



**Evaluation of
Interferon- γ Release Assays
in the Diagnosis of Latent TB Infection in U.S.
Healthcare Workers:**

Preliminary Results of Task Order #18

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On behalf of the
CDC TB Epidemiological Studies
Consortium**

Disclosures

- Advisory Board
 - Cellestis
 - Oxford-Immunotec
- Research Grant
 - Oxford-Immunotec



Background

- LTBI diagnosis and treatment are important components of U.S. TB control
- HCWs are an important group for targeted testing and treatment (~14 million/year)
- QuantiFERON®-TB Gold In-Tube (“QFT”) and T-SPOT®.TB (“T-SPOT”) are FDA-approved
 - Require only 1 client-provider interaction
 - Not affected by BCG
- Limited information on use of these tests longitudinally in HCWs undergoing periodic testing

IGRA Testing in HCWs

Study	N	TST (%)	QFT (%)	T-Spot (%)	Comment
Lee, Taiwan	39	Initial 84.6 Converter 33.3	Initial 10.2 Converter 12.5	–	Contact >1 h associated with + QFT
Stebler, Swiss	777	–	7.6	–	Work place
Khanna, England	171	16.2	7.6	–	Positive result associated with FB for both tests
Casas, Spain	52	0	17.3	23.1	In non BCG vacc. with prev. + TST, associated with degree of exposure and TST diameter
Pollock, □USA	143	100.0	18.0	–	High discordance rates
Vinton, Australia	358	33.0	6.7	–	+ QFT associated with Foreign-birth Time in country High-risk occupation

Serial Testing of 147 HCWs with QFT-in tube



<i>Definition of Conversion % CI)</i>	<i>No. of Conversions</i>	<i>% Incidence of Conversion (95</i>
TST		
1. Increase in ≥ 6 mm to ≥ 10 mm	14	9.5 (5.3-15.5)
2. Increase in ≥ 10 mm to ≥ 10 mm	6	4.1 (1.5-8.7)
QFT		
3. IFN- γ < 0.35 IU/ml to ≥ 0.35 IU/ml	17	11.6 (6.9-17.9)
4. IFN- γ < 0.35 IU/ml to ≥ 0.70 IU/ml	11	7.5 (3.8-13.0)
Combination of TST and QFT		
1 or 3	22	14.9 (9.6-21.8)
2 or 4	11	7.5 (3.8-13.0)
1 and 3	9	6.1 (2.8-11.3)
2 and 4	6	4.1 (1.5-8.7)

Incidence of Reversions Among HCWs*



<i>Baseline IFN-γ response, IU/ml</i>	<i>No. Retested after 18 mo</i>	<i>No. That Received INH (%)</i>	<i>Total Reversions</i>	<i>Incidence of Reversions (%)</i>
0.35-0.69	11	1 (9)	6	6/11 (55)
0.7-1.0	2	0 (0)	1	1/2 (50)
1.1-5.0	9	3 (33)	1	1/9 (11)
>5.0	16	9 (56)	1	1/16 (6)
Total	38	13 (34)	9	9/38 (24%)

* Among HCWs with either QFT+/TST+ results or QFT+/TST- Results at Baseline



Objectives

- To evaluate performance characteristics of QFT and T-SPOT compared with TST for detecting LTBI in HCWs undergoing routine screening
 - Test result stability over time (i.e. conversion, reversion)
 - Reproducibility
 - Test, re-test repeatability
 - Estimated sensitivity and specificity
 - % of failed tests
 - Impact of TST on IGRA results
- To determine costs, cost-effectiveness
- To determine and compare acceptability of tests among participants

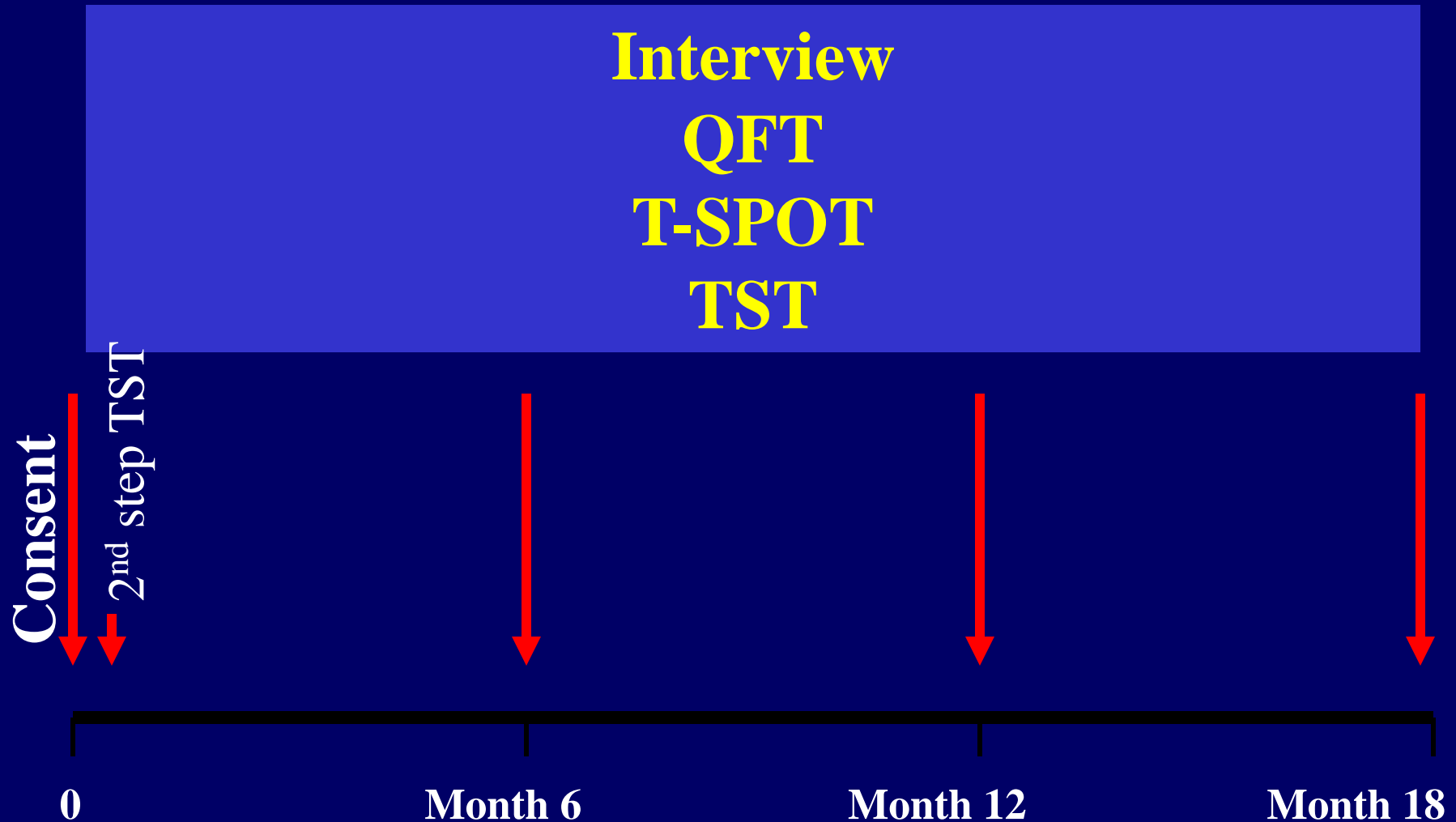


Design and Population

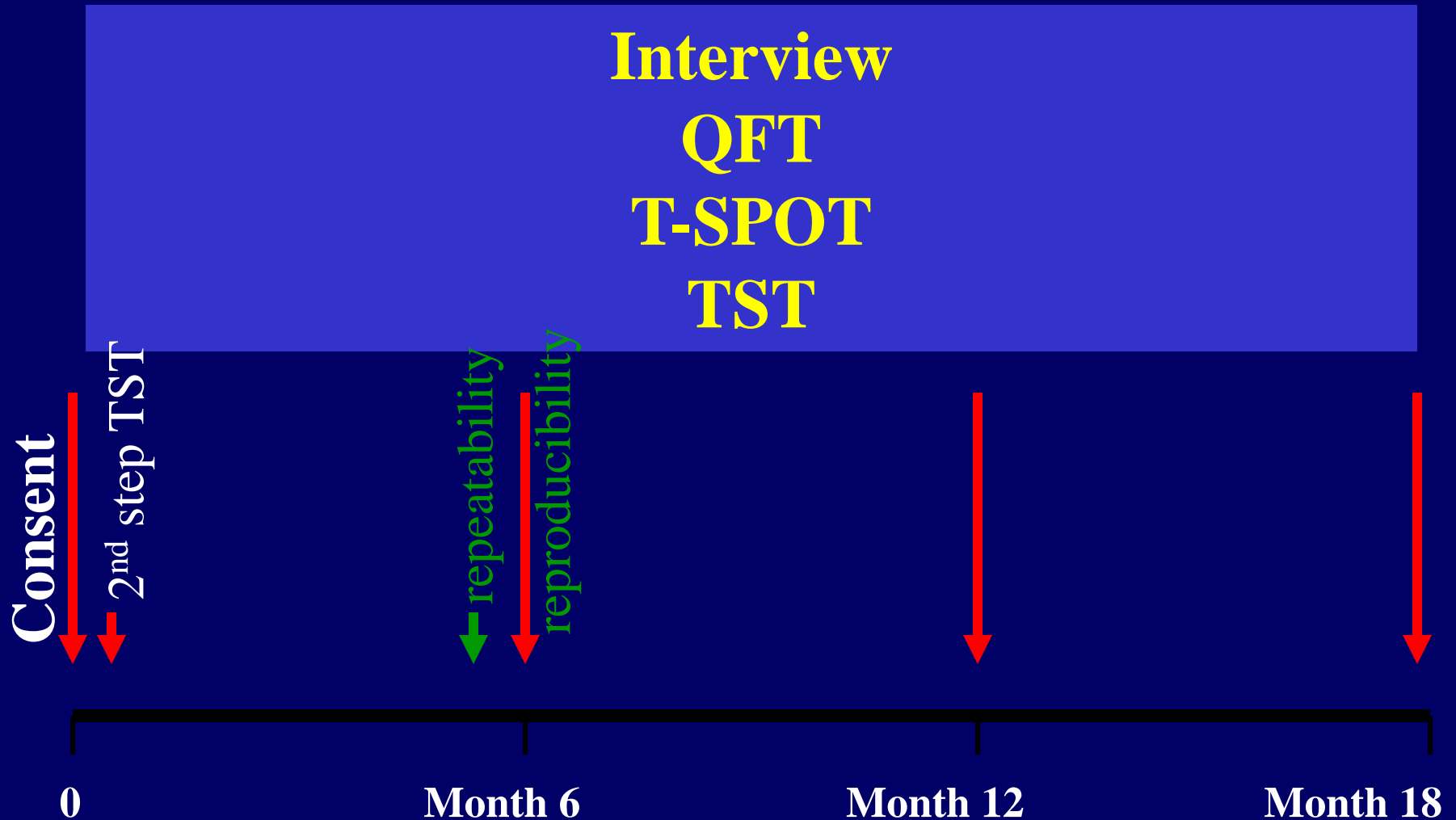
- Longitudinal study
- HCWs undergoing routine LTBI testing
- 4 sites: Denver, Houston, Baltimore, NYC
- Inclusion:
 - ≥ 18 yrs; informed consent; undergoing routine screening
- Exclusion:
 - Current or prior active TB; TST within 6 months prior to enrollment
- Target sample size 2500

Intervention

Target sample size: 2500 enrolled, 2000 completers



Intervention





Testing Methods

- TST
 - Administered, interpreted by study-trained personnel
 - Tubersol
- QuantiFERON®-TB Gold In-Tube (“QFT”) Cellestis, Inc
- T-SPOT®.TB (“T-SPOT”) Oxford Immunotec, Ltd
- Performed, interpreted by trained technologists according to manufacturer package insert
- No financial support or donations have been received from Cellestis or Oxford Immunotec.
- Technical representatives from each company assisted in training study laboratory technologists to perform and interpret the assays.

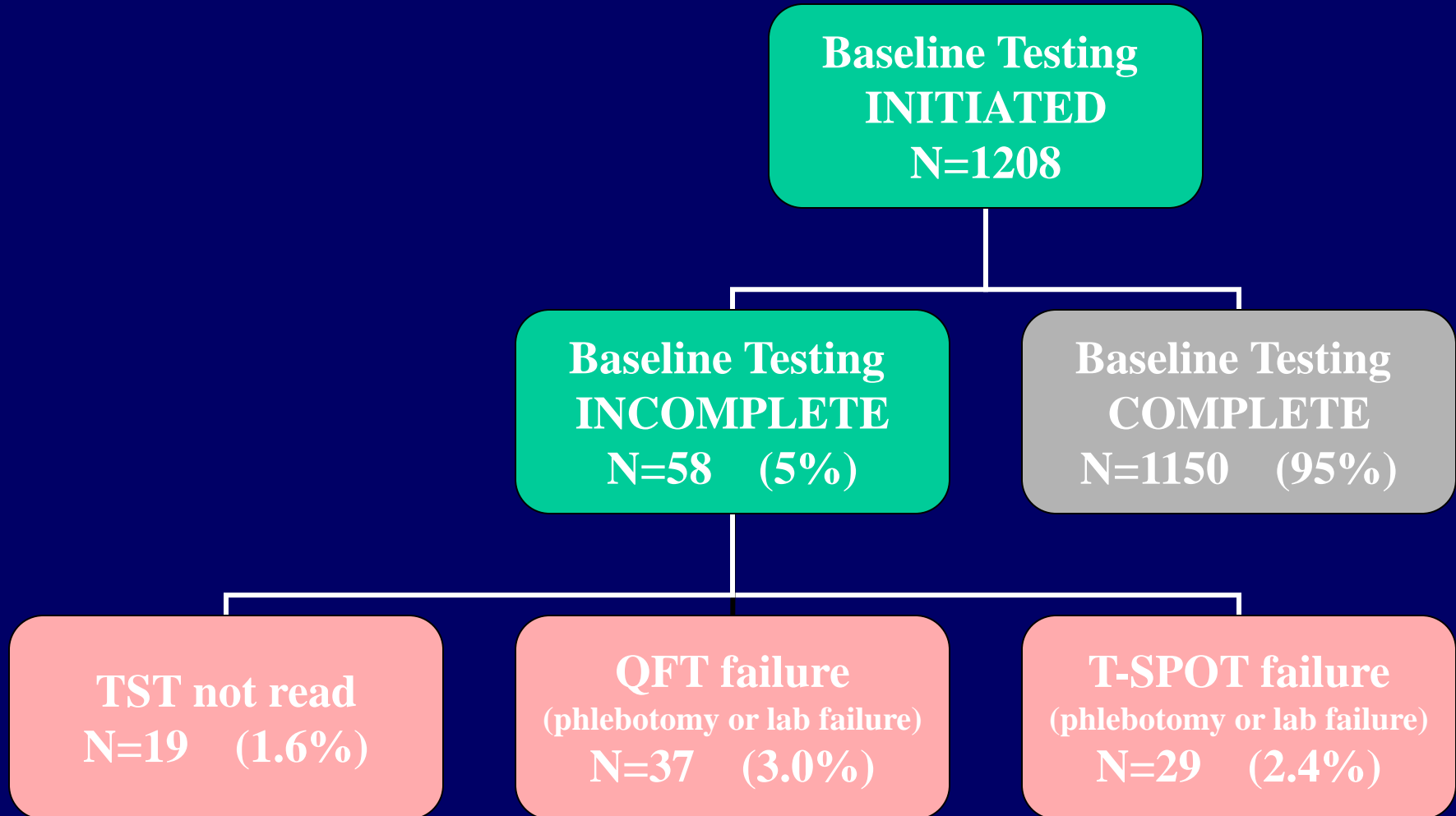
Characteristics of the Study Population (n=1208 to date)



	Number	%
Age (median)	34.5 (range 18-73)	
Female	885	73.5
Race/Ethnicity*		
Hispanic	213	17.6
African-American	163	13.5
Caucasian	701	58.0
Other	94	7.8
Born outside U.S.	186	15.4
h/o BCG vaccine	109	9.5

*37 unknown

Testing Outcomes



*Several incomplete on >1 test



Assay Results, by Method (completed tests with valid results)

	QFT N=1178	T-SPOT N=1171	TST* (10 mm) N=1189
Positive	73 (6.2%)	91 (7.8%)	110 (9.2%)
Negative	1085 (92.0%)	1021 (87.2%)	1079 (90.8%)
Borderline	n/a	49 (4.2%)	n/a
Indeterminate	20 (1.7%)	10 (0.9%)	n/a

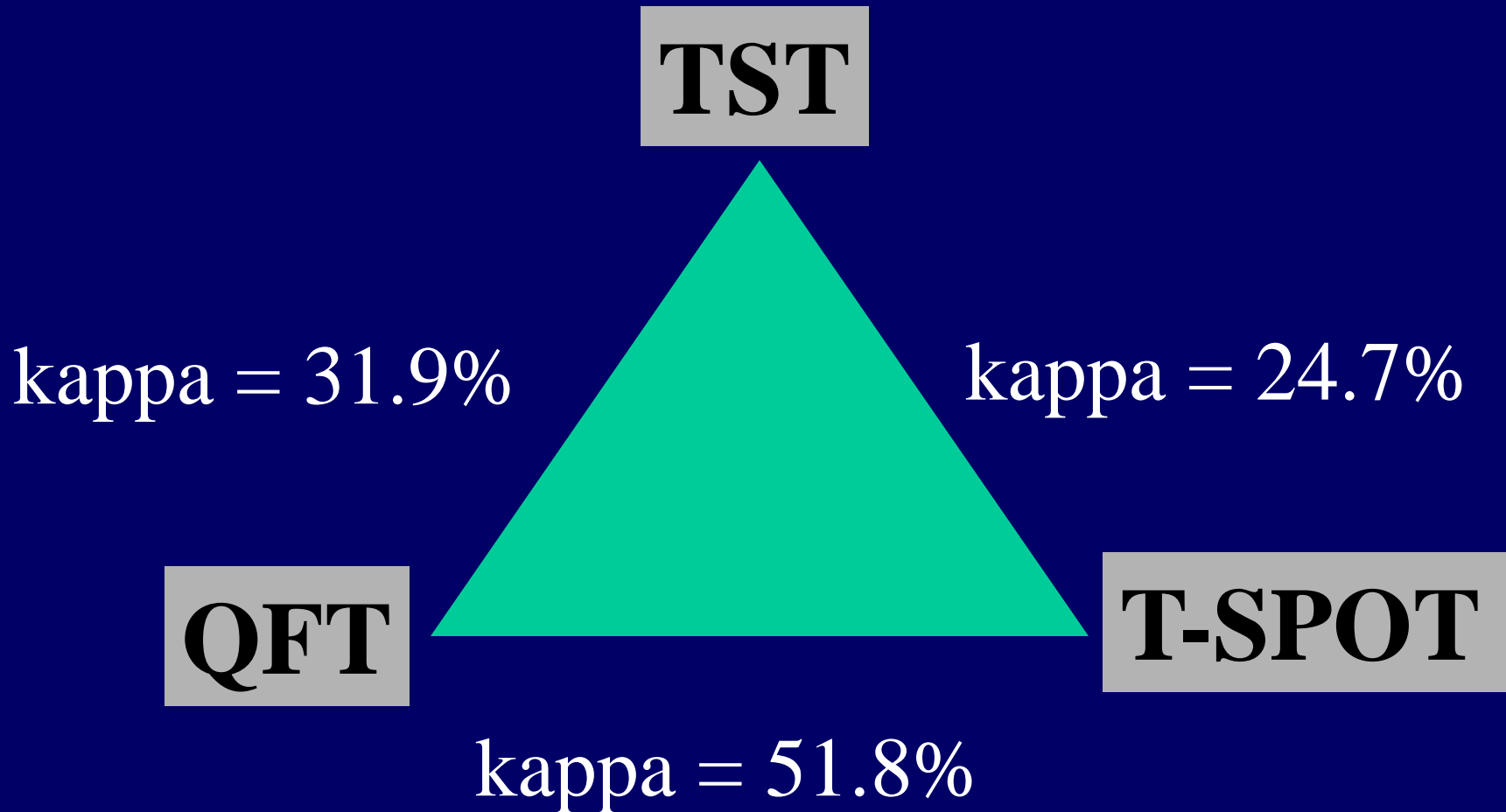
* Includes 2-step results

Test Agreement

QFT	T-SPOT	TST* (10 mm)	N	%
POS	POS	POS	28	2.6
NEG	NEG	NEG	893	83.3
POS	POS	NEG	15	1.4
NEG	NEG	POS	68	6.3
POS	NEG	NEG	17	1.6
NEG	POS	NEG	44	4.1

* Includes 2-step results

Test Agreement





Risk Factors for TST (+) / QFT (-) / TSPOT (-)

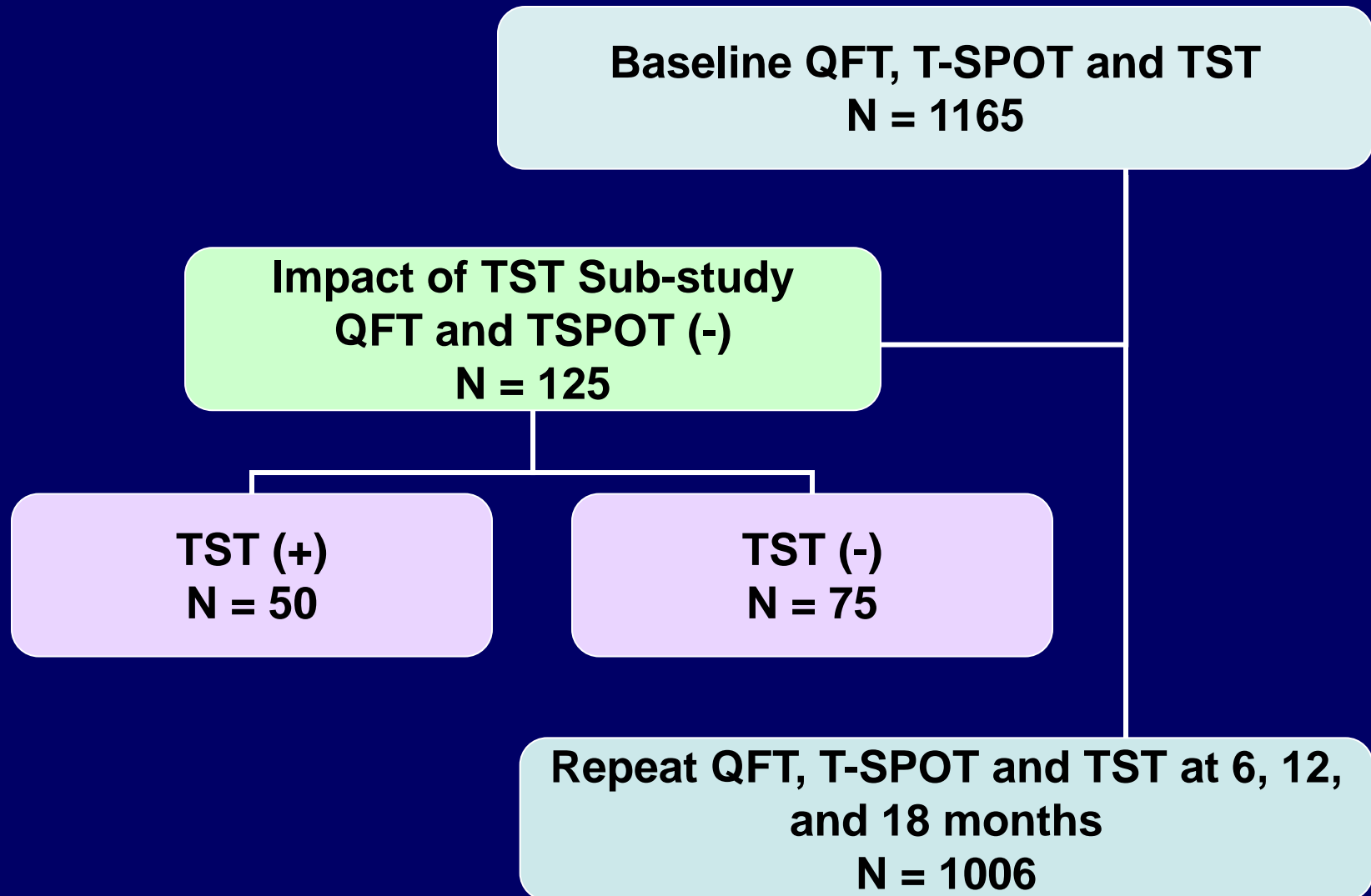
Risk Factor	Total N (%)	TST+, QFT- TSPOT-	OR (95% CI)	Adjusted OR (95% CI)
Hispanic	204 (18)	15 (7)	1.9 (1.0-3.7)	1.0 (0.5-2.2)
African American	154 (14)	5 (3)	0.8 (0.3-2.1)	0.9 (0.3-3.1)
White	669 (60)	25 (4)	REF	REF
Other	89 (8)	20 (23)	7.0 (3.7-13.1)	1.5 (0.7-3.6)
Denver	448 (39)	17 (4)	1.6 (0.4-6.9)	4.7 (0.5-40.9)
Harlem	81 (7)	2 (3)	REF	REF
Maryland	301 (26)	11 (4)	1.5 (0.3-6.9)	3.5 (0.4-31.6)
Texas	320 (28)	38 (12)	5.3 (1.3-22.6)	10.7 (1.3-88.7)
US born	973 (85)	24 (3)	REF	REF
Foreign born	177 (15)	44 (25)	13.1 (7.7-22.2)	1.4 (0.4-4.7)
No BCG	989 (90)	23 (2)	REF	REF
BCG	105 (10)	37 (35)	22.9 (12.9-40.6)	14.1 (4.3-46.5)



Impact of a Recent TST Study Population and Methods

- Target enrollment:
 - 100 TST (-) and 100 TST (+)
- Participants must test negative on both QFT-GIT and T-SPOT at baseline
- Both IGRAs are repeated 1-3 weeks after the baseline TST was placed

Study Design



Demographics – Impact Substudy

	TST (-) N = 75	TST (+) N = 50
Prior TST	67 (91)	46 (94)
Time since last TST, years (med, IQR)	1.6 (1.2, 2.7)	3.9 (1.8, 8.5)
Prior TST Pos	2 (3)	40 (87)
Born outside U.S.	8 (11)	34 (68)
BCG vaccinated	5 (7)	30 (61)
Time between blood draws, days (med, IQR)	14 (7, 18)	15 (9, 19)

Impact Results - Overall

Baseline QFT-GIT and T-SPOT Negative			
	TST (-) n = 75	TST (+) n = 50	Total n (%)
Repeat QFT-GIT			
Negative	71 (95)	39 (78)	110 (88)
Positive	3 (4)	9 (18)	12 (10)
Indeterminate / Failed	1 (1)	2 (4)	3 (2)
Repeat T-SPOT			
Negative	67 (89)	38 (76)	105 (84)
Positive	5 (7)	7 (14)	12 (10)
Borderline	3 (4)	2 (4)	5 (4)
Indeterminate / Failed	0	3 (6)	3 (2)

Impact Results – QFT-GIT

Impact QFT-GIT	Baseline QFT-GIT	
	<0.2	0.2-0.34
<0.2	104	0
0.2-0.34	5	0
0.35-0.49	3	1
0.5-0.69	0	0
≥ 0.7	6	2
Total	118	3

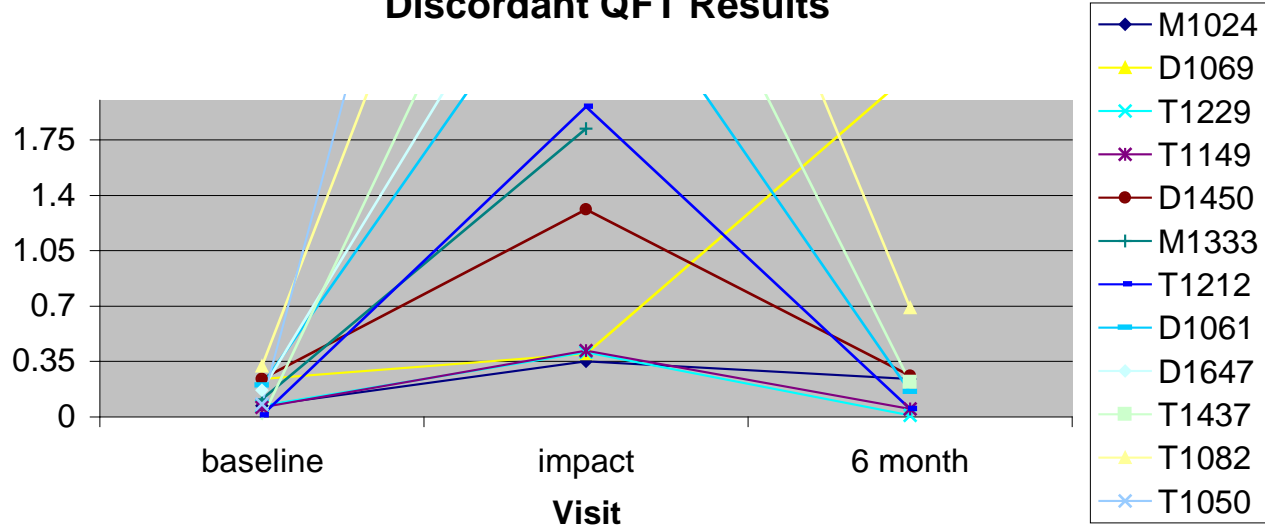


Impact Results – T-SPOT

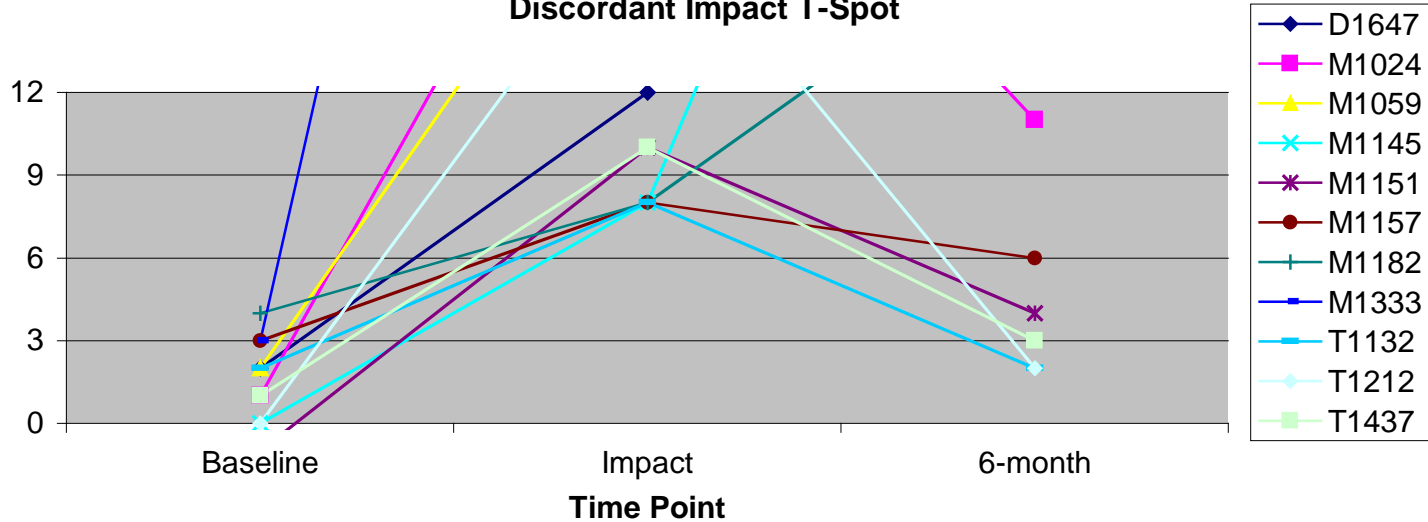
	Baseline T-SPOT		
Impact T-SPOT	≤ 3	4	5-7
≤ 3	97	2	2
4	2	3	0
5-7	5	0	0
8	3	1	0
≥ 9	7	0	0
Total	114	10	2



Impact substudy Discordant QFT Results



Discordant Impact T-Spot



Definitions

- **Conversion:** change from a negative to a positive
- **Reversion:** change from a positive to a negative
- **Reproducibility:** lab variability when 2 samples are drawn simultaneously from an individual
- **Repeatability:** variability in an individual when the IGRAs are repeated within a short time frame (7-21 days)

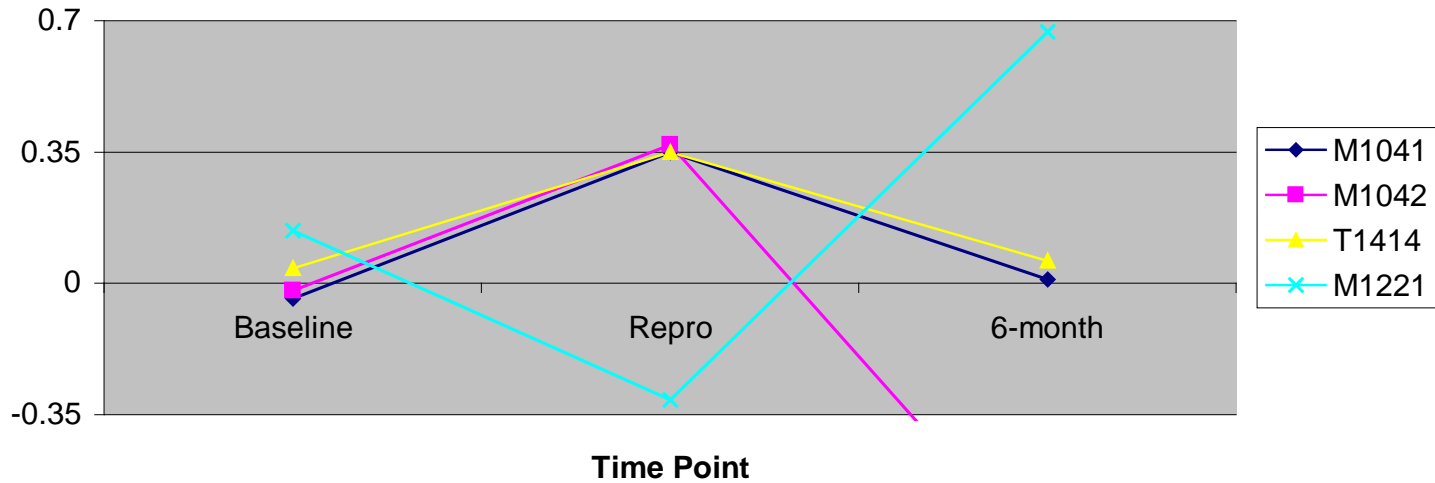
Reproducibility

QFT-GIT		
	n	%
Concordant Negative	91	73
Concordant Positive	29	23
Discordant (Pos/Neg)	5	4
Total	125	

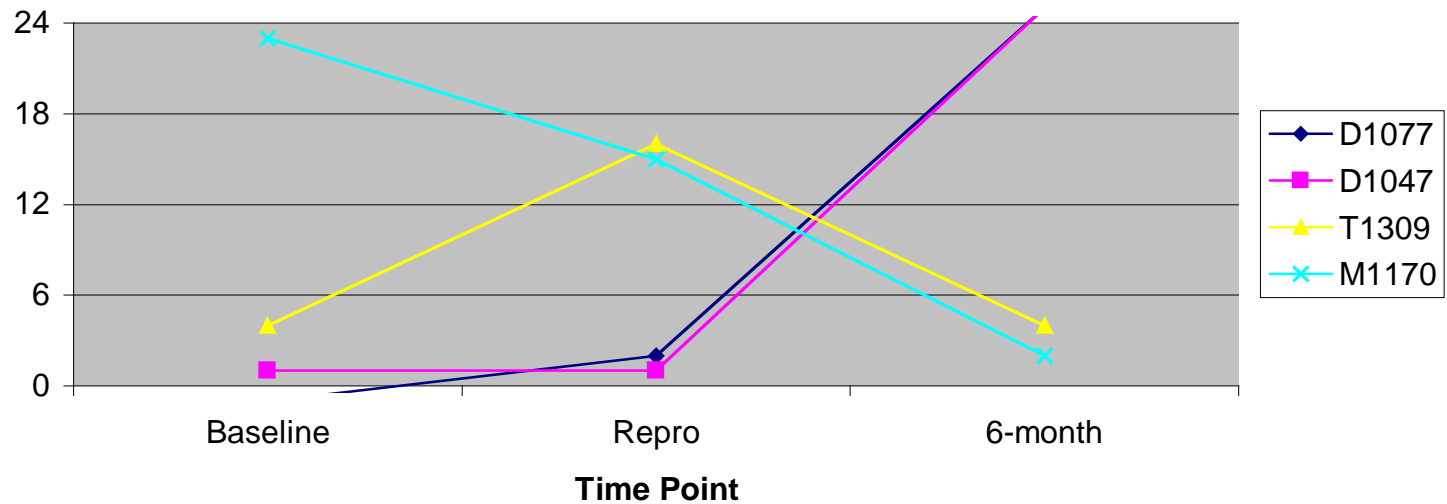
T-SPOT		
	n	%
Concordant Negative	77	65
Concordant Positive	26	22
Concordant Borderline	1	< 1
Discordant		
Pos/Neg	5	4
Border/Neg	5	4
Border/Pos	4	3
Total	118	

Excludes 7 with failed T-Spot

Discordant QFT Reproducibility Results



Discordant T-Spot Reproducibility



Repeatability

	QFT-GIT #2		
QFT-GIT #1	Neg	Pos	Total
Neg	87	3	90
Pos	4	23	27
Total	91	26	117

Conversions: 3/90 (3%)

Reversions: 4/27 (15%)

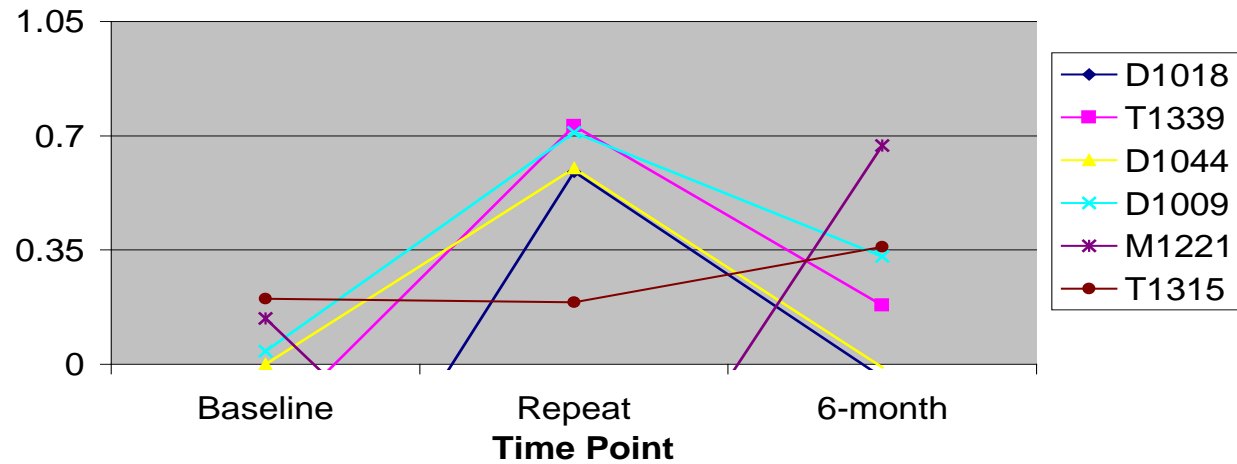
	T-SPOT #2			
T-SPOT #1	Neg	Border	Pos	Total
Neg	64	2	2	68
Border	4	2	2	8
Pos	6	3	20	29
Total	74	7	24	105

Conversions: 2/68 (3%)

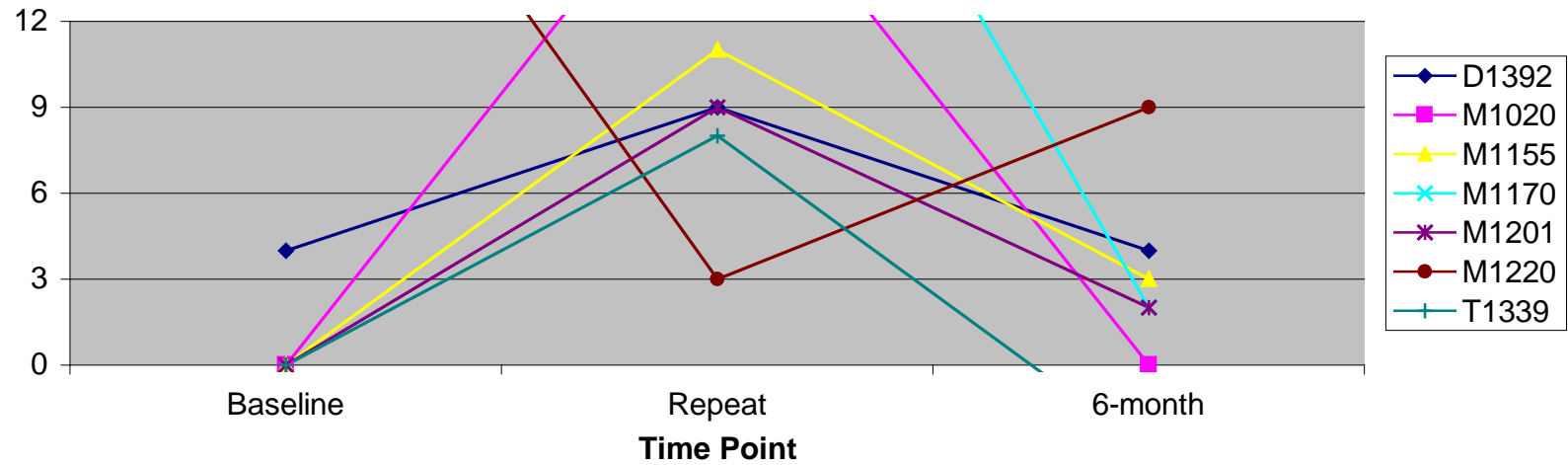
Reversions: 6/29 (21%)

Borderline: 13/105 (12%) with at least one borderline result

Discordant QFT Repeatability Results



Discordant T-Spot Repeatability





	6 month TST			
Baseline TST	Neg	Pos*	Not Done	Total
Neg	869	8	40	917
Pos	16	19	54	89
Total	885	27	94	1006

Conversions: 5/877 (0.65%)
 Reversions: 16/45 (46%)

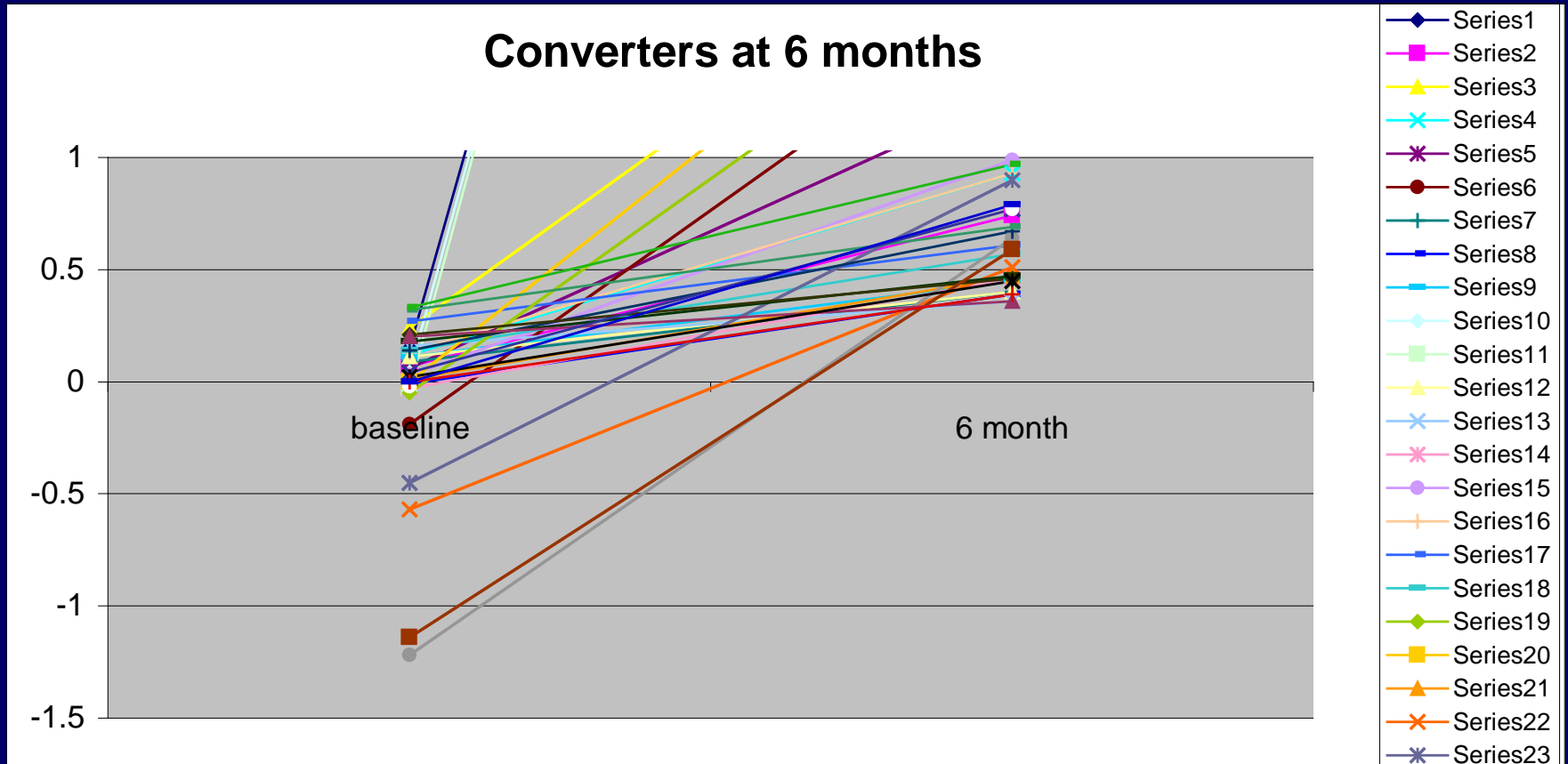
	6 month T-SPOT				
Baseline T-SPOT	Neg	Border	Pos	Failed	Total
Neg	779	39	32	22	872
Border	23	4	11	2	40
Pos	22	10	45	3	80
Total	824	53	88	27	992

Conversions: 32/850 (4%)
 Reversions: 22/77 (29%)

	6 month QFT-GIT			
Baseline QFT-GIT	Neg	Pos	Indeter	Total
Neg	881	33	6	920
Pos	22	45	1	68
Total	903	78	7	988

Conversions: 33/914 (4%)
 Reversions: 22/67 (33%)

Conversion at 6 Months



Outcomes Using Standard and Proposed Criteria

Method		Baseline Positive (%)	Baseline Borderline (%)	6 month Conversion (%)	6 month Reversion (%)	Conversion Criteria
Standard	TST	8.9	-	0.6	45.7	Increase \geq 10 mm
	QFT	6.9	-	3.6	32.8	Value above 0.35
	T-Spot	8.0	4.1	3.8	28.6	8 or more spots
Proposed ¹	QFT	4.6	5.3	1.9	11.1	Increase from <0.35 to >0.70
	T-Spot	6.6	9.0	3.5	35.9	Increase from <6 spots to >9 spots

¹ van Zyl-Smit Am J Resp Crit Care Med, April 2009

– proposed Borderline Ranges: QFT-GIT 0.2 to 0.7, T-SPOT 4 to 8

Summary and Conclusions

- LTBI prevalence is ~3% if defined as positive on all 3 tests; ~17% if defined as any test positive
- Agreement is fair between TST and IGRAs; agreement is slightly better between QFT and T-SPOT
- Prior BCG vaccination is a risk factor for TST positive/IGRA negative
- TST may “boost” a subsequent IGR and the change in IGRAs occurs early (within 2 weeks)
- The impact of TST on IGRAs results affects more than just people whose initial test is near the cut-point

Summary and Conclusions

- Lab variability resulted in discordant results for 4% with QFT-GIT and 11% with T-SPOT.*TB*
- Short-term variability (1-3 weeks) and long-term variability (6 months) for QFT-GIT and T-SPOT.*TB* resulted in “conversions” in 3-4% and “reversions” in 15-33%.
- Conversion rates were 6-fold higher for the IGRAs than the TST
- Alternative criteria establishing a minimum threshold for the amount of change necessary to define a conversion are needed



Thank you to TO #18 Team

- CDC: Paul Weinfurter, Denise Garrett, Grace Thiongo
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