

Interferon Gamma Release Assays Longitudinal Studies

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What is the evidence that can be brought to bear on this critical question at this time?

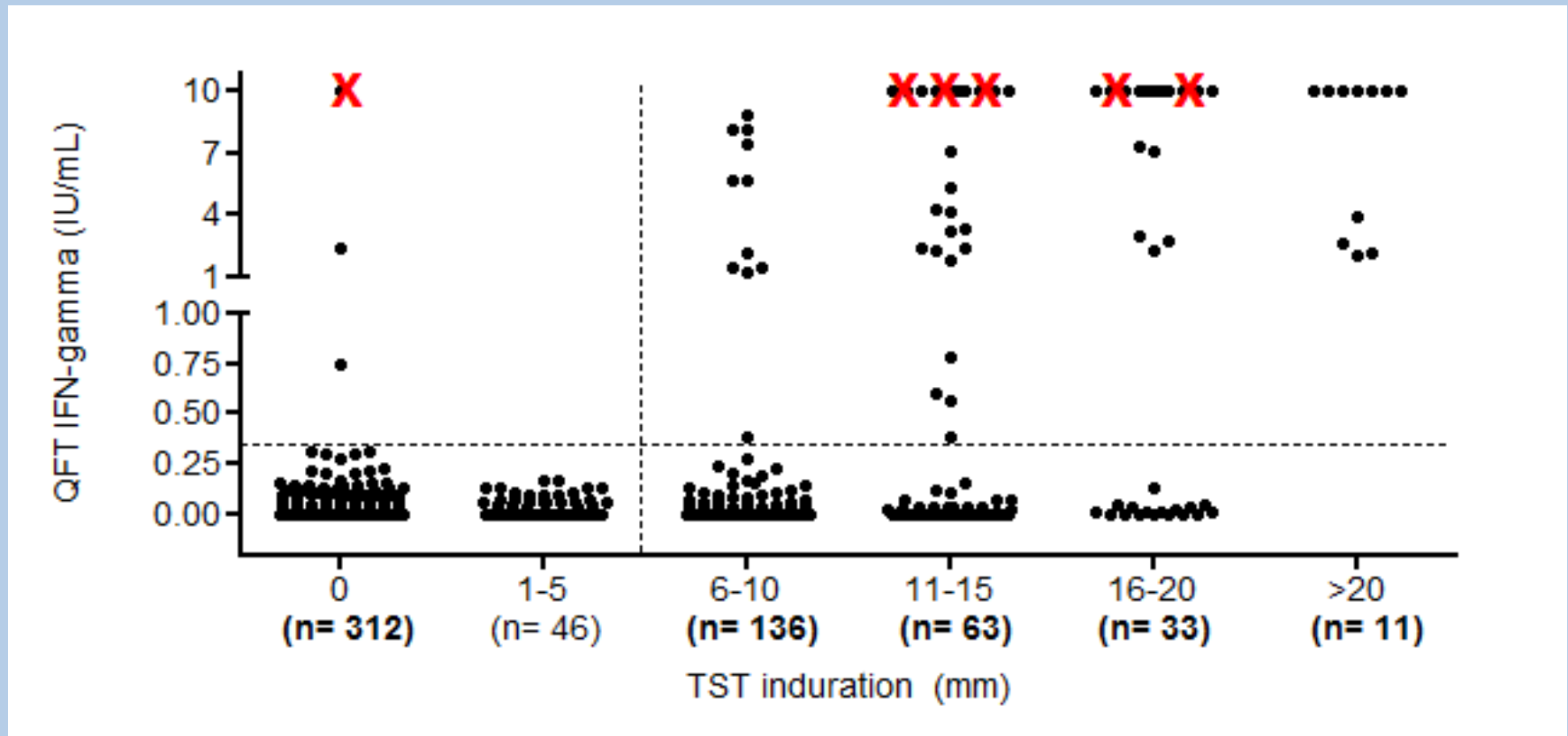
1. The science tells us QFT should be more predictive
 - Antigens highly specific
 - The biology of IFN- γ suggests a central role for this cytokine
2. QFT negative but TST positive have not developed active TB to date
 - Information collected during routine use of QFT
 - Publications exist and more coming
 - Confirm that QFT does not “miss” people
3. Demonstrate that those who do progress are QFT positive
 - Ethically more difficult, if test positive, reactors should be treated
 - Practically more difficult in general progression is slow and requires very large sample size but these are underway in several communities.

Predictive value of QFTG

The Hamburg Experience

- Compare TST and QFTG in 601 close contacts of AFB+ active TB cases
 - 243/601 (40%) TST +
 - 66/601 (26%) QFTG +
 - QFT+ but not TST+ associated with exposure time
 $p < 0.0001$
- Treatment for latent TB was only offered if QFT positive and only if recommended by their pneumonologist
 - As per the recently published German guidelines:*
 - 25 of the 66 QFT positive contacts were treated
 - None of these contacts developed active TB disease
 - Of the other 576 contacts, 6 developed pulmonary TB disease

Comparison of the level of responses for QFT and the TST



The six individuals who developed TB disease are marked by X

Development of TB

TST:

Sensitivity for predicting progression = 83%

Only 2.3% progressed to active TB

One of the TST negative contacts also developed TB

QFT:

Sensitivity for predicting progression = 100%

15% progressed to active TB

None of those QFT negative developed active TB

» *(Still the case a further 18 months later)*

Unpublished data on progression

- Since publication of the Hamburg study, another subject, both QFT and TST positive, has developed culture-confirmed active TB.
- Thus progression rate for QFT is now 7/41 (17%).
 - TST 6/219 (2.7%)
- A 2 year old, QFT positive, child who was not included in the study (as no TST) also developed miliary TB.

Fingerprint confirmation of transmission was made for both cases above.

Max Aichelberg

Medical University of Vienna, Austria

- Predictive Value of QFT in HIV+
- 830 HIV+
 - 70% male
 - 30% female
 - Median age 39 years
 - 71% West or mid Europe
 - 11% African
 - MSM/IVDU
- Initial Screen
 - 44/822 (5.3%) QFT+
 - 7 active TB
 - 47/822 (5.7%) indeterminate
 - 0 active TB
 - 738/822 GFT-
 - 1 had active TB
 - Concordance 93% (5mmTST)
- Follow Up studies
 - 305 followed for 2 years
 - QFT+ & TST+ > 5 developed active TB
 - QFT+ & TST- > 1 developed active TB
 - QFT- & TST- None developed active TB
- Conclusion
 - QFT may be more sensitive than TST for predicting the development of active TB

Hassan Mahomed

University of Cape Town So Africa

- So African TB Vaccine Initiative and Areas
- TB incidence 1,400/100,000
- BCG at birth, no repeats
 - coverage 95%
- HIV prevalence 1%
- Age 12-18 years
- July /2005-April /2007
- 6,363 Enrolled
 - 10% previously Dx of active TB
 - 29.7 currently or previously lived with someone with active TB
 - 19 (0.3%) Dx active TB
 - 22 (0.3%) Rx for active TB
 - Findings at baseline
 - 53.6% QFT +
 - 42.5% TST +
 - agreement 81.4%
 - kappa 0.63
- 5,194 completed 2 year follow up
 - 64 developed active TB
 - 76% started with a +QFT
 - 74% started with + TST (10mm)
- Conclusion
 - TST & QFT equally predictive of TST

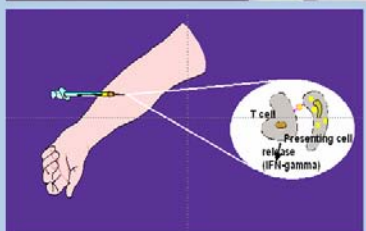
Data from presentation: 2nd Global Symposium on IGRAs

TB Infection Prevalence By Test and Clinic Type

	Homeless	TB Clinic	Methadone	Immigrant
TST (2001-2003)	26%	~50%	10%	37%
QFT-1 (11/03-2/05)	17 % n=1848	48 % n=292	18 % n=346	37 % n=344
QFT-G (3/05-11/08)	7 % n=9166	23 % n=4042	4 % n=1261	14 % n=2505
QFT-IT (4/08-2/09)	6 % n=1625	22 % n=1555	—	20% n=323
Decline in positive rate from TST	↓ 73%	↓ 54%	↓ 60%	↓ 62%

San Francisco TB Control Section

Testing for Latent TB Infection - LTBI



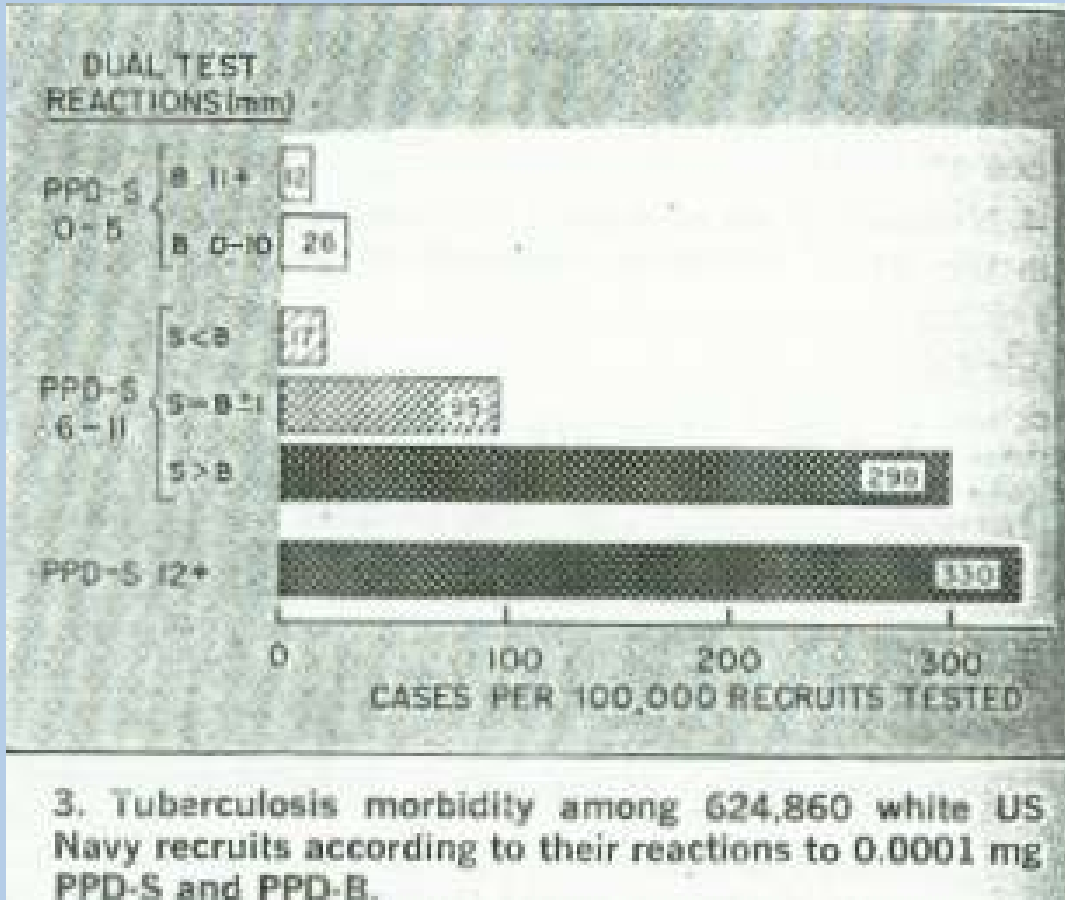
Tuberculosis complex	Antigens		Environmental strains	Antigens	
	ESAT	CFP		ESAT	CFP
M tuberculosis	+	+	M abcessus	-	-
M africanum	+	+	M avium	-	-
M bovis	+	+	M brisbanii	-	-
BCG substrain gothenburg	-	-	M chelonae	-	-
moreau	-	-	M fortuitum	-	-
tice	-	-	M goodii	-	-
tokyo	-	-	M intracellulare	-	-
danish	-	-	M kansasii	+	+
glaxo	-	-	M malmoense	-	-
montreal	-	-	M neoaurum	+	+
pasteur	-	-	M novae	-	-
			M scrofulaceum	-	-
			M smegmatis	-	-
			M szulgai	+	+
			M terrae	-	-
			M vaccae	-	-
			M xenopi	-	-

TST

Interferon Gamma Release Assays

- It is easy to understand that the specificity of the antigens >exquisite specificity of QFT
- Studies Dr Kawamura in San Francisco are convincing that QFT does not overlook people who are at risk of getting TB. No QFT neg people at risk of getting TB have been missed and gone ahead and gotten TB
- Let's look a bit closer at the limitations inherent in using the 'gold standard TST'

USPHS Studies

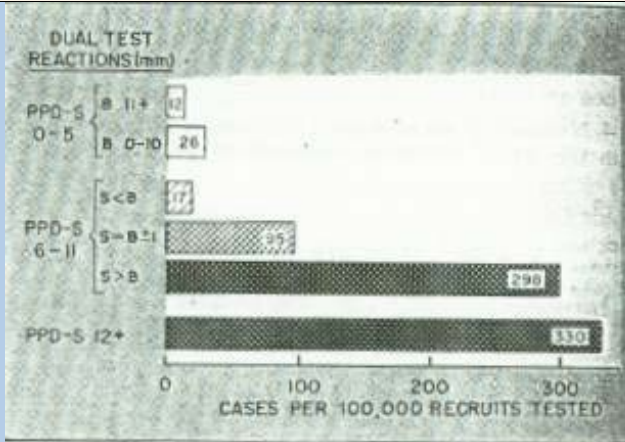


- 19 year follow up study of kids in BCG trials with TST and NOT given BCG
 - TST reactions >6mm in response to 1 or 10 TU
 - 1,400/ 82,269 children developed active TB
 - Rate 90.2/100,000

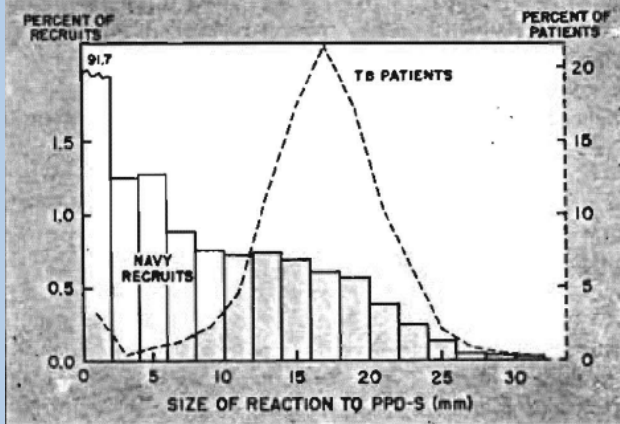
Palmer and Edwards JAMA 202, 1968

Comstock Am J Epi 131, 1974

Data from US Navy Recruits



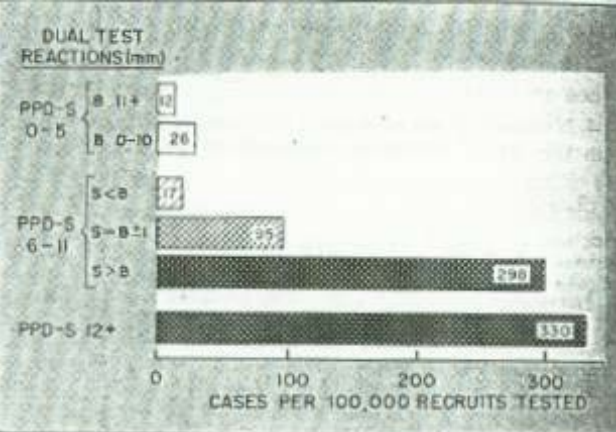
3. Tuberculosis morbidity among 624,860 white US Navy recruits according to their reactions to 0.0001 mg PPD-S and PPD-B.



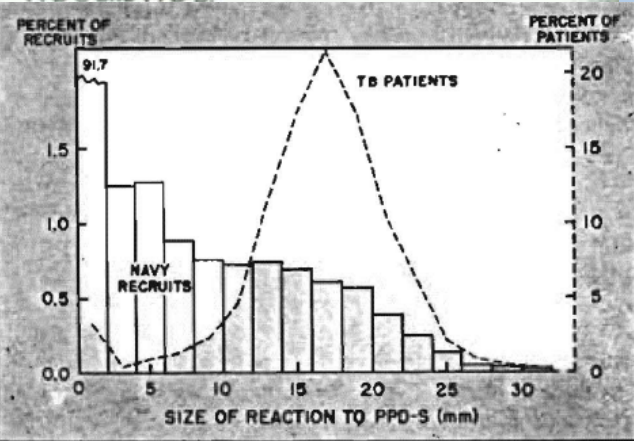
1. Reactions to 0.0001 mg PPD-S in 624,860 white US Navy recruits and in 5,544 tuberculosis patients.

5mm cut off	Active TB	No Active TB
TST >5	732	4,768
TST <5	38	94,462
Total	770	99,230
Sensitivity	95.0%	
Specificity		95.2%

Data from US Navy Recruits



3. Tuberculosis morbidity among 624,860 white US Navy recruits according to their reactions to 0.0001 mg PPD-S and PPD-B.



1. Reactions to 0.0001 mg PPD-S in 624,860 white US Navy recruits and in 5,544 tuberculosis patients.

12 mm cut off	Active TB	No Active TB
TST >12 mm	330	3,070
TST <12 mm	440	96,160
Totals	770	99,230
Sensitivity	42%	
Specificity		96.9%

Data from US Navy Recruits

- TST 5 mm cut off

- Sens 95%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 14,250 true pos
 - 750 false negative

- Spec 95.2%
 - 4,080 false positives in 85,000 uninfected

- Accuracy

- False negatives 750
- True positive 14,250
- False positive 4,080

- Eligible for Rx 18,330

- TST 12 mm cut off

- Sens 42.8%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 6,420 true pos
 - 750 false negative

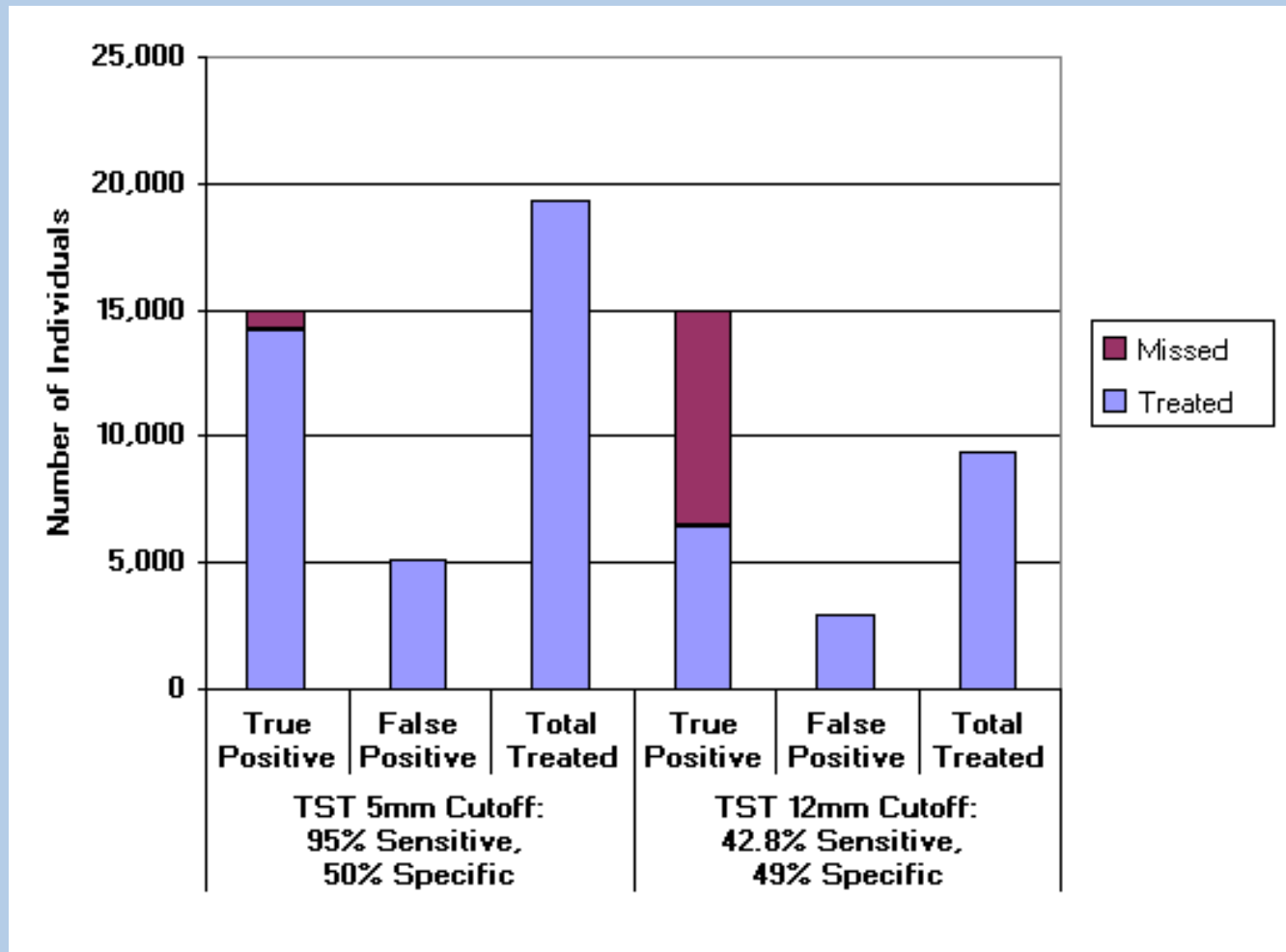
- Spec 96.9%
 - 2,635 false positives in 85,000 uninfected

- Accuracy

- False negatives 8,580
- True positive 6,420
- False Positive 2,635

- Eligible for Rx 9,395

Data from US Navy Recruits



Data from US Navy Recruits

- TST 5 mm cut off
- Sens 95%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 14,250 pos out of 15,000 with LTBI
- Spec 95.2%
 - 4,080 false positives if 85,000 tested
- Accuracy
 - Missed 750
 - True positive 14,250
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- Eligible for Rx 18,330
- TST 12 mm cut off
- Sens 42.8%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 6,420 pos out of 15,000 with LTBI
- Spec 96.9%
 - 2,635 false positives if 85,000 tested
- Accuracy
 - Missed 8,580
 - True positive 6,420
 - False Positive 2,635
- Eligible for Rx 9,395
- Recommendations for all except high risk chose 12 mm cut off

At 12 mm to get fewer false positives 1,445 (4,080 to 2,635)
we accept the identification of fewer true positives that is
7,830 (14,250-6,420) fewer TB infected persons
A loss of 5.4 LTBI (7,830/1,445) for each false pos not identified
OK to miss 5 to not to falsely identify 1 false positive
We pay a huge price in sensitivity to gain specificity

Public Health Departments focuses on contacts of active cases of TB

Aggregate Report of TB Program Evaluation, 2003

- 74% of areas reported nationally
- 115,544 contacts
- 63% were contacts to smear (+) cases
- 1% had active disease at evaluation
- 26% diagnosed with LTBI (+TST)
- 73% started & 59% completed treatment
- Overall 43% success; vs. goal: 85%



U.S. Burden of LTBI Two CDC Studies*

1. Prevalence 9–14 million[†]
2. TBESC** Multi-site (19): 8.6% U.S. TB
 - Examined LTBI practice
 - Estimated 291,000–433,000 persons started on Tx LTBI yearly
 - Prevents 4,000–11,000 cases TB^{††}

*Unpublished, [†]NHANES 1999–2000, **TB Epidemiologic Studies Consortium, ^{††}Assumes 5% lifetime risk and 20–60% Tx efficacy



Roland Diel

Hamburg Department of Health

- Regarding the prediction of TB disease
- Sensitivity
 - TST 88%
 - QFT 100%
- Negative Predictive Value of QFT 100%
- Need Rx of LTBI
 - TST 40% of 601
 - QFT 11% of 601
- Take home message
 - Hypothesis not yet proven but all available evidence support
 - QFT is the better predictor of progression
 - QFT more specific than TST
 - QFT at least as sensitive as TST
 - QFT does not miss people who will progress to active TB
 - QFT has higher Positive Predictive Value for progression to active TB

Conclusion

We have experience with thousands of high risk LTBI (HIV pos and Close contacts of Active TB cases) that demonstrate that the QFT does not miss people who are going to develop active TB

We have many studies that show that the specificity of QFT is far superior to TST

We now have three studies that show that the prognostic value of QFT is at least as good as TST

We have two studies, one in HIV pos one in close contacts of active cases that show superiority of QFT over TST

Tell me in what area are there solid data, information supportable by facts (as distinct from tradition), to support the preferential use of the TST for any application?