Universitätsklinikum Hamburg-Eppendorf

Institute for Health Service Research for Healthcare Workers

TB-screening in Healthcare Workers (HCW)

and

TB-contact tracing

What did we learn from using the Quantiferon Gold in tube (QFT)

Albert Nienhaus

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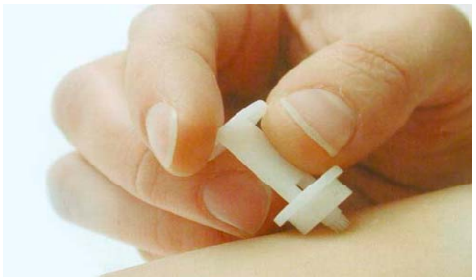
My personal background

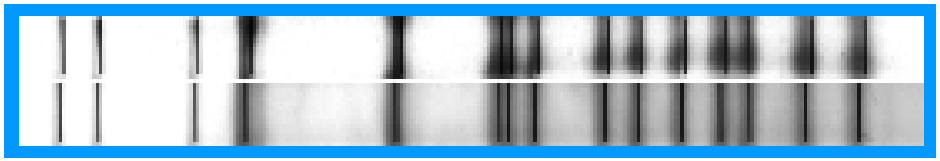
- during my OSH training
  - 45 year old fire fighter and emergency worker
  - 20 years at the fire department
  - positive TST at pre-employment screening
  - 10 chest X-rays since
  - no know TB contact in history
  - BCG vaccination



- My refusal to send him in for his eleventh X-ray decreased my chances for job promotion

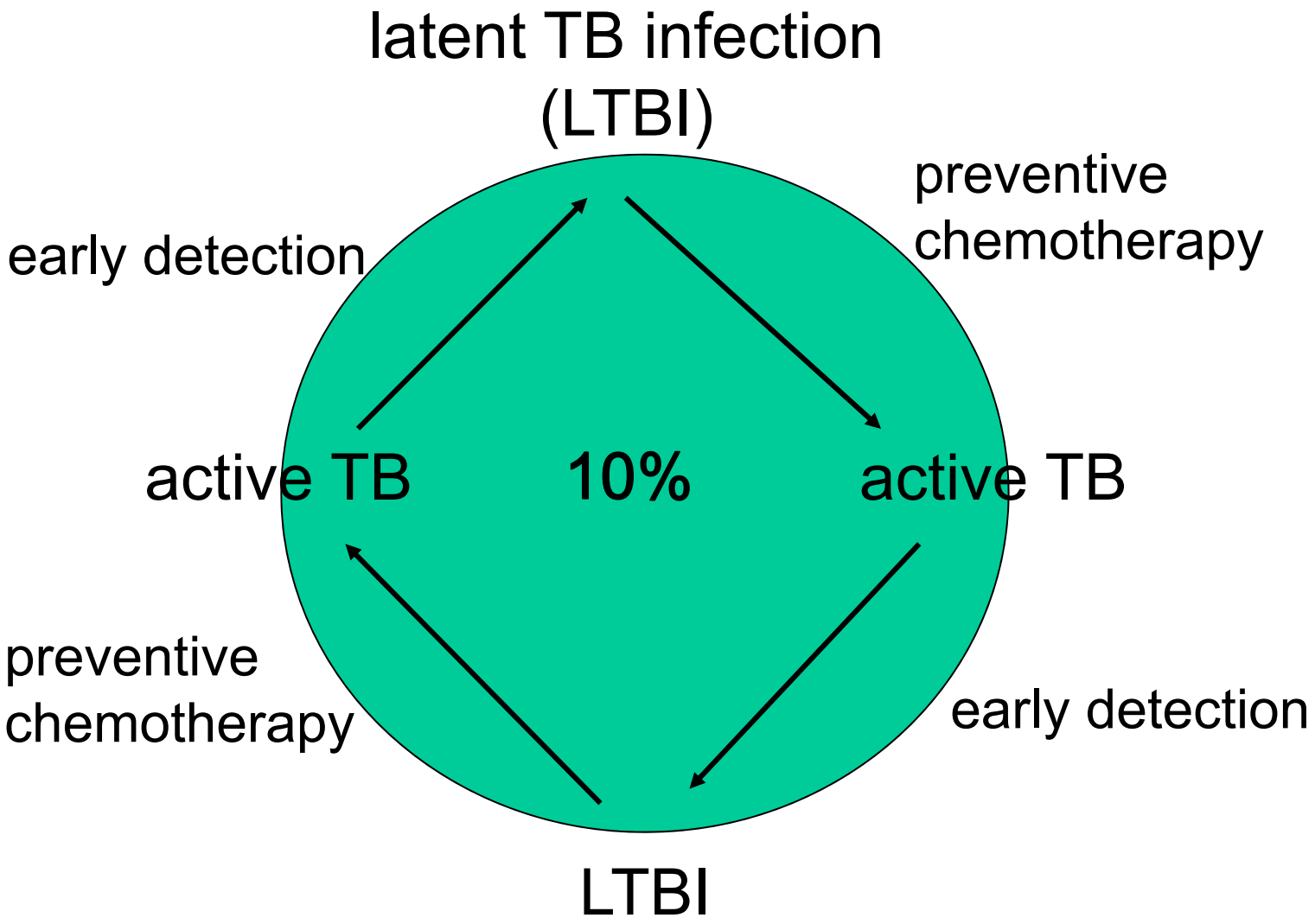
German background 2005

- TB in HCW is most often caused by patient contact

case	age	sex	IS*6110*-DNA-Fingerprint	
1	25	m		Index
2	68	m		ENT-doctor

- Diel R, …, Nienhaus A Resp Research 2005;6:35
- Most physicians refused to perform TST in HCW

Why screen for TB?



TST for diagnosing LTBI

pro

- inexpensive
- no Lab needed

contra

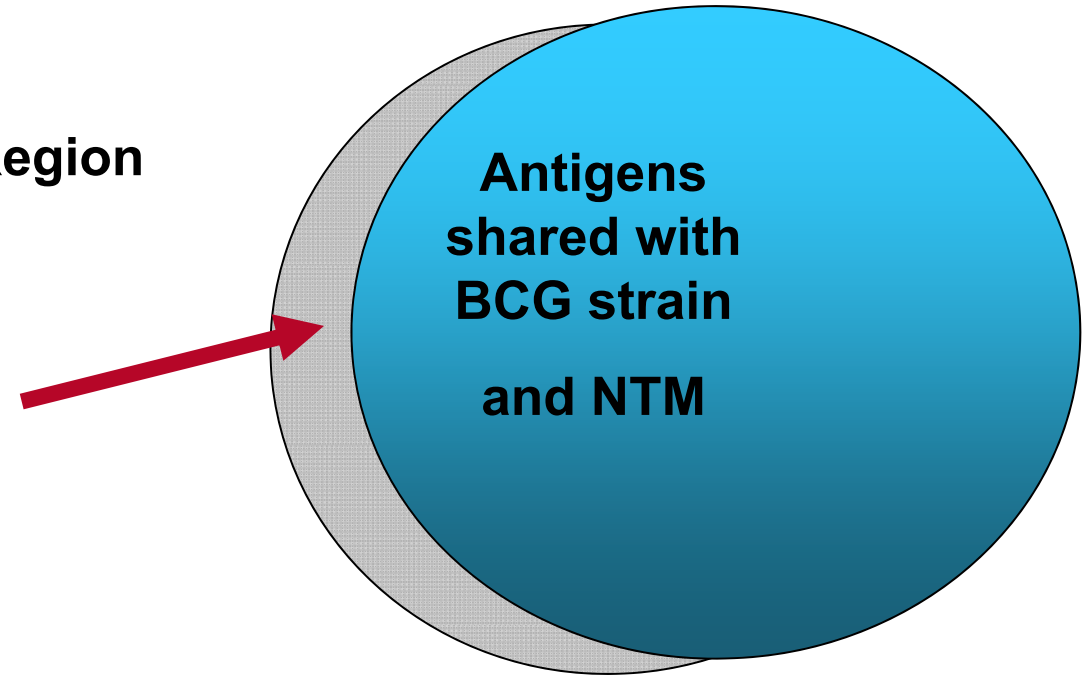
- cross reaction with
  - BCG vaccination
  - NTM
- strong reaction
- second appointment
- boosting in serial testing
- no simple interpretation
  - > 5 mm
  - >= 10 mm
  - > 15 mm
  - increase by 10 mm

Aim: No cross-reaction with BCG and NTM

- QuantiFERON®-Gold In Tube (QFT) (Elisa)

3 Antigens from the Region of Difference (RD1)

- **ESAT-6**
- **CFP-10**
- **TTD7.1**



TST uses Tuberculin with about 200 antigens

TB-NET for HCW in Germany

- HCWs are screened
  - after contact to TB patients
  - every 1-3 years if regular contact to TB patients
    - biologic substances ordinance
- TB-NET in order to evaluate IGRA started in 2006
  - Employer pays the physician
  - Accidents insurance for health service sector pays the test - **QFT** (because at this time it was less expensive)
- 50 physicians
- Cohort of 2,500 HCWs

First results

- positive QFT 9.6%
- positive TST (>5mm) 24.2%
- no active TB in TST+/QFT- participants
- 2 out of 3 X-rays avoidable
  - Nienhaus et al IAOEH 2008;81:295-300

- Acceptance of TST even for study purposes decreased

Agreement between TST and IGRA in HCW

	TST >10mm	IGRA pos	TST confirmed
• Germany	24%	10%	30%
– Nienhaus et al IAOEH 2008			
• France	50%	19%	31%
– Triopldi et al JOMT 2009			
• Portugal	74%	33%	41%
– Torres et al. Eur Respir J 2009			

• Portugal	n (%)	IGRA positive
• TST 0-4 mm	137 (11)	3%
• TST 5-10 mm	178 (15)	12%
• TST 11-15 mm	483 (40)	29%
• TST >15 mm	420 (34)	55%

Reason for discordant results

Nienhaus et al PloS ONE 2008;3(7):e2665

- pooled analysis of 2 German studies
  - Diel et al Eur Respir J 2006;28(1):16-23 (contact tracing)
  - Nienhaus et al IAOEH 2008;81:295-300 (HCW screening)

- 671 observations
  - IGRA- / TST+ 14.0 % (87.5 % explained by BCG vaccination)
  - IGRA+ / TST- 4.2 % (57.1 % explained by age > 40 y)
  - Agreement 81.8 %
- corrected for explained discordance
  - IGRA- / TST+ 3.2 %
  - IGRA+ / TST- 1.8 %
  - Agreement 95.0 %

Waning immunological reaction ?

	TST - / QFT +	Odds Ratio*	95%CI	AF
Age	O (%) [E]			%
14-39 years	8 (1.8) [8]	1	-	
40-49 years	12 (7.1) [3.0]	3.3	1.3 – 8.5	69.7
50-68 years	8 (13.6) [1.1]	5.4	1.8 – 16.1	81.5
Total	28 (4.2) [12.1]			

*** gender, being foreign born, previous TST, BCG vaccination and source population were not associated with TST-/QFT+ discordance**

O = observed, E = expected

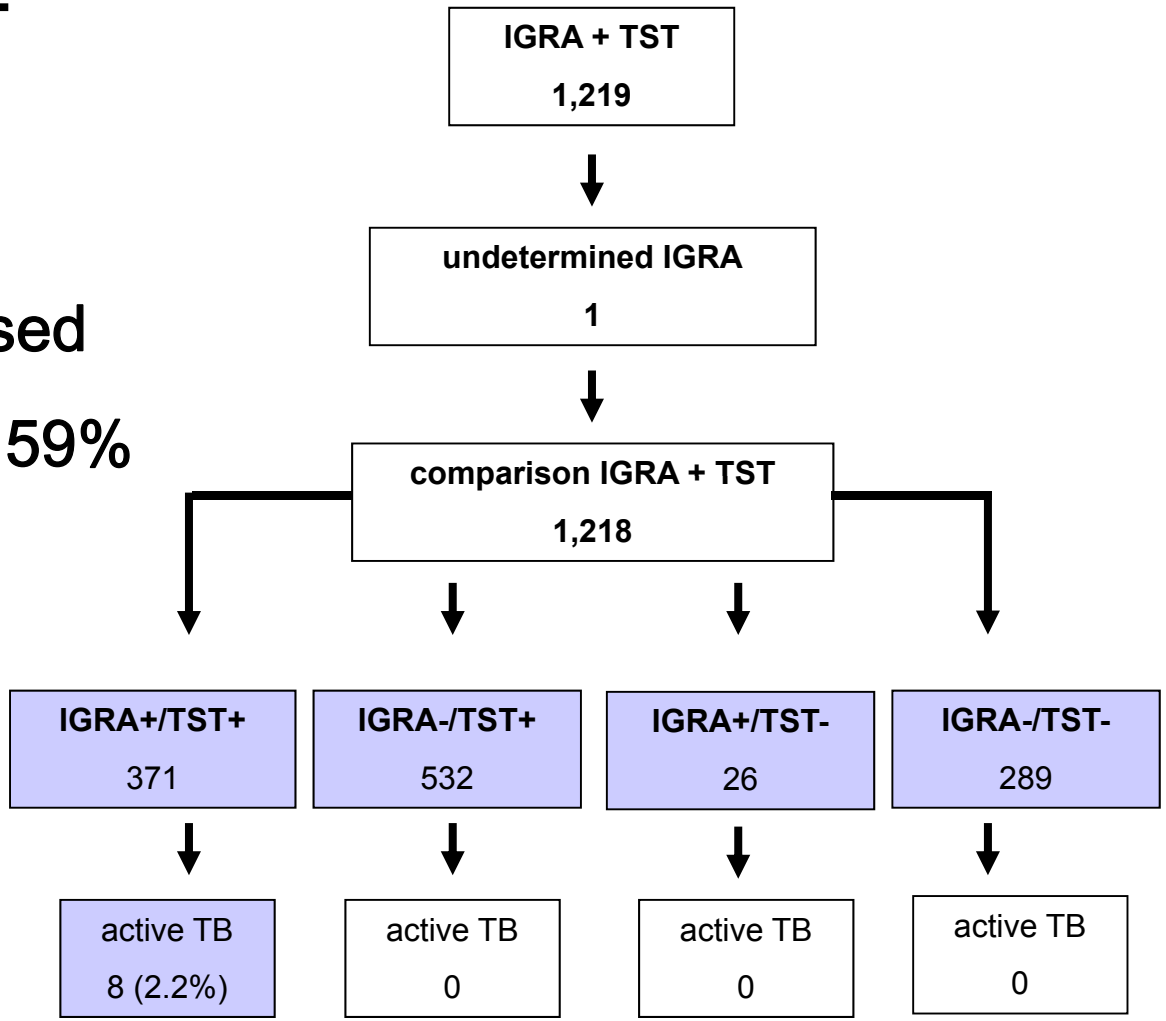
Nienhaus et al PloS ONE 2008;3(7):e2665

Hospital de São João, Porto, Portugal

Screening with QFT 2007/2008

No active TB missed

X-ray reduced by 59%

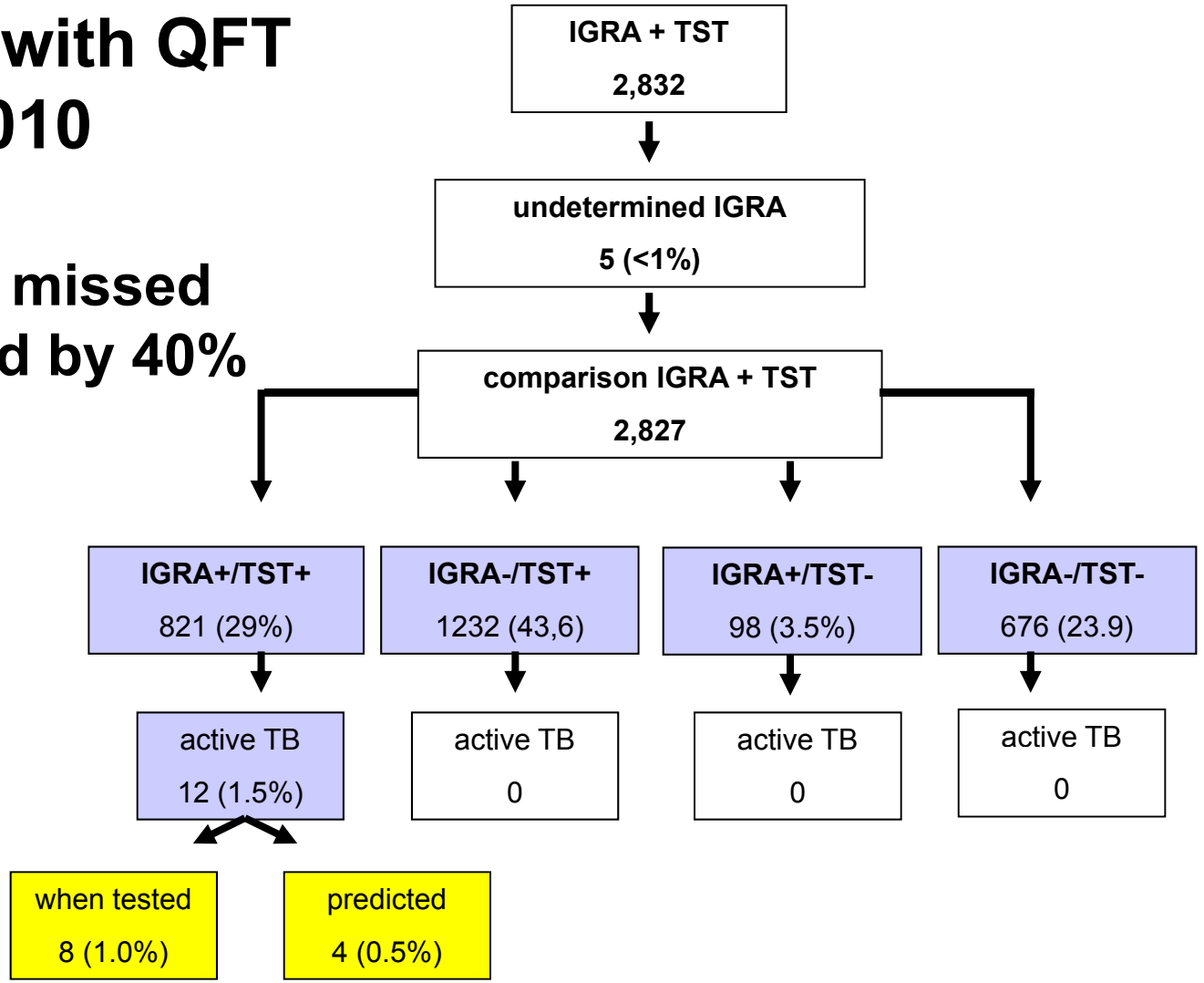


Torres Costa, …, Nienhaus ERJ 2009;34:1423–8

Hospital de São João, Porto, Portugal

- **Screening with QFT 2007- 10/2010**

No active TB missed
X-ray reduced by 40%



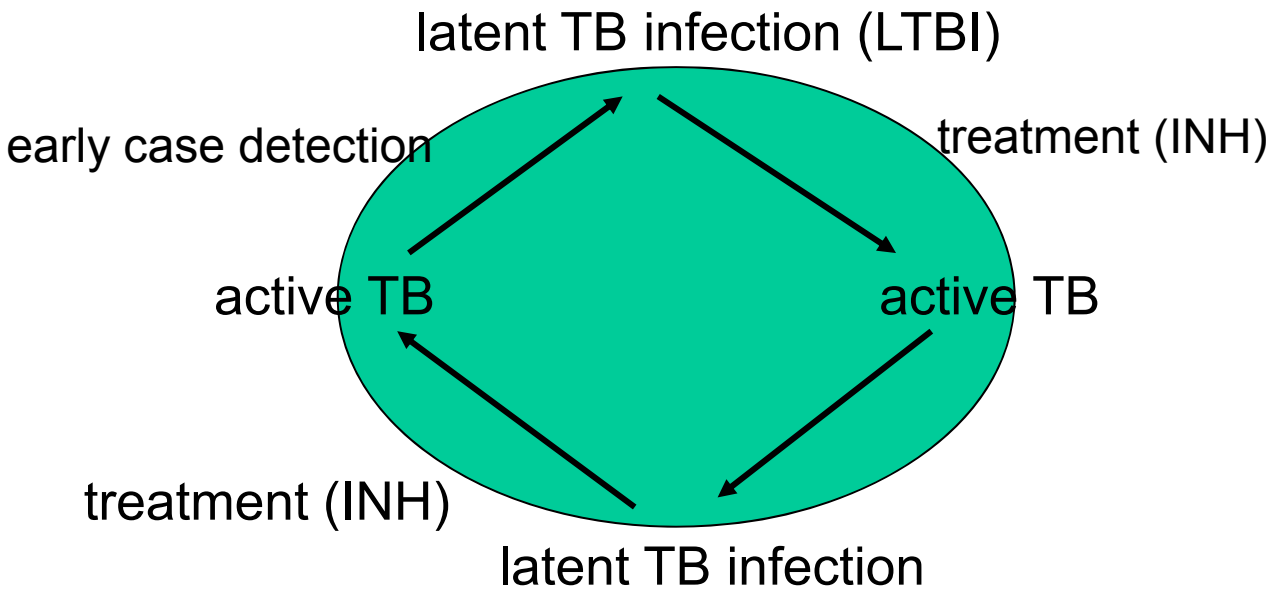
Progression risk in close contacts

- 101 TB cases
- 954 **close contacts** (with 2 years follow up)
  - TST positive 63.3% (n=604)
  - QFT positive 20.8% (n=198)
- 51 chemoprevention (INH/RIF) (2 QFT+/THT-) no active TB
- Progression to active TB
  - TST: 17 out of 555 (3.1%)
  - QFT: 19 out of 147 (12.9%)
    - <16 years old: 6 out of 21 (29%)

Diel, …, Nienhaus: Negative and positive predictive value of a whole blood interferon-γ release …….
AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 182 2010, online first

Number to treat to prevent one active TB

• Effectiveness IHN/RIF	100%	80%
• TST > 5 mm:	33	42
• QFT positive:	8	10



IGRA in patients with TB and in unexposed persons

	QFT-GIT	TST
• Sensitive	84%	70%
• Specific	99%	(15-90%)

CHEST Special Features

Evidence-Based Comparison of Commercial Interferon-γ Release Assays for Detecting Active Tuberculosis

A Metaanalysis

Roland Diel, MD, MPH; Robert Loddenkemper, MD, FCCP; and Albert Nienhaus, MD, MPH

2010; 137 (4): 952-968

Positive predictive value (PPV)

prevalence	**Sensitivity / Specificity of test**		
LTBI	84%/99%	70%/90%	90%/90%
	PPV	PPV	PPV
1%	50%	9%	9%
10%	89%	44%	50%
20%	94%	64%	69%
30%	96%	75%	79%

Specificity of TST increase >= 10mm

	TST-increase	QFT pos
• France (n=148)	8 (5%)	1 (12%)
– Triopldi et al JOMT 2009		
• Portugal (n=690)	61 (9%)	13 (21%)
– Torres et al. IAOEH 2010 December		

Meaning of the value around the cut-off

- Portugal:
- INF-γ >0.35-<1.0 IU/mL

  3 out of 9 HCW with active TB
  - Torres Costa, ,,, Nienhaus Int Arch Occup Environ Health 2010

- Germany contact tracing
- INF-γ 0.35-<1.0 IU/mL: 3 out of 19 predicted cases (progression 5.3%)
- INF-γ >=1.0 IU/mL: 16 out of 19 predicted cases (progression 6.2%)
  - calculated from data of Diel, …; Nienhaus AJRCCM 2010

QFT-GIT and T-SPOT.TB in contact tracing in Germany

- 812 close contacts
- QFT-GIT und T-SPOT.TB, if TST > 5mm
- IGRA positive
  - QFT-GIT 30%
  - T-SPOT.TB 29%
- Agreement 94%, Kappa 0.85

- Diel, …, Nienhaus Chest 2009; 135(4):1010-8

CHEST

Official publication of the American College of Chest Physicians

cost of screening with TST or IGRA

- The unit cost for IGRAs are higher than for TST
  - QFT 20-40 € (German average price)
- What does the picture look like when all costs are taken into account?
  - chest X-ray
  - chemoprevention
  - treatment of active TB

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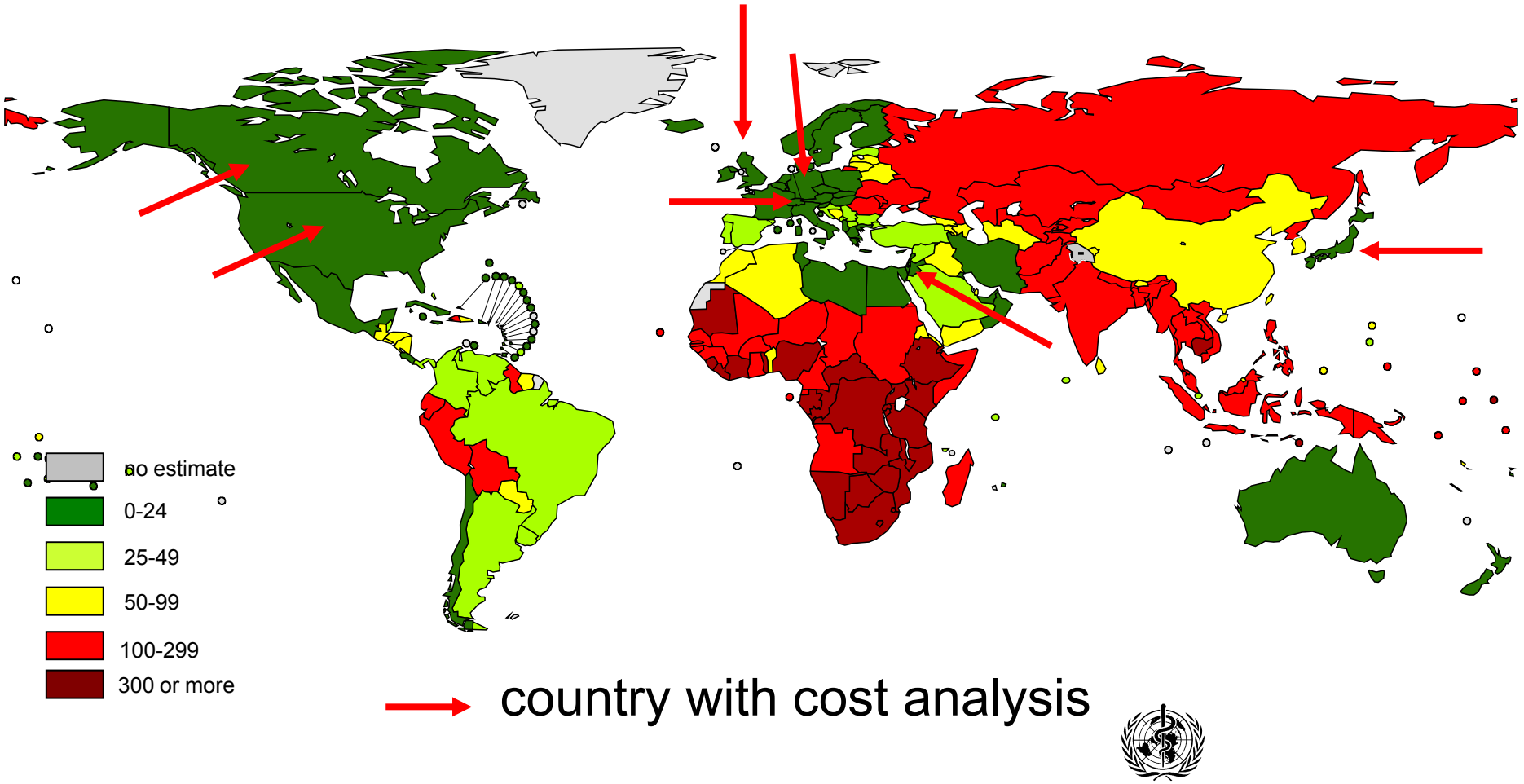
Countries with cost analysis



active TB per 100,000 population

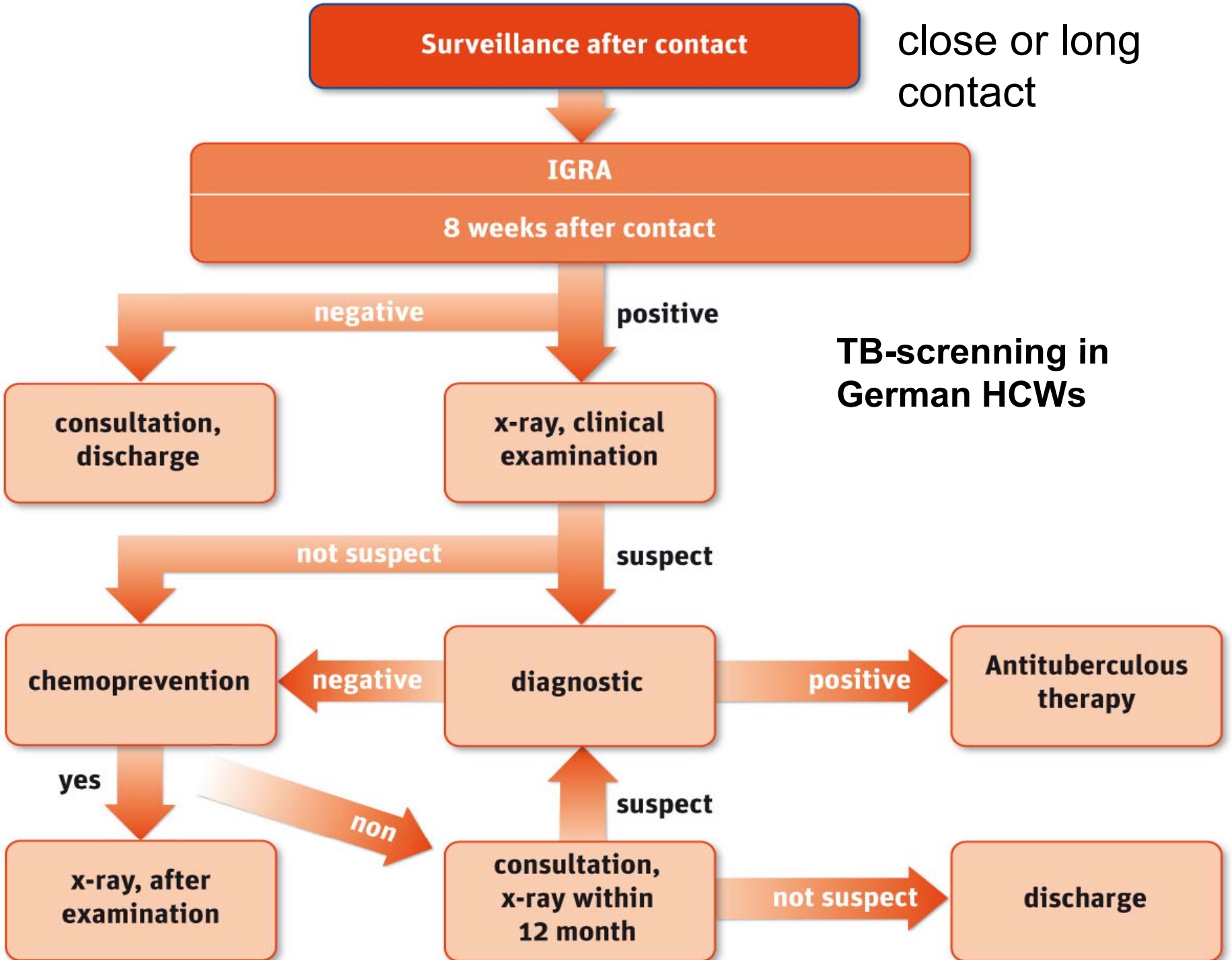
available evidence concerning cost of screening

- 13 publications available on cost
  - 5 cost analysis of screening or LTBI-detection
    - Costs for test, chemoprevention and chest x-ray
    - **Conclusion:** Introduction of IGRAs reduces cost
  - 8 cost-effectiveness analysis of TB-prevention
    - additional costs for treatment of active TB
    - Cohort follow-up: 2 years to life long
    - Survival analysis with Markow Model
    - let us have a closer look

Cost-effectiveness

- 8 cost-effectiveness analyses of TB-prevention
  - 1 compared TST only to QFT only
    - QFT more cost-effective
  - 6 compared TST only, IGRA in TST+ves, IGRA only
    - 4 favour IGRA in TST+ves
    - 3 favour IGRA only
  - how can this be explained?
    - low specificity of TST
      - 15% in Japan with BCG repeated in adults
    - high progression to active TB for QFT+ contacts
      - 14% for QFT+ and 2% for TST+ in two years

close or long contact



TB-screnning in German HCWs

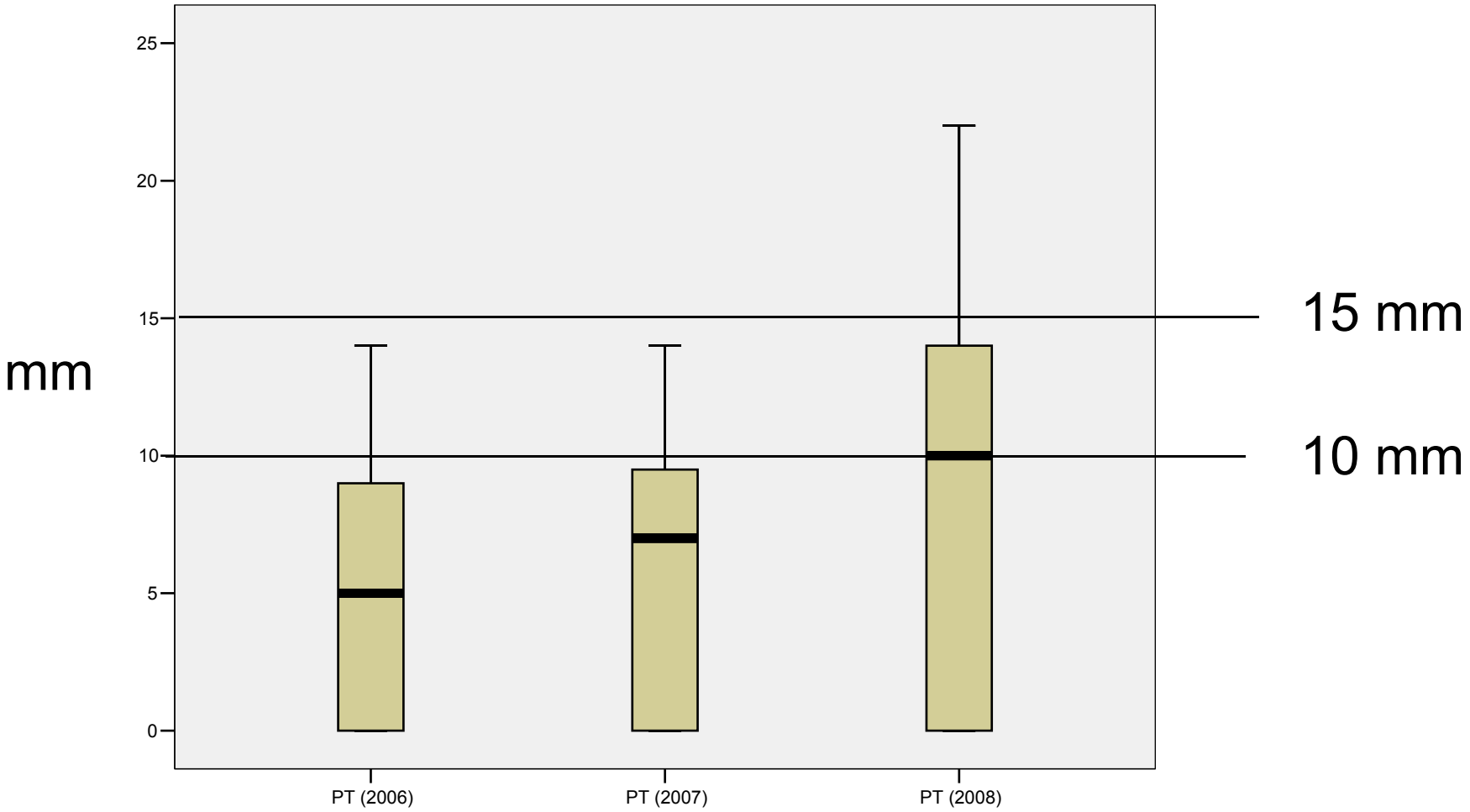
National recommendations HCW screening

- US: TST or IGRA, IGRA if patient is unreliable

- GB: IGRA in TST+, IGRA if patient is unreliable
- Germany contact tracing: IGRA (in TST+)
- Swiss: IGRA or IGRA in TST+ (not in HCW)

- Swiss and Germany HCW: IGRA
  - IGRA instead of TST because of booster effect in serial testing of HCWs
- Why?

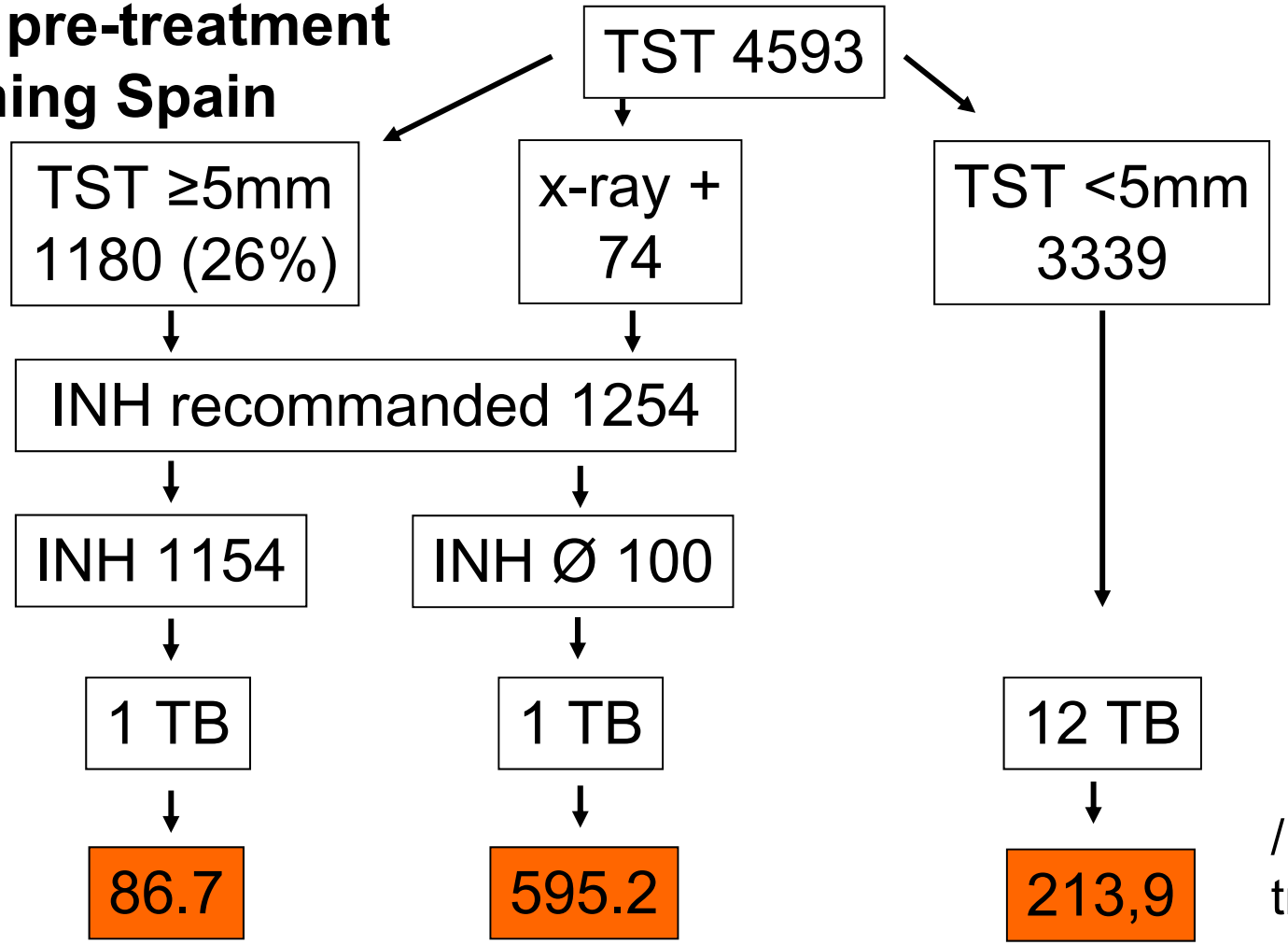
59 HCWs with TSTs (PT) in 2006, 2007, and 2008



Torres et al. ERJ 2009, 34:1423–1428

Risk of TB in TST-

TNF-α pre-treatment screening Spain



/100.000 treatment years

nach: Gómez-Reino et al A&R 2007;57(5):756-761

BIOBADASER

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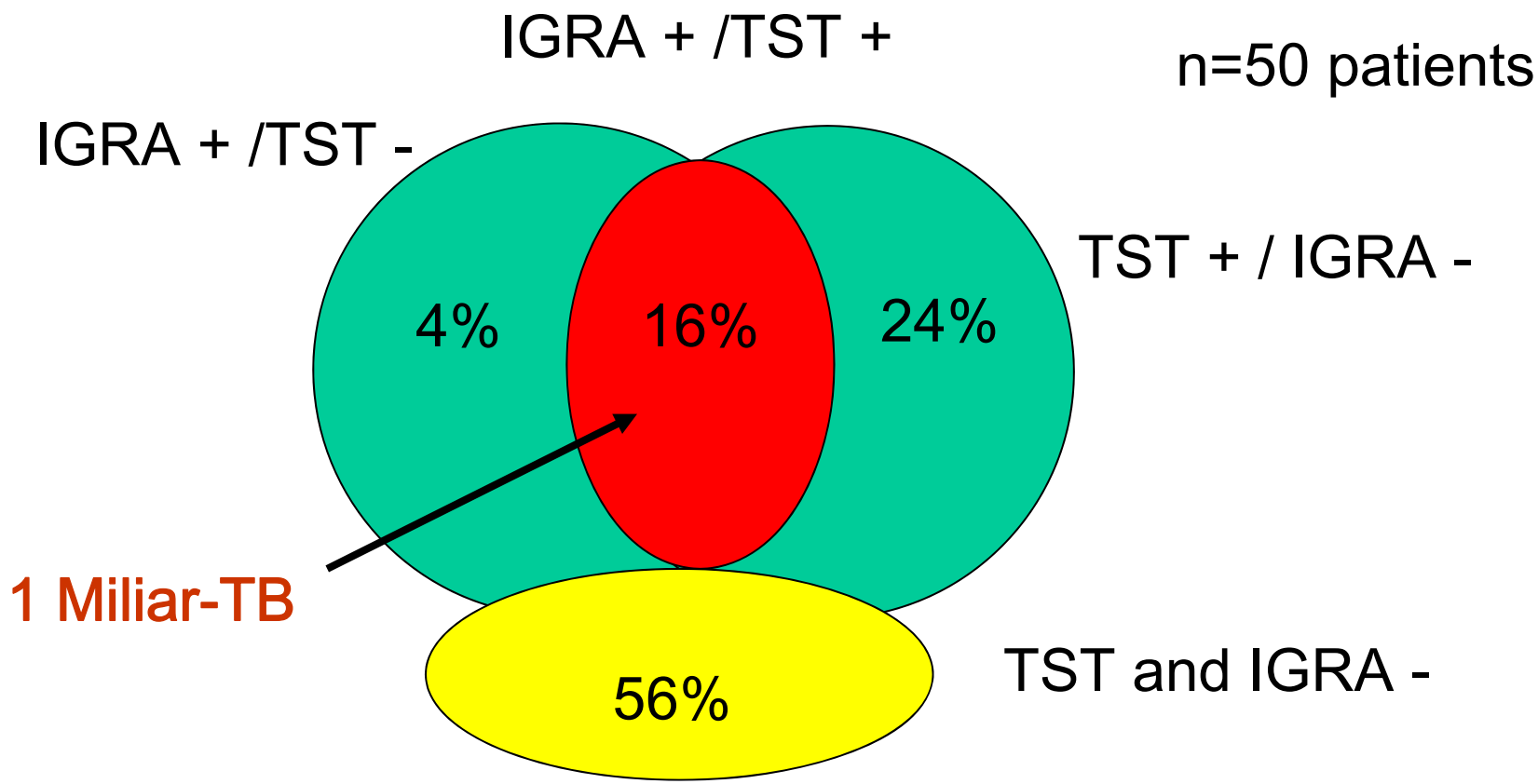
Number to treat with INH in patients for TNF-α Blocker

	Pat-Years	TB-Cases
before 2002	8.671	41
2002-2006	8.717	15 (expected: 41,2)
		(avoided: 26,2

- INH-Treatment
- total: 1.154
- per case avoided: 44 (with QFT they might have done better)

nach: Gómez-Reino et al A&R 2007;57(5):756-761 BIOBADASER

IGRA and TST in patinets with Psoriasis



CLINICAL AND LABORATORY INVESTIGATIONS BJD British Journal of Dermatology

Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-γ release assay vs. tuberculin skin test

E. Laffitte, J.P. Janssens,* P. Roux-Lombard,† A.M. Thielen, C. Barde, G. Marazza, R.G. Panizzon‡ and J.-H. Saurat

Laffitte et al BJD 2008

Reaction after infection
?can we make sense out of reversion?

active TB

Local reaction lung

TB granuloma (LTBI)

Transient infection

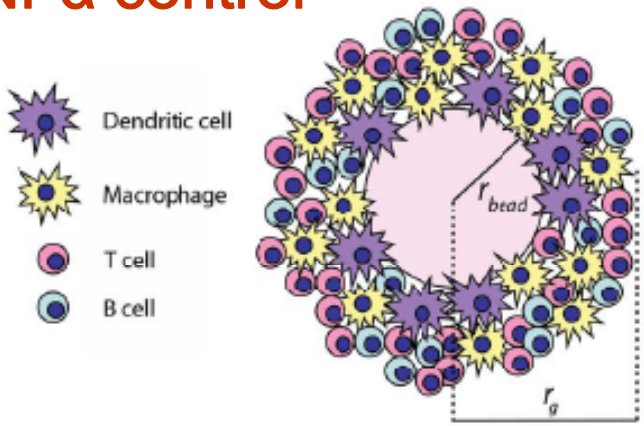
Dormant state

low replication with T-cell stimulation

uncontrolled replication

subclinical or clinical TB

TNFα control



?can we make sense out of reversion?

TB and QFT in HCWs in Portugal

TB	QFT	
	negativ	positive
Old TB	23 (40.4%)	34 (59.6%)
Acute TB	-	8
Predicted TB	-	4
No TB	1908 (67.8)	953 (33.0?)

Torres Costa, …, Nienhaus. unpublished data

Conclusion

- QFT is more sensitive and specific and has a higher positive predictive value for active TB
- QFT increases cost-effectiveness of TB-screening
- X-ray in HCWs can be saved
- Chemoprevention can be performed more targeted

Thank you for your attention

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