Clinical challenges in MDR TB care and systems implications

Sarah K. Brode, MD FRCPC MPH

West Park Healthcare Centre, University Health Network,

University of Toronto

April 25, 2023

MDR-TB: Why is it important?

- Globally, MDR-TB treatment outcomes are much poorer than for drug susceptible TB
  - Higher mortality
  - Lower rates of cure/treatment completion, higher rates of relapse
  - Higher rates of drug related adverse effects
- Costs of treating MDR-TB are substantially higher than costs of treating drug susceptible TB

Global tuberculosis report 2022. Geneva: World Health Organization; 2022.
Blondi et al. ERJ 2014; 44: 1694.

MDR-TB Treatment is evolving

Canadian TB Standards, 8th Ed. (Mar 2022):

- Longer, individualized regimen
- Initially 5 drugs
- Total treatment duration of 18 to 20 months

WHO Guidelines (Dec 2022):

"Shorter regimens are recommended"

- 6 month regimen of 3-4 drugs (BPaL+/-M) (possible extension to 9 months)

OR

- 9 month regimen, initially 7 drugs

OR

- Longer individualized regimen

Canadian TB Standards, 8th Ed. Chapter 8. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine* 2022, Vol. 6, No. s1

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022.

Current clinical challenges

Universal challenges

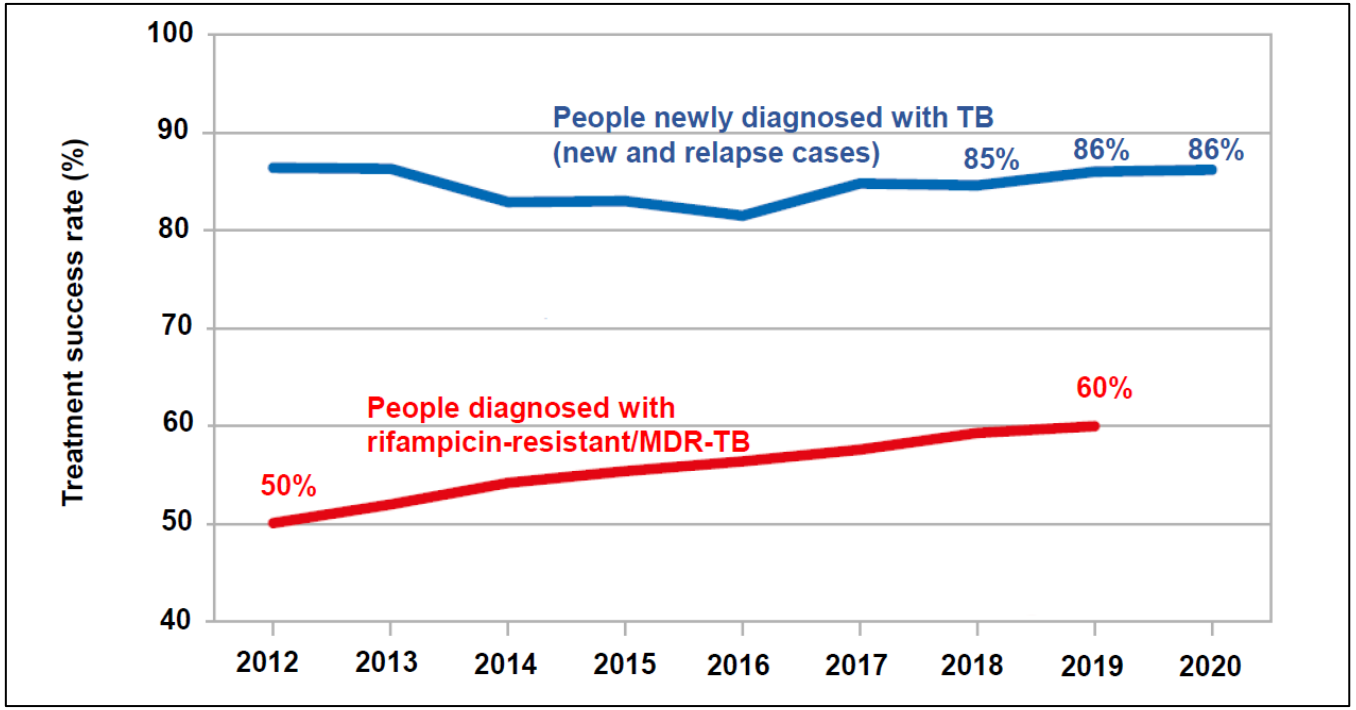
- Treatment outcomes, medication side effects
- Costs (health system & personal), mental health

Canada-specific challenges

- Access to diagnostics
- Access to drugs
- Small numbers of patients, geographically spread, limited experience

Universal challenges

MDR-TB treatment outcomes (Longer regimen)



Global tuberculosis report 2022. Geneva: World Health Organization; 2022.

Treatment outcomes (n=93)

Outcome at end of treatment*	n (%)
Cure or treatment completed	78 (83.9)
Death	3 (3.2)†
Lost to follow-up	1 (1.1)
Treatment failure	1 (1.1)
Not evaluated	10 (10.8)
Outcome after treatment	
Possible relapse	3 (3.2)
Microbiologically confirmed relapse	0 (0)

**As defined by the WHO (20); †Two deaths were unrelated to multidrug-resistant tuberculosis*

Brode et al. Multidrug-resistant tuberculosis: Treatment and outcomes of 93 patients. *Canadian Respiratory Journal* 2015;22(2):97-102.

http://www.trust.org/spotlight/Tuberculosis-the-new-face-of-an-old-disease/

MDR-TB Treatment outcomes
TB PRACTECAL: modified Intention to treat

	SOC N=66	BPaLM N=62	BPaL N=60
Favorable outcome	34 (52%)	55 (89%)	46 (77%)
Unfavorable outcome	32 (48%)	7 (11%)	14 (23%)
-Death	2 (3%)	0	0
-Early discontinuation	28 (42%)	5 (8%)	8 (13%)
-Failure	0	0	0
-Loss to follow up	2 (3%)	2 (3%)	3 (5%)
-Recurrence	0	0	3 (5%)

Nyang'wa, B.-T., et al. (2022). "A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis." New England Journal of Medicine **387**(25): 2331-2343.

MDR-TB Adverse events

TB PRACTECAL: As treated populations

	SOC N=43	BPaLM N=40	BPaL N=43
Serious or grade ≥3 adverse events during treatment and up to 30 days after	25 (58%)	7 (18%)	10 (25%)

Nyang'wa, B.-T., et al. (2022). New England Journal of Medicine **387**(25): 2331-2343.

Individual patient data meta-analysis: **23.5% of patient**s (2027/8622) had at least one drug permanently stopped because of an adverse event Lan Z et al. Lancet Resp Med 2020.

Costs of managing MDR-TB are 8 times higher than DS-TB in Canada

Table 2. Total costs and component costs of managing different forms of TB at 3 treatment centers, Canada, July 2010–June 2016*

Characteristic	Cost, in 2020 Canadian dollars			
	TB infection, n = 90	DS TB, n = 90	INHR TB, n = 71	MDR TB, n = 62
Median (IQR) costs†				
Total costs	804 (587–1,205)	12,148 (4,388–24,842)	19,319 (7,117–41,318)	119,014 (80,642–164,015)
Diagnosis	267 (217–376)	701 (526–1,026)	819 (657–1,049)	1,083 (925–1,331)
Treatment	521 (377–771)	2,145 (1,614–3,187)	2,864 (2,263–3,919)	61,426 (29,840–108,703)
Posttreatment monitoring	0 (0–0)	139 (28–283)	130 (39–195)	193 (39–341)
Hospitalization	0 (0–0)	2,600 (0–15,524)	10,400 (0–27,227)	41,216 (35,178–55,766)
Associated with public health interventions	0 (0–0)	3,174 (632–5,232)	2,885 (1,111–6,174)	6,399 (4,657–6,798)

Campbell JR, et al. Costs of Tuberculosis at 3 Treatment Centers, Canada, 2010–2016. Emerg Infect Dis. 2022;28(9):1814-1823.

Personal costs, mental health concerns

Costs of TB incurred by patients and families in low- and middle-income countries are often catastrophic, and are higher for those with MDR-TB Tanimura T et al. Eur Respir J 2014; **43**:1763–75.

Depression is very common in patients with TB, and the prevalence is higher in patients with MDR-TB (52%, 95% CI 38-66) than in non-MDR-TB (43%, 95% CI 36-51)

Duko B et al. Ann Gen Psychiatry 2020;**19**:30

Canada-specific challenges

Diagnostics: Rapid molecular tests for Rif-R

- **Canadian TB Standards: Rapid molecular tests to predict drug resistance are recommended for every patient newly diagnosed with TB disease[1]**

  --- *but this is not done in most provinces*

- Use of rapid molecular DST reduces time to the start of appropriate therapy[2]
  - Ontario 2010-2016 (50 patients): **Reduced by 19 days** (40 vs. 21 days, p = 0.02)[3]

1. Canadian TB Standards, 8th Ed. Chapter 3. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine* 2022, Vol. 6, No. s1
2. Shin SS. *Int j Tuberc Lung Dis*. 2012;16(11):1538–1543. Jacobson KR. *Clin Infect Dis*. 2013;56(4):503–508. Nair D. *Trans R Soc Trop Med Hyg* 2016; 110(9): 534-41
3. Sabur NF NAR End TB Conference 2019

Diagnostics: Rapid molecular tests for Rif-R

- *Potential* consequences of early initiation of appropriate therapy in Canada (currently only evidence low resource settings)
  - Reduce rates of poor treatment outcomes (mortality, failure, relapse, acquired resistance)
  - Reduce risk of transmission

Shin SS. *Int j Tuberc Lung Dis*. 2012;16(11):1538–1543.
Jacobson KR. *Clin Infect Dis*. 2013;56(4):503–508.
Nair D. *Trans R Soc Trop Med Hyg* 2016; 110(9): 534-41

- *Definite* consequences of early initiation of appropriate therapy in Canada
  - Reduce exposure to less effective drugs that may have side effects
  - Shorten duration of airborne isolation- big impact on patients and families

Diagnostics: Drug susceptibility testing

- **Canadian TB Standards: We strongly recommend that isolates from all TB patients diagnosed with rifampin resistance/multidrug resistance undergo phenotypic drug susceptibility (DST) testing for all anti-TB medicines currently recommended to treat MDR-TB** (*good evidence*).
- Currently bedaquiline and clofazimine DST is not performed in Canada
- The National Microbiology Laboratory (NML) will start offering phenotypic DST for bedaquiline and clofazimine on May 1, 2023

Canadian TB Standards, 8th Ed. Chapter 3. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine* 2022, Vol. 6, No. s1

Diagnostics: Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) testing is not performed in Canada

- Linezolid TDM (when given as part of BPaL(M) regimen) is currently performed by most US experts
- Currently Canadian samples must be sent to US and many centres have difficulty with access, funding, logistics
- Inappropriate linezolid dosing could increase toxicity and/or reduce effectiveness

Therapeutics: Drug access

Majority of drugs used to treat MDR/RR-TB are not licensed in Canada

- Health Canada Special Access Program and manufacturer approval required
- We are at the mercy of the drug manufacturers regarding ongoing access to these drugs
- Delay of a couple of weeks between when drugs are needed and when they are available
  - Bridging regimens needed for sick or infectious patients
  - May expose patient to additional side effects

Canadian TB Standards, 8th Ed. Chapter 3. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine* 2022, Vol. 6, No. s1

MDR-TB Regimens/Drugs (highlighted are not licensed in Canada)

Longer regimen	
Group A	Levofloxacin/Moxifloxacin
	Bedaquiline
	Linezolid
Group B	Clofazimine
	Cycloserine or Terizidone
Group C	Ethambutol
	Pyrazinamide
	Delamanid
	Amikacin
	Imipenem or Meropenem
	Ethionamide
	P-aminosalicylic acid

BPaL (M)
Bedaquiline
Pretomanid
Linezolid
Moxifloxacin

Small numbers of people with MDR/RR-TB in Canada

- Many health care providers have limited experience with the management of drug resistant TB
- Evolving evidence / treatment recommendations add further challenges
- Teams with such experience may not be available where the patient lives
- Patients and families with MDR-TB may feel isolated by lack of peers with similar experiences

Potential opportunities for improvement

For discussion!

End: Questions?