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The Tip of the Iceberg
A Multi Drug Resistant Tuberculosis Case Study

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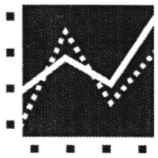
PROTECTING, MAINTAINING AND IMPROVING THE HEALTH OF ALL MINNESOTANS

Abbreviations

- CI = Contact Investigation
- CDC = U.S. Centers for Disease Control and Prevention
- DOT = Directly Observed Therapy
- IGRA = Interferon Gamma Release Assay ("TB blood test")
- MDDR = Molecular Detection of Drug Resistance
- MDH = Minnesota Department of Health
- MDR TB = Multi Drug Resistant Tuberculosis
- QFT = QuantiFERON
- rtPCR = Real time Polymerase Chain Reaction
- TB = Tuberculosis

Outline

- Epidemiology
- Case information
- Contact investigation
- Lessons learned



Epidemiology

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TB Morbidity and Mortality Minnesota, 2014-2018

Year	No. of New Cases (Rate)*	No. of TB Deaths (% of New Cases)**
2014	147 (2.7)	3 (2%)
2015	150 (2.7)	3 (2%)
2016	168 (3.0)	8 (5%)
2017	178 (3.2)	6 (3%)
2018	172 (3.0)	2 (1%)

* Cases per 100,000 population. Rates calculated using state population estimates from the U.S. Census Bureau.
** Represents only deaths due to TB disease or TB drug-induced toxicity; percentages based on the number of new TB cases for each year

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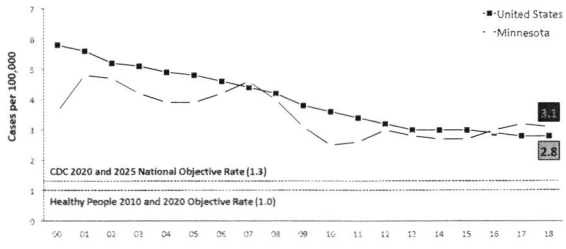
TB Incidence Rates per 100,000 Population United States and Minnesota, 2000-2018



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TB Cases by Race/Ethnicity and Place of Birth Minnesota, 2014-2018

Race / Ethnicity*	Non U.S.-Born Cases No. (%)	U.S.-Born Cases No. (%)
White	18 (3)	43 (32)
Black	383 (56)	42 (31)
Asian	236 (35)	12 (9)
American Indian / Alaska Native	0	15 (11)
Native Hawaiian / Pacific Islander	2 (< 1)	0
Multi-racial	0	2 (1)
Hispanic/Latino	41 (6)	21 (16)
Total	680 (100)	135 (100)

*Race categories do not include persons of Hispanic/Latino ethnicity

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Non-US-Born TB Cases by Top Five Countries of Birth Minnesota, 2014-2018

Country of Birth	No. of Cases (%)
Somalia	186 (27)
Ethiopia	90 (13)
Laos	58 (9)
India	48 (7)
Viet Nam	40 (6)
Other	258 (38)
Total	680 (100)

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TB Cases by Drug Susceptibility Patterns and Year Minnesota, 2014-2018

Year	Cases With Susceptibility Results*	Any Drug Resistance† No. (%)	INH-Resistant** No. (%)	MDR-TB‡ No. (%)
2014	105	25 (24)	19 (18)	1 (1)
2015	115	16 (14)	9 (8)	0 (0)
2016	136	29 (21)	19 (14)	8 (6)
2017	141	32 (23)	22 (16)	9 (6)
2018	134	26 (19)	16 (12)	7 (5)
Total	631	128 (20)	85 (13)	25 (4)

* Culture-confirmed cases with drug susceptibility results available
† Resistance to at least one first-line anti-TB drug [i.e., isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), or ethambutol (EMB)]
** INH-resistant cases may also be resistant to other drugs
‡ Multi-drug resistant TB, defined as resistance to at least INH and rifampin

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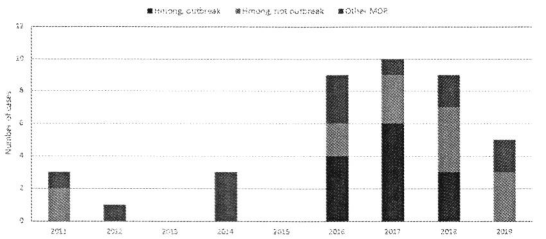
MDR TB Cases*
Minnesota, 2011 - present



* Includes burden cases: patients treated for MDR TB but not included in official CDC statistics (e.g. clinical case with exposure to MDR TB, non-countable case, and patient for which initial susceptibilities could not be done)

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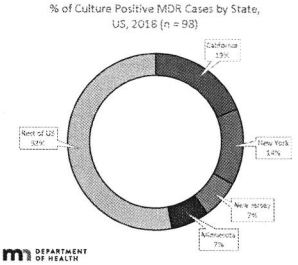
Culture Positive MDR TB Cases
Minnesota, 2018



- MN ranks 16 in total TB cases counted for 2018
  - 2% of US total
- MN ranks T3 [tied for 3] in total culture confirmed MDR TB cases for 2018
  - 7% of US total

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Patient Information

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Case Study (1)

- Lab called on 06.21.16
- Smear positive sputum
- Positive rtPCR for TB
- The rtPCR is a nucleic acid amplification test for TB
- Results are available in 36 to 48 hours

Case Study (2)

- 78 yr. old hospitalized on 06.12.16
- Non-US born Hmong male
- Presented with hemoptysis
- Worsening cough over a month
- Work up for TB

Case Study (3)

- IGRA: QFT positive
- Chest x-ray: bilateral infiltrates
- CT Scan: cavitary
- HIV: negative
- 06.17.16 Sputum : AFB smear positive 2+
- 06.17.16: Treatment initiated with RIPE

Case study (4)

- From a TB-endemic region
- No known TB exposure
- No behavioral risk factors
- No medical conditions
- Not immunocompromised

Case Study (5)

- Came to the US in 2004 as a refugee
- Wat camp in Thailand
- TST positive upon arrival = 10mm
- Chest x-ray normal
- Treated with INH for 9 months in 2005 at a local TB clinic

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Case Study (7)

- Meets our criteria for requesting an MDDR test
  - Allows rapid confirmation of drug resistance
- Sent specimen to CDC for MDDR
- Meets lab definition for active TB and CI was initiated

Case Study (8)

- 06.24.16

MDDR showed resistant mutations for INH, RIF, and EMB

- MDR TB by MDDR
- RIPE was discontinued and second line agents were started on 07.01.16 with a ramp-up

Case Study (9)

- Amikacin 750mg 5x/wk
- Moxifloxacin 400mg daily
- Pyrazinamide 1500 mg daily
- Ethionamide 750mg daily
- Cycloserine 250mg BID
- Para amino salicylic acid 4gm BID
- Vitamin B6 100mg daily

Case Study (10)

- Symptoms improved slowly
- Smear converted on 10.05.16
- 60 day sputum remained culture positive
- 09.26.16 sputum: culture negative on 11.10.16
- Released from isolation 11.18.16

Case Study (11)

Challenges

- Isolation
- Delirium and depression
- Therapeutic drug monitoring [TDM]
- Monitoring for side effects
- Poor food intake
- DOT and adherence after discharge
- International travel and video DOT

Case Study (12)

Treatment Completion

- Stopped Amikacin on 03.24.17
- Stopped all medications on 06.26.18
- Took 720 doses over 24.3 months

Contact Investigation

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Contact investigation (1)

- Patient interview
- Care everywhere
- Record review

- Patient had been in 3 different health systems

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Digging……(1)

- June 2016 presents to the ER
- Patient interviewed about 'chronic cough'
  - He sought care repeatedly
  - Went to a healer but realized that was not helping
  - Went back to a provider

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Digging.....(2)

- January 2015 clinic visit

"C/O chronic cough and wheezing over past 6 months . . . SOB climbing 12 steps . . . no fever, night sweats, weight loss . . . on bronchodilators with some benefit . . .foreman of gravel company in Lacs for 3 years in early 2000s." P.E.: soft expiratory wheezing throughout all lung fields. CXR and CT ordered. Referral to Pulmonology: didn't go.

Digging.....(3)

- February 2015

2/12/15: Chest CT. Indication: cough shortness of breath, abnormal CXR. Comparison: CXRs from 10/2/13 and 6/10/11 and chest CT from 7/23/2011 – Outpatient

'Opacity in the medial aspect of the left lung has been present since at least 6/10/11 and has decreased in size. Much of the process has undergone central cavitation with associated volume loss in the left hemithorax . . . scattered nodular pulmonary opacities peripheral to the opacity at the left hilum have decreased in size, number and extent . . . wall thickening and luminal narrowing in the left upper and low lobar bronchi . . . single right hilar lymph node is enlarged, but stable . . ."

Conclusion: "opacity in the medial aspect of the left lung has decreased in size and extant and undergone cavitation . . . though nonspecific, the chronicity, regression and cavitation favor sequelae of prior infection, including tuberculosis. No findings specific for active infection".

Digging.....(4)

- October 2013

CXR. Indication: Shortness of breath. Comparison: CTA chest 7/23/11

"Moderate infiltrate in the superior segment of the left lower lobe and left upper lobe is again seen, overall this appears mildly decreased when compared to 7/23/11. While some of this may represent residual infiltrate, it is difficult to exclude new superimposed infiltrate. Consider further evaluation with CT."

- June 2013 clinic visit

Cough, afebrile, rales. Dx: Bronchitis and asthma. Given erythromycin.

Digging.....(5)

- July 2011

CT Chest

Indication: Lung infiltrate. Abnormal CXR. Mass vs. pneumonia. Patient short of breath. No comparisons.

"Left lung opacity consistent with dense pneumonia in the left upper lung. No left upper lobe (?). No underlying mass visualized. Right lung negative".

"Conclusion: left lung pneumonia"

Digging.....(6)

- June 2011 CXR

CXR: Indication: Preoperative planning No comparisons. "Dense consolidation throughout the left lower lobe. Findings are most consistent with pneumonia. More focal opacity in the left midlung laterally. Underlying mass cannot be excluded".

- Unrelated surgery, incidental finding
- 2005 on LTBI treatment
- 2004 normal CXR

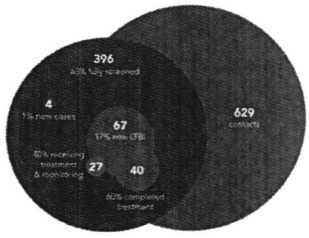
Contact Investigation (2)

- Infectious period
  - 03/10/2011 to 06/17/2016 (when isolated)
  - 5 years
- TB was not in the differential
- No sputum collected
- LTBI was thought to rule out active TB

Contact Investigation (3)

- Extremely complicated and large CI
- Senior center
- Incomplete locating information
- Unknown community exposure

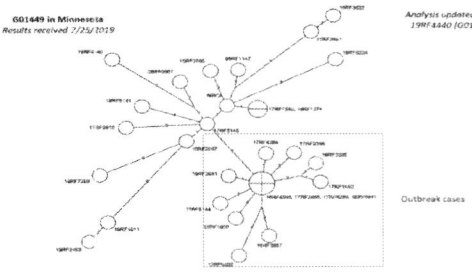
Contact Investigation (4)



Whole Genome Sequencing

- Tool used to sequence an organism's DNA
- More accurate than previous laboratory techniques
- Able to show relatedness and likelihood of patients with recent transmission
- In outbreak settings, augments but does not replace epidemiology

Phylogenetic Tree



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Outbreak Summary

Epi summary of MDR TB cases* in Minnesota, 2016-present
as of 9/30/2019

	2016	2017	2018	2019	Total from 2016 to date
Total MDR TB cases	9	9	7	6	31
Total Hmong MDR TB cases	9	8	7	3	24
Hennepin County	0	0	1	1	2
Ramsey County	5	8	6	2	21
Washington County	1	0	0	0	1
Link to Ramsey senior center	3	6	2	0	11
Dec – all causes	3	3	1	0	7
Died from TB	1	2	0	0	3
*Outbreak cases = related cluster of Hmong MDR TB (based on WGS, epidemiology, and clinical information)***	4	6**	3	0	13**
Ramsey County	4	6	3	0	13
Link to senior center	3	5	2	0	10
Dec – all causes	2	2	1	0	5
Died from TB	0	1	0	0	1

*Includes burden cases; patients treated for MDR TB but not included in official CDC statistics (e.g. clinical case with exposure to MDR TB, non-countable case, and patient for which initial susceptibilities could not be done)

**One Hmong MDR case in 2017 (patient #12) with link to senior center was excluded from these outbreak numbers due to different mutations for drug resistance, distance from other outbreak cases on WGS map, and possible MDR TB exposure in Wat refugee camp; patient is still included in "Total MDR TB cases" and "Total Hmong MDR TB cases" totals at the top of the table.

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Lessons Learned

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Lessons Learned (1)

- NOT over because of the unknown community exposure and the unavailable attendance roster
  - Keep reminding our providers
  - Keep educating the community
  - Educate the nurses
- Maintain close relationships and partnerships with the local ID providers and IP of hospitals.

Lessons Learned (2)

- Low threshold for specimen collection
- A test result is as good as the specimen
- rtPCR and MDDR for all Hmong patients
  - Pulmonary and non-pulmonary
  - HAIN and MIC – Florida lab [if MDR]
- Quick turnaround time for MDR diagnosis

Resources

Resources

- CDC: https://www.cdc.gov/tb/topic/drtb/default.htm
- COE: https://sntc.medicine.ufl.edu/TrainingOnline.aspx
- MDH: https://www.health.state.mn.us/tb
- Curry International TB Center https://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition

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Thank you.

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