Con-LTBI treatment for IGRA-positive Healthcare Workers

전남의대 내과
권용수

Contents

1. High LTBI prevalence in HCW
2. Limitations of IGRAs
3. Some concerns about of LTBI treatment

Positive and conversion rate of IGRA in HCWs

Year	Test center	age	N	TST+	QFT+	1-yr follow up	
						TST+	QFT+
2007	아산병원	23	196	52%	14%	21%	14%
2009	세브란스	28	82	38%	23%	NA	NA
2009-2011	세브란스	30	53	38%	17%	0%	9%
2008	삼성병원	24	322	26%	10%	NA	6%
2012	8개병원	30	493	37%	17%	NA	NA

Infect Control Hosp Epidemiol 2009;30:1218-1222. Scand J Infect Dis. 2010;42:672-8.
Infection 2013;41:511–516. Scand J Infect Dis. 2010;42: 943–945. Tuberc Respir Dis 2013;75:18-24

LTBI in healthy population

- 국민건강영양조사
- 제7기 1차, 2016

Age	TST> 10 mm	TST > 15 mm
20-29	11%	3%
30-39	36%	17%
40-49	46%	25%

- 군인, 신병교육대,
- 2005 (Mean age: 20)

Risk	TST> 10 mm	TST > 15 mm
Low risk	28%	8%
Casual contract	27%	13%
Close contract	40%	15%

- INT J TUBERC LUNG DIS 10(12):1342–1346

- 건강 참여자
- 2004

Risk	Age	TST>10 mm	QFT+
Low risk	25	51%	4%
Casual contract	28	60%	10%
Close contract	41	71%	44%

- JAMA. 2005;293:2756-2761

Sensitivities of IGRAs and TST

Test	Sensitivity				Specificity			
	No. of Studies	Participants, No.	Pooled Estimate (95% CI)	I^2, %	No. of Studies	Participants, No.	Pooled Estimate (95% CI)[a]	I^2, %
TST induration threshold, mm								
5	8	803	0.79 (0.69-0.89)	94.6	4	47[40]	0.30 (0.19-0.44)	NA
						2848[65]	0.95 (0.94-0.96)	
						1750[76]	0.94 (0.92-0.95)	
						551[77]	0.97 (0.95-0.98)	
10	11	988	0.79 (0.71-0.87)	91.4	9[b]	9651	0.97 (0.96-0.99)	94.3
15	7	740	0.52 (0.35-0.68)	95.5	12	9640	0.99 (0.98-0.99)	91.7
IGRA								
T-SPOT.*TB*	16[c]	984	0.90 (0.87-0.93)	63.6	5	1810	0.95 (0.92-0.98)	79.1
QuantiFERON TB Gold	17	1073	0.77 (0.74-0.81)	55.3	4	699	0.98 (0.90-1.0)[d]	NA[d]
QuantiFERON TB Gold In-Tube	24	2321	0.80 (0.77-0.84)	74.3	4	2053	0.97 (0.94-0.99)	93.4

JAMA. 2016;316(9):970-983.

Results of QFT-GIT

- 1264 culture confirmed TB (>18 yrs of age) in 6 university hospitals
- 2007.5.1~2014.2.31

	n (%)
Positive	1082 (85.6)
Negative	142 (11.2)
Indeterminate	40 (3.2)

PLoS One. 2015 Jun 12;10(6):e0129792

High risk of TB in recent infection

Table 1. Annual Risk of Reactivation Tuberculosis.*

Size of Induration on Tuberculin Skin Test	Age				
	0–5 Yr	6–15 Yr	16–35 Yr	36–55 Yr	≥56 Yr
	percent (95 percent confidence interval)				
Persons with nonconversion positive result					
5–9 mm	0.06 (0.03–0.11)	0.04 (0.03–0.06)	0.12 (0.05–0.32)	0.07 (0.03–0.19)	0.07 (0.03–0.16)
10–14 mm	0.19 (0.12–0.28)	0.08 (0.06–0.11)	0.15 (0.08 –0.29)	0.10 (0.05–0.19)	0.10 (0.06–0.17)
≥15 mm	0.24 (0.19–0.30)	0.14 (0.12–0.17)	0.19 (0.10–0.34)	0.12 (0.07–0.21)	0.12 (0.08–0.20)
Persons with recent conversion or contacts of patients with active tuberculosis					
5–9 mm	0.29 (0.08–0.74)	0.06 (0.02–0.18)	0.30 (0.18–0.50)	0.23 (0.10–0.44)	0.12 (0.02–0.44)
10–14 mm	0.37 (0.16–0.71)	0.12 (0.05–0.25)	0.37 (0.26–0.53)	0.28 (0.17–0.45)	0.15 (0.04–0.39)
≥15 mm	0.54 (0.27–0.95)	0.12 (0.07–0.23)	0.56 (0.41–0.76)	0.42 (0.28–0.62)	0.17 (0.05–0.42)

- N Engl J Med 2004;350:2060-7.

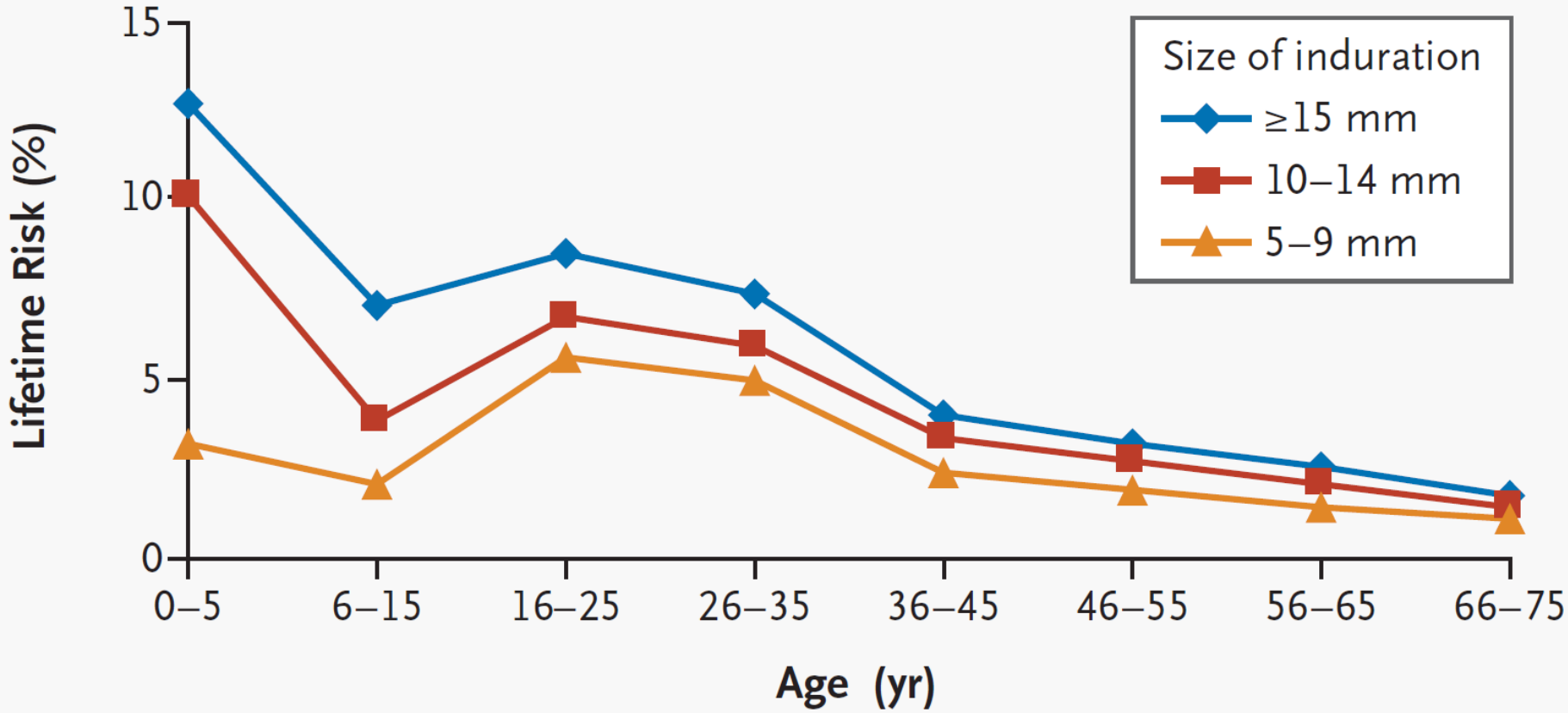


Figure 1. Lifetime Risk of Active Tuberculosis among Persons with a Non-conversion Positive Tuberculin Skin Test.

Risks were calculated with the assumption of a decrease in risk of 10 percent per decade.

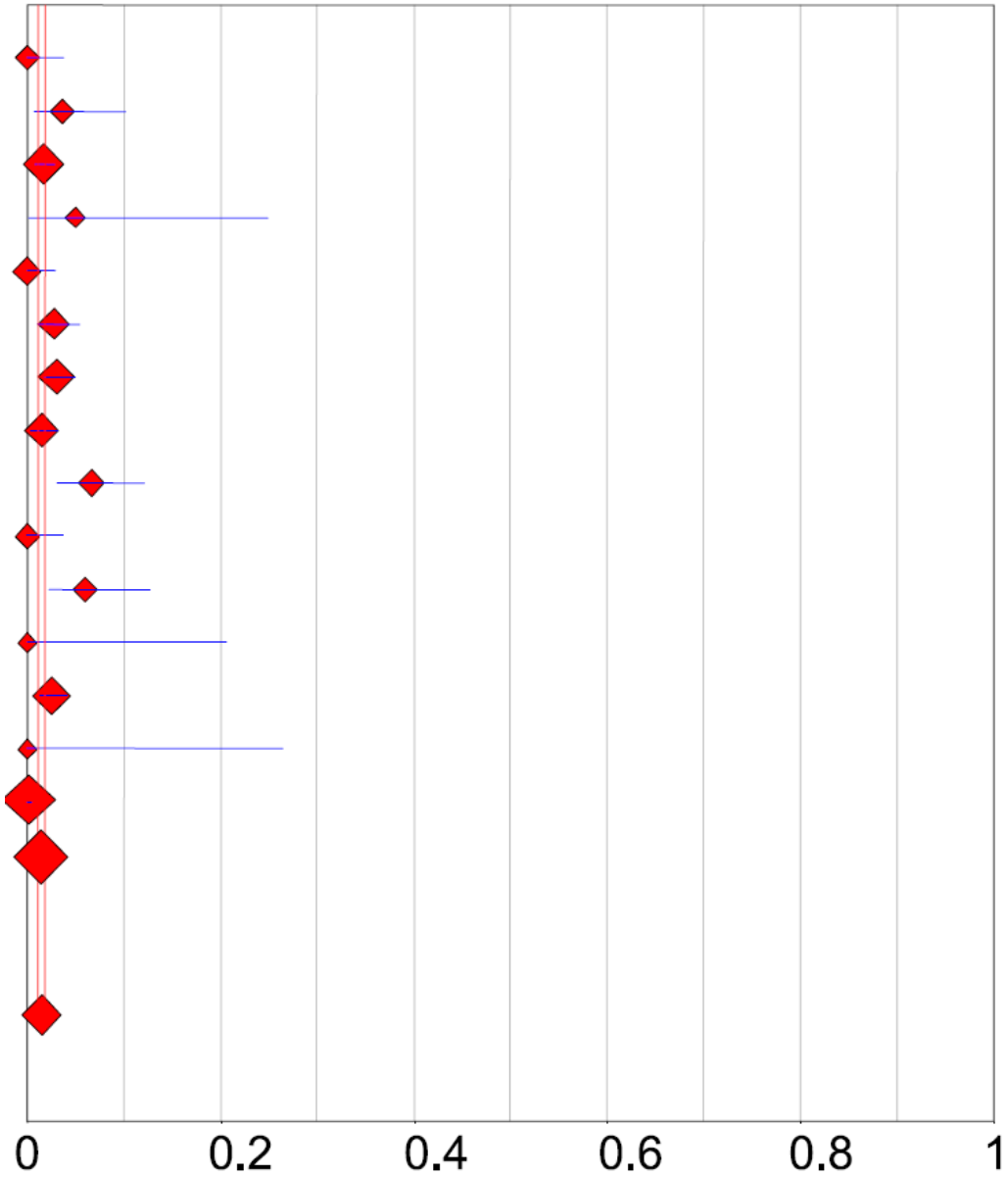
- N Engl J Med 2004;350:2060-7.

However, IGRA has no discriminating ability of recent from remote *Mtb* infection

Poor prediction about progression to active TB in IGRAs positive subjects

- A meta-analysis of 28 studies
- Follow-up duration: 1 year to 46 months
- Pooled PPV for progression: 2.7% (95% CI, 2.3%-3.2%)
- Containing high risk group: 6.8% (95% CI, 5.6%-8.3%)
    - CHEST 2012; 142(1):63–75

- A meta-analysis of 15 studies
- N=26,680
- Follow-up duration: 4 years (IQR 2–6)
- Pooled unadjusted incidence rate ratios: 2.10 (95% CI, 1.42–3.08)
    - Lancet Infect Dis 2012; 12: 45–55



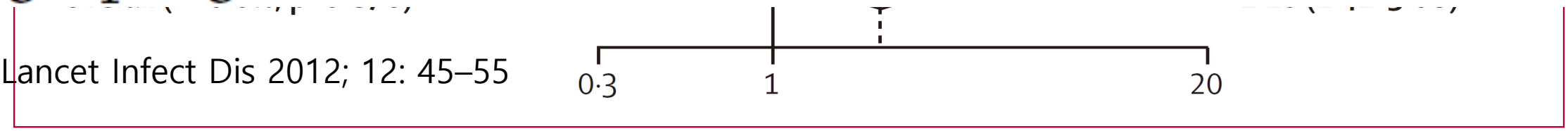
	PPV	(95% CI)	n/N
Higuchi 2007[20]	0.00	(0.00 – 0.04)	0/95
Bakir 2008[16]	0.04	(0.01 – 0.10)	3/83
Hill 2008[17]	0.02	(0.01 – 0.03)	14/843
Lee 2009[13]	0.05	(0.00 – 0.25)	1/20
Higuchi 2009[21]	0.00	(0.00 – 0.03)	0/200
Kik 2009[14]	0.03	(0.01 – 0.05)	8/288
Diel 2011[27]	0.03	(0.02 – 0.05)	17/555
Harstad 2010[28]	0.01	(0.01 – 0.03)	6/415
Leung 2010[38]	0.07	(0.03 – 0.12)	9/136
Thomas 2010[29]	0.00	(0.00 – 0.04)	0/100
Song 2011[34]	0.06	(0.02 – 0.13)	6/99
Chang 2011[30]	0.00	(0.00 – 0.21)	0/16
Lienhardt 2010[19]	0.03	(0.01 – 0.04)	16/629
Silvermann 2007[23]	0.00	(0.00 – 0.26)	0/12
Torres Costa 2011[35]	0.00	(0.00 – 0.00)	4/2094
Mahomed 2011[31]	0.01	(0.01 – 0.02)	40/2894

Pooled PPV for progression = 0.015 (0.012 to 0.017)
Chi-square = 89.22; df = 15 (p = 0.0000)
Inconsistency (I-square) = 83.2 %

CHEST 2012; 142(1):63–75

Figure 4: Unadjusted incidence rate ratios for positive versus negative interferon-γ release assay results, by type of assay

The incidence of tuberculosis, even in IGRA-positive individuals, was low, suggesting that most IGRA-positive individuals did not progress to tuberculosis disease during follow-up. This finding is similar to that for TST in this meta-analysis and in historical studies.[14] Thus, the most important finding in this review is that no available tests for latent *M tuberculosis* infection have high prognostic value.



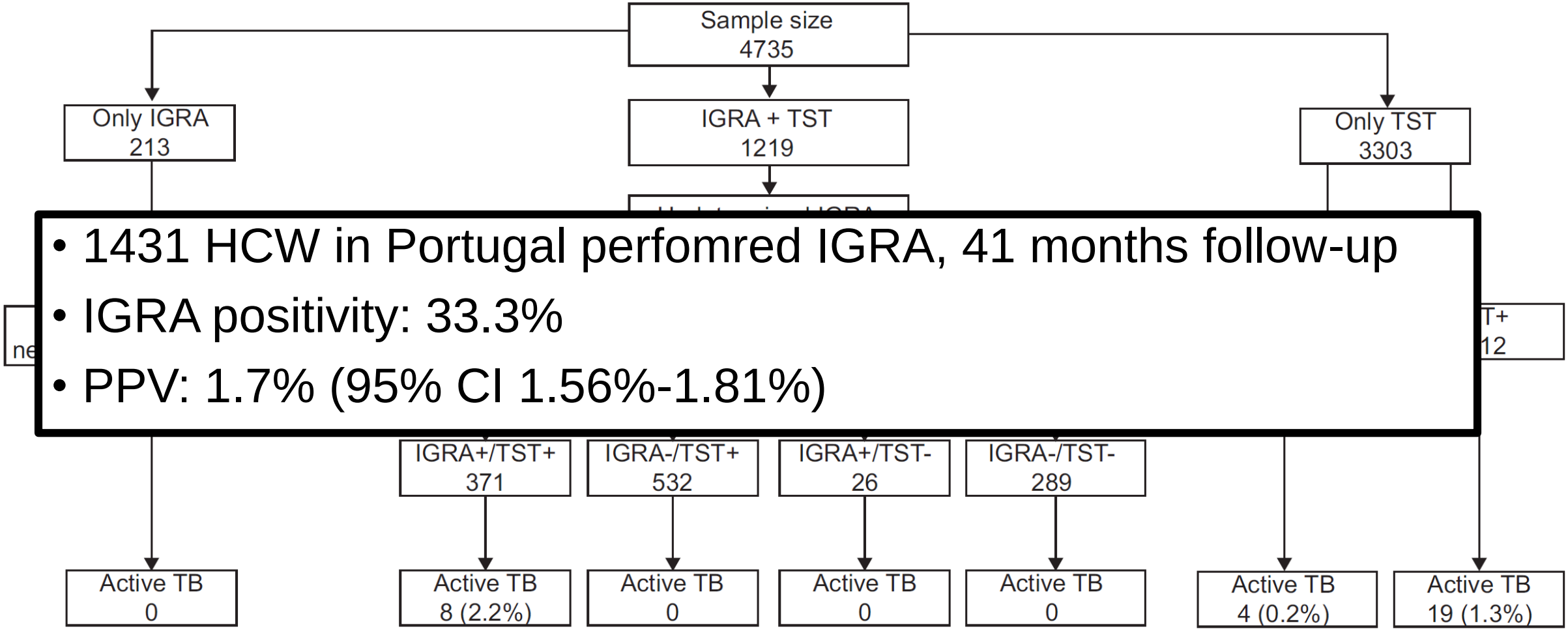
Lancet Infect Dis 2012; 12: 45–55

Eur Respir J 2009; 34: 1423–1428
DOI: 10.1183/09031936.00053809

Tuberculosis screening in Portuguese healthcare workers using the tuberculin skin test and the interferon-γ release assay

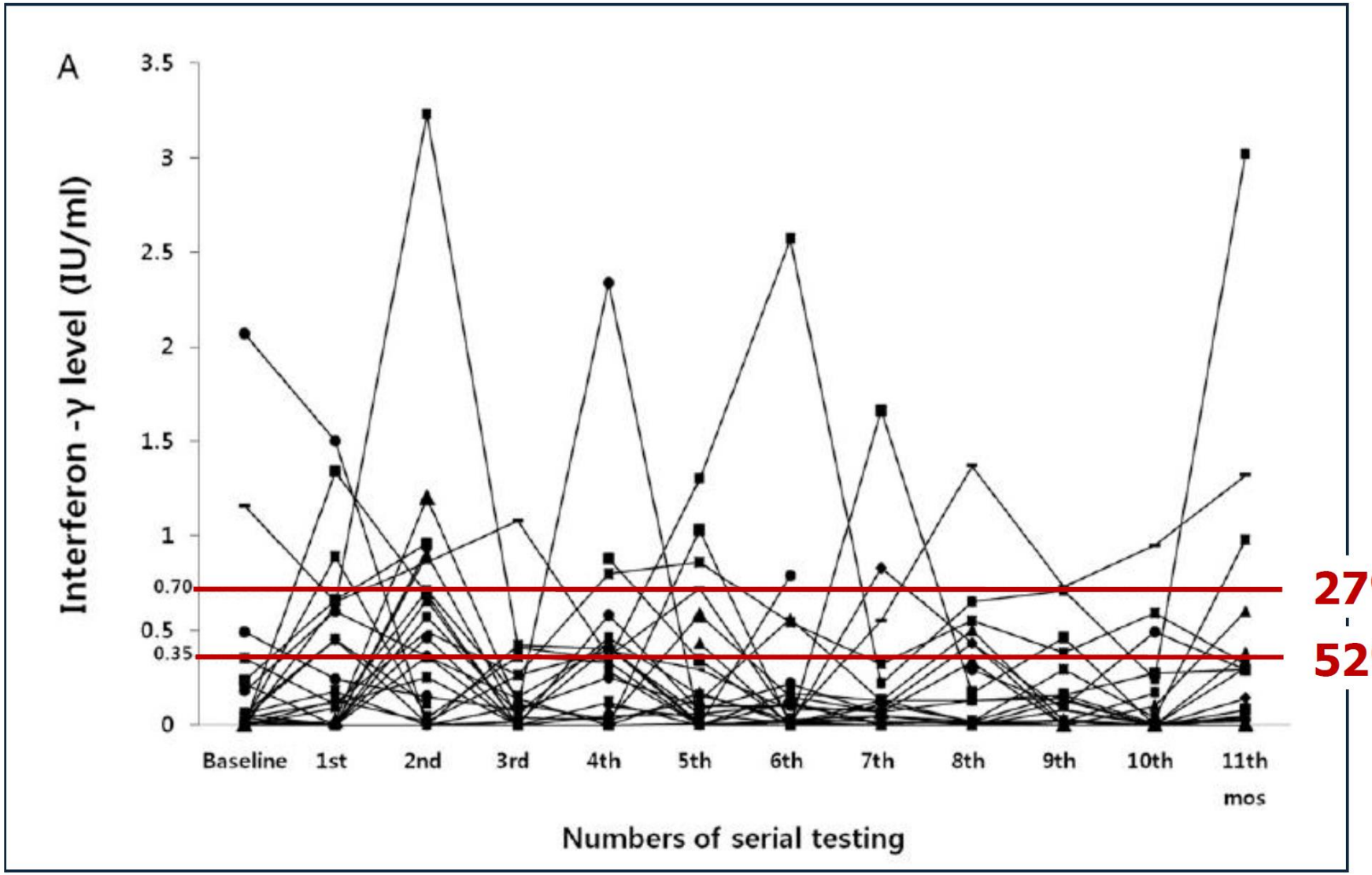
J. Torres Costa*,#,¶, R. Sá*, M.J. Cardoso¶,+, R. Silva*,#,¶, J. Ferreira*, C. Ribeiro*, M. Miranda*,#,¶, J.L. Plácido*,# and A. Nienhaus§

- Annual incidence HCW 191/100,000
- General population 32/100,000



- 1431 HCW in Portugal perfomred IGRA, 41 months follow-up
- IGRA positivity: 33.3%
- PPV: 1.7% (95% CI 1.56%-1.81%)

Conversion and reversion in serial testing



CHEST 2012;142:1461-8.

False positive in serial testing

- A cross sectional study
- 2008.2~2011.3
- 4 health care centers in US
- N=2418
- Conversion
- QFT-GIT: 6.1%
- T-SPOT: 8.3%

→ 76% reversion at 6 m later

- TST: 0.9%

Am J Respir Crit Care Med 2014;189:77-87

- A retrospective study
- 2006~2011
- Stanford University Medical center
- N=9153
- Conversion
- QFT-GIT: 4.4%

→ 65% reversion in short-term testing

- Historical TST conversion: 0.4%

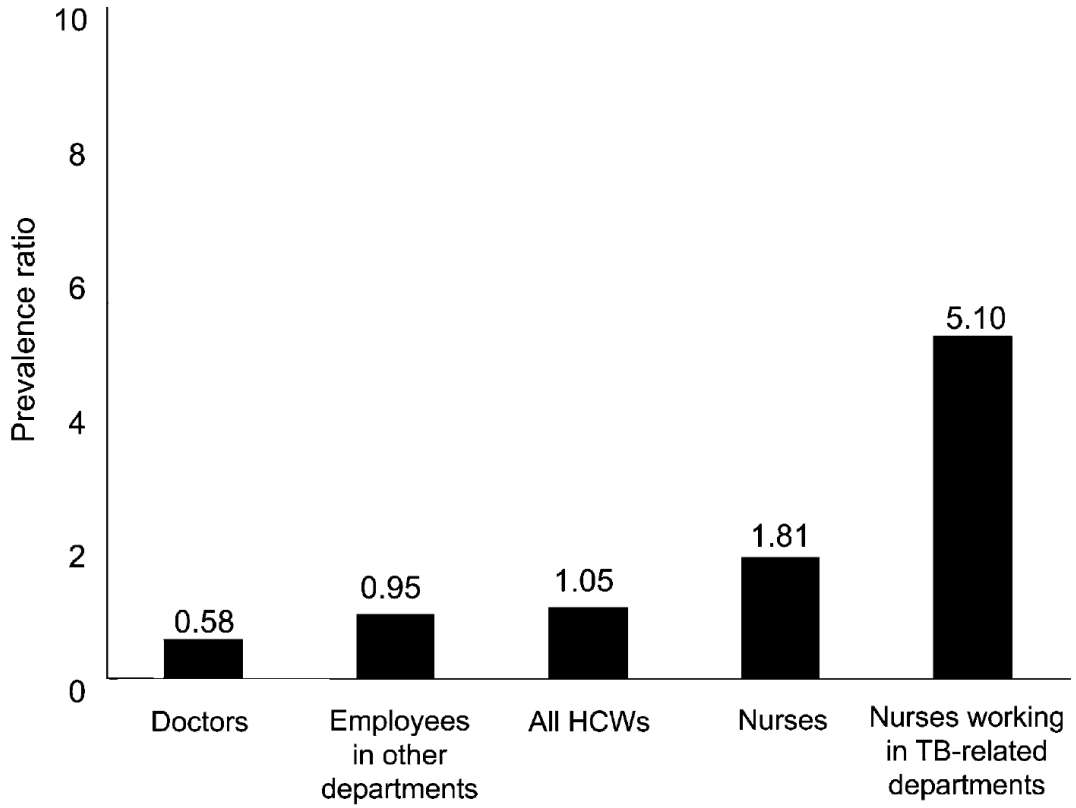
Am J Respir Crit Care Med 2013;188:1005-1010

Other limitations of IGRAs

- No ability for detecting reinfection after treatment
- No ability for discriminating active vs. latent TB
- No ability for identifying MDR-TB infection
- No ability for determining cure in LTBI treatment

Incidence of active TB in HCW

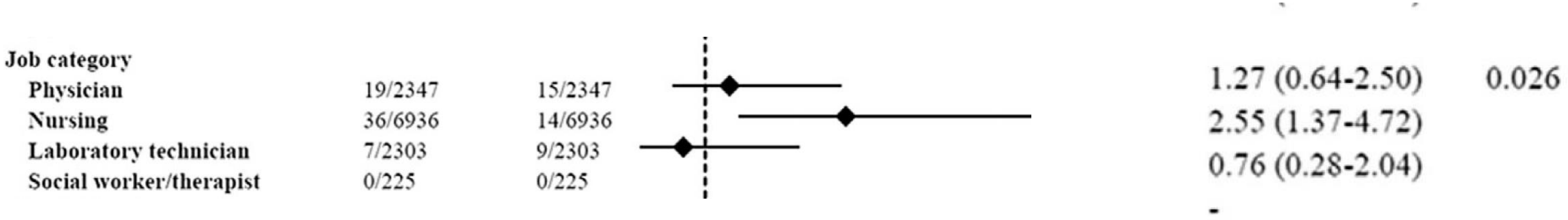
- 아산병원
- Prevalence ratio=1.05 (95% CI, 0.80–1.35).
- Nurses working in TB-related department was 5.1 (95%CI 3.23–8.42).
- Doctors and Nurses Age: 27.9±3.9
  - INT J TUBERC LUNG DIS 12(4):436–44



Incidence of active TB in HCW

- A nationwide, population-based cohort study in Taiwan
- aHR=1.62 (95% CI, 1.08-2.43)
- Job category: Nursing: aHR=2.55 (1.37-4.72)
- Mean age of HCW: 30

- Journal of Infection (2014) 69, 525-532



Job category				
Physician	19/2347	15/2347	1.27 (0.64-2.50)	0.026
Nursing	36/6936	14/6936	2.55 (1.37-4.72)	
Laboratory technician	7/2303	9/2303	0.76 (0.28-2.04)	
Social worker/therapist	0/225	0/225	-	

Mass Isoniazid Preventive Therapy for Tuberculosis Control

- A cluster-randomized trial in 3 gold-mining companies in South Africa
- Intervention: 9 months INH treatment

Table 3. Direct Effect of Isoniazid Preventive Therapy as Shown by Tuberculosis Incidence, According to the Time Interval after Enrollment.*

Time Interval	Control Cohort (N=6263)		Isoniazid Cohort (N=4646)		Rate Ratio (95% CI)			
	Cases	Rate†	Cases	Rate†	Unadjusted	P Value	Adjusted‡	P Value§
	no./no. of person-yr	*per 100 person-yr*	*no./no. of person-yr*	*per 100 person-yr*				
Overall	382/13,776	2.77	175/9163	1.91	0.77 (0.52–1.15)	0.18	0.82 (0.58–1.15)	0.23
0–9 mo¶	133/4,564	2.91	37/3358	1.10	0.38 (0.19–0.75)	0.01	0.42 (0.20–0.88)	0.03
>9–18 mo	115/4,243	2.71	74/3156	2.34	0.97 (0.57–1.65)	0.89	0.93 (0.53–1.61)	0.93
>18 mo	134/4,970	2.70	64/2649	2.42	0.83 (0.54–1.27)	0.35	0.95 (0.62–1.46)	0.95

N Engl J Med 2014;370:301-10

CHEST

Original Research

TUBERCULOSIS

The Role of Chest CT Scanning in TB Outbreak Investigation

Sei Won Lee, MD; Yoon Soo Jang, MD; Chang Min Park, MD; Hee Yoon Kang; Won-Jung Koh, MD; Jae-Joon Yim, MD; and Kyeongman Jeon, MD

CHEST 2010; 137(5):1057–1064

- Contact investigation of 96 soldiers

→ 18 active TB: 9 normal CXR but TB lesions in HRCT

Combined use of QuantiFERON®-TB Gold assay and chest computed tomography in a tuberculosis outbreak

W. J. Lew,* Y. J. Jung,† J-W. Song,‡ Y. M. Jang,‡ H-J. Kim,* Y-M. Oh,† S. D. Lee,† W. S. Kim,† D. S. Kim,† W. D. Kim,† T. S. Shim†

INT J TUBERC LUNG DIS 13(5):633–639

- Contact investigation of 1044 high school students

→24 QFT+ and normal CXR: 6 TB in HRCT

22 TST+ and normal CXR: 5 TB in HRCT

Preventive therapy and risk of resistant TB

- A meta-analysis of 13 studies (n=18095 in INH vs. n=17985 in control)
- RR for resistance: 1.45 (95% CI 0.85–2.47)
- DST 시행율: 28% (158/564 TB case) in INH

  32% (328/1034 TB case) in Control

separately. Analyses were limited by small numbers and incomplete testing of isolates, but findings do not exclude an increased risk for isoniazid-resistant TB after IPT. The diagnosis of active TB should be excluded before IPT. Continued surveillance for isoniazid resistance is essential.

Emerg Infect Dis. 2006 May;12(5):744-51.

Poor compliance and ADRs

Table I. Summary of LTBI regimens in common use

Regimen	Efficacy (relative to placebo)#	Completion of therapy	Serious adverse events	
			Type	Rate
INH: 6 months	69%[12]	50%[6,8,54]	Hepatitis	1 -5%[23,68]
INH: 9-12 months	90 – 93%[12,17]	<50%[31,33,34,69]	Hepatitis	1 -5% [23,31,34,68]
RIF&PZA: 2 months	Equal to 6 -12INH[27,63]	6% > 6-12INH[*27]	Hepatitis	3 -5%[27,68,70]
INH&RIF: 3-4 months	Equal to 6INH[30,36]	6% > 6-12INH[**36]	Hepatitis†	1 – 5% [36,37]
RIF: 3-4 months	65% [##30]	22% > 9INH[***31-34,71]	Rash	1- 2%[31,34]
			Hepatitis	<1% [31,32,34]

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY MAY 2015, VOL. 36, NO. 5

ORIGINAL ARTICLE

Determinants of Tuberculosis Infection Control–Related Behaviors Among Healthcare Workers in the Country of Georgia

Veriko Mirtskhulava, MD, MPH;[1,4,*], Jennifer A. Whitaker, MD, MSc;[2,*] Maia Kipiani, MD;[1] Drew A. Harris, MD;[3] Nino Tabagari, MD, PhD;[4] Ashli A. Owen-Smith, PhD;[5] Russell R. Kempker, MD, MSc;[6] Henry M. Blumberg, MD[6,7]

- 240 HCWs (48% physicians; 39% nurses)
- 52% of HCWs were willing to undergo annual LTBI screening
- 48% were willing to undergo LTBI treatment
- Accept annual LTBI screening
  - HCWs who worried about acquiring MDR-TB infection (aOR=1.7, 95% CI 1.28–2.25)
  - Who thought screening contacts of TB cases is important (aOR,3.4; 95% CI, 1.35–8.65)
  - Who were physicians (aOR, 1.7; 95% CI, 1.08–2.60)
- Perceived a high personal risk of TB reinfection (aOR, 0.5; 95% CI, 0.37–0.64) were less likely to accept LTBI treatment.

Infect Control Hosp Epidemiol 2015;36(5):522–528

Tuberculosis Risk among Medical Trainees, Pune, India

- 1,300-bed public teaching hospital in Pune in the state of Maharashtra, India
- June 2012–December 2013
- 1,886 HCWs → 47 TB → 26 trainees (14 in residents and 12 in interns) among 662 medical trainees, who had 793 person-years of follow-up.
- 9 (35%) had PTB, 17 (65%) had EPTB
- MDR TB was 44% (4/9 cases of culture-positive TB); 3 trainees had TB with single-drug resistance to isoniazid
- 15-fold higher estimated incidence of TB among medical trainees

Emerging Infectious Diseases 2016;22(3):541–543

International Journal of Infectious Diseases 32 (2015) 147–151

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Why healthcare workers are sick of TB

Arne von Delft [a,b,*], Angela Dramowski [a,c], Celso Khosa [a,d], Koot Kotze [a,e], Philip Lederer [a,f], Thato Mosidi [a,g], Jurgens A. Peters [a], Jonathan Smith [a,h,i,j], Helene-Mari van der Westhuizen [a,e], Dalene von Delft [a], Bart Willems [a,e], Matthew Bates [k], Gill Craig [l], Markus Maeurer [m], Ben J. Marais [n], Peter Mwaba [k], Elizabete A. Nunes [o], Thomas Nyirenda [p], Matt Oliver [q], Alimuddin Zumla [a,r]

SUMMARY

Dr Thato Mosidi never expected to be diagnosed with tuberculosis (TB), despite widely prevalent exposure and very limited infection control measures. The life-threatening diagnosis of primary extensively drug-resistant TB (XDR-TB) came as an even greater shock. The inconvenient truth is that, rather than being protected, Dr Mosidi and thousands of her healthcare colleagues are at an increased risk of TB and especially drug-resistant TB. In this viewpoint paper we debunk the widely held false belief that healthcare workers are somehow immune to TB disease (TB-proof) and explore some of the key factors contributing to the pervasive stigmatization and subsequent non-disclosure of occupational TB. Our front-line workers are some of the first to suffer the consequences of a progressively more resistant and fatal TB epidemic, and urgent interventions are needed to ensure the safety and continued availability of these precious healthcare resources. These include the rapid development and scale-up of improved diagnostic and treatment options, strengthened infection control measures, and focused interventions to tackle stigma and discrimination in all its forms. We call our colleagues to action to protect themselves and those they care for.

random? Neither. The alarming reality is that she was led to believe that she, and all of her 'healthy' colleagues, were somehow immune to TB or 'TB-proof' – a phenomenon characterized by a heightened awareness of the disease among others, but a low perception of self-risk. An alternative explanation may be that the HCW's perception of risk is gradually eroded by habituation to the risks of working in a TB-endemic setting.[16]

day. We frequently hear seniors say to younger trainees, "Why are you wearing that (N95) mask? I have worked here for many years and have never gotten TB." Nervous laughter ensues, and the trainee's respirator is absent the next day. That attitude of 'battle-hardened' invincibility often filters down to younger HCWs, who internalize these reassuring but false beliefs. But as cases of

A systematic review of TB incidence in low- and middle-income countries estimated the annual risk of TB infection in HCWs to range from 3.9% to 14.3% (with between 2.6% and 11.3% attributable to occupational exposure).[17] A subsequent meta-analysis estimated that the average annual risk of developing TB disease was three times higher (95% confidence interval 2.43–3.51) for HCWs (across all settings) compared to the general population.[18] A delay in DR-TB diagnosis, less effective treatment for DR-TB, and longer periods of healthcare contact for DR-TB patients, increase the potential for transmission of DR-TB strains to HCWs. Accordingly, HCWs are up to six times more likely to be hospitalized for DR-TB than the population they care for (incidence rate ratio 5.46 for MDR and 6.28 for XDR).[19] Furthermore, HCWs with DR-TB are diagnosed late and have poor treatment outcomes, even when HIV-uninfected.[20,21]

6. The stain of stigma

Stigma, fed by a combination of fear and denial, aggravates delays in diagnosis and treatment, and sustains an unspoken culture of 'don't ask, don't tell'.[22] When HCWs contract TB and are (eventually) diagnosed, they frequently seek treatment secretly. They dread public disclosure of their TB diagnosis, fearing a backlash from colleagues, who themselves are afraid of contracting TB. Among TB patients, it has been shown that disclosure is more likely to occur when the patient is assured that they will not be stigmatized.[23]

8. Safety first: improving implementation of TB infection control measures

How can Dr Mosidi and her colleagues claim back a safe working environment? The pre- (and post-) antibiotic solution is rigorous implementation of TB IC programmes. This goal is achievable, even in countries with resource limitations.[34] Unfortunately the resources for and implementation of TB IC are often poorest in countries with the greatest TB burden. Two recent South African studies found less than 50% compliance with IC recommendations[35] and that 55% of HCWs did not wear personal respiratory protective equipment when indicated.[36]

XDR-TB

- 진폐병원에 입원, CRF on HD
- 2015.12월 결핵배양
- 2016.8.26 DST 확인, AFB 4+

◆ 약제 감수성 검사 결과

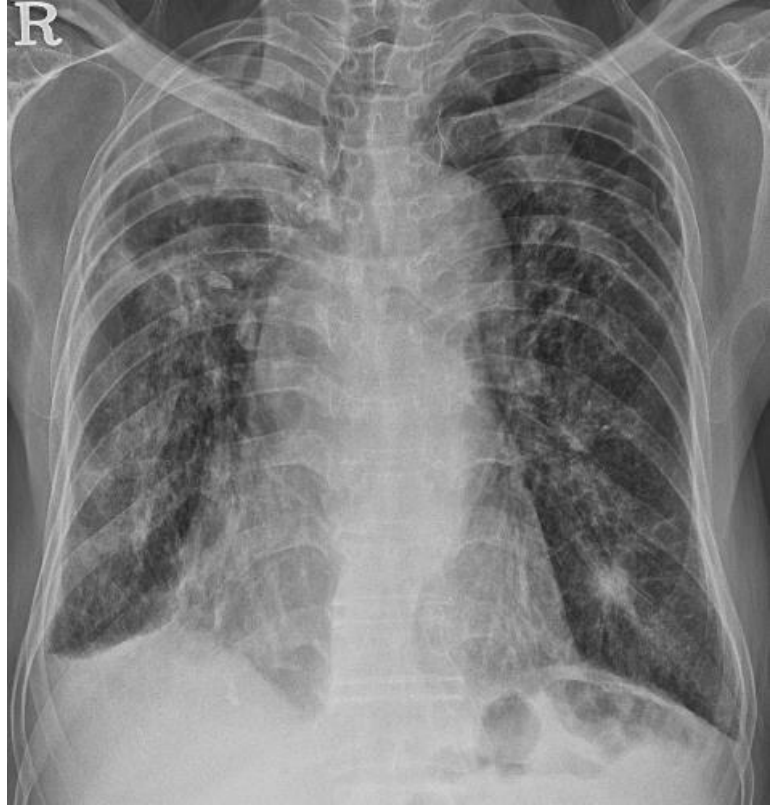
※ 대조배지상 발육정도 2+

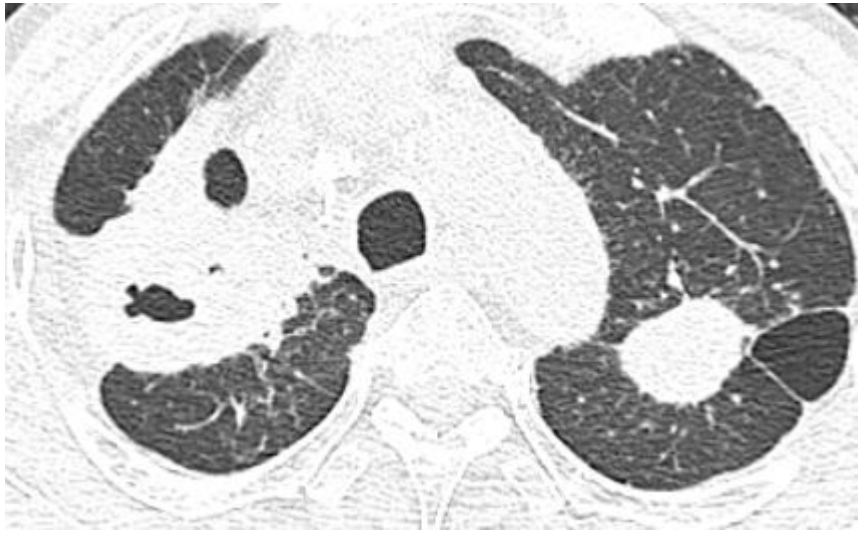
약제명	기준농도 (㎍/mL)	균발육정도	판정결과	약제명	기준농도 (㎍/mL)	균발육정도	판정결과
INH	0.2	2+	R	TH	40.0	2+	R
RMP	40.0	2+	R	CS	30.0	2+	R
SM	10.0	2+	R	OFLX	4.0	2+	R
EMB	2.0	2+	R	PAS	1.0	-	S
KM	30.0	2+	R	CPM	40.0	2+	R
RBT	20.0	2+	R	MXF	2.0	2+	R
AMK	30.0	2+	R	LFX	2.0	2+	R

Pyrazinamidase Test (R) ※S : 감수성, R : 내성

균발육표시법 -, No Growth; 1+, ≤100; 2+, 101-200; 3+, 201-500 colonies; 4+, 3+이상융합발육

◆ 결핵균 감별검사 : *Mycobacterium tuberculosis*





의료기관내 결핵감염관리

- Environmental control & Personal protection
- 객담부스
- 음압격리실
- 결핵환자 진료를 독립된 공간에서 하는가?
- 응급실 진료는?

Summery

1. 국내 의료종사자들에서 잠복결핵감염률 및 발생률이 높다.
2. IGRA는 많은 제한점이 있다.
   - 낮은 민감도
   - 활동성 결핵 발생 예측도가 낮다
   - False positive in serial testing
   - 최근 감염과 오래된 감염을 구별할 수 없음
   - 활동성 결핵을 감별할 수 없음
   - 내성결핵 감염을 확인할 수 없음
   - 잠복결핵 치료 후 반응 평가 할 수 없음.
   - 치료 후 재감염을 확인할 수 없음
3. 잠복결핵 치료 전 활동성 결핵에 대한 철저한 조사가 필요
4. 잠복결핵 치료의 낮은 순응도 개선 필요
5. 의료기관내 결핵 감염관리가 우선 필요