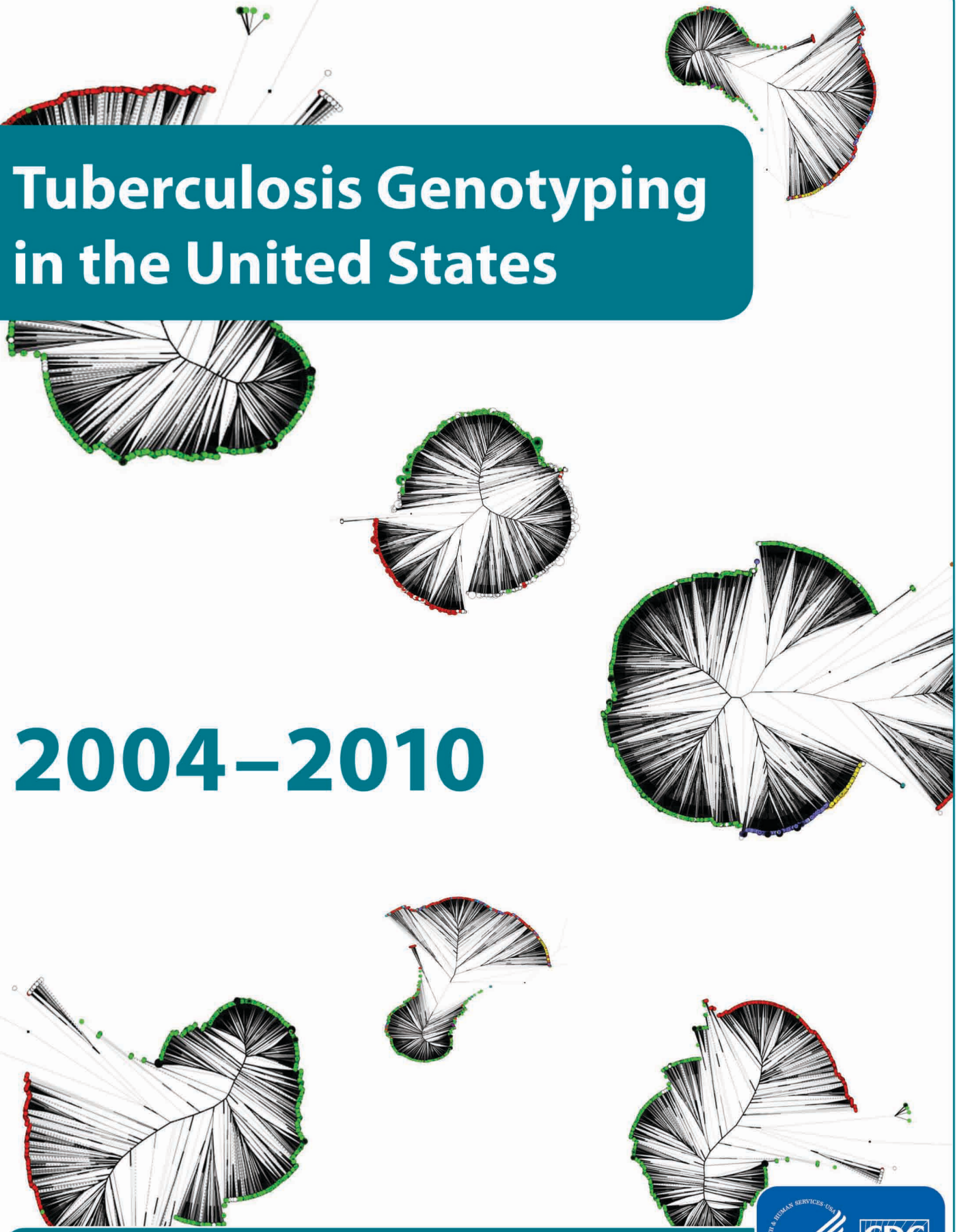
Tuberculosis Genotyping in the United States



2004–2010

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Executive Commentary

Executive Commentary

Tuberculosis (TB) genotyping is a laboratory-based analysis of the genetic material of the bacteria that causes TB disease, *Mycobacterium tuberculosis* complex. Genotyping has become a standard component of TB control measures, and most jurisdictions now use genotyping during routine TB control activities.[1] The Centers for Disease Control and Prevention (CDC) established the National TB Genotyping System (NTGS) in 2004 to provide TB genotyping to local and state TB control programs. Since then, over 70,000 *Mycobacterium tuberculosis* isolates have been successfully genotyped through partnerships between CDC, national genotyping laboratories, and 58 reporting areas.

One of the most significant accomplishments of NTGS has been the increase in national genotyping surveillance coverage (the proportion of cases with positive cultures with at least one genotyped isolate). Coverage has increased by 72% from 2004 (51.3%) to 2010 (88.2%)[2], nearing the national target of 94%.[3] This increase can be attributed to the collaborative efforts of staff at local, state, and federal TB programs and public health laboratories, as well as a growing recognition of the utility of genotyping in TB control.

The TB Genotyping Information Management System (TB GIMS), launched in March 2010, is a secure online database that makes genotyping data available to users in a form easily applicable to TB control activities, and links genotyping data to patient surveillance records.[4] In the first 9 months of implementation, use of TB GIMS has grown rapidly, with over 28,000 logins by 349 state and local users as of December 31, 2010.

CDC continues to focus on improving TB GIMS to meet users' needs. Timeliness of complete records (i.e., records with linked genotype and surveillance data) in TB GIMS has been identified as an area for improvement. Unpublished analysis of TB GIMS system data has shown that delays in availability of genotyping results are affected by two primary factors unrelated to the national genotyping laboratories:

- Time to arrival of isolate at genotyping laboratories
- Time until a genotype result is linked to a surveillance record.[1]

CDC has worked with local and state users in these issues, and timeliness has improved. In June 2010, complete records were available a median of 22 weeks after specimen collection. This time period has been shortened by half, reaching a median of 11 weeks for specimens collected in December 2010.

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TB Genotyping Overview

TB Genotyping Overview

GENOTYPING BACKGROUND

Tuberculosis (TB) genotyping is a laboratory-based analysis of the genetic material of the bacteria that causes TB disease, *Mycobacterium tuberculosis* complex. The total genetic content is referred to as the genome. Specific sections of the genome contain distinct genetic patterns that help distinguish different strains of *M. tuberculosis*.[1]

Applications of Genotyping

TB genotyping results, when combined with epidemiologic data, help identify persons with TB disease involved in the same chain of recent transmission. This information adds value to conventional TB control activities. Below are some applications of TB genotyping:[2]

- Detect contamination events involving clinical specimens or laboratory cultures, or errors in specimen handling or labeling
- Distinguish new TB disease from recurrence or relapse of previously diagnosed disease
- Discover unsuspected transmission relationships between TB patients and confirm known transmission relationships
- Determine completeness of contact investigations
- Identify unknown or difficult to investigate transmission settings, such as bars or clubs, instead of traditional settings like home and workplace
- Uncover inter-jurisdictional transmission
- Identify outbreaks
- Establish criteria for outbreak-related case definitions.

TB control efforts directed at preventing TB transmission differ from efforts to prevent activation of latent TB infection.[3,4] Genotyping offers a useful tool to help direct the application of efforts focused on preventing transmission.[3,5]

History of TB Genotyping Surveillance in the United States

In 1993, the U.S. Centers for Disease Control and Prevention (CDC) funded regional genotyping laboratories to support TB control programs for outbreak detection and epidemiologic studies.[6] CDC started the National Tuberculosis Genotyping Surveillance Network (NTGSN) in 1996, a 5-year initiative that established the utility of genotyping in TB control efforts.[7] In 2004, based on the knowledge gained from the network and related studies,[8] CDC established the National TB Genotyping Service (NTGS) and funded two national genotyping laboratories, located in Michigan and California, to genotype at least one *M. tuberculosis* isolate collected from each culture-positive TB case reported in the United States.[9] All TB control programs may use NTGS at no cost to the patients, healthcare providers, or health departments.[2] CDC pays for the shipping of isolates from public health laboratories to the national genotyping laboratories.[6] NTGS participation is voluntary, with individual programs determining how genotyping data will be used for their TB control activities.[5]

In March 2010, the TB Genotyping Information Management System (TB GIMS) was launched by CDC as a secure Web-based system to support ongoing use of TB genotyping data in TB control activities. TB GIMS facilitates systematic data collection of TB genotyping results and integrates genotyping results with epidemiologic data collected by the National TB Surveillance System (NTSS) to form a national and centralized database.

TB GIMS allows users the following functions:[9]

- Create, submit, track, and manage genotyping data for *M. tuberculosis* isolates in the United States
- Link isolate genotype records with patient surveillance records
- Query line-listed isolate genotype and patient surveillance data
- Generate summary reports and maps of genotype clusters, including national genotype distributions, and national, state, and county maps
- Monitor and receive notifications on genotype clusters that may represent recent transmission or outbreaks.

Genotyping-based Outbreak Detection

Genotyping-based outbreak detection involves the use of geospatial analysis to identify patterns of TB cases with matching genotypes that deviate from expected patterns and may represent outbreaks. TB control programs can use outbreak detection information to help allocate and prioritize resources for investigation and intervention on specific TB genotype clusters.

Currently, CDC's outbreak detection methods are primarily based on identifying higher than expected geospatial concentrations of a TB genotype in a specific county, compared to the national distribution of that genotype. This method calculates a log-likelihood ratio (LLR); the higher the LLR, the greater the possibility that the local genotype cluster within the county represents an unexpected geospatial concentration, which might indicate recent transmission of TB. The LLR can be used to compare and prioritize TB genotype clusters.

Genotyping Terminology

In NTGS, a genotype is defined as a unique combination of spacer oligonucleotide typing results (spoligotype) and 12-locus mycobacterial interspersed repetitive unit–variable number tandem repeat typing (MIRU–VNTR) results. Each unique combination of spoligotype and 12-locus MIRU-VNTR results is assigned a ''PCRType.'' PCRType is designated as ''PCR'' followed by five digits, which are assigned sequentially to every genotype identified in the U.S. (e.g., PCR01974). This nomenclature is designed for convenience and ease of communication, but the specific numbers assigned have no additional significance outside of NTGS.

In April 2009, MIRU-VNTR analysis was expanded from 12 loci to 24 loci. The complete set of 24 loci is referred to as 24-locus MIRU-VNTR. The addition of these 12 loci increases our ability to distinguish between strains of *M. tuberculosis* and correctly identify chains of transmission (an increase in specificity of genotyping results). The additional 12 loci examined in 24-locus MIRU-VNTR are interpreted with equal weight as the initial 12 loci (from 12-locus MIRU-VNTR); the inclusion of the additional 12 loci is not a subtyping method.

To fully integrate the additional 12 loci into routine use, a new national terminology system has been developed. Each unique combination of spoligotype and 24-locus MIRU-VNTR has been assigned a GENType, formatted as "G" followed by five digits (e.g., G00056). New unique combinations will be assigned GENTypes sequentially as they are identified. Because the majority of all genotype results tested before April 2009 do not have 24-locus MIRU-VNTR, PCRTypes will continue to be assigned to spoligotype/12-locus MIRU-VNTR combinations during a transition period of not less than 2 years.

National TB Genotyping Surveillance Coverage in the United States

National TB genotyping surveillance coverage refers to the proportion of culture-positive TB cases with a genotyped *M. tuberculosis* isolate. High levels of coverage in the United States can provide a better understanding of the epidemiology of TB transmission within a specific geographic area, as well as the entire country. The current national objective for TB genotyping surveillance coverage is 94%.[10] In 2004, when the NTGS was initiated, 51% of all reported culture-positive TB cases in the United States had genotyping information reported by voluntary participants. In 2010, this proportion had increased to 88%.

TECHNICAL NOTES

National Tuberculosis Genotyping Service (NTGS)

NTGS laboratories primarily use two genotyping methods: spoligotyping and MIRU–VNTR.[3] Both methods require only a small amount of culture material, provide digital results, and are relatively quick.[11,12] IS6110-restriction fragment length polymorphism (IS6110-RFLP) and retrospective 24-locus MIRU-VNTR for older isolates can be performed, if requested, and may help in differentiating genotype clusters.[3] All isolates are prepared for long-term storage at genotyping laboratories.[3]

Tuberculosis Genotyping Information Management System (TB GIMS)

Primary users of TB GIMS include TB laboratories that submit isolates for genotyping, national genotyping laboratories in California and Michigan, state and local TB control programs, and CDC.[2]

Results of genotyping from the national genotyping laboratories are uploaded into TB GIMS as they become available. Line-listed data from the NTSS are also uploaded into TB GIMS at least biweekly. Users at the state or local level must log in to TB GIMS in order to link genotype results to surveillance data. Once genotyping results have been linked to individual patient surveillance data in TB GIMS, the record is considered complete. Complete records are essential for most of the applications of TB genotyping, including using the outbreak detection system to identify potential outbreaks; therefore, it is critical that complete records be available in TB GIMS in a timely manner. The dates associated with the steps to create a complete are summarized below:

- **Genotype Report Date** is the date that genotyping results were entered by the genotyping lab into TB GIMS.

- **Surveillance Upload Date** is the date that surveillance data (initially reported to CDC by individual jurisdictions) were uploaded from the CDC NTSS to TB GIMS. Many jurisdictions are moving towards reporting cases to CDC on a continuous basis, rather than quarterly or annually.

- **Linking Date** refers to the date the state case number (of the case from which the genotyped isolate was collected) was entered into TB GIMS by the state TB program to link genotype results to surveillance records.

- **Record Completion Date** defines the date in which a) genotyping results are available, b) surveillance data has been uploaded, and c) linking has occurred in TB GIMS; once all three steps are complete, the record is available to TB GIMS users.

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TB Genotyping Tables

Table 1. National Tuberculosis Genotyping Surveillance Coverage[1] by Year: United States[2], 2004–2010[3]

Year	Number of Reported Culture-Positive Cases	Number With Any Genotype Result	Percent Coverage (%)
2004	11,326	5,796	51.2
2005	10,995	7,019	64.1
2006	10,746	7,381	68.7
2007	10,425	8,355	80.1
2008	10,029	8,118	80.9
2009	8,885	7,566	85.2
2010	8,413	7,424	88.2
All years (2004–2010)	70,779	51,659	73.0

[1] The proportion of positive cultures with at least one genotyped isolate
[2] Includes 50 states and the District of Columbia
[3] Ghosh S, Moonan PK, Cowan L, Grant J, Kammerer S, Navin TR. Tuberculosis Genotyping Information Management System: Enhancing tuberculosis surveillance in the United States. Infect Genet Evol. 2012;12(4):782–788.

Table 2. Tuberculosis Genotyping Surveillance Coverage[1] by Reporting Areas[2]: United States, 2004–2010

Year	Reporting Areas with Coverage					
	<50%		50% - 80 %		>80%	
	No.	(%)	No.	(%)	No.	(%)
2004	15	(29.4)	10	(19.6)	26	(51.0)
2005	8	(16.0)	8	(16.0)	34	(68.0)
2006	7	(13.7)	13	(25.5)	31	(60.8)
2007	4	(7.8)	13	(25.5)	34	(66.7)
2008	4	(7.8)	8	(15.7)	39	(76.5)
2009	1	(2.0)	13	(25.5)	37	(72.5)
2010[3]	0	(0.0)	8	(16.7)	40	(83.3)

[1] The proportion of positive cultures with at least one genotyped isolate
[2] Includes 50 states and the District of Columbia
[3] Excluding 3 states due to technical delays

Table 3. Most Frequently Reported Tuberculosis Genotypes Based on PCRType[1]: United States, 2010

PCRType	Spoligotype	12-locus MIRU-VNTR	Cases		No. Reporting Areas[2] with PCRType
			No.	(%)	
PCR00002	000000000003771	223325173533	301	(4.1)	35
PCR00041	677777477413771	254326223432	286	(3.9)	30
PCR00015	777776777760601	224325153323	132	(1.8)	27
PCR00022	777777777720771	225325153323	92	(1.2)	31
PCR00019	777777777760771	223425153322	60	(0.8)	19
PCR00617	777777607760771	224226153321	57	(0.8)	16
PCR00309	000000000003771	222325173543	56	(0.8)	20
PCR00093	000000000003771	223325163533	49	(0.7)	16
PCR00091	000000000003771	223325153533	38	(0.5)	17
PCR00117	677777477413771	254326223422	38	(0.5)	11

[1] Unique combination of spoligotype and 12-locus MIRU-VNTR results
[2] Includes 50 states and the District of Columbia

Table 4. Most Frequently Reported Tuberculosis Genotypes Based on GENType[1]: United States, 2010

GENType	PCRType[2]	Spoligotype	24-locus MIRU-VNTR		Cases		No. Reporting Areas[3] with GENType
					No.	(%)	
G00010	PCR00002	000000000003771	223325173533	444534423428	61	(0.8)	15
G00011	PCR00015	777776777760601	224325153323	444234423337	39	(0.5)	18
G00012	PCR00002	000000000003771	223325173533	445644423328	33	(0.4)	14
G00013	PCR00016	700036777760731	222325143223	434534412334	29	(0.4)	12
G00014	PCR00051	776037777760771	223125163324	242434223525	27	(0.4)	12
G00015	PCR11884	000000000003771	223326171531	445544423228	25	(0.3)	8
G00016	PCR00041	677777477413771	254326223432	14A843263217	25	(0.3)	7
G00017	PCR00803	000000000003771	222325173533	445644423328	24	(0.3)	9
G00018	PCR00036	000000000003771	223425173563	344644623337	24	(0.3)	7
G00019	PCR00309	000000000003771	222325173543	445644423328	23	(0.3)	13
G00020	PCR01328	776377777760751	333325153222	351544223229	23	(0.3)	9

[1] Unique combination of spoligotype and 24-locus MIRU-VNTR results
[2] Corresponding unique combination of spoligotype and 12-locus MIRU-VNTR results
[3] Includes 50 states and the District of Columbia

Table 5. Number of County-based Tuberculosis Genotype Clusters[1] by Cluster Size: United States[2], 2008–2010

Cluster Size	No.	Percent of Clusters (%)[3]
2	1,281	58.7
3	398	18.2
4	178	8.2
5–6	148	6.8
7–9	79	3.6
10–14	49	2.2
15–19	18	0.8
≥20	33	1.6
TOTAL NUMBER OF CLUSTERS	2,184	

[1] Genotype cluster is defined as two or more *M. tuberculosis* isolates that share matching genotypes in a jurisdiction during a specified time period.
[2] Includes 50 states and the District of Columbia
[3] Percentages do not add to 100% due to rounding

Table 6. County-based Tuberculosis Genotype Clusters[1] by Reporting Area: United States, 2008–2010

Reporting Area	No. Culture-Positive Cases	Genotyping Surveillance Coverage[2]	No. Clusters	Cluster Size	
				Median	Range
Alabama	401	>80	33	2	2–20
Alaska[3]	127	n/a	n/a	n/a	n/a
Arizona	541	>80	61	2	2–18
Arkansas	191	>80	12	3	2–7
California	5,971	>80	514	2	2–100
Colorado	180	>80	11	2	2–5
Connecticut	239	>80	20	2	2–4
Delaware	43	50–80	0	n/a	n/a
District of Columbia	112	<50	4	3	2–5
Florida	2,041	50–80	135	2	2–28
Georgia	942	>80	64	3	2–22
Hawaii	273	>80	18	2	2–39
Idaho	33	>80	2	3	2–3
Illinois	973	50–80	64	2	2–18
Indiana	257	>80	21	2	2–19
Iowa[3]	99	n/a	n/a	n/a	n/a
Kansas	128	>80	6	2	2–4
Kentucky	216	>80	16	2	2–5
Louisiana	498	50–80	38	3	2–7
Maine	16	>80	1	2	n/a
Maryland	555	>80	44	2	2–8
Massachusetts	550	>80	36	2	2–10
Michigan	402	>80	29	3	2–15
Minnesota	379	>80	38	2	2–8
Mississippi	251	>80	18	2	2–40
Missouri	229	>80	12	2	2–5
Montana	16	>80	2	3	2–3
Nebraska[3]	61	n/a	n/a	n/a	n/a
Nevada	215	>80	19	2	2–20
New Hampshire	37	>80	3	2	2–2
New Jersey	944	>80	73	2	2–8
New Mexico	140	>80	13	2	2–3
New York	2,294	>80	213	2	2–32
North Carolina	668	>80	38	2	2–21
North Dakota	13	50–80	0	n/a	n/a
Ohio	454	>80	21	3	2–14
Oklahoma	199	>80	18	2	2–7
Oregon	194	>80	16	2	2–6
Pennsylvania	637	50–80	25	2	2–10
Rhode Island	59	>80	4	3	2–3
South Carolina	359	50–80	17	2	2–14
South Dakota	33	>80	2	5	3–7
Tennessee	464	>80	45	2	2–12
Texas	3,340	>80	350	2	2–83
Utah	70	>80	4	2	2–3
Vermont	12	>80	0	n/a	n/a
Virginia	649	>80	53	2	2–9
Washington	592	>80	56	2	2–19
West Virginia	55	>80	2	3	2–4
Wisconsin	167	>80	6	2	2–3
Wyoming	8	>80	0	n/a	n/a

[1] Genotype cluster is defined as two or more *M. tuberculosis* isolates that share matching genotypes in a jurisdiction during a specified time period.

[2] The proportion of positive cultures with at least one genotyped isolate

[3] States excluded due to technical delays (n =3)

NOTE: “n/a” = “not applicable”

Table 7. Percent of County-based Tuberculosis Clusters[1] with a Medium or High Alert Level[2] Based on PCRType: United States, 2005–2010

3-year Period Used to Determine Clustering	Total No. Clusters	Clusters with Medium Alert Level		Clusters with High Alert Level	
		No.	(%)	No.	(%)
2005–2007	2,202	304	(14)	111	(5)
2006–2008	2,269	342	(15)	122	(5)
2007–2009	2,268	340	(15)	118	(5)
2008–2010	2,184	279	(13)	99	(5)

[1] Genotype cluster is defined as two or more *M. tuberculosis* isolates that share matching genotypes in a county during a specified time period.
[2] The alert level is determined by the log likelihood ratio (LLR) for a given cluster over a 3-year period of time. This is calculated automatically by TB GIMS and is updated whenever a new case is added to a genotype cluster. A medium alert level is based on LLR of 5.1–10. A high alert level is based on LLR >10.

Table 8. Number of Users[1] and Logins per Month: Tuberculosis Genotyping Information Management System, July–December 2010

Month	No. Unique Users	No. Logins
July	289	2,667
August	312	2,938
September	318	2,958
October	341	2,618
November	348	2,652
December	349	2,173

[1] Only includes users at the state and local level, as well as national genotyping laboratory users. CDC users are not included.

Table 9. Timeliness of Tuberculosis Genotyping Results: Tuberculosis Genotyping Information Management System[1], July–December 2010

Time	Median Time (weeks)	Interquartile Range (weeks)
From specimen collection until receipt at genotyping lab	8.9	6.1–12.3
From receipt at genotyping lab until genotyping result	1.4	0.6–1.3

[1] N=2,746

Table 10. Timeliness of Tuberculosis Genotyping Surveillance and Reporting: Tuberculosis Genotyping Information Management System[1], July–December 2010

Time	Median Time (weeks)	Interquartile Range (weeks)
From specimen collection until genotype report date[2]	11.9	8.1–16.3
From specimen collection until surveillance upload date[3]	11.6	7.4–17.7
From specimen collection until linking date[4]	13.6	9.2–19.0

[1] N=2,746
[2] Genotype Report Date: date genotyping results entered by the genotyping lab into TB GIMS
[3] Surveillance Upload Date: date surveillance data reported to CDC uploaded from NTSS to TB GIMS
[4] Linking Date: date the state case number (for a specific genotyped isolate) entered into TB GIMS by the state TB program to link genotype results to surveillance records

Table 11. Time from Specimen Collection to Record Completion Date[1]: Tuberculosis Genotyping Information Management System[2], July–December 2010

Month	Median Time (weeks)	Interquartile Range (weeks)
July	22	15–30
August	20	14–26
September	19	13–22
October	16	12–19
November	13	10–15
December	11	9–14

[1] Record completion date defines the first date a) genotyping results are available, b) surveillance data has been uploaded, and c) linking has occurred in TB GIMS—once all three steps are complete, the record is available to TB GIMS users.
[2] N=2,746

TB Genotyping Slide Set

TB Genotyping Slide #1

Tuberculosis Genotyping in the United States

Tuberculosis Genotyping Information Management System
Highlights from 2004–2010

Division of Tuberculosis Elimination
Centers for Disease Control and Prevention

Nomenclature for Tuberculosis Genotyping in the United States

Spoligotype:
00000000003771

Initial 12-locus MIRU-VNTR:
223325173533

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

PCRType:
PCR00002

\+

Additional 12-locus MIRU-VNTR:
444534423428[1]

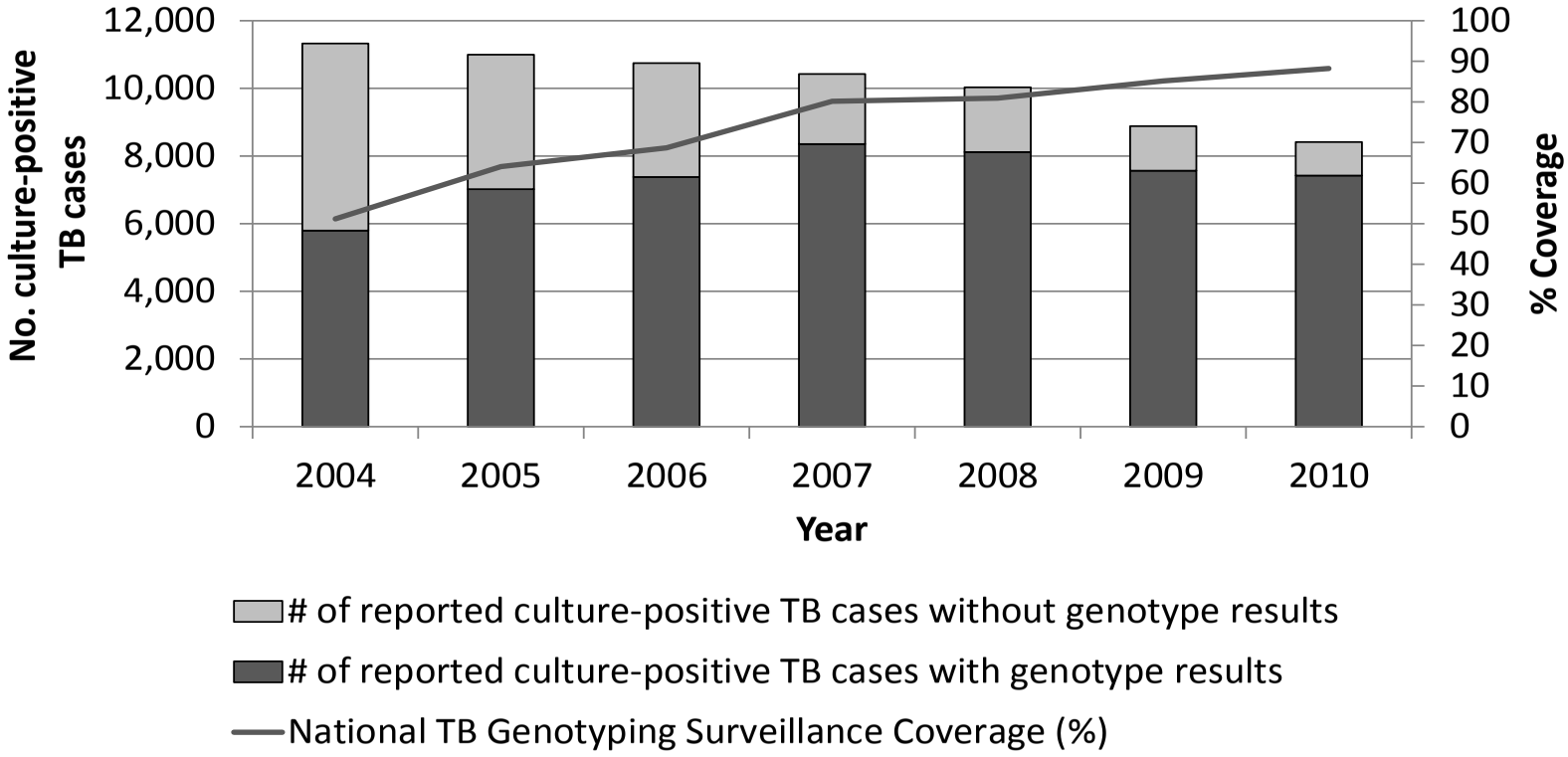
Sequentially assigned for each unique spoligotype and 24-locus MIRU-VNTR combination

GENType
G00010

[1] The complete set of 24 loci is referred to as 24-locus MIRU-VNTR. The additional 12 loci are interpreted with equal weight as the initial 12 loci.

TB Genotyping Slide #3

National Tuberculosis Genotyping Surveillance Coverage[1] by Year: United States[2], 2004–2010[3]

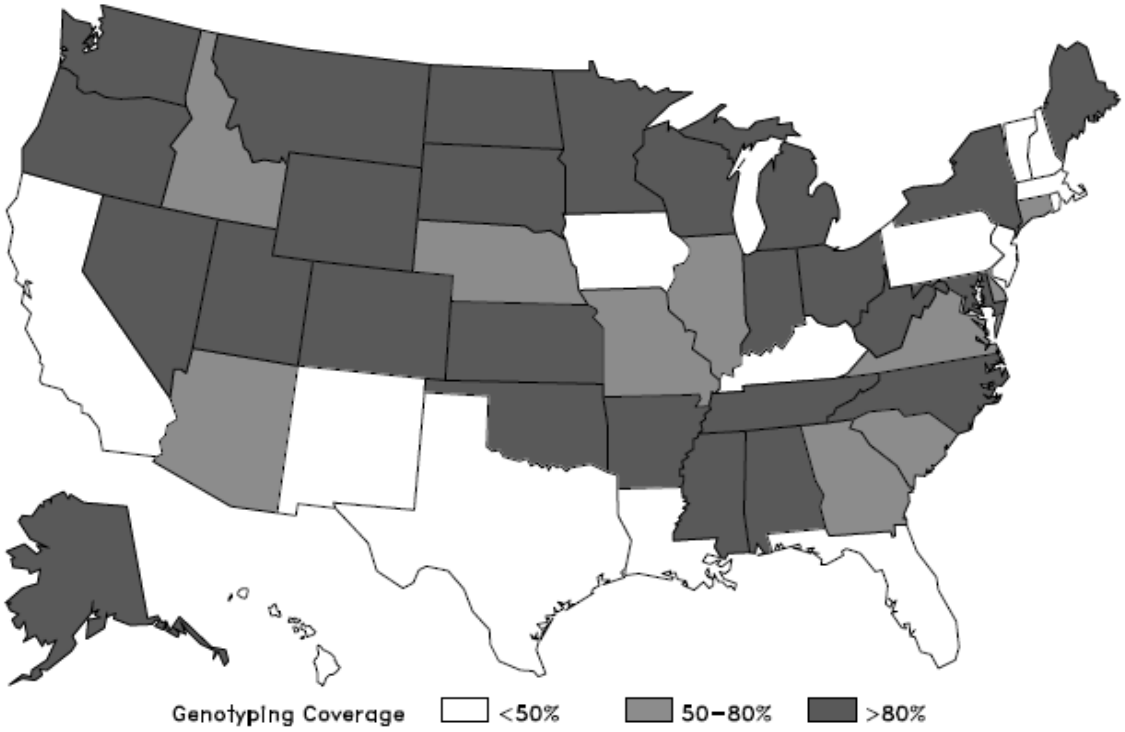


[1] The proportion of positive cultures with at least one genotyped isolate

[2] Includes 50 states and the District of Columbia

[3] Ghosh S, Moonan PK, Cowan L, Grant J, Kammerer S, Navin TR. Tuberculosis Genotyping Information Management System: Enhancing tuberculosis surveillance in the United States. Infect Genet Evol. 2012;12 (4):782–788.

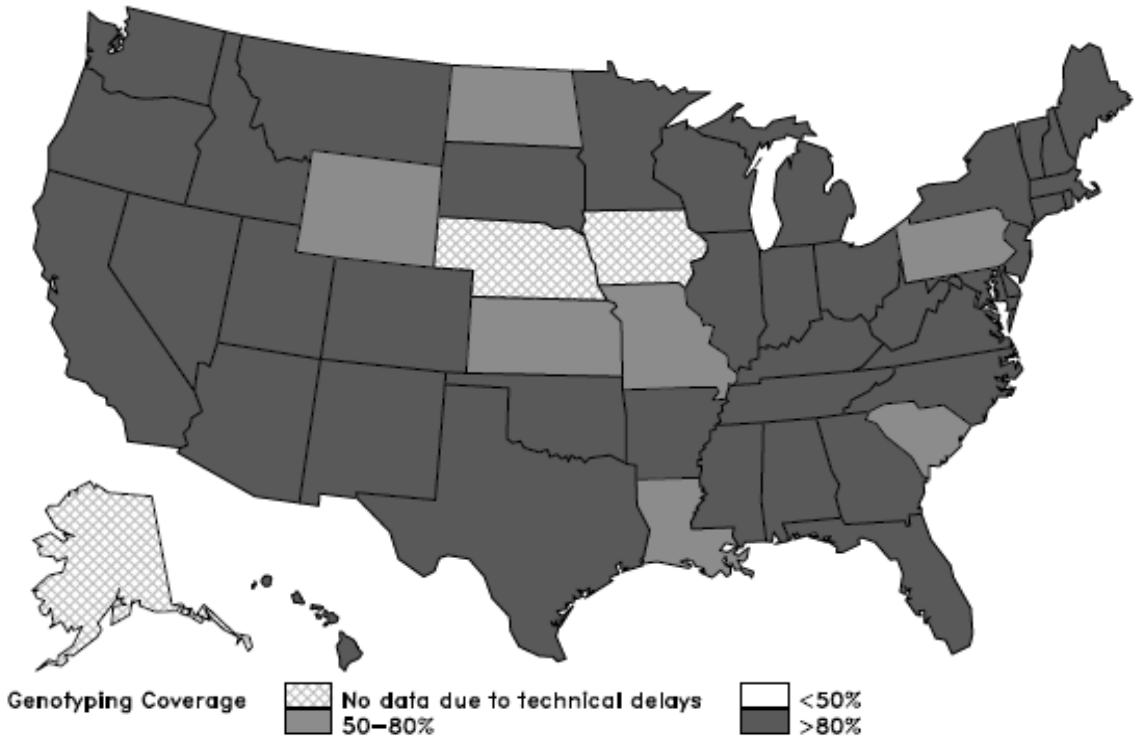
Tuberculosis Genotyping Surveillance Coverage[1]: United States, 2004



[1] The proportion of positive cultures with at least one genotyped isolate

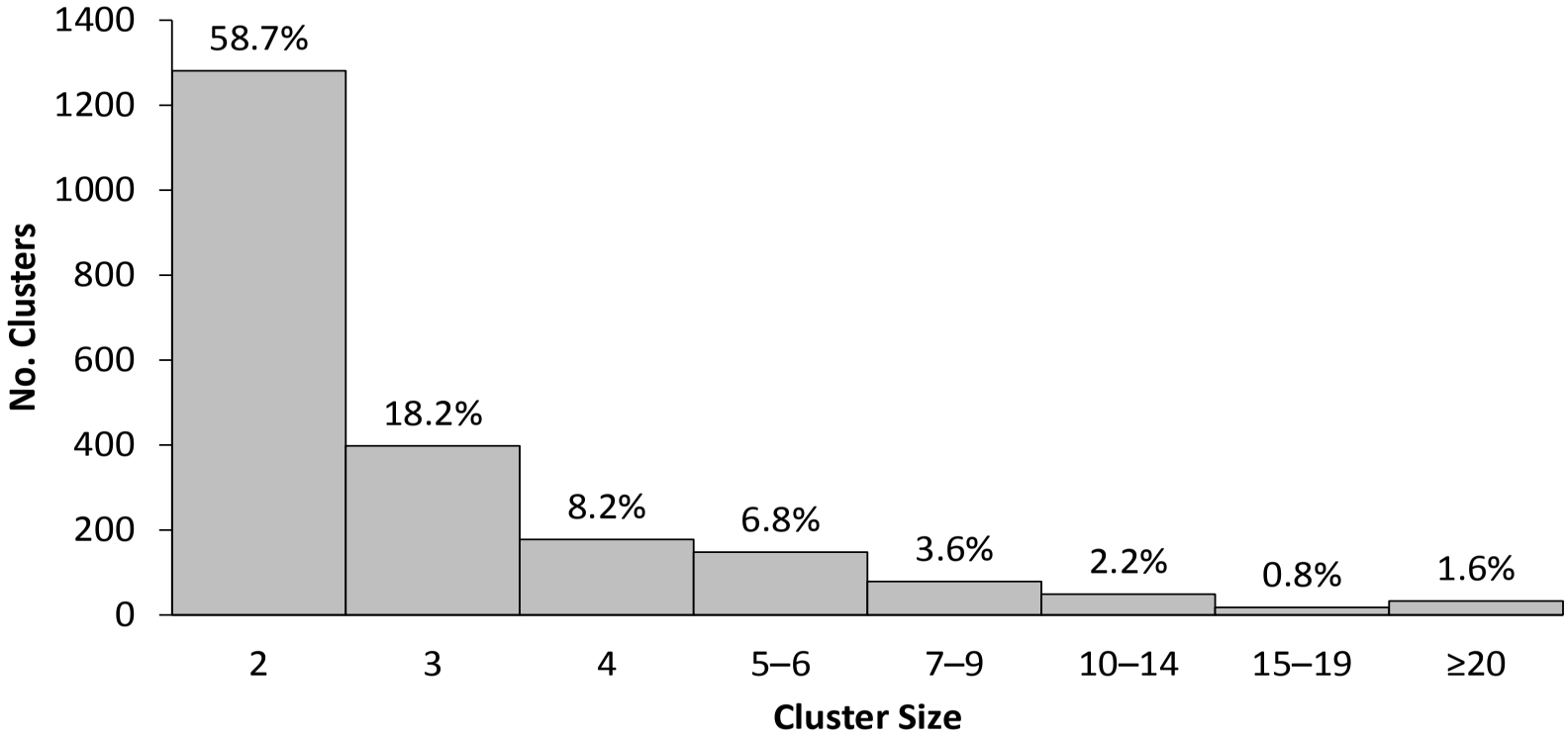
TB Genotyping Slide #5

Tuberculosis Genotyping Surveillance Coverage[1]: United States, 2010



[1] The proportion of positive cultures with at least one genotyped isolate

Number of County-based Tuberculosis Genotype Clusters[1] by Cluster Size: United States[2], 2008–2010

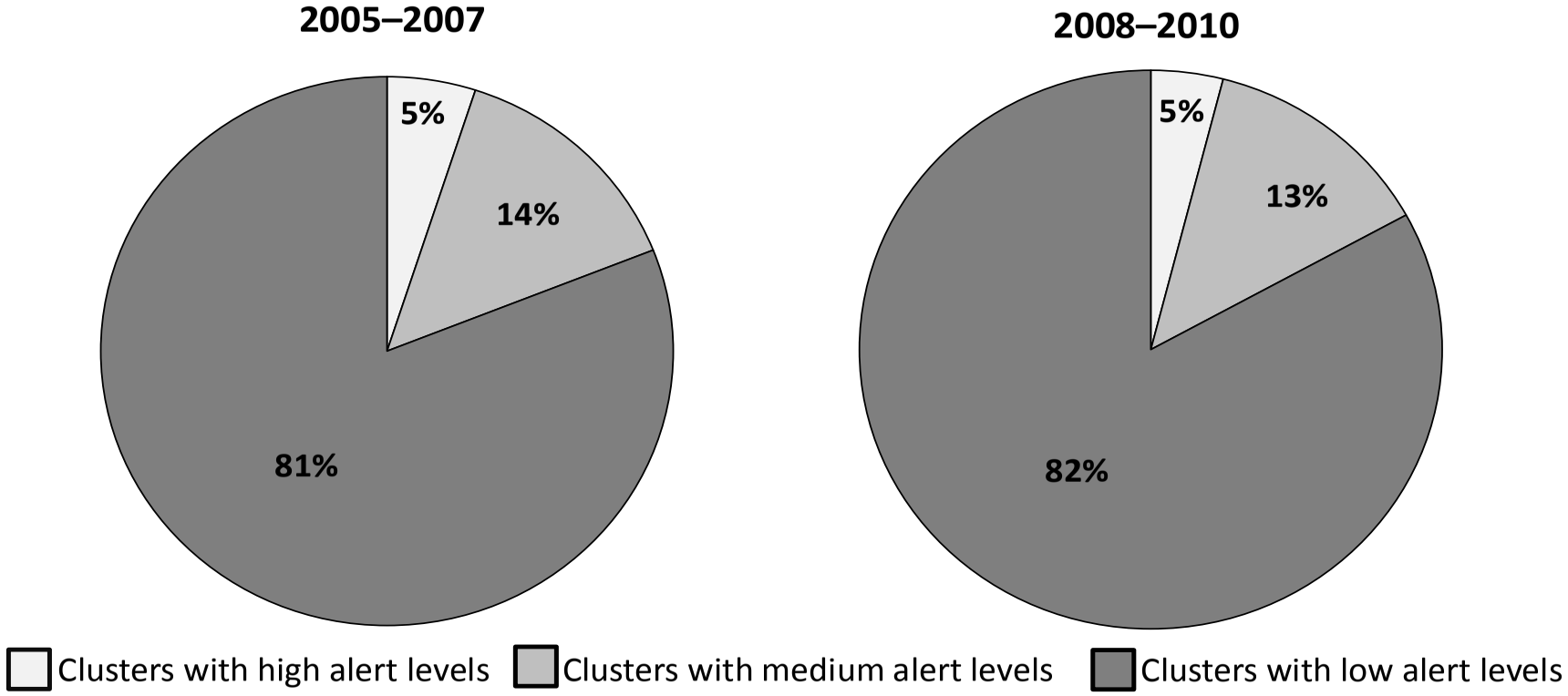


[1] Genotype cluster is defined as two or more *M. tuberculosis* isolates that share matching genotypes in a county during a specified time period.

[2] Includes 50 states and District of Columbia

TB Genotyping Slide #7

Percent of County-based Tuberculosis Clusters[1] by Alert Level[2,3] : United States, 2005–2010

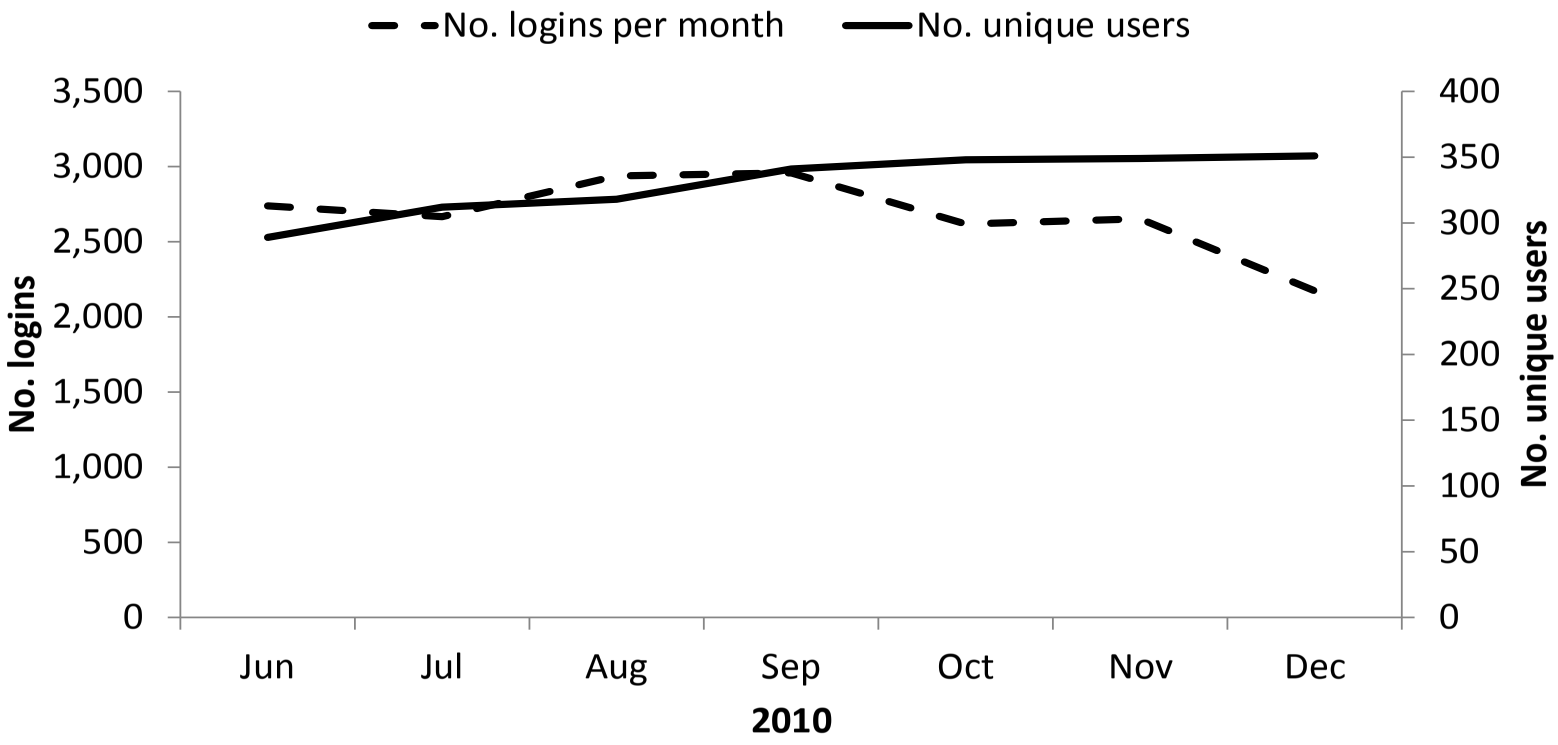


[1] Genotype cluster is defined as two or more *M. tuberculosis* isolates that share matching genotypes in a county during a specified time period.

[2] The alert level is determined by the log likelihood ratio (LLR) for a given cluster over a 3-year period of time. A low alert level is based on LLR <5.1. A medium alert level is based on LLR of 5.1–10. A high alert level is based on LLR >10.

[3] Based on PCRType

Number of Users[1] and Logins per Month in TB GIMS[2]: July–December 2010

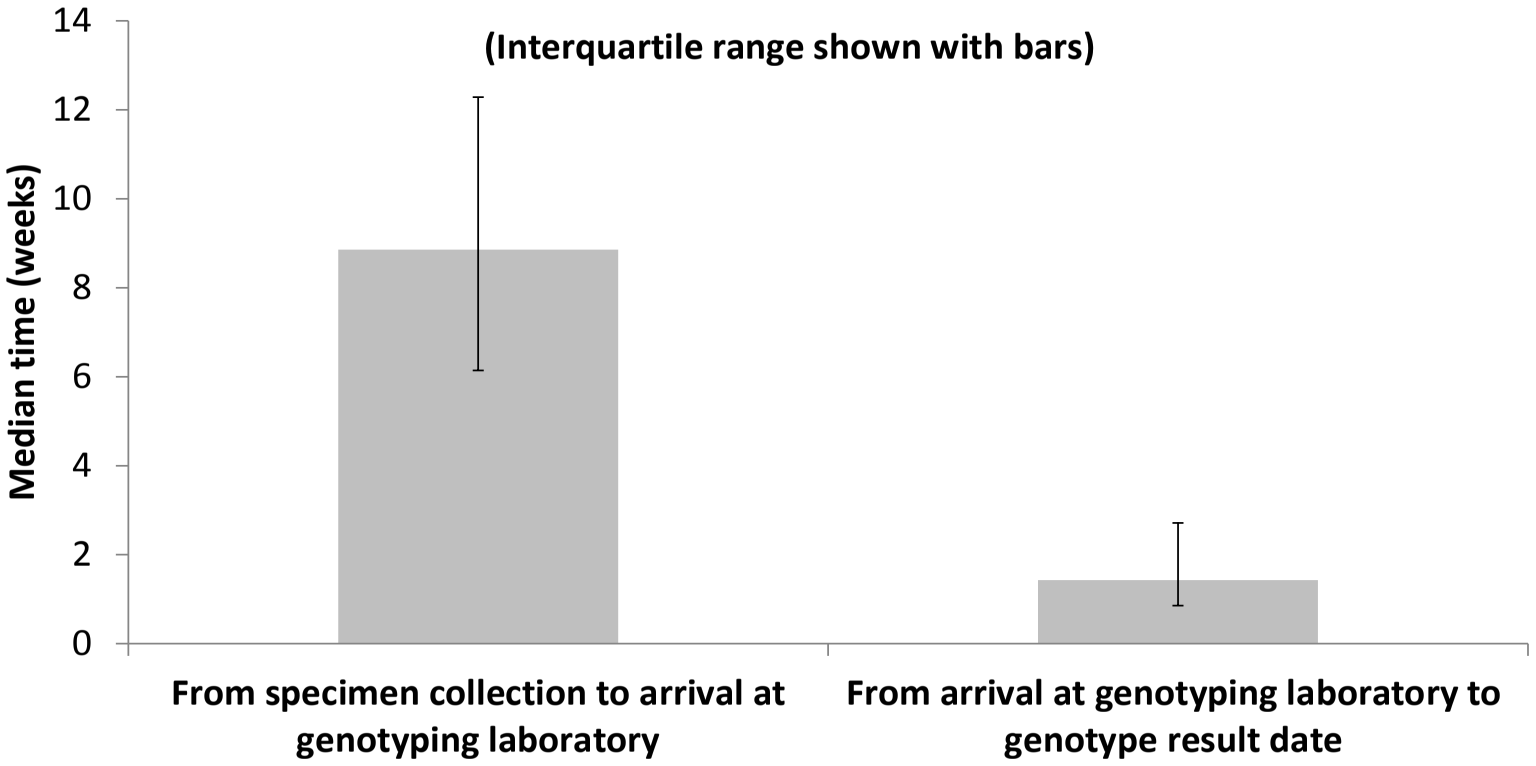


[1] Only includes users at the state and local level, as well as national genotyping laboratory users. CDC users are not included.

[2] Tuberculosis Genotyping Information Management System

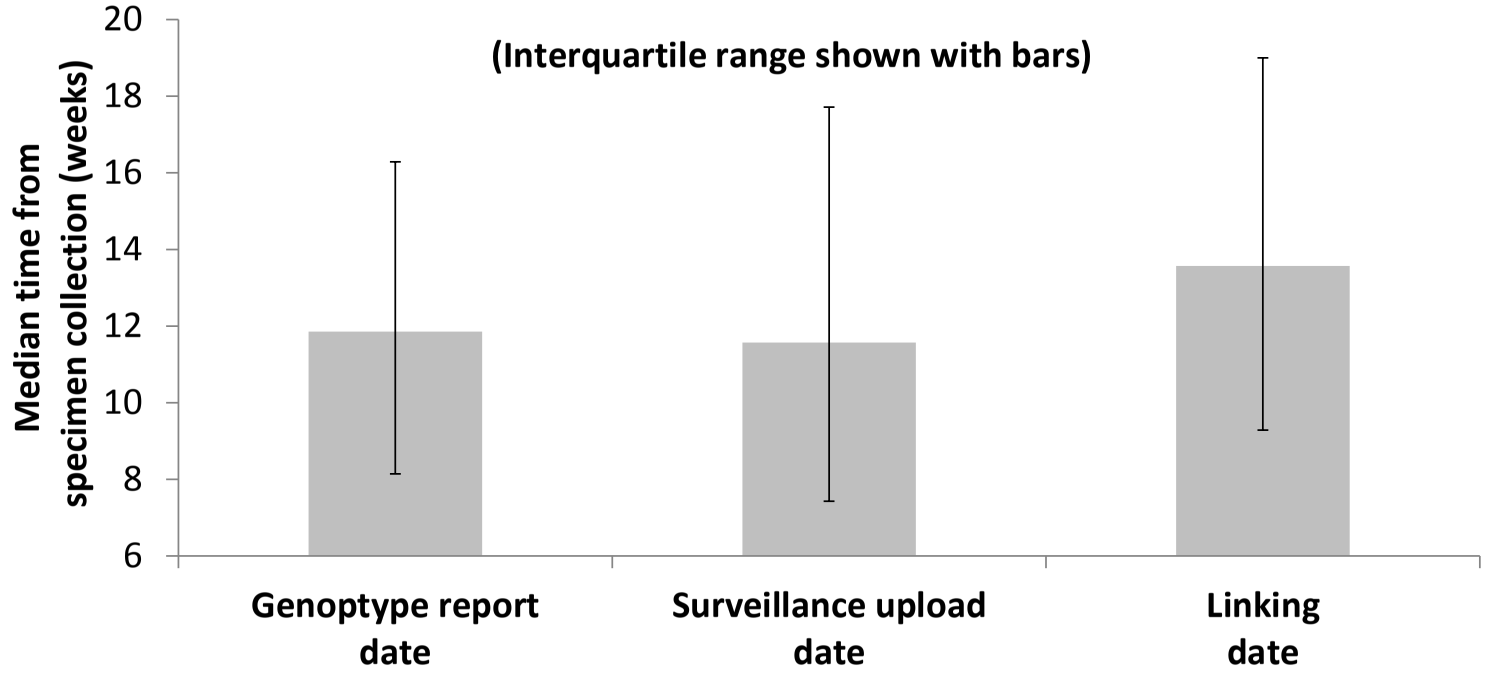
TB Genotyping Slide #9

Timeliness of Genotyping Results in TB GIMS[1]: July–December 2010 (N=2,746)



[1] Tuberculosis Genotyping Information Management System

Timeliness of Genotyping Surveillance and Reporting in TB GIMS[1]: July–December 2010 (N=2,746)



[1] Tuberculosis Genotyping Information Management System

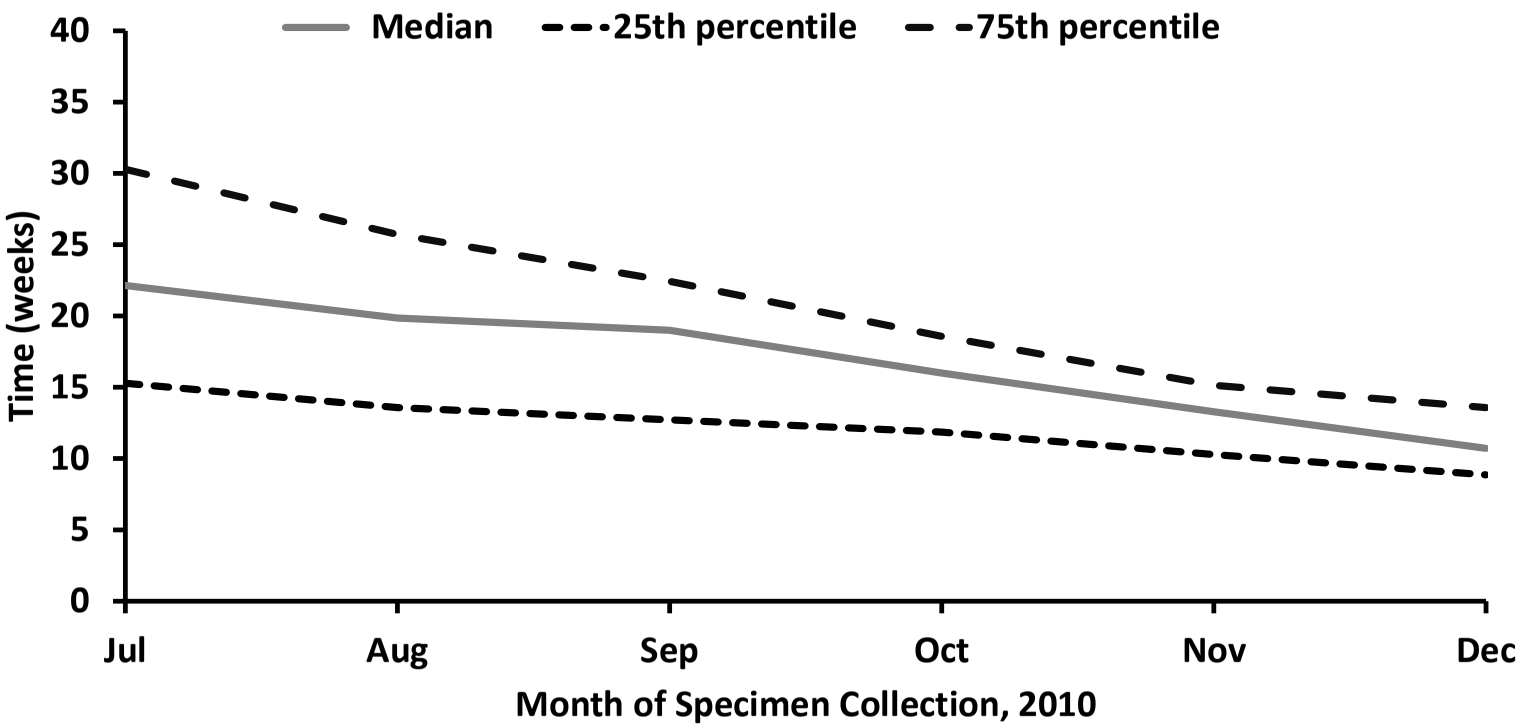
Genotype report date: Date genotyping results entered by the genotyping lab into TB GIMS

Surveillance upload date: Date surveillance data reported to CDC uploaded from NTSS to TB GIMS

Linking date: Date the state case number (for a specific genotyped isolate) entered into TB GIMS by the state TB program to link genotype results to surveillance records

TB Genotyping Slide #11

Time From Specimen Collection to Record Completion Date[1] in TB GIMS[2]: July–December 2010 (N=2,746)



[1] Record completion date defines the first date a) genotyping results are available, b) surveillance data has been uploaded, and c) linking has occurred in TB GIMS—once all three steps are complete, the record is available to TB GIMS users.

[2] Tuberculosis Genotyping Information Management System

Glossary

Glossary

Alert Level
A mechanism used by TB GIMS to notify users of genotype clusters, possibly representing TB outbreaks, in a specific county. The alert level is determined by the log likelihood ratio (LLR) for a given cluster. This is calculated automatically by TB GIMS and is updated whenever a new case is added to a genotype cluster. Email notifications are generated whenever an alert level changes from a "low" LLR (0–5) to "medium" LLR (5.1–10) or "high" LLR (>10), or from a "medium" LLR to a "high" LLR.

Cluster investigation
A cluster investigation identifies epidemiologic links between TB patients whose isolates have matching genotypes. It may consist of reviewing information from public health and medical records and interviewing case managers and outreach workers. It can also involve re-interviewing TB patients.

DNA genotyping
DNA genotyping is a laboratory approach that provides a description of the genetic makeup of a *M. tuberculosis* complex isolate.

Epidemiologic link (epi link)
An epidemiologic link is a characteristic that two TB patients share that explains where, when, and how *M. tuberculosis* could have been transmitted between them. An epidemiologic link could be a location where the two persons spent time together or an activity that brought them together.

Geospatial analysis
Geospatial analysis is an approach to applying statistical methods and to geographically based data. The log likelihood ratio utilizes the geospatial concentration of a given TB genotype in comparison to geospatial distribution of other TB genotypes.

Genotype
The designation that represents one or more of the three genotyping techniques used for *M. tuberculosis*: spoligotyping, MIRU-VNTR analysis, and IS6110-based RFLP. These designations were developed to facilitate communication of genotyping information within and between TB programs.

Genotyping cluster
A genotyping cluster consists of two or more cases in a jurisdiction during a specified time period with *M. tuberculosis* isolates that share matching genotypes. The jurisdiction and time period used vary based on the specific application of the term cluster. Within TB GIMS, a single county and a 3-year time period are used to define a cluster.

GENType
A designation for each a unique combination of spoligotype and 24-locus MIRU–VNTR results. GENType is designated as ‘‘G’’ followed by five digits, which are assigned sequentially to every genotype identified in the U.S. (e.g., G00017).

IS6110 RFLP
Insertion sequence 6110 (read "I-S-sixty-one-ten") is a genetic element unique to members of the *M. tuberculosis* complex. IS6110-based restriction fragment length polymorphism (RFLP) analysis was the first widely used method for genotyping *M. tuberculosis* isolates.

LLR (log likelihood ratio)
The measure of the geographic concentration of a specific genotype in a county, compared to the national distribution of that same genotype over a 3-year period. The higher the LLR, the greater the possibility that the local genotype cluster within the county represents an unexpected geospatial concentration, which might indicate recent transmission of *M. tuberculosis*.

Linking
In TB GIMS, linking refers to the process of connecting genotyping results with a reported TB case from the National TB Surveillance System (NTSS). This step is essential to ensuring that risk factor and geographic data can be viewed in TB GIMS for genotype clusters.

MIRU-VNTR
Mycobacterial interspersed repetitive unit–variable number tandem repeat typing analysis. MIRU-VTNR is a PCR-based genotyping assay. The CDC genotyping program currently performs 24-locus MIRU-VNTR analysis on every isolate submitted by one of the national genotyping laboratories.

***M. tuberculosis* complex**
Often abbreviated MTC, a group of closely related mycobacterial species that can cause LTBI and TB disease (i.e., *M. tuberculosis, M. bovis, M. bovis BCG, M. africanum, M. canetti, M. microti, M. pinnipedii,* and *M. mungi*). In humans, most TB is caused by *M. tuberculosis*.

NTGS
The National TB Genotyping Service has provided TB genotyping to local and state TB control programs since 2004. Two national genotyping laboratories, located in Michigan and California, provide genotyping services at no cost to the patients, healthcare providers, or health departments.

NTSS
National TB Surveillance System administered by CDC. NTSS collects surveillance data through an electronic reporting registry. Data collected include socio-demographic, clinical, and risk factor variables.

PCR
Polymerase chain reaction. The national genotyping laboratories routinely use two PCR-based techniques, spoligotyping and MIRU-VNTR analysis.

PCRType
A designation for each a unique combination of spoligotype and 12-locus MIRU–VNTR results. PCRType is designated as ‘‘PCR’’ followed by five digits, which are assigned sequentially to every genotype identified in the U.S. (e.g., PCR01974).

Relapse vs. reinfection
A case of relapsed TB represents a worsening of signs and symptoms of disease after a period of improvement, caused by the same strain of *M. tuberculosis*. TB that represents a reinfection is disease caused by a second infection (often with a strain that is different from the strain that caused the initial infection). Genotyping the initial and the subsequent *M. tuberculosis* isolate might distinguish these two possibilities.

RFLP
Restriction fragment length polymorphism. A genotyping technique based on measuring the number and length of specific DNA fragments that are cut using specific restriction enzymes.

RVCT
Report of a Verified Case of TB. National surveillance data on patients with tuberculosis is recorded on this form, and subsequently reported to CDC’s National TB Surveillance System (NTSS).

Spoligotyping
Spacer oligonucleotide genotyping. A genotyping technique based on spacer sequences found in the direct repeat region in the chromosomes (genetic makeup) of the *M. tuberculosis* complex. The “spoligotype” is reported as a 15-digit number.