Annual ICOT Conference

PRE-XDR TB

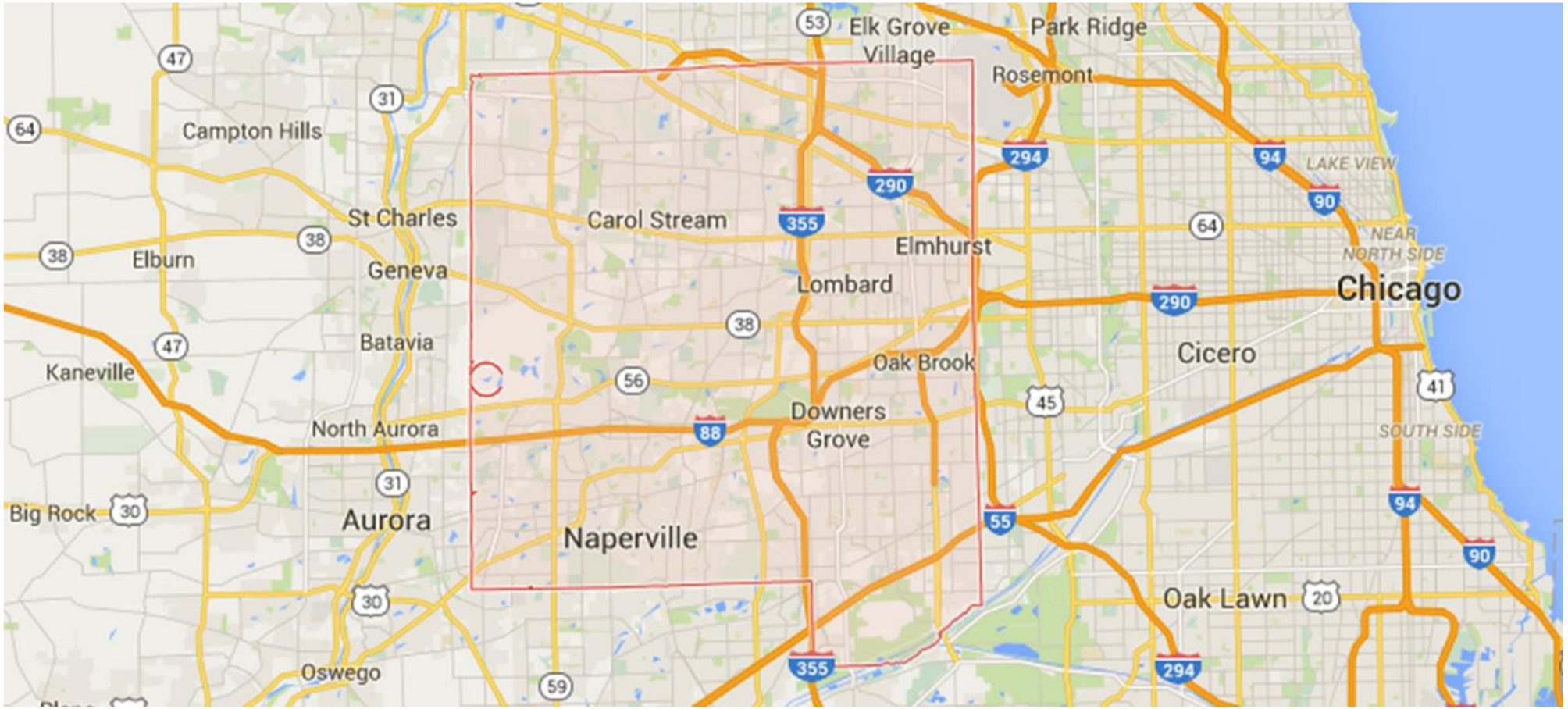
Dean Schraufnagel, MD – Director, Tuberculosis Care and Prevention, DCHD

Tamam Jada, RN – Public Health Services Supervisor, DCHD

Objective

Participants will be able to gain knowledge about nurse case management of Extensively Drug-Resistant Tuberculosis.

DuPage County



DuPage County Health Department (DCHD)

- Over 500 employees at multiple locations.
- Accredited by The Joint Commission for Behavioral Health and the Public Health Accreditation Board (one of 75 out of 3000 health departments).
- Range of services including: community based programming, environmental health, behavioral health, and clinical services.
- TB clinic is core responsibility of local health departments. Statutory responsibility.

DCHD Tuberculosis Program

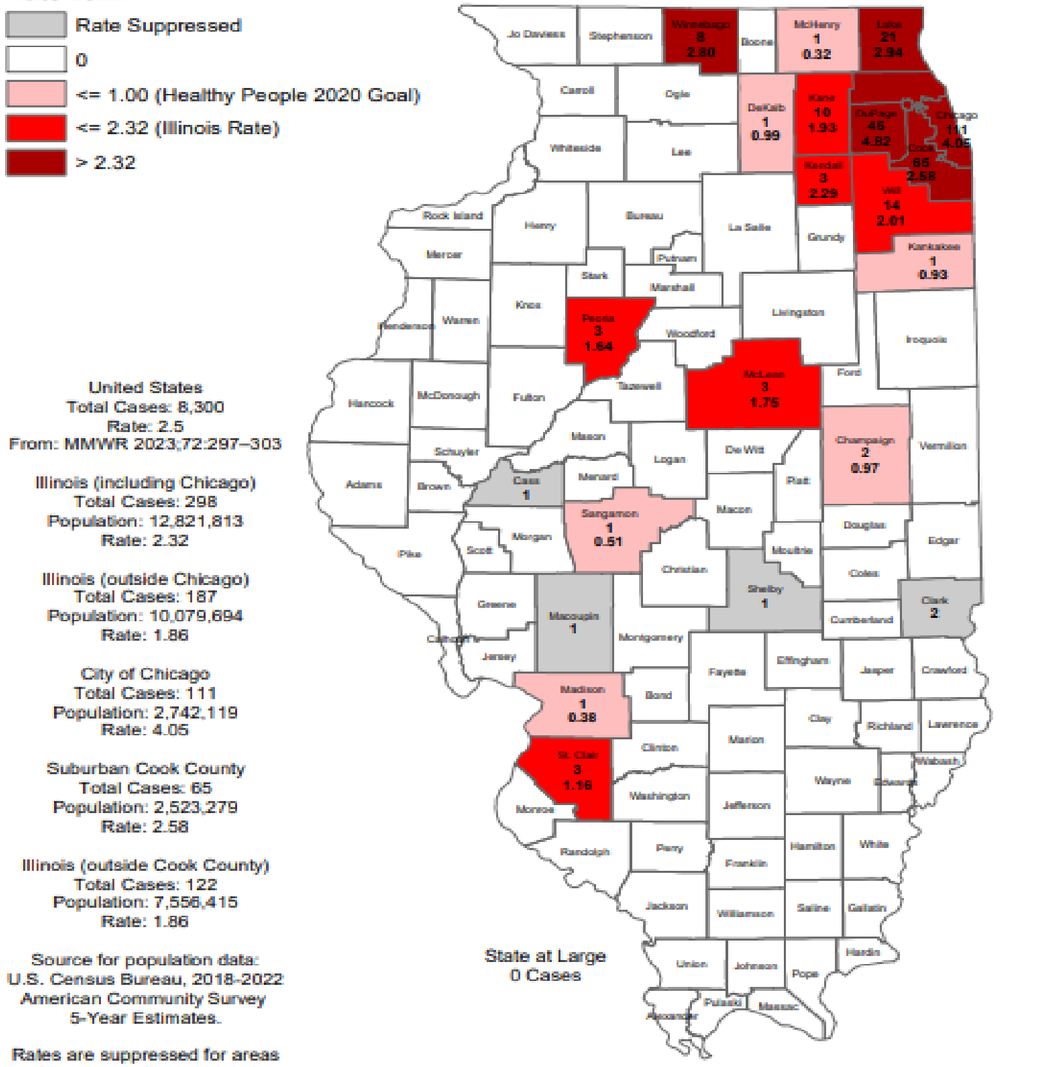
- 4 full-time TB Nurse Case Managers
  - Ewa Bridgeforth
  - Ruth Woodworth
  - Kayli Braun
  - Maria Tinoco-Manriquez
- 1 Nurse Supervisor
  - Tamam Jada
- 3 Clinic Assistants
- 1 TB Medical Director – Dean Schraufnagel
  - 10 TB Fellows
- Assistant Director of Public Health Services
  - Ashley Matese

- **616** unduplicated clients served in the TB program in 2022.
- **122** Latent cases treated in 2022
- **6706** VOT/DOT Visits in 2022
  - Some clients we DOT through entirety of treatment depending on circumstances.

DuPage County Active Cases

Year	# of Active Cases	Rate
2017	42	4.51
2018	50	5.37
2019	46	4.94
2020	30	3.23
2021	31	3.35
2022	46	4.62

Source IDPH: https://dph.illinois.gov/topics-services/diseases-and-conditions/infectious-diseases/tb.html



Extensively Drug-Resistant TB (XDR)

Tamam Jada, RN, DCHD

Extensively Drug-Resistant TB (XDR)

WHAT: Drug-resistant tuberculosis (DR-TB) is a deadly communicable disease caused by *Mycobacterium tuberculosis* (MTB). DR-TB poses a serious global health threat, impacts individual patients and their families, and imposes tremendous burdens on overextended public health systems. Treatment for DR-TB is associated with more adverse events than treatment for drug-susceptible TB and requires intensive patient-centered case management and support.

HOW: DR-TB can be spread through person-to-person transmission. Drug resistance may develop when TB treatment is inadequate, to include:

- full course of TB treatment not completed;
- incorrect TB treatment (i.e., prescribed regimen, dose or length of time);
- TB drugs not available; or
- drug susceptibility testing not done.

WHO: Drug resistant TB is more common in persons who:

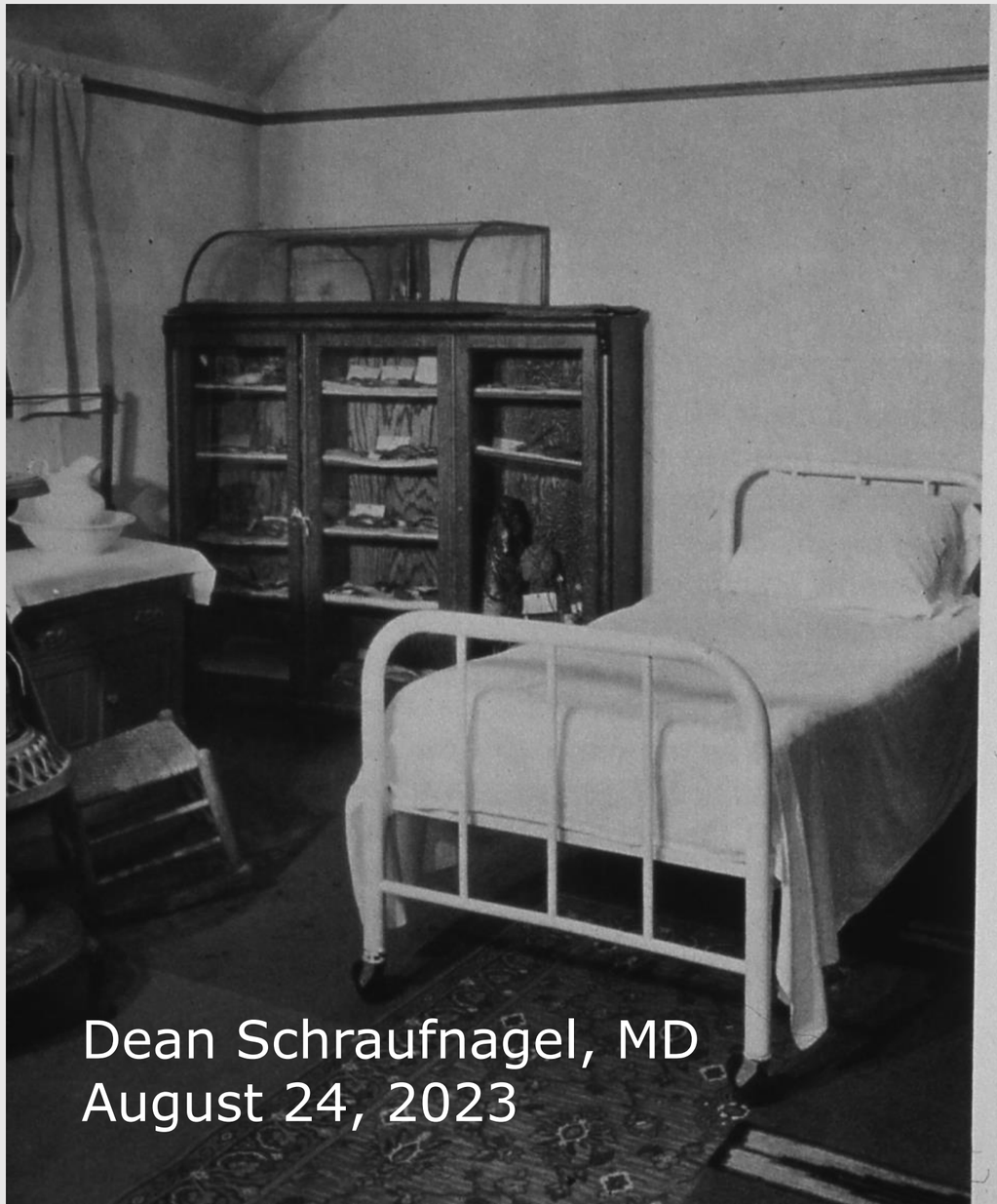
- do not take their TB drugs regularly;
- do not take all of their TB drugs;
- develop TB disease again after previous treatment;
- come from places where DR-TB is common;
- have been exposed to a person that had DR-TB; or
- have poor absorption of TB drugs.

WHERE: About 500,000 new cases of RR/MDR TB are estimated to emerge each year. India, China and the Russian Federation account for one half of the global burden. www.who.int/news-room/fact-sheets/detail/tuberculosis

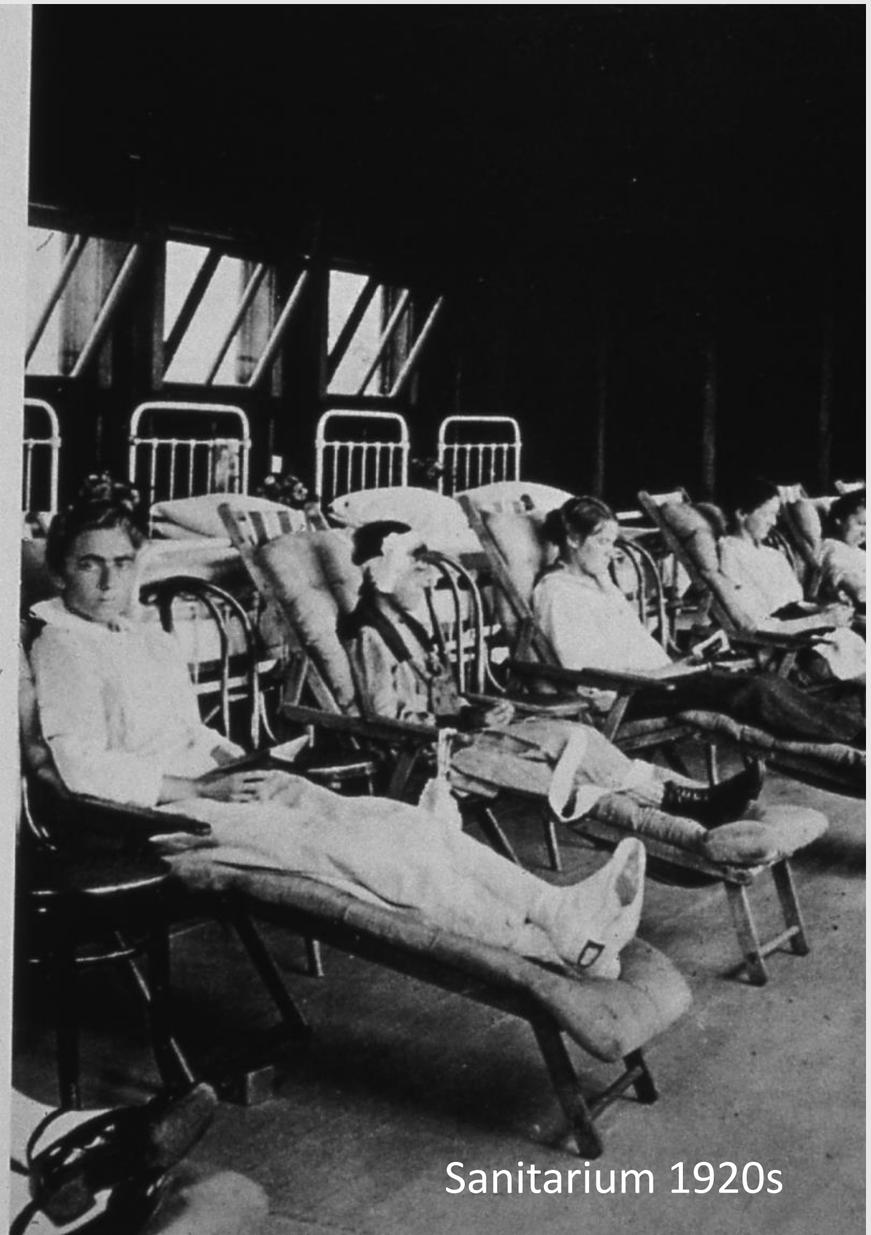
WHO List of 30 Countries with a High Burden of MDR/RR-TB MDR-TB

https://www.heartlandntbc.org/

Drug-resistant tuberculosis



Dean Schraufnagel, MD
August 24, 2023



Sanitarium 1920s

Case presentation

Pharmacy 1920s

Background

- 59 ♂ immigrated in 2018 (Hyderabad)
- BCG as infant
- Diabetes >10 years; HTN;↑cholesterol
  - DM poorly controlled, on insulin 7 years
- Work: pharmacy tech, delivering meds
- No tobacco or alcohol

April 2022

- Angina → 3-vessel angioplasty and stent
- Ticagrelor (Brilanta™)

November 2022

- Progressive cough

- December 2, 2022: hemoptysis
  - 2 L of blood → LUL lobectomy

- December 3, 2022: AFB
  - INH, RFM, PZA, EMB, piperacillin

Drug-Sensitivity Testing

- Resistant to RFM, INH, PZA, EMB, FQ
  - Continued meds until Dec 15

- Started bedaquiline, pretomanid, linezolid (BPaL) on January 1, 2023

Course (March 7 visit)

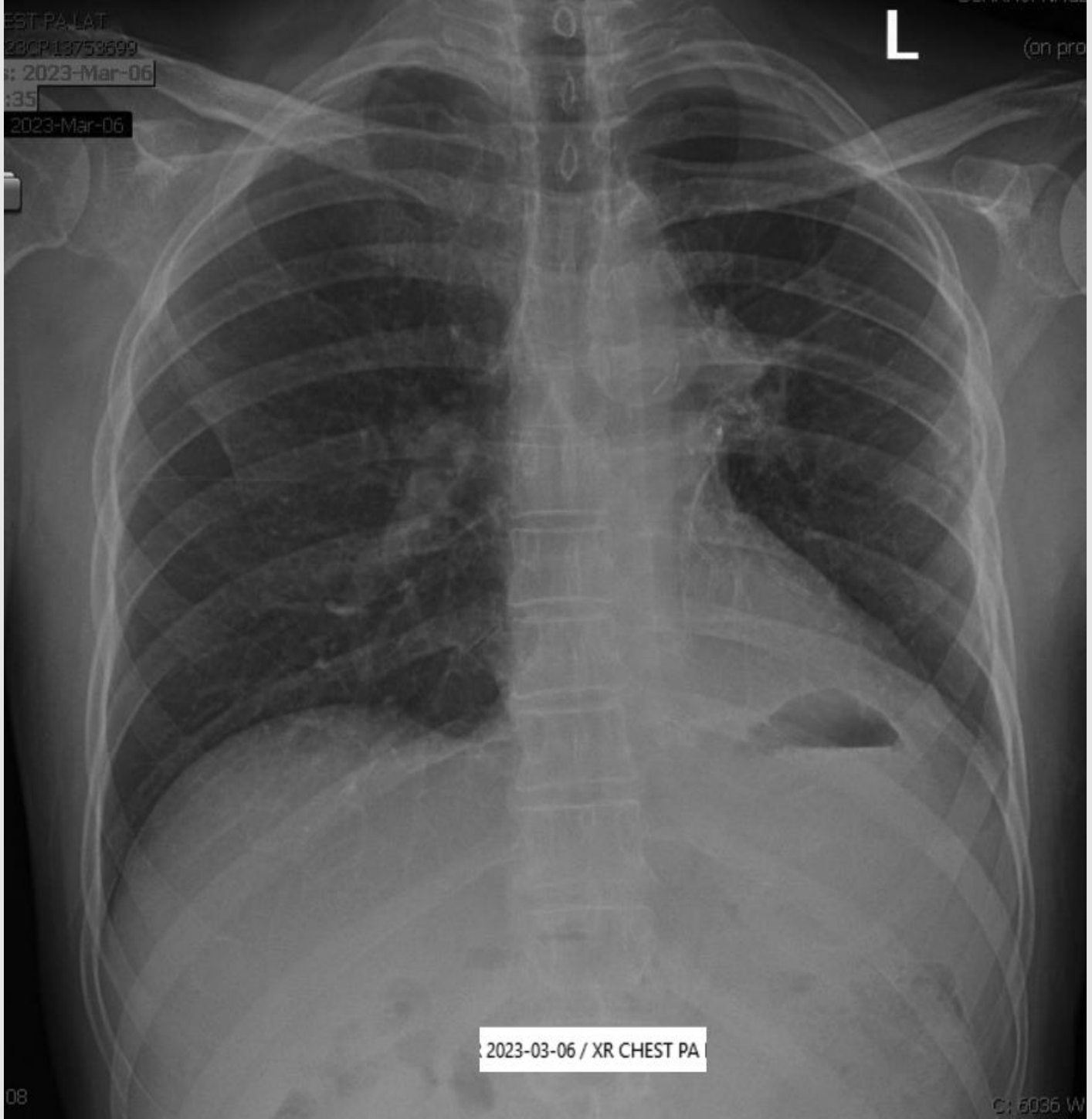
- Greatly improved
- Drugs more tolerable, “nausea gone”
- Cough disappeared, gaining weight
- Surgery site pain; 1 flight doe
- ROS: leg pain in bed (old), heartburn

Physical Exam

- Slender, in no distress
- VS normal
- Scattered crackles in right lung
- No cardiac abnormality or edema
- Neurologic (sensation, reflexes) intact
  - Vision and vibratory sense mildly↓

Chest Radiograph

- April 4, 2022
  - Portable reported normal
- Dec 3, 2023 CT
  - LUL consolidation
  - Scattered ground-glass and airspace
- March 7, 2023
  - Decreased volume,
  - Bilateral hilar fullness, RUL bronchiectasis
  - Granulomata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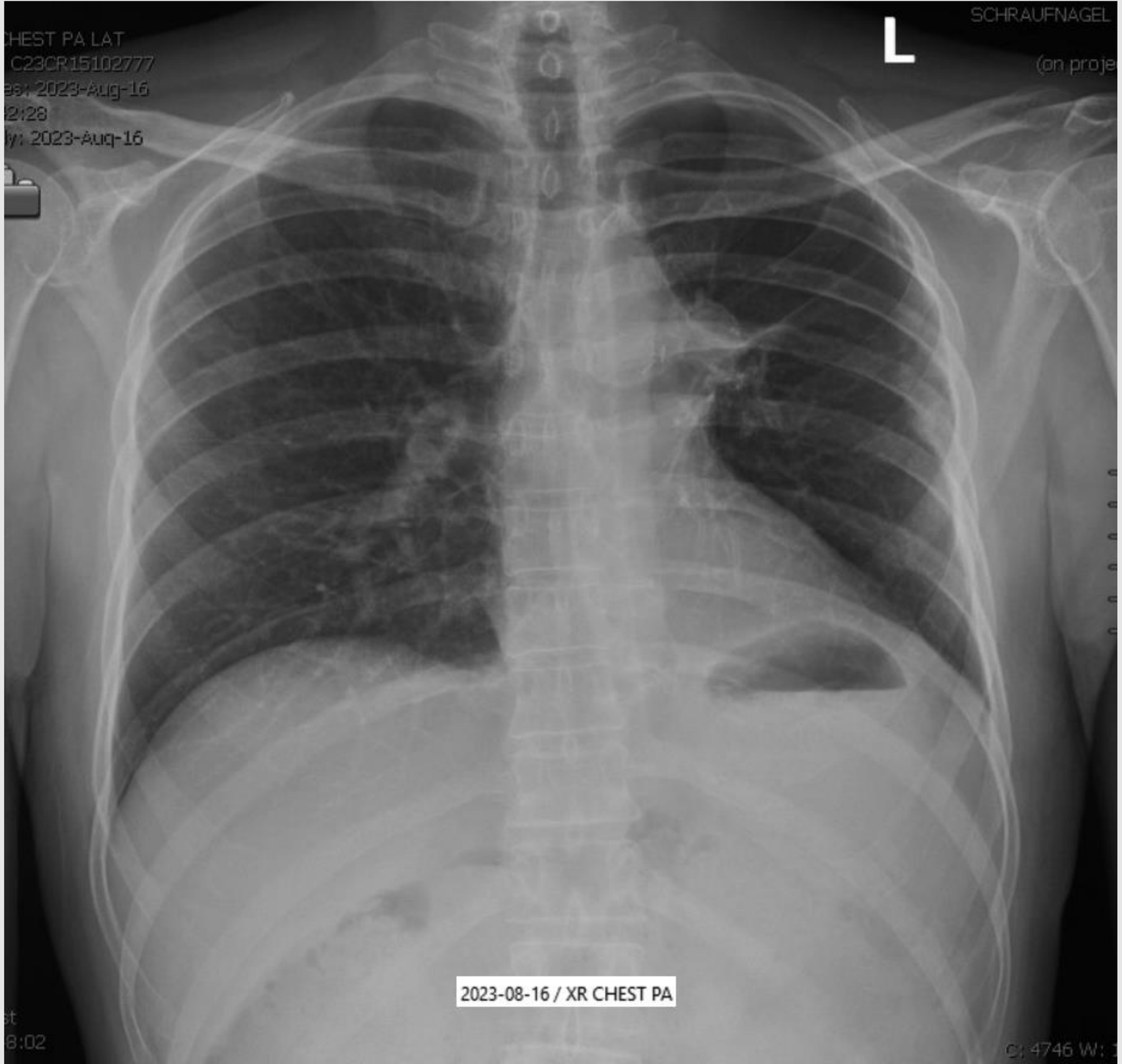
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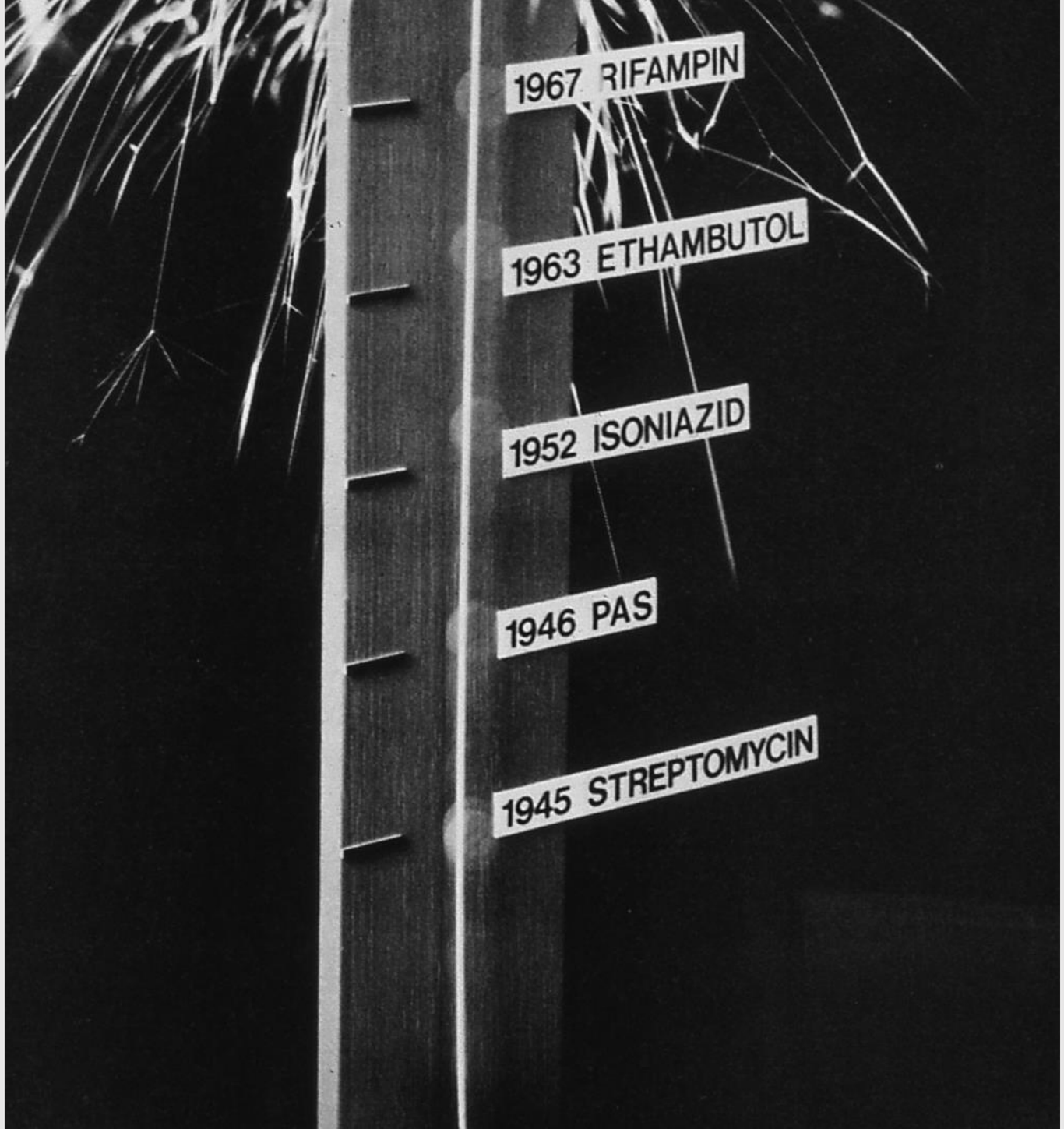
How drug resistance develops

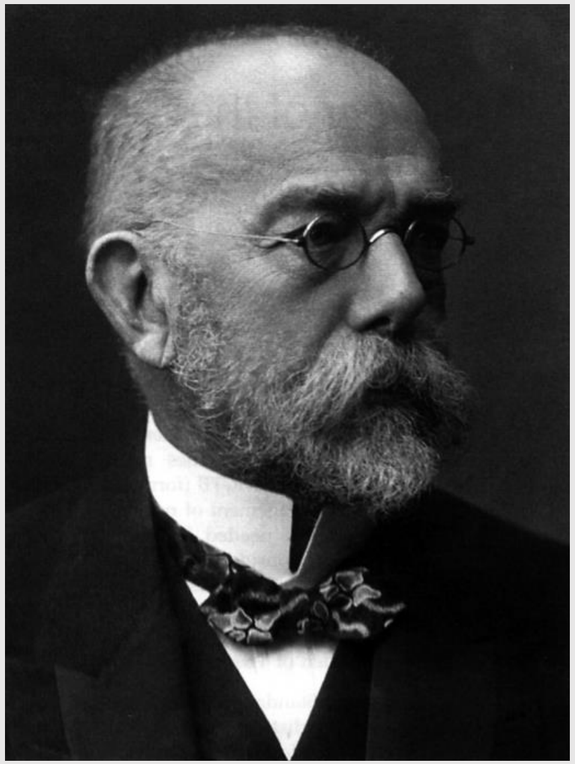


TB Scourge

- Leading cause of death in 18th and 19th centuries
  - Affecting up to 30% of certain populations
- Many causes hypothesized
- Cure unattainable
  - Sunlight, clean air
    - Murray, Schraufnagel, Hopewell. Annals ATS 2015;12:1749-59

Breakthroughs

Jean Villemin: 1860s TB contagious



Robert Koch discovered bacillus 1882

Sanitorium era

Drug Resistant TB History

- Streptomycin (1944)
  - Miracle cure for TB
  - 1-3 months later resistant disease returned
    - Youmans et al., Proc Mayo Clinic 1946;21:126
    - Pyle. Proc Mayo Clinic 1947;22:465
- PAS → Lasting cure (1951)
- Overshadowed by INH (1952)

First randomized control trial

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli *in vitro*, and the results of treatment in experimental tuberculous infection in guinea-pigs, had been reported; these results were strikingly better than those with any previous chemotherapeutic agent in tuberculosis. Preliminary results of trials in clinical tuberculosis had been published (Hinshaw and Feldman, 1945; Hinshaw, Feldman, and Pfuetze, 1946; Keefer *et al.*, 1946); the clinical results in pulmonary tuberculosis were encouraging but inconclusive.

The natural course of pulmonary tuberculosis is in fact so variable and unpredictable that evidence of improvement or cure following the use of a new drug in a few cases cannot be accepted as proof of the effect of that drug. The history of chemotherapeutic trials in tuberculosis is filled with errors due to empirical evaluation of drugs (Hart, 1946); the exaggerated claims made for gold treatment, persisting over 15 years, provide a spectacular example. It had become obvious that, in future, conclusions regarding the clinical effect of a new chemotherapeutic agent in tuberculosis could be considered valid only if based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature) reported negative therapeutic results (Amberson, McMahon, and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.

The many difficulties of planning and conducting a trial of this nature are important enough to warrant a full description here of the methods of the investigation.

Plan and Conduct of the Trial

Type of Case

A first prerequisite was that all patients in the trial should have a similar type of disease. To avoid having to make allowances for the effect of forms of therapy other than bed-rest, the type of disease was to be one not suitable for other forms of therapy. The estimated chances of spontaneous regression must be small. On the other hand, the type of lesion should be such as to offer some prospect of action by an effective chemotherapeutic agent; for this reason old-standing disease, and disease with thick-walled

How Resistance Develops

- Natural selection → fittest survive
- Mutations – independent events for *M. tb*
- Assume infection has 10^9 organisms &
- Assume 10^3 bacteria are resistant
  - Varies with drug, strain from 10^{-2} to 10^{-8}
- Of 10^9, 10^6 killed → 10^3 resistant
  - 10^3 resistant multiply → drug resistant TB
- 2 drugs → 10^{-3} X 10^{-3} =10^{-6}
- 2 drugs → 10^{-5} X 10^{-5} =10^{-10}

Mutation Rates and Estimated Number of Organisms

Table 8.1 Number of bacilli required for the appearance of a mutant resistant to different drugs

Isoniazid	1×10^5–10^6 bacilli
Rifampicin	1×10^7–10^8 bacilli
Streptomycin	1×10^5–10^6 bacilli
Ethambutol	1×10^5–10^6 bacilli
Pyrazinamide	1×10^2–10^4 bacilli
Fluoroquinolone	1×10^5–10^6 bacilli
Other drugs	1×10^3–10^6 bacilli

Table 8.2 Estimated bacterial populations in the different tuberculosis lesions

Smear-positive tuberculosis	10^7–10^9 bacilli
Cavitary tuberculosis	10^7–10^9 bacilli
Infiltrating	10^4–10^7 bacilli
Nodules	10^4–10^6 bacilli
Adenopathies	10^4–10^6 bacilli
Renal tuberculosis	10^7–10^9 bacilli
Extra-pulmonary tuberculosis	10^4–10^6 bacilli

Caminero JA. Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis 2013 p74

Resistance Develops

- Misdiagnosis–missing active TB
  - Treating with one drug
- Premature stopping
  - Stopping one
- Inattention to missed medication
  - Lost to follow up
  - Patient selecting drugs
  - Drug supply
- Risk ∝ bacterial load & dividing orgs
  - Why latent risk is low

Our Patient

- Delivering drugs would allow contact
  - Person with MDRTB
  - Not a bit from different patients
- DM (HIV, etc.) →↑ latent to active
  - Less known about exposure-to-latent
  - Usually, risks lumped in
- BDQ risk

Worsening Patient?

- Immune reconstitution
- Wrong Dx or 2^{ndary} diagnosis
- Failure to take medicine
- Malabsorption
- Failure to improve ∝ severity
  - >80% clear by 2 months

Care, Nursing, Public Health

- This patient posed several problems that needed attention

Client Medications

Home Medications

- Aspirin
- Atorvastatin
- Jardiance
- Gabapentin
- Insulin
- Losartan
- Metoprolol
- Prasugtel

TB Medications

- 12/15/2022
  - Isoniazid 300mg
  - Rifampin 600mg
  - Ethambutol 800mg
  - Pyrazinamide 100mg
- 12/17/2022
  - Levofloxacin 750mg

Multi Drug-Resistance

Definitions of Drug-Resistance

X identifies resistance

	Centers for Disease Control and Prevention (CDC)						World Health Organization (WHO)			
Drug	**MDR**	**Pre-XDR[3]**		**XDR[3]**			**RR/MDR**	**Pre-XDR**	**XDR[3]**	
Isoniazid (INH)	X	X	X	X	X	X	P or N*	P or N*	P or N*	P or N*
Rifampin (RIF)	X	X	X	X	X	X	X	X	X	X
Fluoroquinolone (FQN)[1]	-	X	-	X	X	X	-	X	X	X
Bedaquiline (BDQ)	-	-	-	X	-	-	-	-	X	P or N*
Linezolid (LZD)	-	-	-	-	X	-	-	-	-	X
2nd line injectable[2]	-	-	X	-	-	X				

RR-Rifampin resistant MDR-Multidrug resistant XDR - Extensively drug resistant

P - Positive N - Negative

*By WHO definition, resistance to these drugs can be positive or negative when the patient is being considered for MDR, Pre-XDR, or XDR.

[1]Levofloxacin or Moxifloxacin

[2]Amikacin, Capreomycin, Kanamycin

[3]Each column indicates one combination of drug resistance that meets the respsective definition of pre-XDR or XDR TB.

Treatment of Multi Drug-Resistant TB

- ✓ January 31, 2023 - BPaL initiated
- ✓ Bedaquiline 400mg daily for the first 14 days followed by 200mg trice weekly
- ✓ Linezolid 600mg daily
- ✓ Pretomanid 200 mg daily

Multi Drug-Resistant TB Treatment - BPaL

6-Month Standardized Regimens	
Regimen and Description	**Considerations**

BPaLM regimen
• 6 months of bedaquiline, pretomanid, linezolid (600mg), and moxifloxacin
 	
BPaL regimen
• 6 months of bedaquiline, pretomanid, and linezolid (600 mg)
 	
Treatment Length: Treatment can be extended beyond 26 weeks up to 9 months (39 weeks), based on delayed treatment response within the first 8 weeks (assessed by time of culture conversion and clinical response to treatment) and other underlying clinical factors, or modifications based on adverse events.
 	
Linezolid Dose:
• Data from the ZeNix study suggest that optimal dosing is 600 mg daily.
• WHO recommends attempting to maintain a 600 mg dose throughout treatment, with dose reduction possible due to toxicity or poor tolerability.
• Many experts use therapeutic drug levels to adjust linezolid dose or dosing interval.
• Early evidence suggests fewer adverse effects with trough level <2 mcg/ml. Peak concentration is ≥ 12mcg/ml.
	• BPaLM may be used in patients with MDR/RR-TB who:
	  • are 15 years or older; AND
	  • are not pregnant, AND
	  • have pulmonary or non-severe extrapulmonary TB AND
	  • have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure).
	• BPaL may be used in patients who meet these criteria who also have intolerance or resistance to a fluoroquinolone.
	• Experience in extrapulmonary TB is limited.
	• BPAL or BPaLM can be used in people with HIV if compatible with ART regimen.
	
	(Note: Pretomanid does not have an approved indication for use in pregnant patients.)

Nurse Case Management of a Pre-XDR TB Case

Nurse Case Mangement

Case Management II

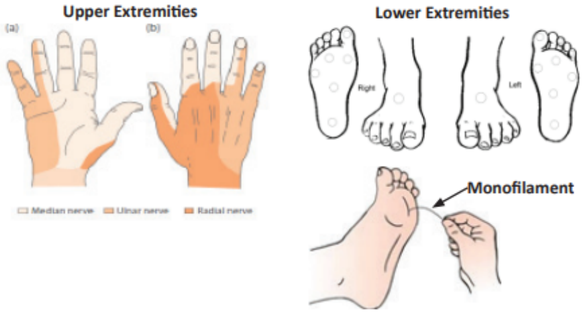
Critical Components of Monthly Nurse Assessment for 2nd-Line Drugs

Additional information for selected nurse assessment (see complete toxicity assessment tool)

Peripheral Neuropathy

Peripheral neuropathy may be painful and is often non-reversible. Neuropathy usually manifests initially in the lower extremities, with sensory disturbances, but may also involve the upper extremities. Disturbances are often bilateral. Assess for:

- numbness (using a monofilament or other available tool) or tingling
- burning pain
- temperature sensation
- unsteady gait/balance
- decreased or absent deep tendon reflexes



Vestibular Toxicity

Vestibular damage is often non-reversible. Assess for balance and walking:

- balance (Romberg)/gait/heel-toe walking
- past pointing
- lateral nystagmus

Behavior and Mood

Some TB medications may contribute to depression and in rare cases, suicidal ideation. Depressive symptoms may fluctuate during therapy. Although the risk may be increased in those with a past history of depression, it is not an absolute contraindication to the use of cycloserine. Some patients with depression at baseline improve on cycloserine, as they respond to treatment.

- Use a mental health assessment tool at least monthly.
- Facilitate access to psychological support for patients and family, including antidepressant therapy at usual doses, if needed.
- Review drug-drug interactions with linezolid that may lead to serotonin syndrome.

Hearing

Hearing loss, tinnitus, or fullness in the ears are signs of auditory toxicity which is associated with total cumulative dose of aminoglycosides; however, change can be detected early. Patients with hearing loss at

Vision

Optic neuritis may exhibit as change in color vision or visual acuity. Loss of red-green color distinction may be detected first, however, a decrease in visual acuity is more common. Changes are usually reversible if detected early and medication is discontinued.

Nurse Case Management

February 15, 2023 – Client is transferred to DuPage County

- Client attends monthly visit with DCHD MD
- Neuropathy assessment
- F/U CXR
- CBC/CMP Q 2 wks to monthly
- Monthly EKG

Direct Observation Therapy

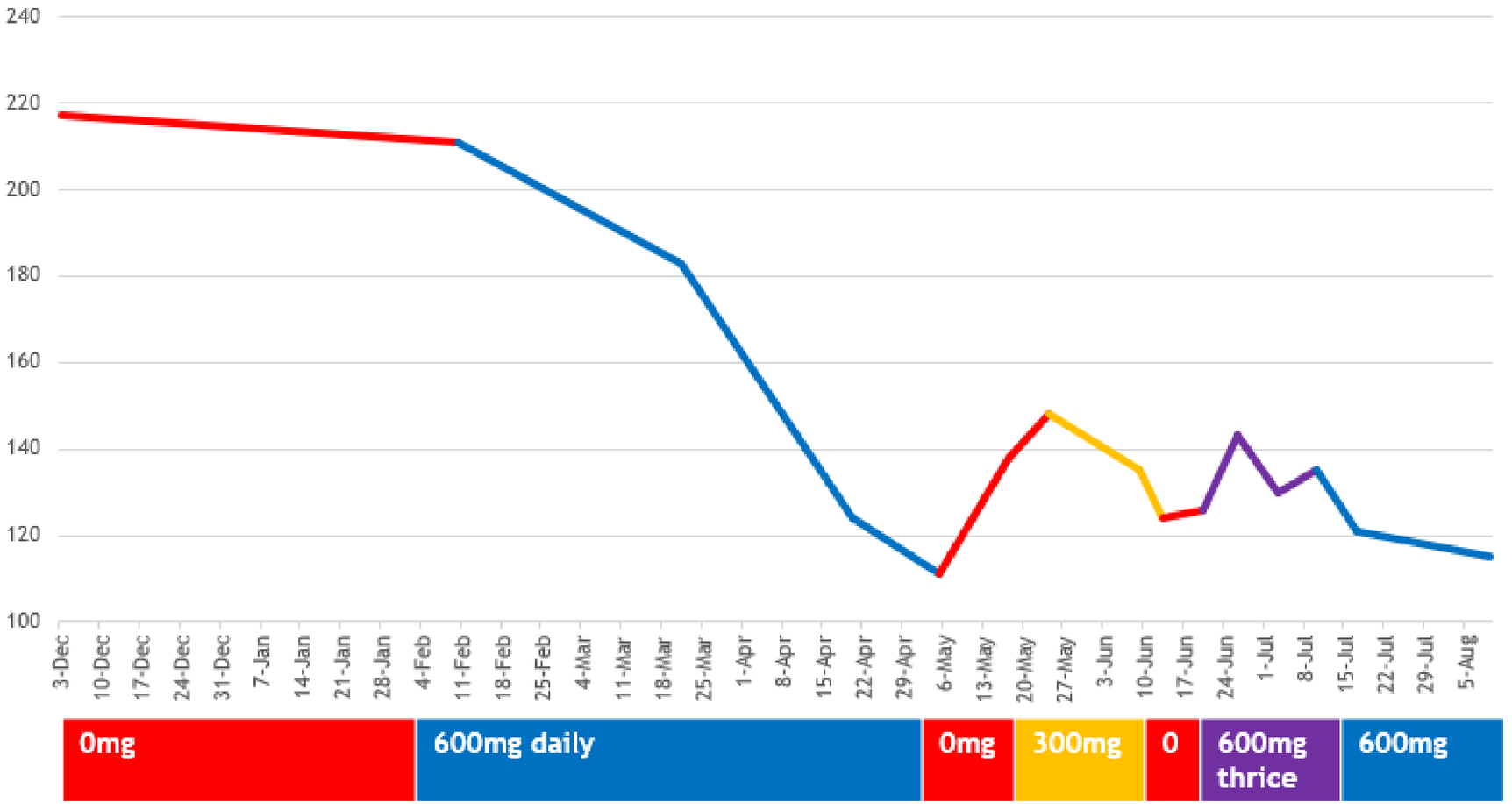
Daily DOT visits for 6 months to monitor for side effects of TB medications:

- Number of attempted visits = 122
- Number of completed visits = 121
- Total Number of Doses = 172

ECG Results

Monthly ECG		
DATE	**QT**	**QTC**
5-Apr	432	409
31-May	434	407
21-Jun	408	410
19-Jul	466	412

Platelet Levels on Linezolid



Pre-XDR TB
Contact Investigation

Social History

- Lives with:
  - Wife
  - 2 college age daughters
  - Son
  - Son-in-law
  - 4-month-old grandson

- Nonsmoker
- No HIV risks
- No illicit drugs
- No alcohol use

- Worked as a Pharmacy Tech
- Currently unemployed

Contact Investigation

Multiple home visits completed. Findings included:

- Family was initially non-compliant
- Identified 6 close contacts (family members) that live in DuPage County
- 4-month-old who lives in the same household
- Household members completed initial testing by Cook County
- Son-in-law (household member) refused testing initially

Initial Contact Investigation

Contact investigation was initiated by Suburban Cook Health Department

- 5 out of 6 household members completed their initial testing by Cook County
  - Son-in-law refused testing

- **Wife** – **Positive** QFT, **Normal** CXR
- **2 adult aged daughters** – Received 3HP LTBI treatment in 2021 and CXR's reported as normal.
- **20 y/o son** – **Negative** QFT, **Normal** CXR

DCHD Contact Investigation

- **20 y/o son** – Refused retesting
  - Attempted QFT retesting multiple times, many CXR referrals given to client

- **Son-in-law** – Made many attempts to test but refused.
  - June 2023, needed immigration clearance – Had borderline positive QFT, negative CXR. Repeated QFT was **negative**.

DCHD Contact Investigation

- **Wife** – Repeated QFT = **Positive** results. **Normal** CXR
  - No LTBI medication initiated due to index case multi drug-resistance
  - Wife will be monitored with repeated CXR Q 4 months for 2 years

- **4-month-old baby** – Reevaluated by the MD, received new TST and CXR – **Negative** results

Treatment Outcome of BPaL Therapy

TB meds discontinued August 16, 2023

- Cough and shortness of breath resolved
- Client regained a total of 4kg(9lbs) with increased appetite
- Overall CXR improved/scar remains
- Successfully completed treatment
- Most family members were evaluated
- Client is ready to return to work

Obstacles, Challenges, and Successes

Obstacles and Challenges

- ✓ Uncooperative family with contact investigation
  - ✓ Unable to evaluate 4-month-old baby and son-in-law
- ✓ Language barrier
- ✓ Client moved from another jurisdiction
  - ✓ Transitioning care and medications
- ✓ Medications
  - ✓ Expensive

Successes

- ✓ Client's symptoms resolved, can return to work
- ✓ Received medications at little to no cost
- ✓ Majority of close contacts evaluated
- ✓ Collaboration with Suburban Cook County with the transition of care.

Questions?

Dean Schraufnagel, MD

schrauf@uic.edu

Tamam Jada, RN

Tamam.Jada@dupagehealth.org