

The Value of Sensitivity vs. The Value of Specificity

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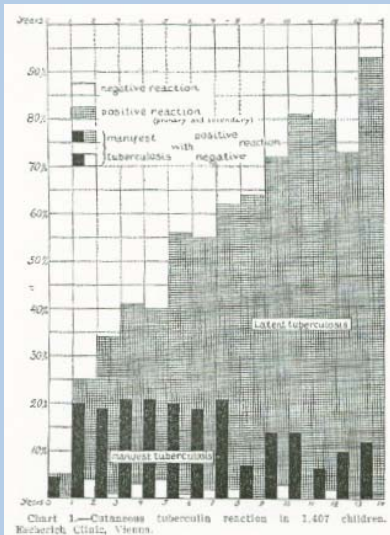
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Original definition of Latent TB



Clemens Freiherr von Pirquet
1909 First use of the term Latent
TB Infection
Solid bars indicate children with
active disease

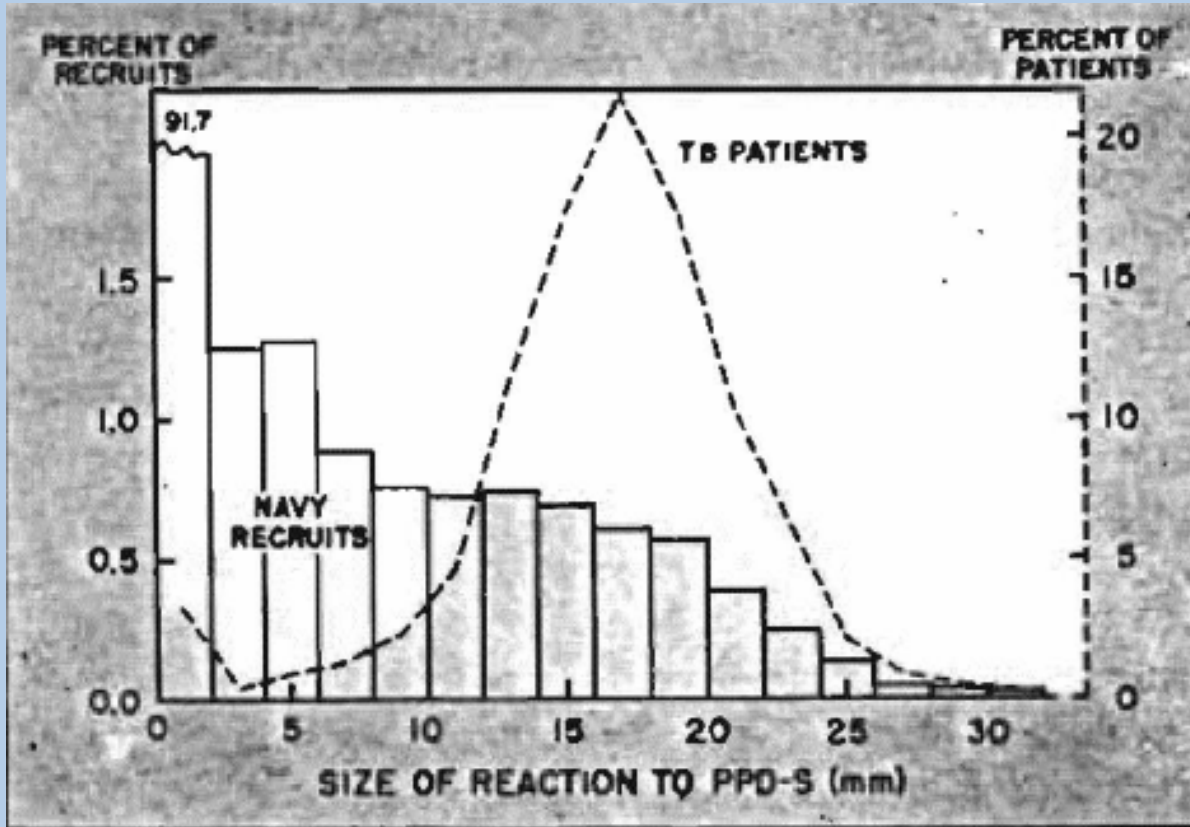


Shaded areas indicate asymptomatic
children who he called latent TB

Von Pirquet JAMA Feb 27, 1909



Data from US Navy Recruits

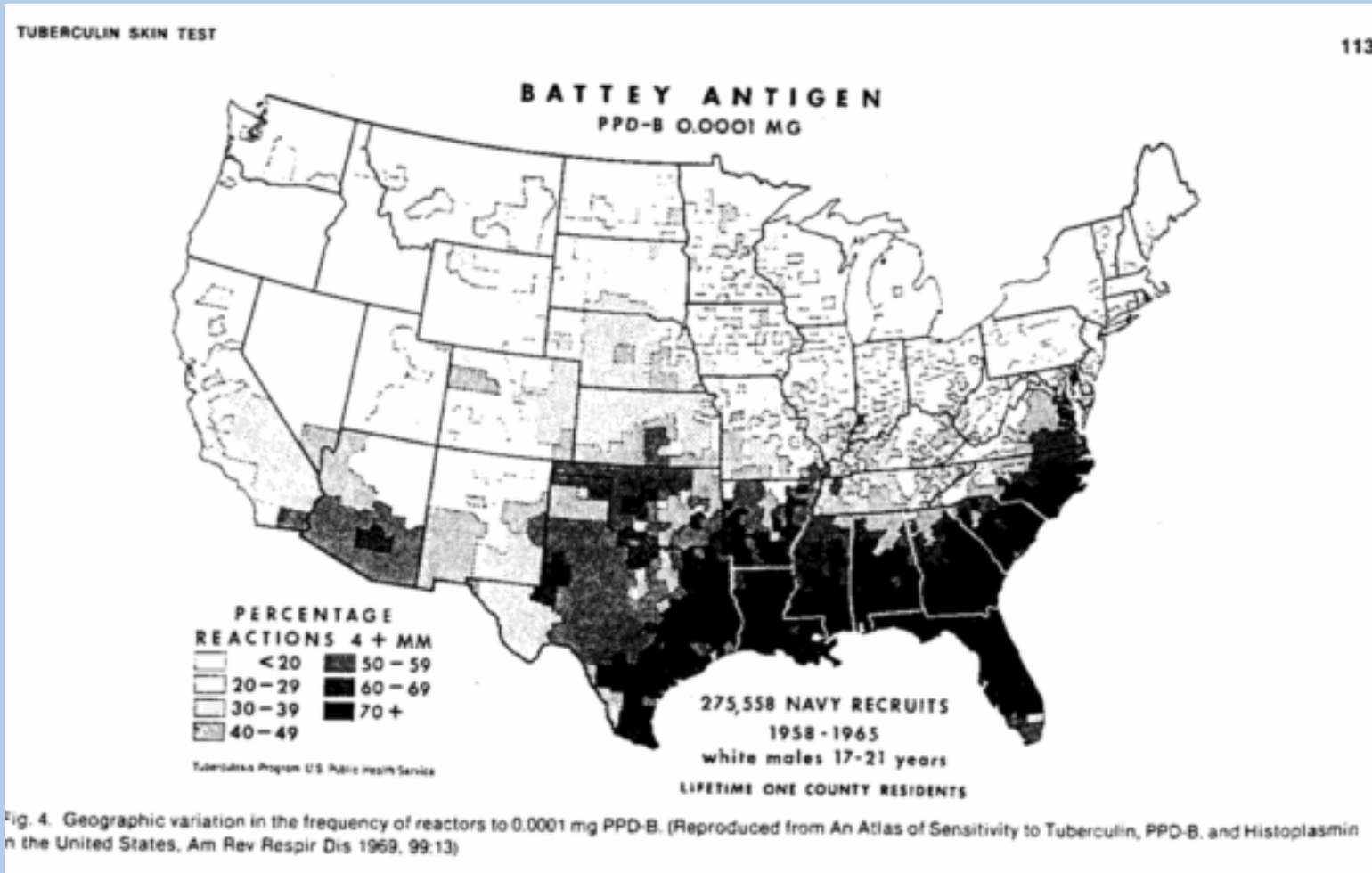


1. Reactions to 0.0001 mg PPD-S in 624,860 white US Navy recruits and in 5,544 tuberculosis patients.

Palmer and Edwards JAMA 202, 1968



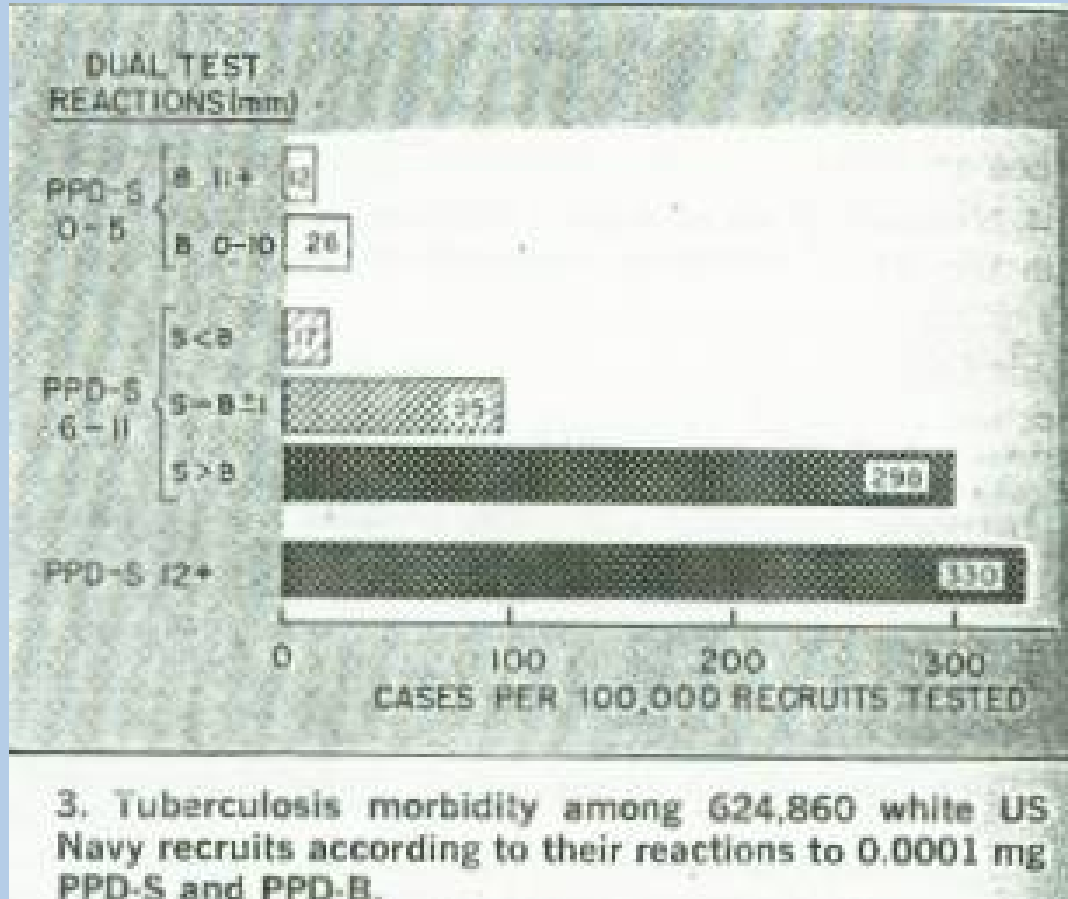
Data from US Navy Recruits



Palmer and Edwards JAMA 202, 1968



USPHS Studies



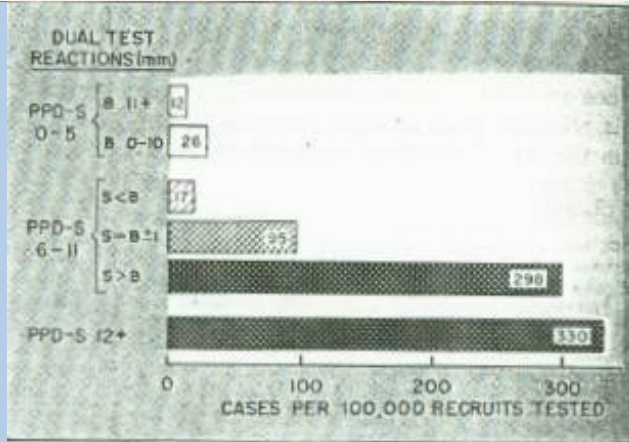
- 19 year follow up study of TST reactors not given BCG
 - TST reactions >6mm in response to 1 or 10 TU
 - 1,400/ 82,269 children developed active TB
 - Rate 90.2/100,000

Palmer and Edwards JAMA 202, 1968

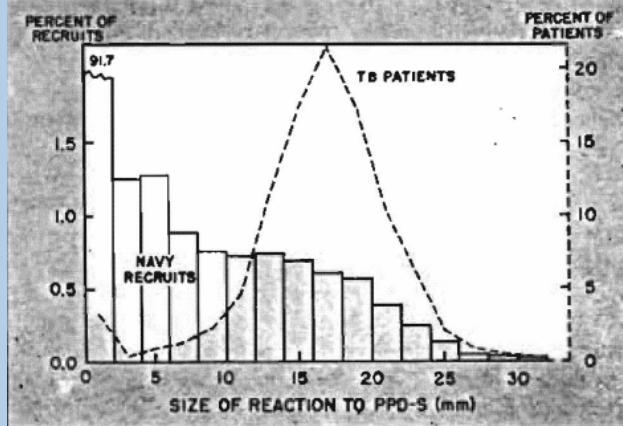
Comstock Am J Epi 131, 1974



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.

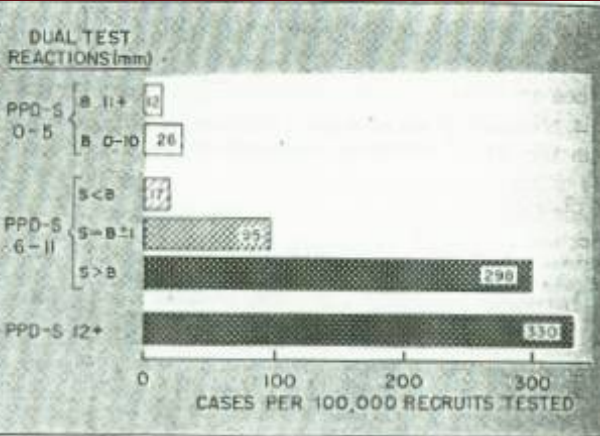


1. Reactions to 0.0001 mg PPD-S in 624,860 white US Navy recruits and in 5,544 tuberculosis patients.

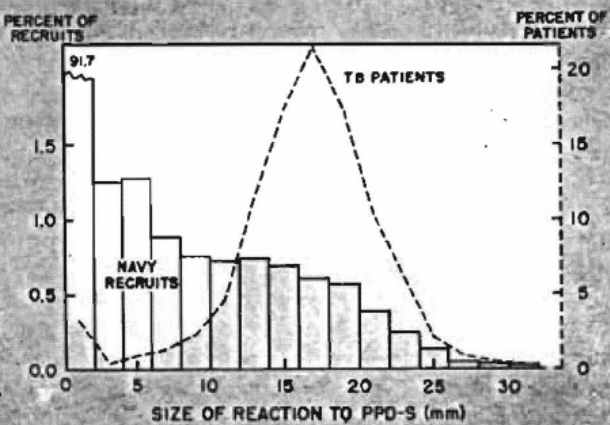
5mm cut off	Active TB	No Active TB
TST >5 mm	732	4,768
TST <5 mm	38	94,462
Total	770	99,230
Sensitivity	95.0%	
Specificity		95.2%



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

- Sensitivity 95%

- If prevalence of LTBI is 15% then 15,000 have LTBI
- 14,250 true positives
- 750 false negatives

- Specificity 95.2%

- 4,080 false positives in 85,000 uninfected

- Accuracy

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

- Eligible for Rx 18,330

- TST 12 mm cut off

- Sensitivity 42.8%

- If prevalence of LTBI is 15% then 15,000 have LTBI
- 6,420 true positives
- 750 false negatives

- Specificity 96.9%

- 2,635 false positives in 85,000 uninfected

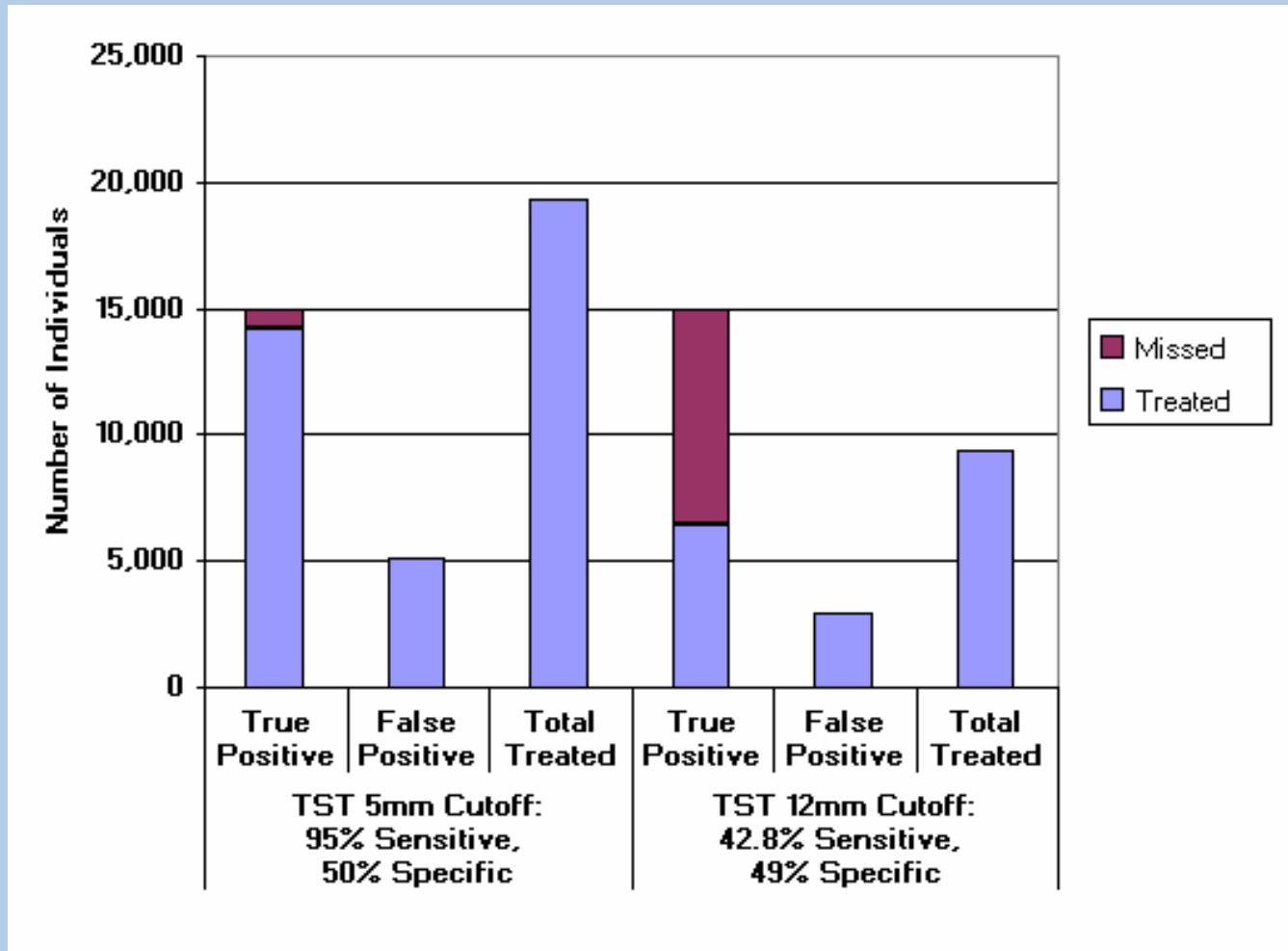
- Accuracy

- False negatives 8,580
- True positives 6,420
- False positives 2,635

- Eligible for Rx 9,395



Data from US Navy Recruits



Data from US Navy Recruits

- TST 5 mm cut off
- Sensitivity 95%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 14,250 positives out of 15,000 with LTBI
- Specificity 95.2%
 - 4,080 false positives if 85,000 tested
- Accuracy
 - Missed 750
 - False positive 4,080
 - True positive 14,250
- Eligible for Rx 18,330
- TST 12 mm cut off
- Sensitivity 42.8%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 6,420 positives out of 15,000 with LTBI
- Specificity 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 positive not identified

OK to miss 5 to not to falsely identify 1 false positive

We pay a huge price in sensitivity to gain specificity



Comparing TST to QuantiFERON Gold

PPD vs. highly specific TB antigens: ESAT-6 & CFP-10

- **TST**

- **Sensitivity**

- Active TB 82%
- LTBI 95%

- **Specificity**

- Non BCG Pop 98%
- BCG @ birth 92%
- BCG later 60%

- **QFT-G**

- **Sensitivity**

- Active TB 82%
- LTBI 95%

- **Specificity**

- All pop 98%

In the next series of slides I will assume we are testing a population of 100,000

Oxlade, Schwartzman and Menzies, IJTLD, 16, 2007



Oxlade, Schwartzman and Menzies IJTLD, 16, 2007 'No BCG'

- QFT-G
 - Sensitivity 95%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 14,250 true positives
 - 750 false negatives
 - Specificity 98 %
 - 1,700 false positives in 85,000 uninfected
 - Accuracy
 - False negatives 750
 - False positives 1,700
 - True positives 14,250
 - Eligible for Rx 15,950
- TST
 - Sensitivity 95%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 14,250 true positives
 - 750 false negatives
 - Specificity 98 %
 - 1,700 false positives in 85,000 uninfected
 - Accuracy
 - False negatives 750
 - False positives 1,700
 - True positives 14,250
 - Eligible for Rx 15,950



Oxlade, Schwartzman and Menzies IJTLD, 16, 2007 'BCG during infancy'

- QFT-G
 - Sensitivity 95%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 14,250 true positives
 - 750 false negatives
 - Specificity 98 %
 - 1,700 false positives in 85,000 uninfected
 - Accuracy
 - False negatives 750
 - False positives 1,700
 - True positives 14,250
 - Eligible for Rx 15,950
- TST
 - Sensitivity 95%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 14,250 true positives
 - 750 false negatives
 - Specificity 92 %
 - 6,800 false positives in 85,000 uninfected
 - Accuracy
 - False negatives 750
 - False positives 6,800
 - True positives 14,250
 - Eligible for Rx 21,050

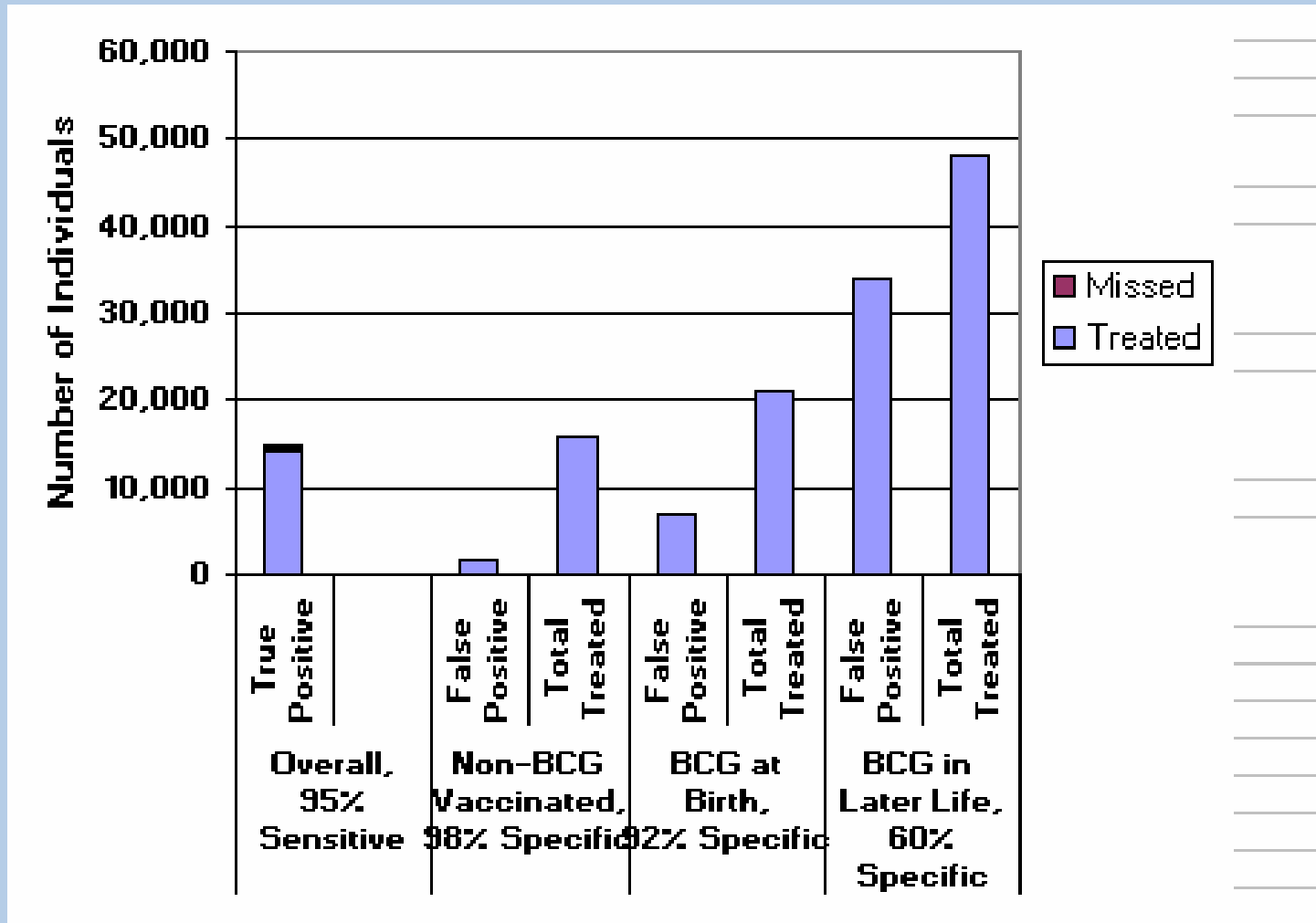


Oxlade, Schwartzman and Menzies IJTLD, 16, 2007 'BCG later in life'

- QFT-G
 - Sensitivity 95%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 14,250 true positives
 - 750 false negatives
 - Specificity 98 %
 - 1,700 false positives in 85,000 uninfected
 - Accuracy
 - False negatives 750
 - False positives 1,700
 - True positives 14,250
 - Eligible for Rx 15,950
- TST
 - Sensitivity 95%
 - If prevalence of LTBI is 15% then 15,000 have LTBI
 - 14,250 true positives
 - 750 false negatives
 - Specificity 60 %
 - 34,000 false positives in 85,000 uninfected
 - Accuracy
 - False negatives 750
 - False positives 34,000
 - True positives 14,250
 - Eligible for Rx 48,250

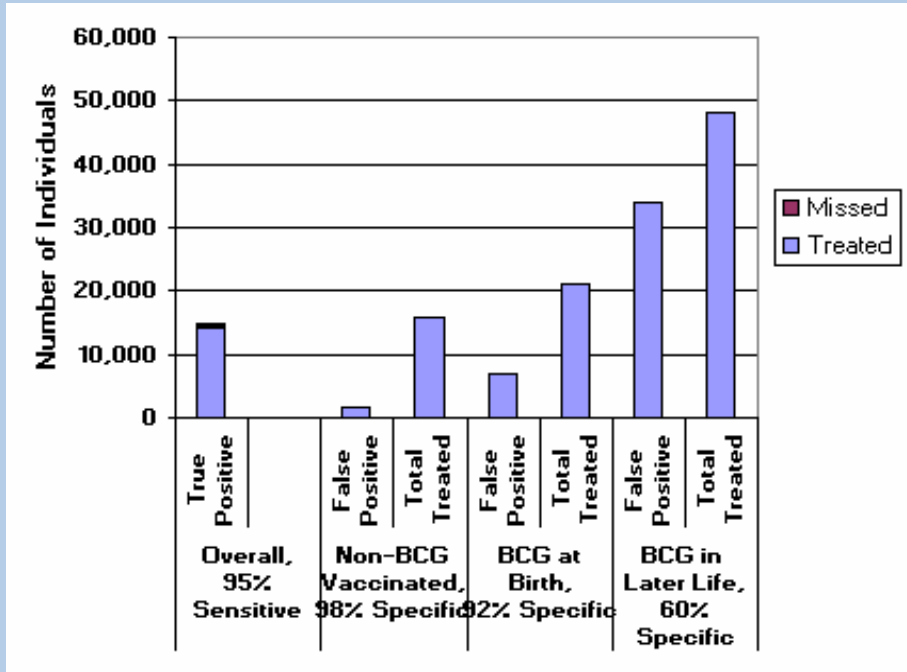


Calculations using the data from Oxlade *et.al.*

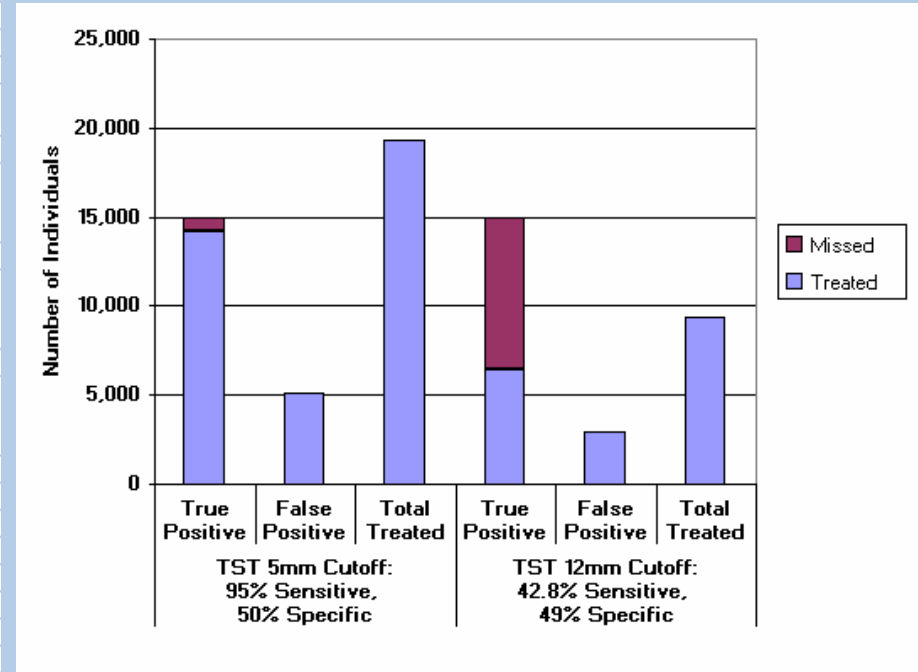


The trade off when NTM infections present

With TST you may chose sensitivity or specificity



TST or QFT
Sensitivity 95%, Specificity 98%
If no BCG



With BCG Specificity plummets
If increase cut off Sensitivity plummets



Burden vs. Risk of TB in USA

- Risk
 - LTBI
 - 10%-0.1%
 - Immunosuppressed esp. HIV
 - 10% year for HIV
 - Close Contacts of Active Cases
 - 1% first year
 - HCW
 - 0.1%
- Burden
 - LTBI
 - 15 million
 - Immunosuppressed esp. HIV
 - 1,000,000 at risk
 - LTBI ?
 - Close Contacts of Active Cases
 - 156,140
 - HCW
 - Approximately 4.5,000,000
 - LTBI ?

43% of contacts who need Rx for LTBI complete Rx



Conclusion

- Sensitivity of the *in vitro* tests is likely as good or better than intradermal testing
- Specificity is clearly greatly improved when the highly specific antigens from Mtb are used
- Resulting in:
 - Increase in number of latent TB infected persons actually treated, and
 - Reduction in risk of treatment by not exposing false positive reactors to unnecessary treatment.



Acknowledgments

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