TB GENOTYPING AND CLUSTERS IN MICHIGAN

Shona Smith, MPH

TB Epidemiologist
Michigan Department of Health and Human Services

Disclosures

- None of the speakers or planners involved in this activity has any relevant conflict of interest.

- Approval status does not imply endorsement by the provider, ONA, MSMS, or any products displayed in conjunction with an activity.

- The use of trade names and commercial sources during this presentation is for identification only, and does not imply endorsement.

- No commercial support has been received for this program.

Objectives

1. Provide a brief overview of genotyping and how it is used with *M. tuberculosis* specimens

2. Review the TB GIMS system and its application of genotyping for identifying outbreak clusters

3. Examine prominent TB clusters in Michigan

4. Discuss best practices for investigating clusters

Content

- Genotyping overview for Tuberculosis
  - Best practices for cluster investigations
  - Using genotype information to assist in contact investigations
- TB GIMS
  - Overview of cluster reports
  - Interpretation of cluster reports
- Genotype clusters in MI
  - Trends in primary Michigan clusters
  - Compare with clusters nationwide
- Intro to new cluster survey tool

OVERVIEW OF GENOTYPING FOR TUBERCULOSIS

National Tuberculosis Genotyping Surveillance Coverage* by Year: United States**, 2004–2014

Proportion of culture confirmed TB cases genotyped (%)

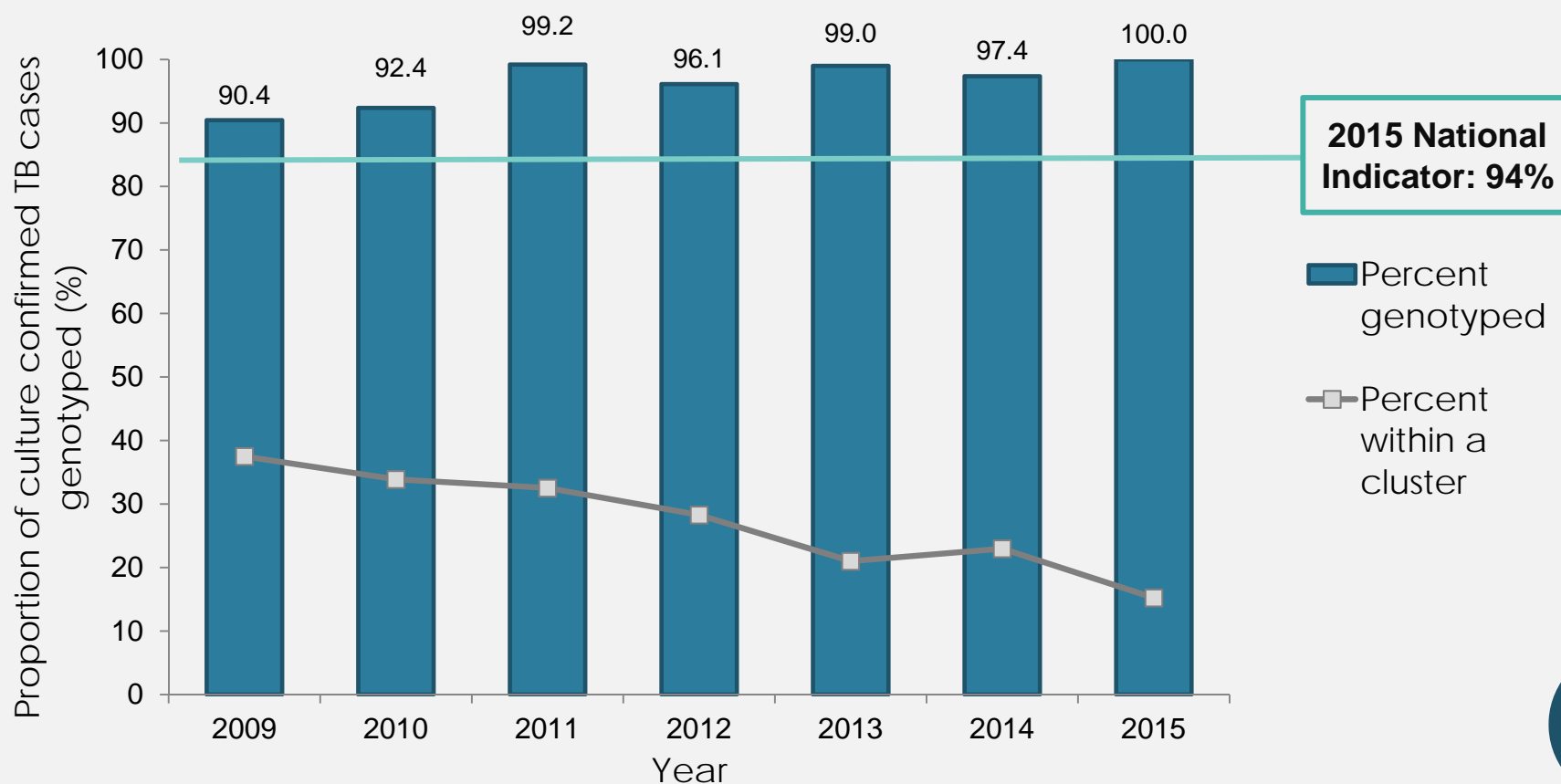| Year	Value
2004	52.6
2005	68.5
2006	70.1
2007	80.9
2008	81.6
2009	86.8
2010	91.6
2011	94.2
2012	94.8
2013	95.6
2014	95.3

National Indicator 94%

* The proportion of positive cultures with at least one genotyped isolate.
** Includes 50 states and the District of Columbia.

Genotyping Coverage for Culture Positive TB Cases
Michigan, 2010-2015

QUESTION:
What is TB Genotyping?

a. Laboratory method to detect TB infection

b. A blood test to detect drug-resistant TB

c. Laboratory approach to analyze genetic material (DNA) of *Mycobacterium tuberculosis* *(M. tuberculosis)*

d. Tool to help understand transmission of *M. tuberculosis*

e. Both c and d

DNA = deoxyribonucleic acid

ANSWER:
TB Genotyping Is

a. Laboratory method to detect TB infection

b. A blood test to detect drug-resistant TB

c. Laboratory approach to analyze genetic material (DNA) of *M. tuberculosis*

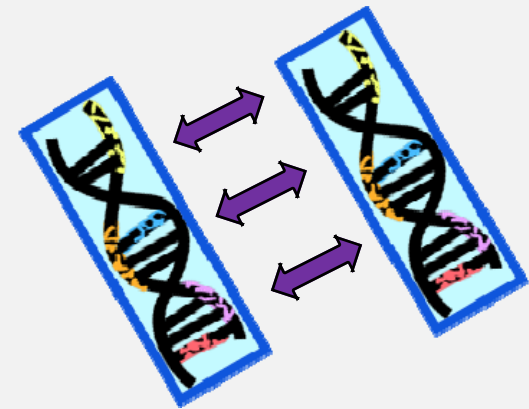d. Tool to help understand transmission of *M. tuberculosis*

e. Both c and d

DNA = deoxyribonucleic acid

TB Genotyping

- Only for culture-confirmed TB
  - The technique requires material from a culture

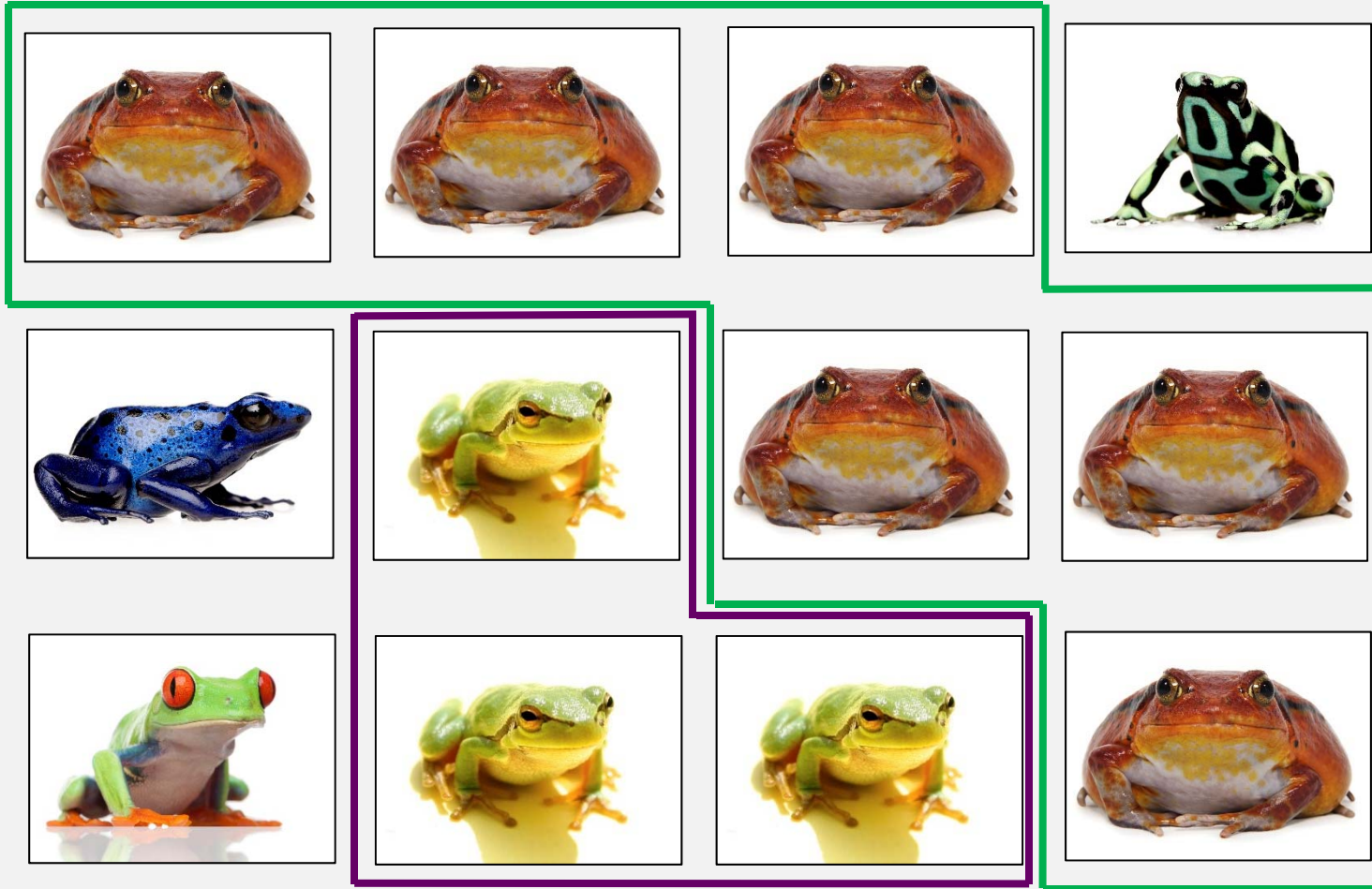- Matching genotypes may indicate that TB cases are related

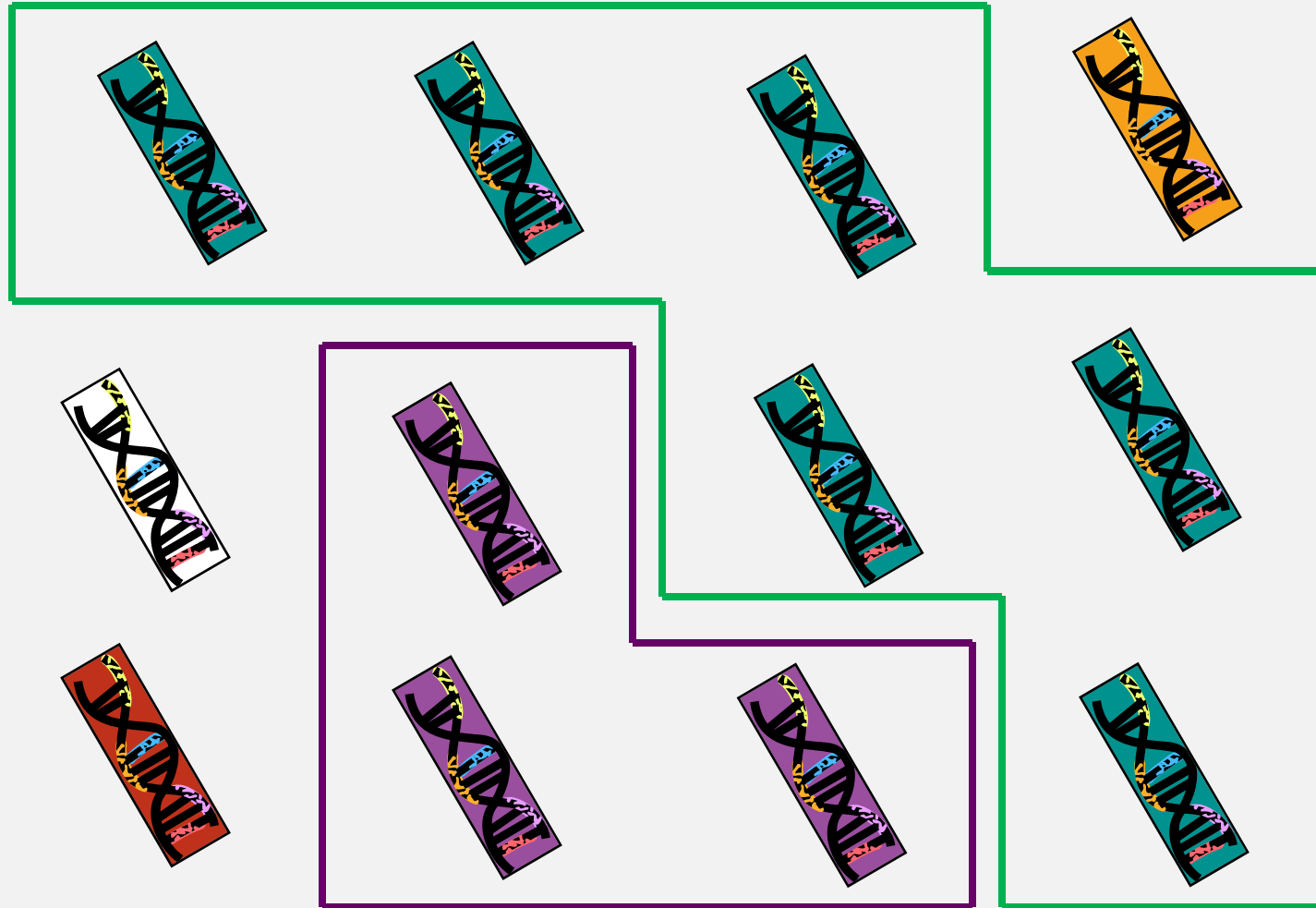# Genotypes and M. tuberculosis Transmission

- Genotyping helps us understand transmission relationships between TB cases

- We expect genotypes from transmission-related TB cases

Matching Game –
Do the Pictures Match?

Genotype Clusters

How Can Genotyping be Useful in TB Control?

- Assist with contact investigations

  - Confirm or refute patient connections

- Find previously unidentified contacts

- Detect and prevent outbreaks

- Refute outbreaks

- Distinguish relapse from new infection

- Detect false-positive culture results
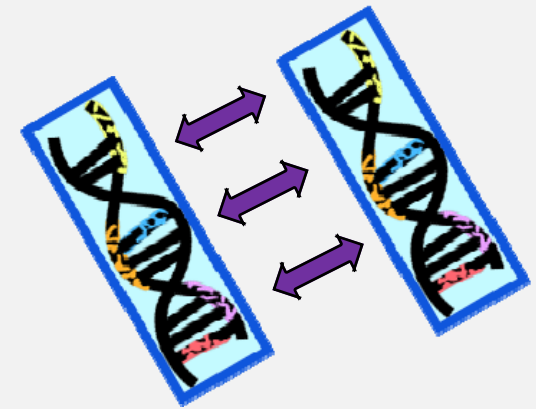
Case Scenario 1: A Household
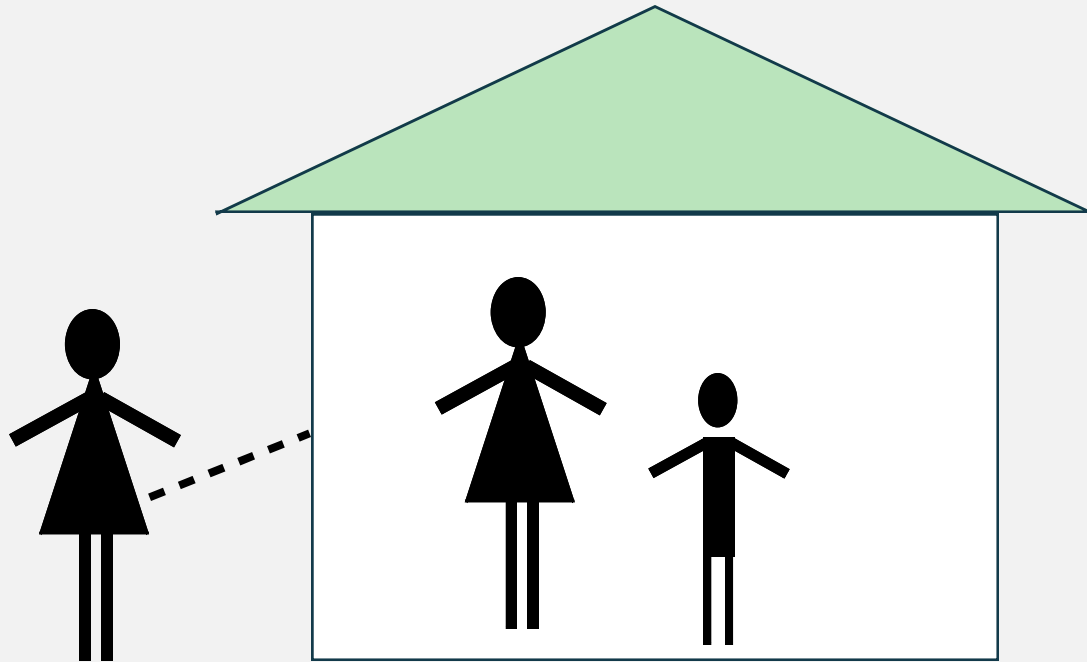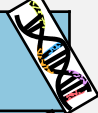
Persons diagnosed with TB spent most of their time together at the same house

- *Likely related by transmission*

Case Scenario 1: A Household

Genotype results for TB cases linked to household

Mother	G08464
Son	G08464
Neighbor	G08464

Case Scenario 1: A Household
Interpretation of Genotyping Results

- All cases had matching genotypes

- All spent time together in the same house

- These cases were likely transmission-related

Case Scenario 1: A Household
Back to the Household

- Contact investigation did not find any other cases

- Two other family members were diagnosed and treated for TB infection

- Neighbor with TB did not identify any other contacts aside from family
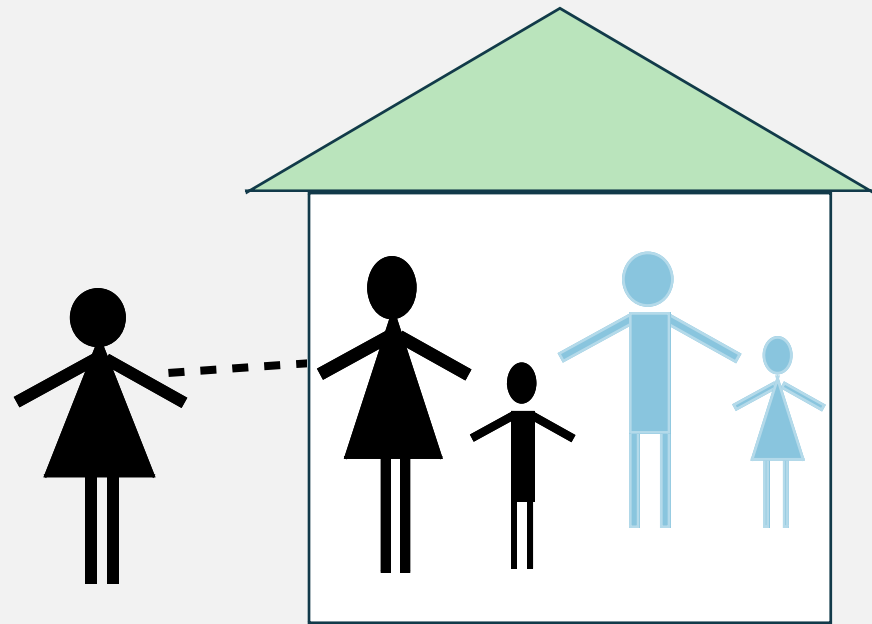
Case scenario 1: A Household Review of Genotype Data for County A – 2013

Mother	G08464
Son	G08464
Neighbor	G08464
Patient A	G08464
Patient B	G08464

Case Scenario 1: A Household
What do the Genotype Results Indicate?

- Five cases with matching genotypes within 6 months

- Cases may all be related by transmission, but
  - *When?*
  - *Where?*

- More information is needed

Case Scenario 1: A Household
Next Steps

- Investigate to understand relationship of Patient A and Patient B to the other patients in the cluster

  - *Identify likely locations of transmission*

  - *Determine if there are missed contacts*

- Review

  - *Public health records*

  - *Contact investigation logs*

  - *Estimated infectious periods*

  - *Re-interview TB patients and contacts*

Case Scenario 2: A Workplace
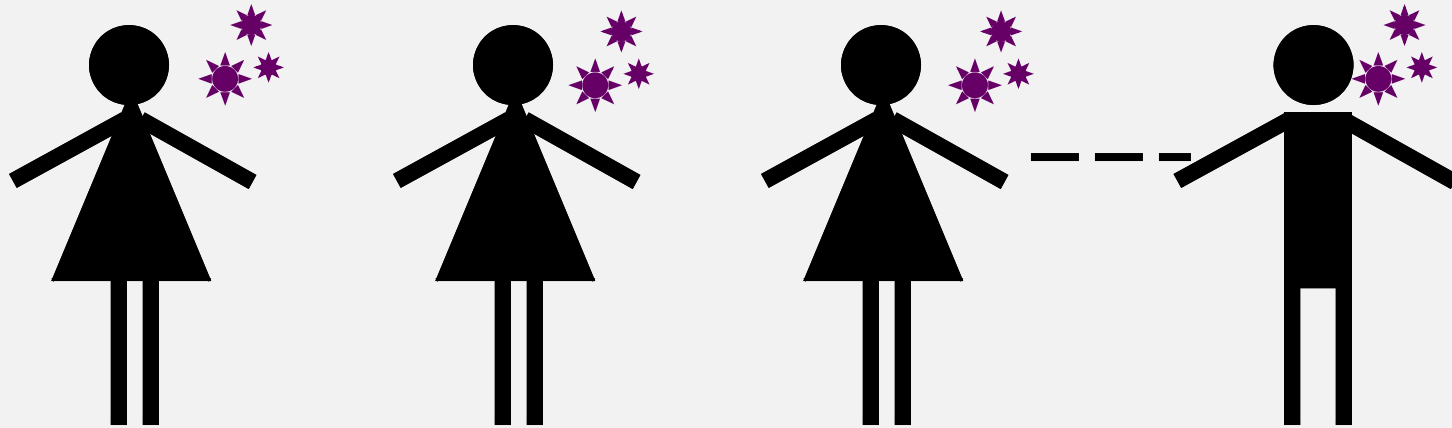
- Within one month
  - *Three women diagnosed with TB*
  - *All work at the same casino*
  - *All work on the same evening shift*
- One woman's boyfriend also diagnosed with TB

Case Scenario 2: A Workplace
QUESTION:

Are these TB cases related by transmission?

a. Yes

b. No
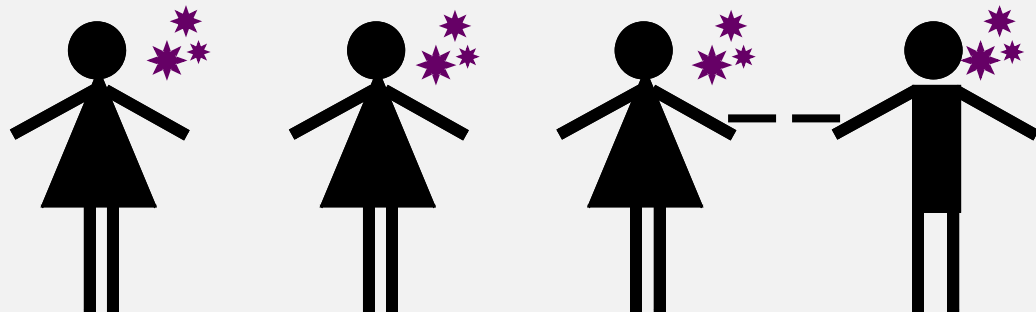
c. Maybe

Case Scenario 2: A Workplace
ANSWER:

Are these TB cases related by transmission?

a. Yes
b. No
c. Maybe!

24
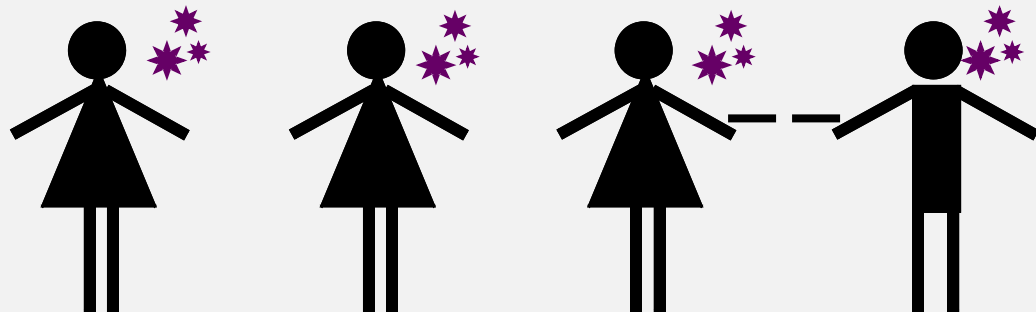
Case Scenario 2: A Workplace
Genotype Results for TB Cases Linked to Casino

Employee 1	G08464
Employee 2	G15185
Employee 3	G00010
Boyfriend	G16470

Case Scenario 2: A Workplace
QUESTION:

How to interpret the genotype results?

a. The genotype data are wrong

b. The genotype data could be wrong, since cases are linked epidemiologically

c. These cases are not related by transmission

d. I don't know

Case Scenario 2: A Workplace

ANSWER:

How to interpret the genotype results?

a. The genotype data are wrong

b. The genotype data could be wrong, since cases are linked epidemiologically

c. These cases are not related by transmission

d. I don't know

Case Scenario 2: A Workplace
Interpretation of Genotype Results

- Genotype results from all cases were different

  - *These cases are not related by transmission*

  - *This was a coincidence*

- Four contact investigations are needed

  - *Three in same work site*

- Not an outbreak

How is it created?

THE COMPOSITION OF A GENOTYPE

How are Genotyping Results Obtained?
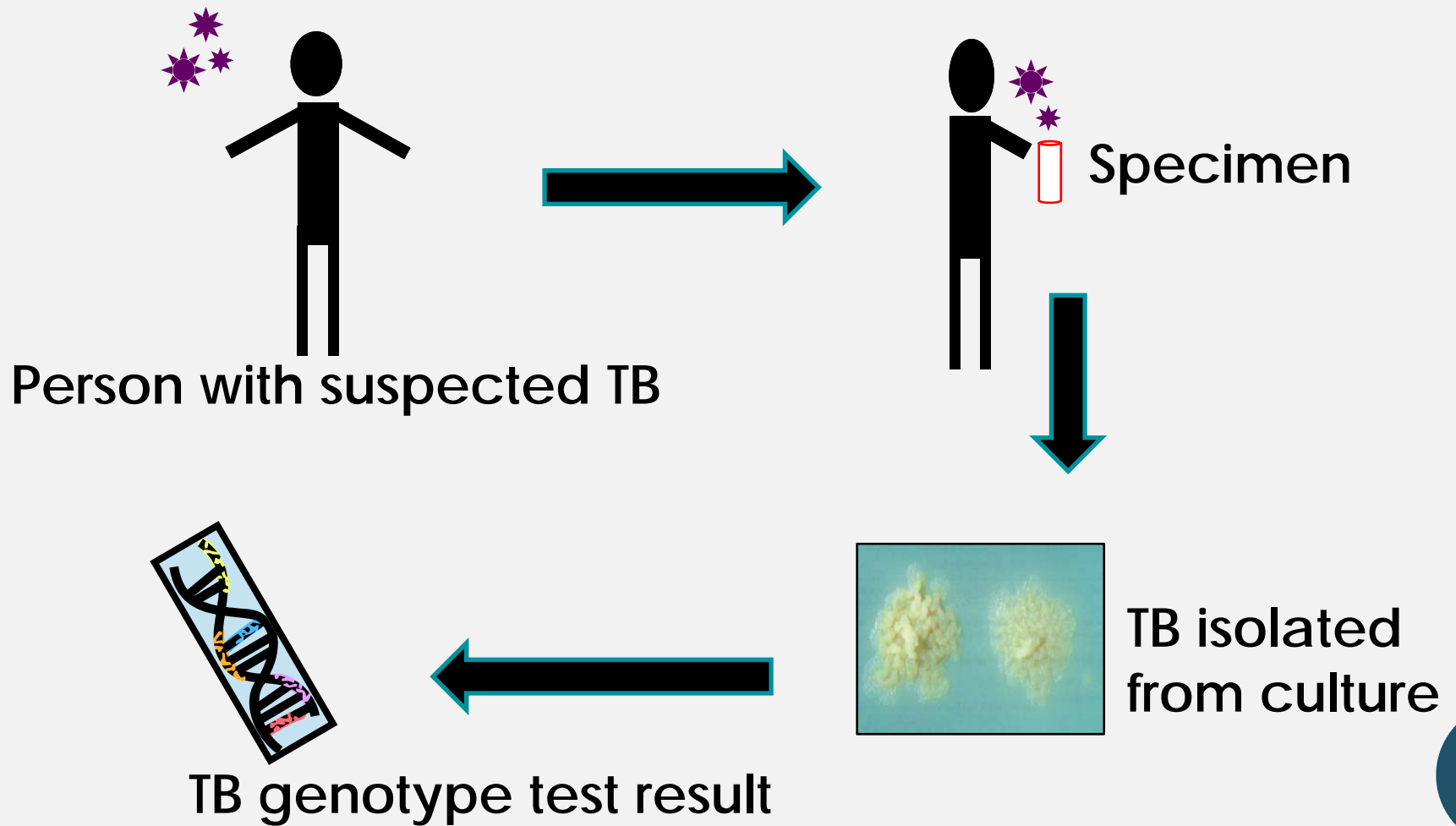
Definition for Tuberculosis Genotyping in the United States

Spoligotype: 000000000003771

Initial 12-locus MIRU-VNTR[1]: 223325173533

Sequentially assigned for each unique spoligotype and initial 12-locus MIRU-VNTR combination

PCRType: PCR00002

+

Additional 12-locus MIRU-VNTR (MIRU2): 444534423428[2]

Sequentially assigned for each unique spoligotype and 24-locus MIRU-VNTR combination

GENType: G00010

[1] Mycobacterial interspersed repetitive unit–variable number tandem repeat.

[2] The complete set of 24 loci is referred to as 24-locus MIRU-VNTR and is used for GENType designation for genotype in the United States.

A Few Examples

GENType	PCRType	ClusterName2	Spoligotype	MIRU	MIRU2
G16470	PCR00766	MI_0065_001	777777777760771	228325163423	236234223736
G11100	PCR00743	MI_0011_001	777776777760771	224225153324	433434423638
G15185	PCR00291	MI_0008_001	777777777760700	223325133224	242524224225
G15165	PCR00013	MI_0004_001	777777777760600	223325133224	242524224225
G00010	PCR00002	MI_0016_001	000000000003771	223325173533	444534423428
G01835	PCR00012	MI_0002_001	000000000003771	322325173543	445544423329
G00012	PCR00002	MI_0016_003	000000000003771	223325173533	445644423328
G23048	PCR00012		000000000003771	322325173543	44554442332%
G15184	PCR00291	MI_0008_002	777777777760700	223325133224	242424224225
G00392	PCR00803		000000000003771	222325173533	345544423328
G24832	PCR17412		000000000003771	2233251b3533	444744423348
G23020			No Result	234325152324	241334223128
G25354	PCR22382		703777740003771	224425183523	224 -- 4223248

Differences by Spoligotype

GENType	PCRType	ClusterName2	Spoligotype	MIRU	MIRU2
G16470	PCR00766	MI_0065_001	77777**7**7777760771	228325163423	236234223736
G11100	PCR00743	MI_0011_001	77777**6**7777760771	224225153324	433434423638
G15185	PCR00291	MI_0008_001	7777777777760**7**00	223325133224	242524224225
G15165	PCR00013	MI_0004_001	7777777777760**6**00	223325133224	242524224225
G00010	PCR00002	MI_0016_001	00000000003771	223325173533	444534423428
G01835	PCR00012	MI_0002_001	00000000003771	322325173543	445544423329
G00012	PCR00002	MI_0016_003	00000000003771	223325173533	445644423328
G23048	PCR00012		00000000003771	322325173543	44554442332%
G15184	PCR00291	MI_0008_002	77777777760700	223325133224	242424224225
G00392	PCR00803		00000000003771	222325173533	345544423328
G24832	PCR17412		00000000003771	2233251b3533	444744423348
G23020			No Result	234325152324	241334223128
G25354	PCR22382		70377740003771	224425183523	224 - - 4223248

Differences by MIRU

GENType	PCRType	ClusterName2	Spoligotype	MIRU	MIRU2
G16470	PCR00766	MI_0065_001	777777777760771	228325163423	236234223736
G11100	PCR00743	MI_0011_001	777776777760771	224225153324	433434423638
G15185	PCR00291	MI_0008_001	777777777760700	223325133224	242524224225
G15165	PCR00013	MI_0004_001	777777777760600	223325133224	242524224225
G00010	PCR00002	MI_0016_001	000000000003771	**2**23325173**5**3**3**	444534423428
G01835	PCR00012	MI_0002_001	000000000003771	**3**2**2**325173**5**4**3**	445544423329
G00012	PCR00002	MI_0016_003	000000000003771	**2**23325173**5**3**3**	445644423328
G23048	PCR00012		000000000003771	**3**2**2**325173**5**4**3**	44554442332%
G15184	PCR00291	MI_0008_002	777777777760700	223325133224	242424224225
G00392	PCR00803		000000000003771	222325173533	345544423328
G24832	PCR17412		000000000003771	2233251b3533	444744423348
G23020			No Result	234325152324	241334223128
G25354	PCR22382		703777740003771	224425183523	224 -- 4223248

Differences by MIRU2

GENType	PCRType	ClusterName2	Spoligotype	MIRU	MIRU2
G16470	PCR00766	MI_0065_001	777777777760771	228325163423	236234223736
G11100	PCR00743	MI_0011_001	777776777760771	224225153324	433434423638
G15185	PCR00291	MI_0008_001	777777777760700	223325133224	242**5**24224225
G15165	PCR00013	MI_0004_001	777777777760600	223325133224	242524224225
G00010	PCR00002	MI_0016_001	000000000003771	223325173533	44**453**4423**4**28
G01835	PCR00012	MI_0002_001	000000000003771	322325173543	445544423332**9**
G00012	PCR00002	MI_0016_003	000000000003771	223325173533	44**564**4423**3**28
G23048	PCR00012		000000000003771	322325173543	44554442332**%**
G15184	PCR00291	MI_0008_002	777777777760700	223325133224	242**4**24224225
G00392	PCR00803		000000000003771	222325173533	345544423328
G24832	PCR17412		000000000003771	2233251b3533	444744423348
G23020			No Result	234325152324	241334223128
G25354	PCR22382		703777740003771	224425183523	224--4223248

How is it used?

TB GENOTYPING INFORMATION SYSTEM (TB GIMS) REPORTS

Cluster Snapshot for G15185

Cluster Definition

GENType: G15185

PCRType: PCR00291

Lineage: EuroAmerican (L4)

State Cluster Name2: MI_0008_001

Date Range: 10/11/2012 - 10/11/2015

Date Type: Count Date

 # cases in cluster: 10

State/County/Region: MICHIGAN

Data Completeness

Genotype Coverage: 96.8%

#Patients with PCRType but no MIRU2 result: 0

#Isolates with no linked surveillance record: 0

Genotype report date of most recent isolate without surveillance record:

Cluster Detection

Alert Level: N/A

Recent change in alert level:

Alert level and LLR are only available for single county areas.

Cluster Snapshot for G15185

Time
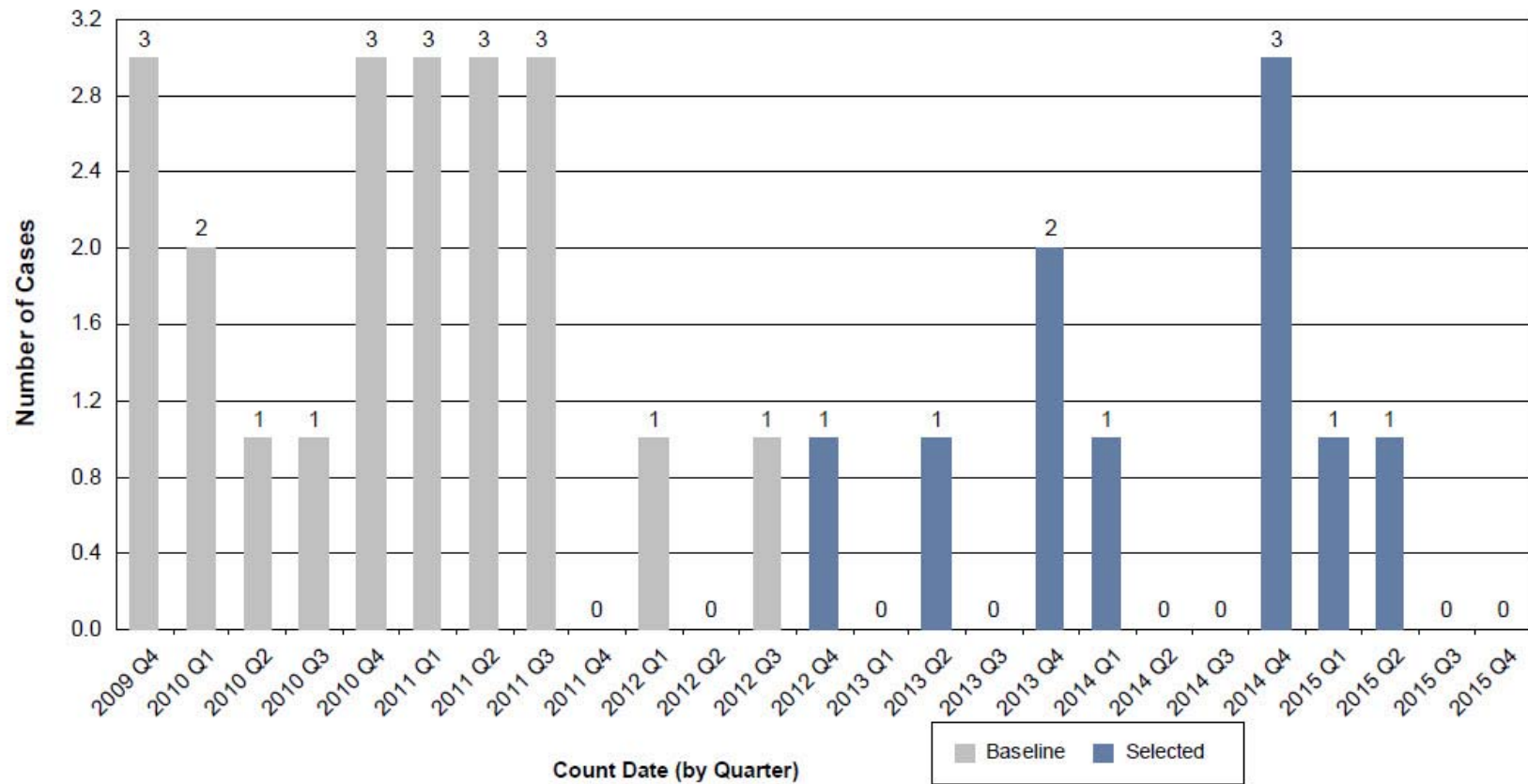
The Epidemic Curve has been expanded to display the historical occurrence of cases for 3 years prior to dates selected. The first blue column will include all cases in the quarter regardless of whether they are in selected timeframe or are part of baseline period. 0 out of 1 cases are from the baseline period.

Geography

# cases in rest of state: N/A	% of all cases in this state with this genotype: 4.10
Five other counties with most cases: N/A	
# cases in adjacent states: 0	Adjacent states with cases:
# cases in entire rest of U.S.: 2	% of all cases in U.S. with this genotype: 0.06

Cluster Snapshot for G15185

Person

Comparative demographics (selected jurisdiction vs. rest of U.S.) n(%)

Characteristic	MICHIGAN	Rest of U.S. n (%)
Race/Ethnicity		
Black	9 (90.0%)	2 (100.0%)
White	1 (10.0%)	0 (0.0%)
Gender		
Female	1 (10.0%)	1 (50.0%)
Male	9 (90.0%)	1 (50.0%)
Birth		
US Born	10 (100.0%)	2 (100.0%)

High risk characteristics of transmission or poor outcome n(%)

Characteristic	n (%)
Case with smear positive and cavitary pulmonary disease	5 (50.0%)
Homeless	3 (30.0%)
Corrections	0 (0.0%)
Long Term Care Facility	1 (10.0%)
Any substance abuse	5 (50.0%)
Alcohol abuse	4 (40.0%)
Non-IDU	4 (40.0%)
IDU	0 (0.0%)
MDR	0 (0.0%)
INH resistance only	0 (0.0%)
Child (<5 years)	0 (0.0%)
Child (5-14 years)	0 (0.0%)
HIV	0 (0.0%)
Dead at diagnosis or died while on therapy	3 (30.0%)

There are no foreign born cases for the selected criteria.

Cluster Snapshot for G15185

Line List

StateCaseNo	Cnt.Date	County	Age3	RaceHisp	CountryLN	YrsInUS2	Smear	Cavity	DrugRes	HIV	SubAbus	Corr	Homeless	ReasEval
2015MID00000050	05/01/2015	WAYNE	45-64	BLACK	UNITED STATES		NEG	UNK	None	NEG	Y	N	N	TBSYMP
2015MI000000002	01/01/2015	WAYNE	45-64	WHITE	UNITED STATES		POS	N	None	NEG	Y	N	Y	TBSYMP
2014MID00000110	12/01/2014	WAYNE	25-44	BLACK	UNITED STATES		POS	Y	None	NEG	N	N	N	ABXRAY
2014MID00000081	10/01/2014	WAYNE	45-64	BLACK	UNITED STATES		POS	Y	None	NEG	Y	N	Y	TBSYMP
2014MID00000083	10/01/2014	WAYNE	45-64	BLACK	UNITED STATES		POS	Y	None	NEG	N	N	N	TBSYMP
2014MID00000016	03/01/2014	WAYNE	65+	BLACK	UNITED STATES		POS	N	None	NEG	N	N	N	TBSYMP
2013MID00000137	11/01/2013	WAYNE	45-64	BLACK	UNITED STATES		NEG	N	None	NEG	Y	N	N	TBSYMP
2013MID00000104	10/01/2013	WAYNE	65+	BLACK	UNITED STATES		POS	Y	None	NEG	N	N	N	TBSYMP
2013MID00000033	04/01/2013	WAYNE	45-64	BLACK	UNITED STATES		POS	Y	None	NEG	N	N	N	ABXRAY
2012MID00000138	12/01/2012	WAYNE	45-64	BLACK	UNITED STATES		POS	N	None	UNK	Y	N	Y	TBSYMP

National Distribution of G15185

Spoligotype: 777777777760700 **24-locus MIRU-VNTR:** 223325133224 242524224225

Number of cases with this genotype in U.S. (Z): 12

Percent of all genotyped cases in the U.S. with this genotype: 0.06 **PCRType:** PCR00291

Number of States reporting this genotype: 3 **Family Name:** EuroAmerican (L4)

Date Range: 08/19/2012 - 08/19/2015 **Date Type:** Count Date

	No. of cases with this genotype in state (X)	All cases with any genotype in state (Y)	% of all cases in state with this genotype (X/Y)	% of U.S. cases with this genotype in the state (X/Z)
FLORIDA	1	1362	0.07	8.33
IOWA	1	86	1.16	8.33
MICHIGAN	10	243	4.12	83.33

Surveillance Summary of G15185

State: MICHIGAN
County: ALL
Region: NA
Spoligotype: 777777777760700
Date Range: 03/03/2005 - 03/03/2015

Family Name: EuroAmerican (L4)
City: NA
PCRType: PCR00291
24-locus MIRU-VNTR: 223325133224 242524224225
Date Type: Count Date

	MICHIGAN		Other US	
	n	%	n	%
Age (years)				
0 - 4	0	0.0	0	0.0
5 - 14	0	0.0	0	0.0
15 - 24	3	7.3	0	0.0
25 - 44	10	24.4	1	50.0
45 - 64	26	63.4	1	50.0
65+	2	4.9	0	0.0
Unknown	0	0.0	0	0.0
Sex				
Male	34	82.9	1	50.0
Female	7	17.1	1	50.0
Birth				
US-Born	41	100.0	2	100.0
Foreign-Born	0	0.0	0	0.0
Unknown	0	0.0	0	0.0
Race/Ethnicity				
Hispanic	1	2.4	0	0.0
American Indian/Alaska Native	0	0.0	0	0.0
Asian	0	0.0	0	0.0
Black	40	97.6	2	100.0
Native Hawaiian/Pacific Islander	0	0.0	0	0.0
White	0	0.0	0	0.0
Multiple Race	0	0.0	0	0.0
Unknown	0	0.0	0	0.0
Homeless in past year				
Yes	16	39.0	1	50.0
Excessive Alcohol Use				
Yes	14	34.1	1	50.0
Drug Use (injecting/non-injecting)				
Yes	13	31.7	0	0.0
Incarcerated at Diagnosis				
Yes	4	9.8	0	0.0
HIV Status				
Positive	5	12.2	0	0.0
Negative	31	75.6	2	100.0
Other/Unknown	5	12.2	0	0.0
TOTAL	41		2	

*Note: 'County: ALL' refers to all the counties in the state.

Surveillance Summary of G01835

State: MICHIGAN
County: ALL
Region: NA
Spoligotype: 000000000003771
Date Range: 08/06/2012 - 08/06/2015

Family Name: East Asian (L2)
City: NA
PCRType: PCR00012
24-locus MIRU-VNTR: 322325173543 445544423329
Date Type: Count Date

	MICHIGAN		Other US	
Drug Susceptibility Results	n	%	n	%
Susceptible to initial testing of first line drugs[1]	2	100.0	5	71.4
INH resistant only	0	0.0	1	14.3
RIF resistant only	0	0.0	0	0.0
PZA resistant only	0	0.0	0	0.0
MDR[2]	0	0.0	0	0.0
XDR[3]	0	0.0	0	0.0
Other resistance pattern[4]	0	0.0	0	0.0
Missing/unknown for first line of drugs[5]	0	0.0	1	14.3
TOTAL	**2**		**7**	

1.Includes INH, RIF, and EMB. PZA is included when results are available.
2.MDR indicates resistance to at least RIF and INH. May be resistant to other drugs, but not meet criteria for XDR.
3.XDR indicates resistance to RIF, INH, any fluoroquinolone and at least one injectable TB drug.
4.Any other combination of resistance patterns to the four first line drugs that do not fit into other categories.
5.Any patient with unknown/missing for RIF, INH or EMB, with or without PZA results.

*Note: 'County: ALL' refers to all the counties in the state.

Surveillance Summary of G01835

There are no US born cases born outside the 50 states and DC.

*Note: 'County: ALL' refers to all the counties in the state.

Surveillance Summary of G01835

State: MICHIGAN
County: ALL
Region: NA
Spoligotype: 000000000003771
Date Range: 08/06/2012 - 08/06/2015

Family Name: East Asian (L2)
City: NA
PCRType: PCR00012
24-locus MIRU-VNTR: 322325173543 445544423329
Date Type: Count Date

Country of Birth for Foreign-Born TB Cases

Country	MICHIGAN		Other US	
	n	%	n	%
VIETNAM	0	0.0	1	100.0
Total	0	0	1	100

*Note: 'County: ALL' refers to all the counties in the state.

PRIMARY GENOTYPE CLUSTERS IN MICHIGAN

# Genotyped and Clustered Cases, 2012-2014

United States

- 21,075 Genotyped Cases
- 4,544 (22%) Clustered Cases

Michigan

- 273 Genotyped Cases
- 241 GENTypes
- 33 Clusters
- 66 (24%) Clustered Cases

| GENType	MI Cluster Name	No. in MI	No. in Rest of US
G15185	MI_0008_001	10	2
G15165	MI_0004_001	5	0
G01835	MI_0002_001	5	6
G08464	MI_0047_001	4	2
G16470	MI_0065_001	4	7
G00010	MI_0016_001	4	173
G00012	MI_0016_003	1	139
G05056		1	114
G00013	MI_0046_001	1	86
G12500		1	58
G10508		1	52
G00734		1	45
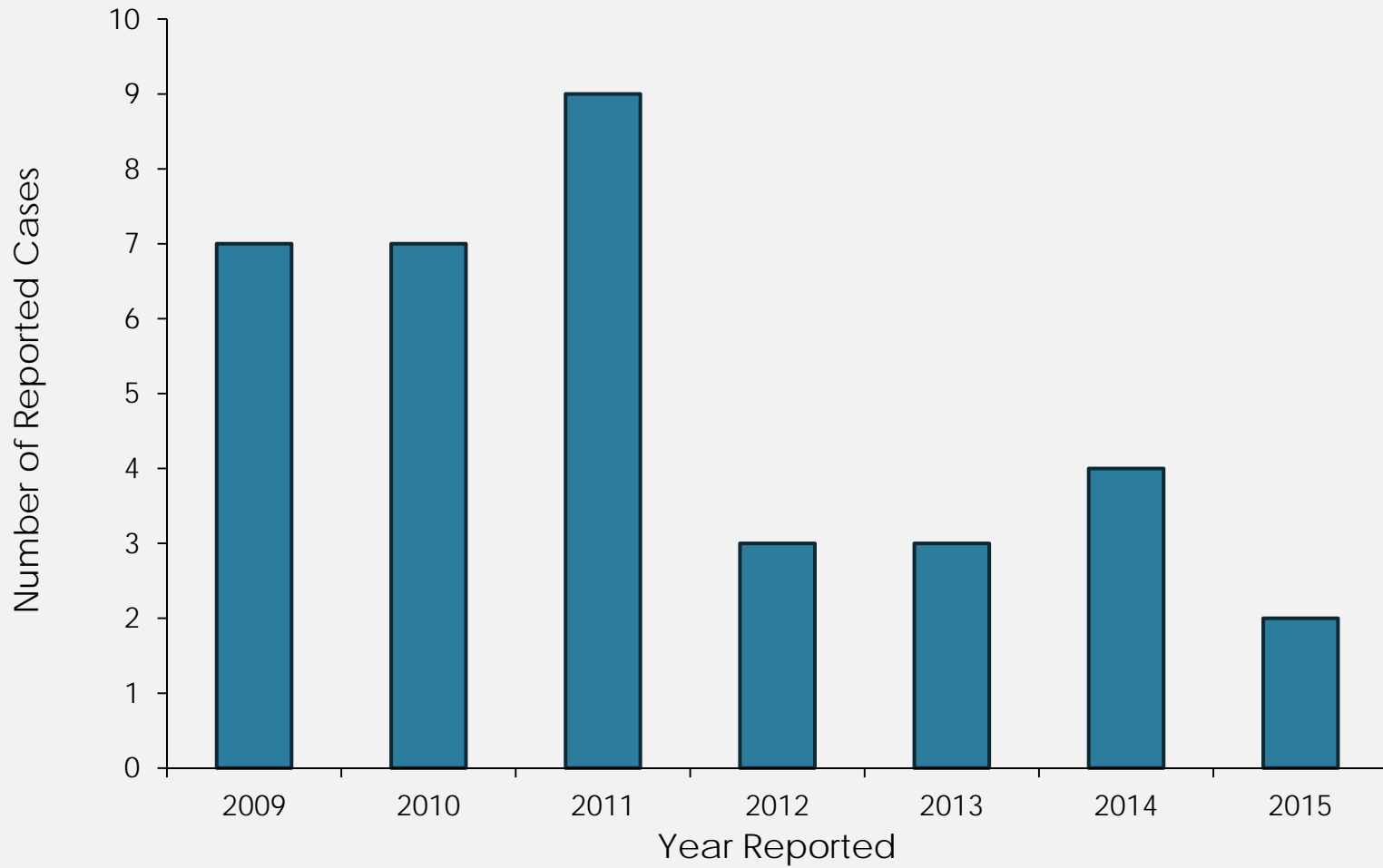
Cases of TB in Genotype Cluster G01835
Michigan vs. Rest of U.S., 2009-2015
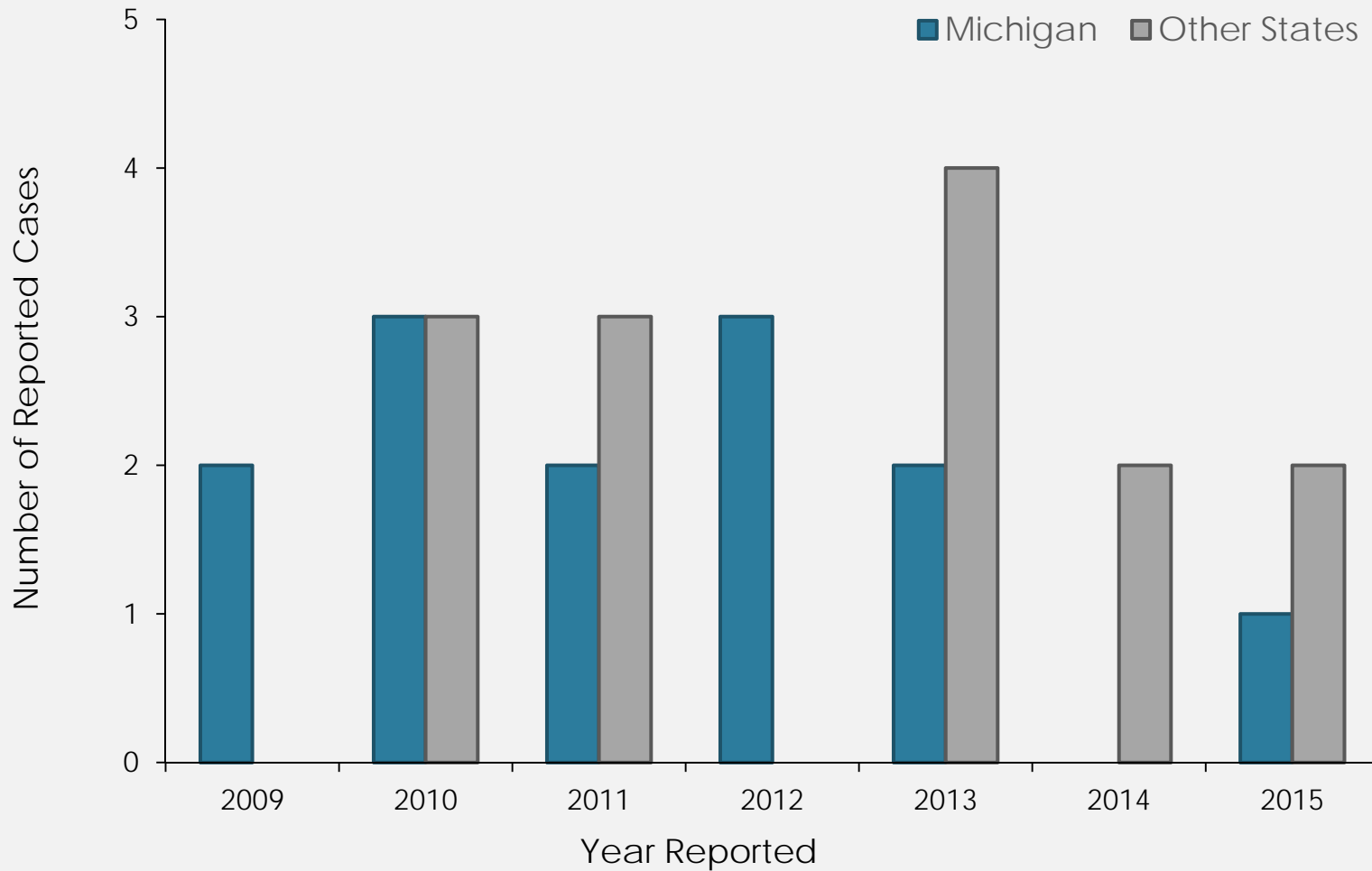
Cases of TB in Genotype Cluster G00010
Michigan vs. Rest of U.S., 2009-2015
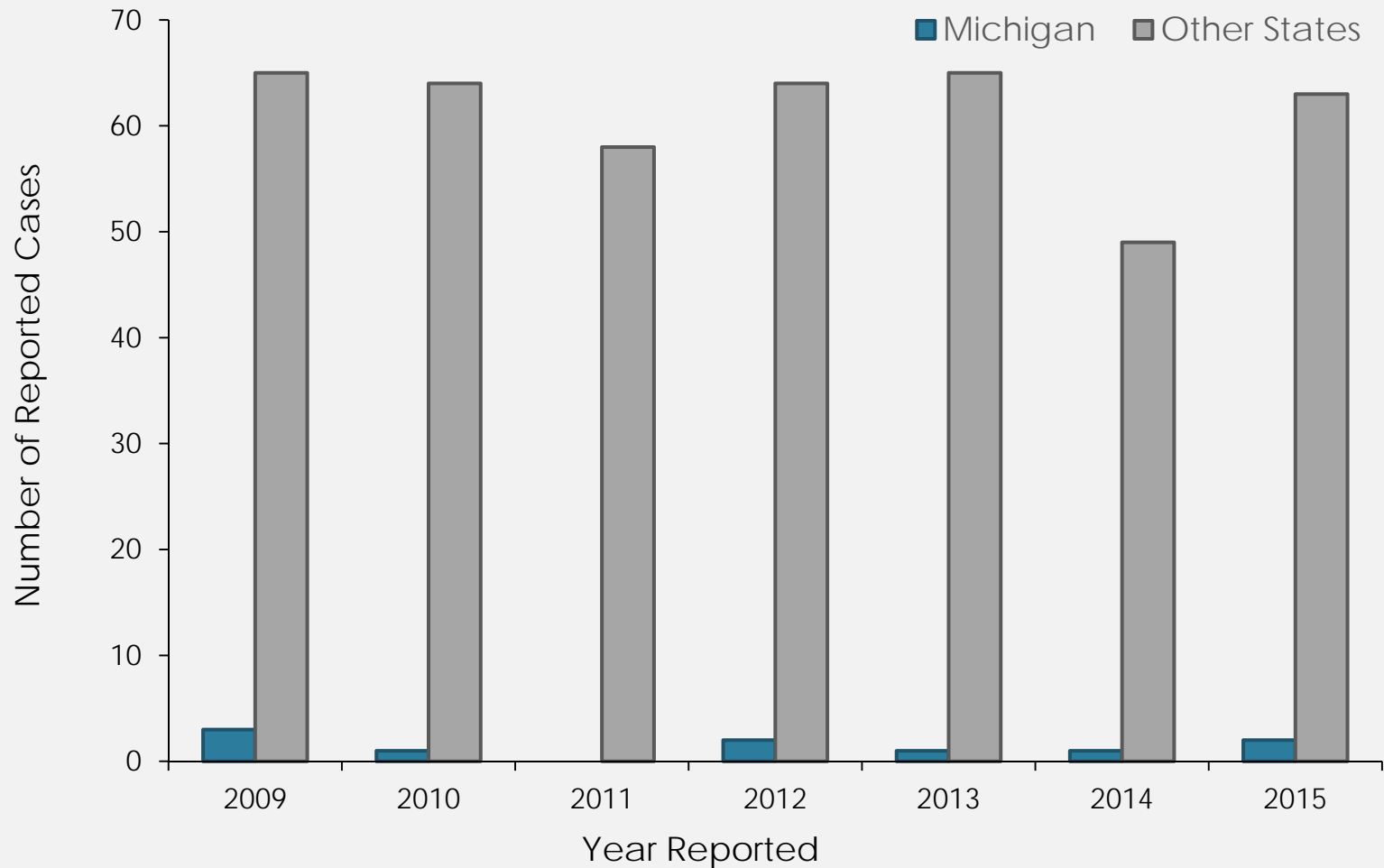
What else can be done?

CLUSTER INVESTIGATION TOOL

Take Home Points

- TB genotyping can be useful in TB control
  - *Find additional contacts*
  - *Detect and prevent outbreaks*
  - *Refute outbreaks*
- Interpreting genotyping results can be as simple as, "Do the pictures match?"
- The number and proportion of clustered genotype cases in Michigan decreases each year"

CDC Resources on Genotyping

- **CDC TB genotyping website**

  www.cdc.gov/tb/programs/genotyping/default.htm

- **TB genotyping best practices**

  www.cdc.gov/tb/publications/factsheets/statistics/Genotyping_BestPractices.pdf

- **TB Genotyping Information Management System (TB GIMS)**

  https://ajtv-nifm-web2.cdc.gov/TBGIMS/

- **Email CDC**

  tbgenotyping@cdc.gov

Thank You!

Acknowledgements

- CDC's Division of Tuberculosis Elimination

- MDHHS TB Units

References

- Introduction to Tuberculosis Genotyping Facilitator Guide http://www.cdc.gov/tb/programs/genotyping/default.htm

- TB GIMS Reports

Contact

smiths79@michigan.gov