Extract lesions from all 320 study PET/CT scans:
Developing automated extraction method using machine learning from manual extractions (ongoing)

Derive PET/CT 1\textsuperscript{st} and 2\textsuperscript{nd} order statistics to categorize lesions into pharmacokinetically-relevant units (ongoing)

Apply these statistics to categorize all extracted lesions from participant scans

Measure delta signature of 14-day PET/CT changes across each lesion unit for each participant

Prediction of all NexGen participant treatment arms based on these signatures
Comparison with microbiology and immunology data
4) Low in Everything

1) High in PC1

2) High in PC2

3) High in PC3

NG009_base_R6_lesion

NG039_base_L4_lesion_2

NG111_base_L1-5_lesion

NG019_base_R4_R5_lesion
The next four years...
rewriting the rules for Phase 2 TB Rx studies
Conclusions

• TB remains a persistent global health threat
• “Latent” TB is a wide spectrum with very different risks of progressing to active disease
• Preventing at-risk LTBI patients from developing disease using simple blood markers may soon be a reality
• “Personalized” TB therapy of appropriate drugs and treatment times should optimize use of the scarce resources available for TB control
• Improved drugs and clinical trial methodologies to combine them are being developed