USE OF NUCLEIC ACID AMPLIFICATION TESTS FOR DETERMINING RISK OF TUBERCULOSIS TRANSMISSION

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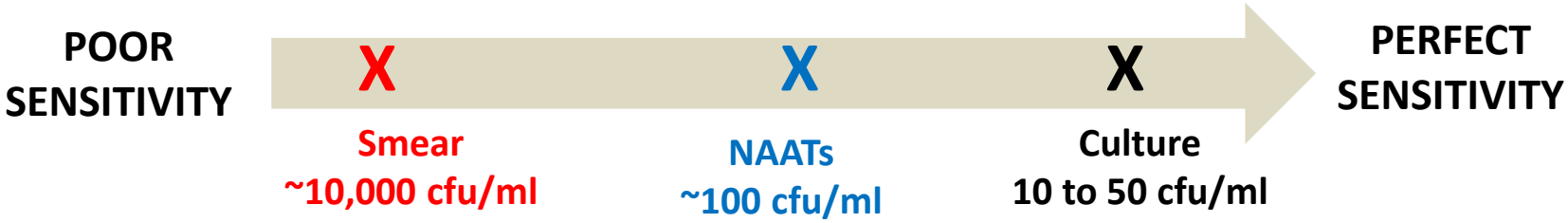
Background

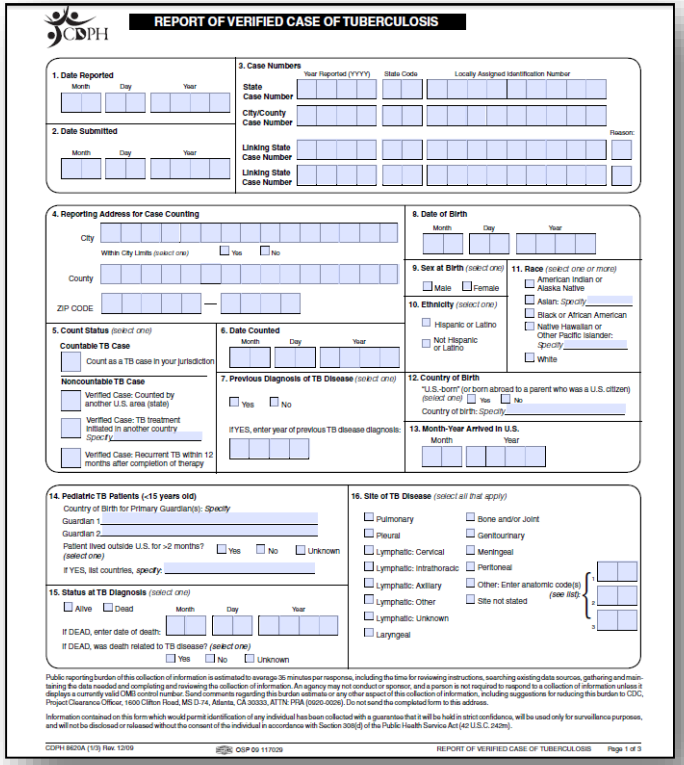
- Public health management of TB patients based heavily on sputum smear microscopy
- However, smear-negative patients contribute considerably to TB transmission
  - Behr et al, Lancet 1999;353:444
- Emergence of **nucleic acid amplification tests (NAATs)** more sensitive for detecting TB
  - Enhanced Amplified Mycobacterium Tuberculosis Direct Test ('MTD', Gen-Probe, CA)
  - Xpert MTB/RIF (Cepheid, CA; FDA-cleared, being rolled out globally)



For pulmonary TB patients in the state of Maryland from Jan 2004 to Sept 2009 (when MTD and genotyping was routinely performed on TB isolates)…
We can compare the infective potential of sputum NAAT-negative vs. sputum NAAT-positive patients, using *Mtb* genotyping as a proxy for transmission

Source documents

1. RVCT



REPORT OF VERIFIED CASE OF TUBERCULOSIS

CDPH

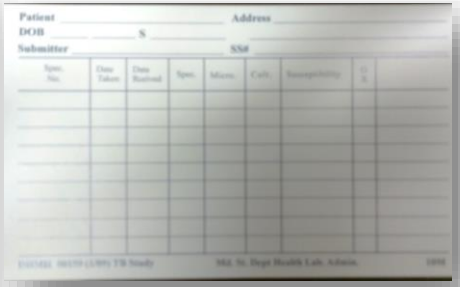
1. Date Reported — Month / Day / Year
2. Date Submitted — Month / Day / Year
3. Case Numbers — Year Reported (YYYY) / State Code / Locally Assigned Identification Number
State Case Number
City/County Case Number
Reason:
Linking State Case Number
Linking State Case Number
4. Reporting Address for Case Counting
City
Within City Limits (select one) Yes No
County
ZIP CODE
5. Count Status (select one)
Countable TB Case
Count as a TB case in your jurisdiction
Noncountable TB Case
Verified Case: Counted by another U.S. area (state)
Verified Case: TB treatment initiated in another country
Specify
Verified Case: Recurrent TB within 12 months after completion of therapy
6. Date Counted — Month / Day / Year
7. Previous Diagnosis of TB Disease (select one) Yes No
If YES, enter year of previous TB disease diagnosis:
8. Date of Birth — Month / Day / Year
9. Sex at Birth (select one) Male Female
10. Ethnicity (select one) Hispanic or Latino; Not Hispanic or Latino
11. Race (select one or more) American Indian or Alaska Native; Asian: Specify; Black or African American; Native Hawaiian or Other Pacific Islander: Specify; White
12. Country of Birth "U.S.-born" (or born abroad to a parent who was a U.S. citizen) (select one) Yes No
Country of birth: Specify
13. Month-Year Arrived in U.S. — Month / Year
14. Pediatric TB Patients (<15 years old)
Country of Birth for Primary Guardian(s): Specify
Guardian 1
Guardian 2
Patient lived outside U.S. for >2 months? (select one) Yes No Unknown
If YES, list countries, specify:
15. Status at TB Diagnosis (select one)
Alive Dead — Month / Day / Year
If DEAD, enter date of death:
If DEAD, was death related to TB disease? (select one) Yes No Unknown
16. Site of TB Disease (select all that apply)
Pulmonary; Pleural; Lymphatic: Cervical; Lymphatic: Intrathoracic; Lymphatic: Axillary; Lymphatic: Other; Lymphatic: Unknown; Laryngeal; Bone and/or Joint; Genitourinary; Meningeal; Peritoneal; Other: Enter anatomic code(s) (see list); Site not stated

Public reporting burden of this collection of information is estimated to average 35 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to CDC, Project Clearance Officer, 1600 Clifton Road, MS D-74, Atlanta, GA 30333, ATTN: PRA (0920-0026). Do not send the completed form to this address.

Information contained on this form which would permit identification of any individual has been collected with a guarantee that it will be held in strict confidence, will be used only for surveillance purposes, and will not be disclosed or released without the consent of the individual in accordance with Section 308(d) of the Public Health Service Act (42 U.S.C. 242m).

CDPH 8639A (1/3) Rev. 12/09 — OSP 09 117029 — REPORT OF VERIFIED CASE OF TUBERCULOSIS — Page 1 of 3

2. Laboratory

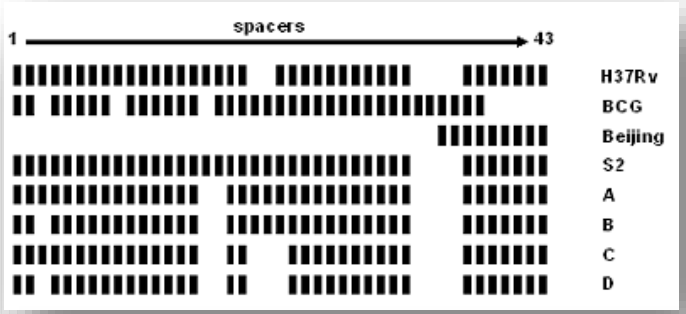


Patient — Address
DOB — S
Submitter — SS#

Spec. No.	Date Taken	Date Received	Spec.	Micro.	Cult.	Susceptibility	C S

MTD/Smear/Culture:
Dates when first specimen for culture/smear used to determine chronology

3. Genotyping



	MIRU locus name											
	02	04	10	16	20	23	24	26	27	31	39	40
No. of repeats	2	3	2	2	3	4	2	5	3	3	2	2

MIRU designation: 232234253322

Epidemiologic Linking
To approximate transmission clusters (12-loci MIRU VNTR + spoligotyping)

Descriptive:
Examines characteristics (homeless, HIV, imaging data, occupation, etc) of participants

4. Contact Investigation Records

Priority for Investigation	*High/Med*	*Low*
Number of Contacts	5	0
Number Evaluated	4	0
TB Disease	0	0
Window Treatment	0	0
Latent Infection	1	0
Candidates for TLTBI	1	0
Started Treatment	1	0

Design/Methods: Definitions

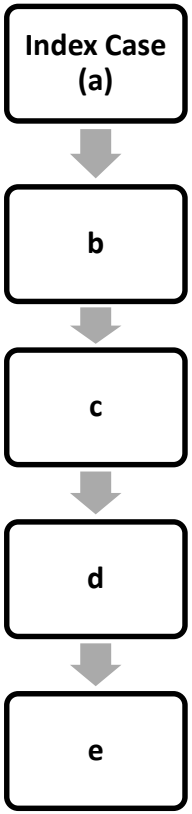
- NAAT negative: at least **2** neg NAAT (MTD) results at time of 1st culture-pos specimen (if any positive MTD = NAAT positive)
  - *An MTD (-) result was repeated 94% of time, of which 83% remained MTD (-)*

- Smear negative: at least **3** neg smear microscopy results at time of 1st culture positive specimen (if any positive smear= smear positive)

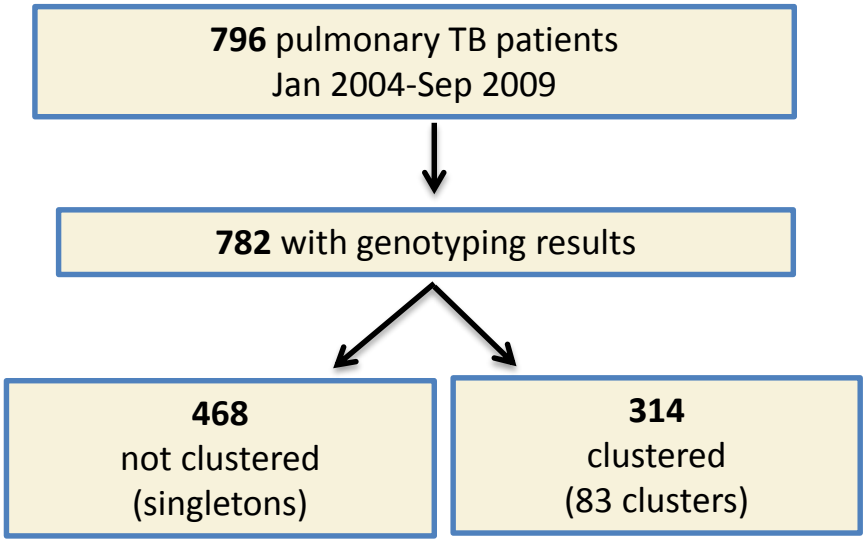
Design/Methods

Primary Analysis: Transmission approximated by genotypic links

1) Cases with *Mtb* isolates having the same fingerprint (spoligo + MIRU 12-loci) assigned to clusters.
2) Cases ordered chronologically by date of 1st culture-positive sputum.
3) Cluster categorized according to index case (1st case in the cluster)
4) Clusters excluded from respective analysis if index case smear or NAAT unknown



RESULTS:



NAAT NEG	NAAT POS	NAAT UNK		SM NEG	SM POS	SM UNK
N=39	N=418	N=325		N=167	N=483	N=132
39	42	49	**Age**	41	42	50
79%	71%	65%	**Born outside USA**	80%	70%	61%
5%	**12%**	**12%**	**HIV pos**	**11%**	**11%**	**19%**
15%	**50%**	**14%**	**CXR cavitation**	**12%**	**55%**	**19%**
13.5	**2.3**	**13.4**	**Days to Rx start**	**15.7**	**2.2**	**10.2**

RESULTS: Primary Analysis

	RR of starting a cluster	RR of transmitting as a cluster case	Interpretation
Behr et al, 1999 SMEAR (-) vs. (+)		***0.22*** *(95% CI: 0.16-0.32)*	*SM(-)* ***78%*** *less likely to transmit TB than SM(+)*
SMEAR (-) vs. (+)	**0.82** (95% CI: 0.49-1.42)	**0.29** (95% CI: 0.25-0.41)	*SM(-)* ***71%*** *less likely to transmit TB than SM(+)*

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NAAT (-) vs. (+)	**0.40** (95% CI: 0.02-1.72)	**0.17** (95% CI: 0.01-0.06)	*NAAT(-)* ***83%*** *less likely to transmit TB than NAAT(+)*
Among SM (-): NAAT (-) vs. (+)	**0.67** (95% CI: 0.02-3.95)	**0.50** (95% CI: 0.02-2.80)	*NAAT(-)/SM(-) maybe less likely to transmit TB than NAAT(+)/SM(-)*

Relative transmission risk for NAAT(-)/ NAAT(+) compared with that of SM(-)/SM(+) is 0.59

Revisiting our Definitions

- *<u>NAAT negative</u>: at least **2** neg NAAT (MTD) results at time of 1st culture-pos specimen (if any positive MTD = NAAT positive)*
- *<u>Smear negative</u>: at least **3** neg smear microscopy results at time of 1st culture positive specimen (if any positive smear= smear positive)*

NOW…

- **As we found no cases of SMEAR(+)/NAAT (-), assume that SMEAR (+) implicates NAAT (+)**
  → <u>46</u> previously NAAT-unknown are now NAAT (+)

RESULTS: if SM(+) implies MTD(+)

		RR of starting a cluster	RR of transmitting as a cluster case	Interpretation
SMEAR (-) vs. (+)		**0.82** (95% CI: 0.49-1.42)	**0.29** (95% CI: 0.25-0.41)	*SM(-) **71%** less likely to transmit TB than SM(+)*
NAAT (-) vs. (+)	**SM(+) ≠ NAAT (+)**	**0.40** (95% CI: 0.02-1.72)	**0.17** (95% CI: 0.01-0.06)	*NAAT(-) **83%** less likely to transmit TB than NAAT(+)*
	SM(+) → NAAT(+)	**0.39** (95% CI: 0.02-1.72)	**0.13** (95% CI: 0.01-0.06)	*NAAT(-) **87%** less likely to transmit TB than NAAT(+)*
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	SM(+) → NAAT(+)	**0.72** (95% CI: 0.02-3.95)	**0.54** (95% CI: 0.02-3.88)	

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- *<u>Smear negative</u>: at least **3** neg smear microscopy results at time of 1st culture positive specimen (if any positive smear= smear positive)*

NOW…

☑ As we found no cases of SMEAR(+)/NAAT (-), assume that SMEAR (+) implicates NAAT (+)

→ <u>46</u> previously NAAT-unknown are now NAAT (+)

☐ **Redefine NAAT negative to require only 1 MTD (-) result (on 1st culture-positive specimen)**

→ For this definition, can no longer assume SMEAR(+) implies NAAT (+)

RESULTS: Require only 1 NAAT (-) test

		RR of starting a cluster	RR of transmitting as a cluster case	Interpretation
SMEAR (-) vs. (+)		**0.82** (95% CI: 0.49-1.42)	**0.29** (95% CI: 0.25-0.41)	*SM(-) **71%** less likely to transmit TB than SM(+)*
NAAT (-) vs. (+)	**NAAT (-) x 2**	**0.40** (95% CI: 0.02-1.72)	**0.17** (95% CI: 0.02-0.60)	*NAAT(-)x2 **83%** less likely to transmit TB than NAAT(+)*
	NAAT (-) x1	**0.49** (95% CI: 0.13-1.24)	**0.21** (95% CI:0.15-0.46)	*NAAT(-) x1 **79%** less likely to transmit TB than NAAT(+)*
Among SM (-): NAAT (-) vs. (+)	**NAAT (-) x 2**	**0.67** (95% CI: 0.02-3.95)	**0.50** (95% CI: 0.02-2.80)	*NAAT(-)/SM(-) maybe less likely to transmit TB than NAAT(+)/SM(-)*
	NAAT (-) x1	**0.88** (95% CI: 0.02-3.95)	**0.66** (95% CI:0.17-2.56)	

RESULTS: Require only 1 NAAT (-) test

		RR of starting a cluster	RR of transmitting as a cluster case	Interpretation
SMEAR (-) vs. (+)		**0.82** (95% CI: 0.49-1.42)	**0.29** (95% CI: 0.25-0.41)	*SM(-) **71%** less likely to transmit TB than SM(+)*
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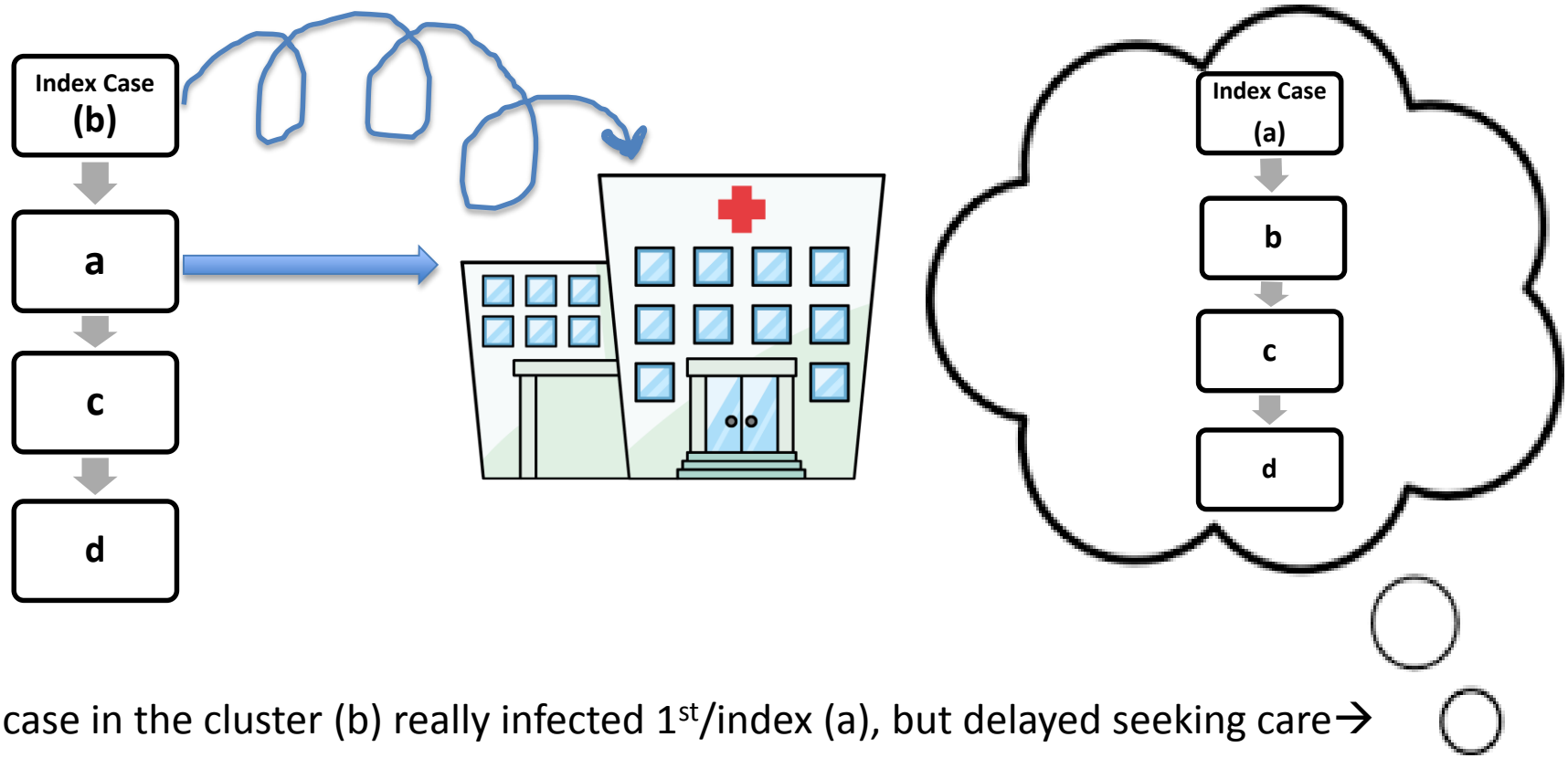
	NAAT (-) x1	**0.88** (95% CI: 0.02-3.95)	**0.66** (95% CI:0.17-2.56)	

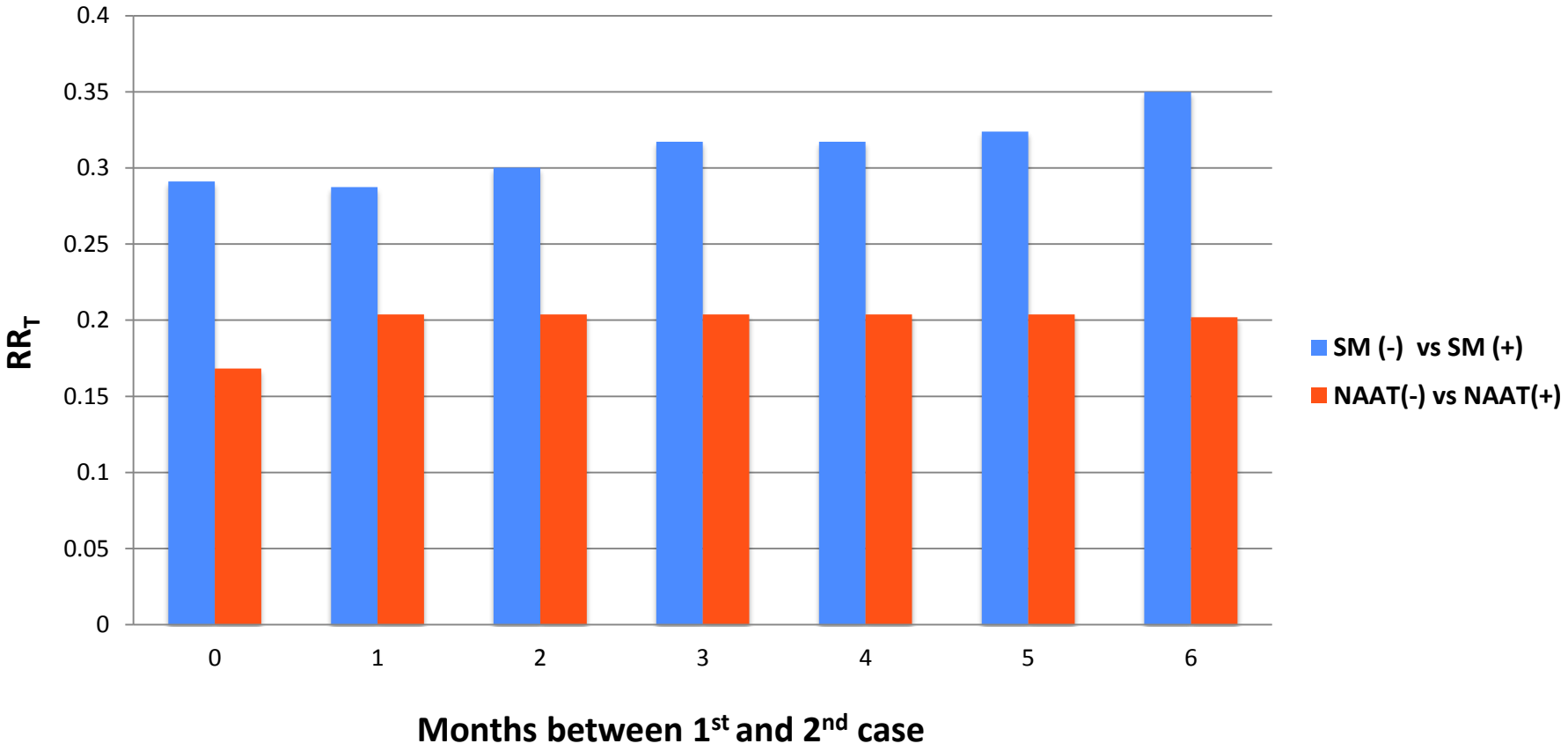
Chronologic Misclassification Bias



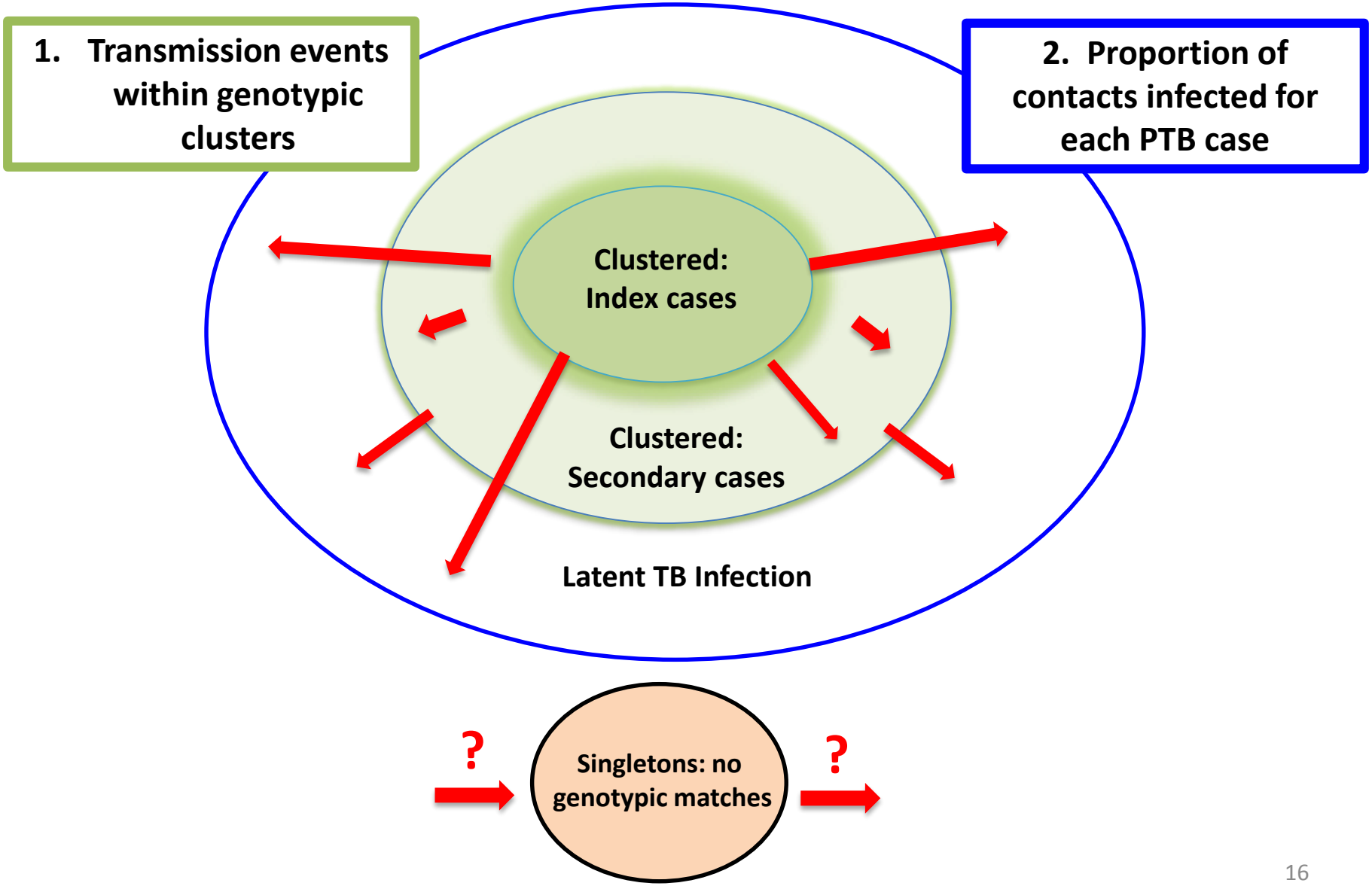
2nd case in the cluster (b) really infected 1st/index (a), but delayed seeking care→

Misclassification of transmission source

Sensitivity Analysis: Relative transmission risk (RR_T) recalculated



How to approximate transmission?



Design/Methods

Secondary Analyses: Transmission approximated by infected contacts

Using contact investigation data for each active case (available for study cases after 2007), we looked at proportion of contacts evaluated who were found to have **a) active b) latent c) active or latent** TB infection

Relative Risk of transmission (RR_T) calculated as:

$$\frac{\text{\# NAAT (-) contacts infected/total \# NAAT (-) contacts evaluated}}{\text{\# NAAT (+) contacts infected/total \# NAAT (+) contacts evaluated}}$$

**Calculation of RR_T also performed based on smear status

Secondary Analysis: RR_T from Contact Investigation

	RR_T Active TB	RR_T Latent TB I	RR_T ALL
SM-/SM+	**0.35 (95% CI 0.02-2.46)**	1.43	1.41
NAAT (-) X1 vs. (+)	**0.00 (95% CI 0.00-12.20)**	1.19	1.15
NAAT (-) X2 vs. (+)	**0.00 (95% CI 0.00-3.86)**	1.42	1.38

Relative risk of active disease in contacts of Smear (-) vs Smear (+) in other developed countries:

Saskatchewan: **0.28** (Gryzbowski et al. Bull Int Union Tuberc 1975; 50: 90-106)

Spain: 0**.47** (Vidal R et al, med clin barc 1997; 108: 361-365)

CONCLUSIONS

1. Transmission risk from sputum NAAT (-) pulmonary TB patients **substantially less (79% if 1 negative NAAT test, 83-87% if 2 negative NAAT tests)** than that from sputum NAAT (+) pulmonary TB patients.

2. Relative order of transmission risk likely:
   smear(+)/ NAAT(+) > smear (-)/NAAT (+) > smear (-)/NAAT (-)

3. Transmission risk approximated from proportion of actively infected contacts may suggest similar findings but statistically inconclusive.

4. Limitations of this study include:
   a) Potential bias due to geographic or temporal undersampling→ sens. analysis
   b) Small number of NAAT (-) patients

5. Findings likely applicable to **GeneXpert MTB/RIF,** which has similar sensitivity as MTD for TB detection[5] and has widely supplanted use of MTD in its global rollout.

NAATs may be valuable public health tools by refining our ability to identify the least transmissible pulmonary TB patients.

REFERENCES

1. Behr M, et al. Lancet 1999;353:444
2. Gryzbowski S, et al. Bull Int Union Tuberc 1975; 50: 90-106
3. Vidal R, et al. Med Clin Barc 1997; 108: 361-365
4. Coll PI, et al. Int J Tuberc Lung Dis. 2003 Sep;7(9):886-91.
5. Boehme CC, et al. N Engl J Med. 2010 Sep 9;363(11):1005-15.

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