잠복결핵의 치료와 효과

가톨릭대학교 의과대학 내과학교실
인천성모병원 호흡기내과
김주상

순서

1. 국가결핵관리에서 잠복결핵감염치료의 중요성
2. 잠복결핵치료와 효과
3. 외국 진료지침의 소개
4. 국내 잠복결핵진단 및 치료 현황

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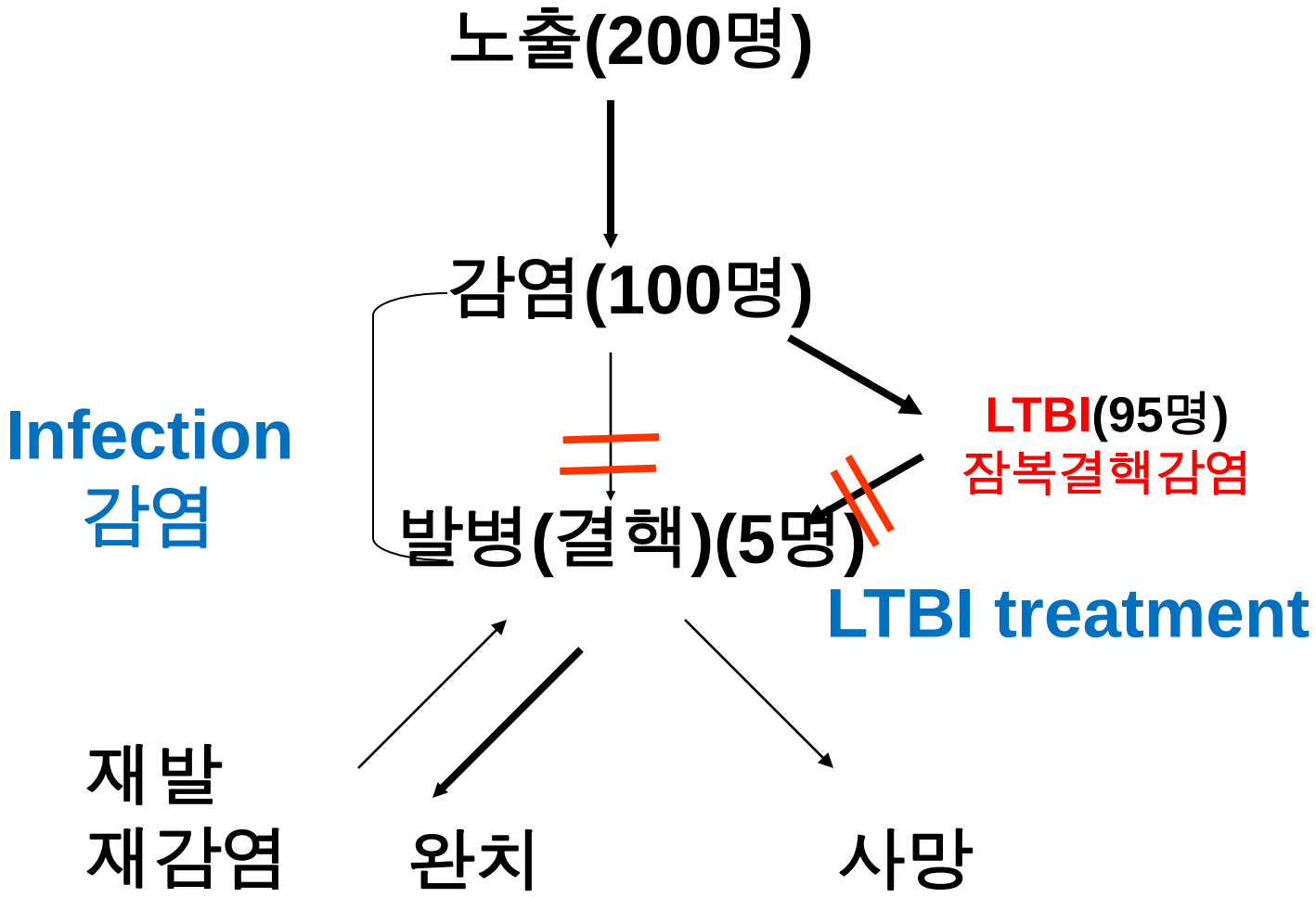
결핵의 자연 경과


노출(200명)
감염(100명)
Infection
감염
LTBI(95명)
잠복결핵감염
발병(결핵)(5명)
LTBI treatment
재발
재감염
완치
사망

결핵의 전염

Table 2 Prevalence of TB infection among contacts according to degree of intimacy with the index case

Degree of intimacy	No. (%) infected	Total	OR (CI 95%)
Close[a]	488 (55.9)	872	3.54 (2.68–4.69)*
Casual[b]	94 (26.4)	356	
Total	582 (47.4)	1228	

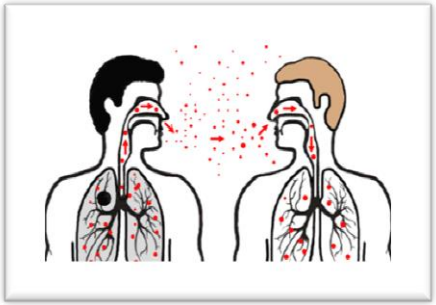
Table 4 New TB cases among contacts according to degree of intimacy with the index patient

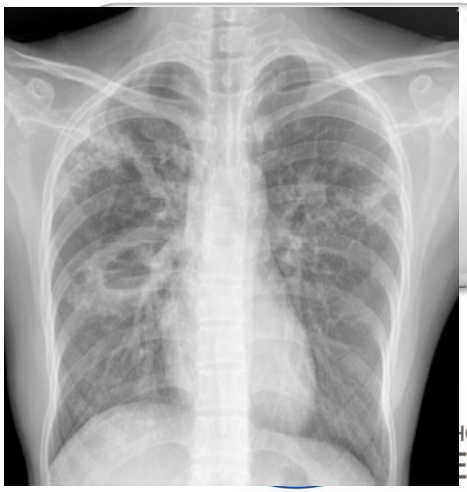
Degree of intimacy	No. (%) with TB disease	Total	OR (CI 95%)
Close[a]	40 (4.6)	872	8.51 (2.18–73)*
Casual [b]	2 (0.6)	356	
Total	42 (3.4)	1228	

Eur J Clin Microbiol Infect Dis (1999) 18 :790–7951.

결핵의 발병주기

접촉



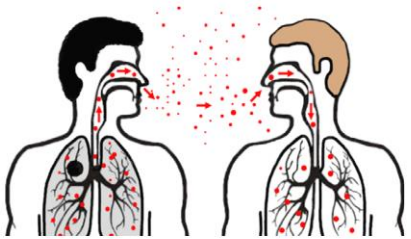


LTBI

TB elimination

Early detection & high success rate

접촉



Increasing of Contact investigation rate

발병

LTBI

LTBITx

TB control strategies

TB management

- Infection prevention

- Early diagnosis and early treatment

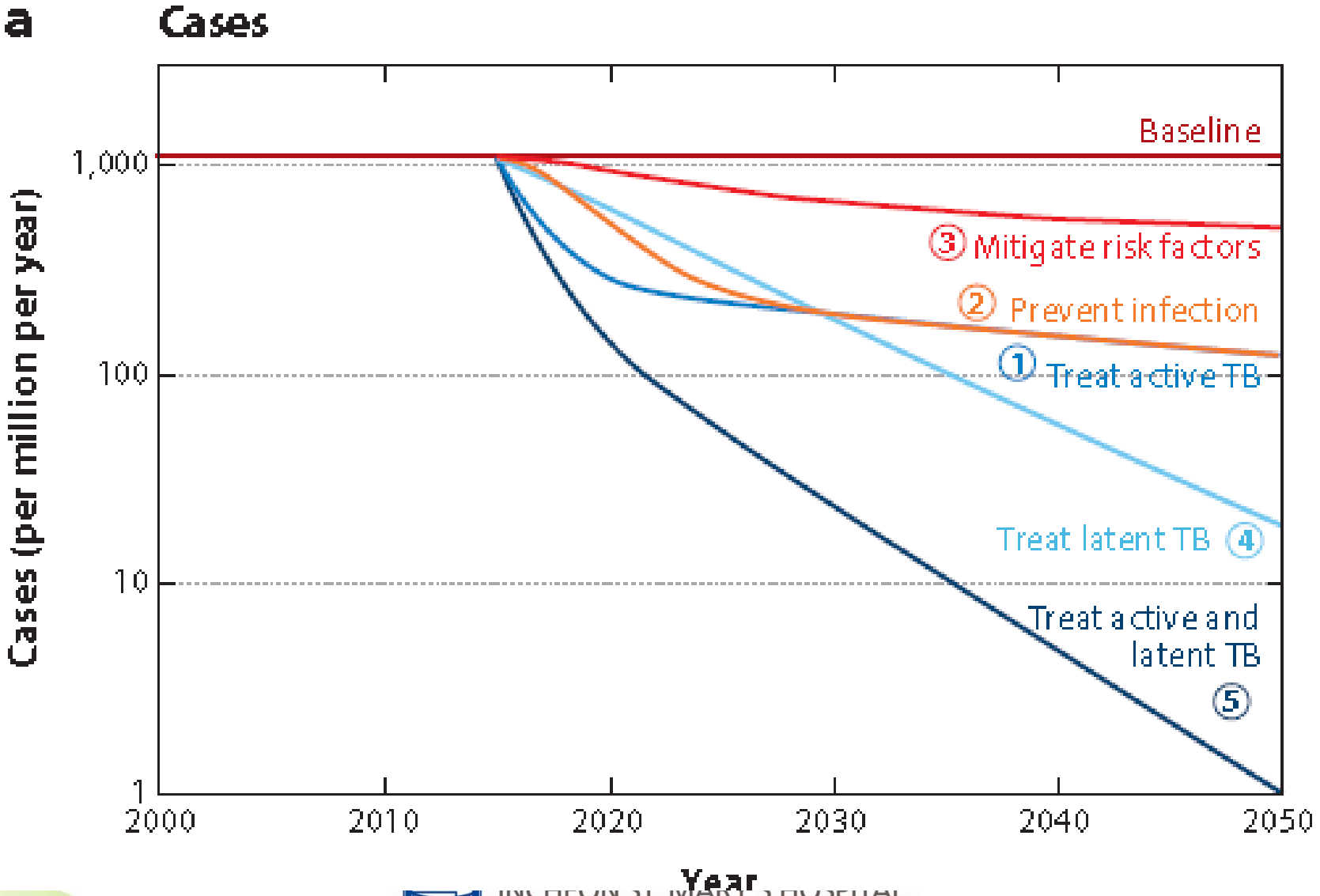
TB elimination

- Disease prevention

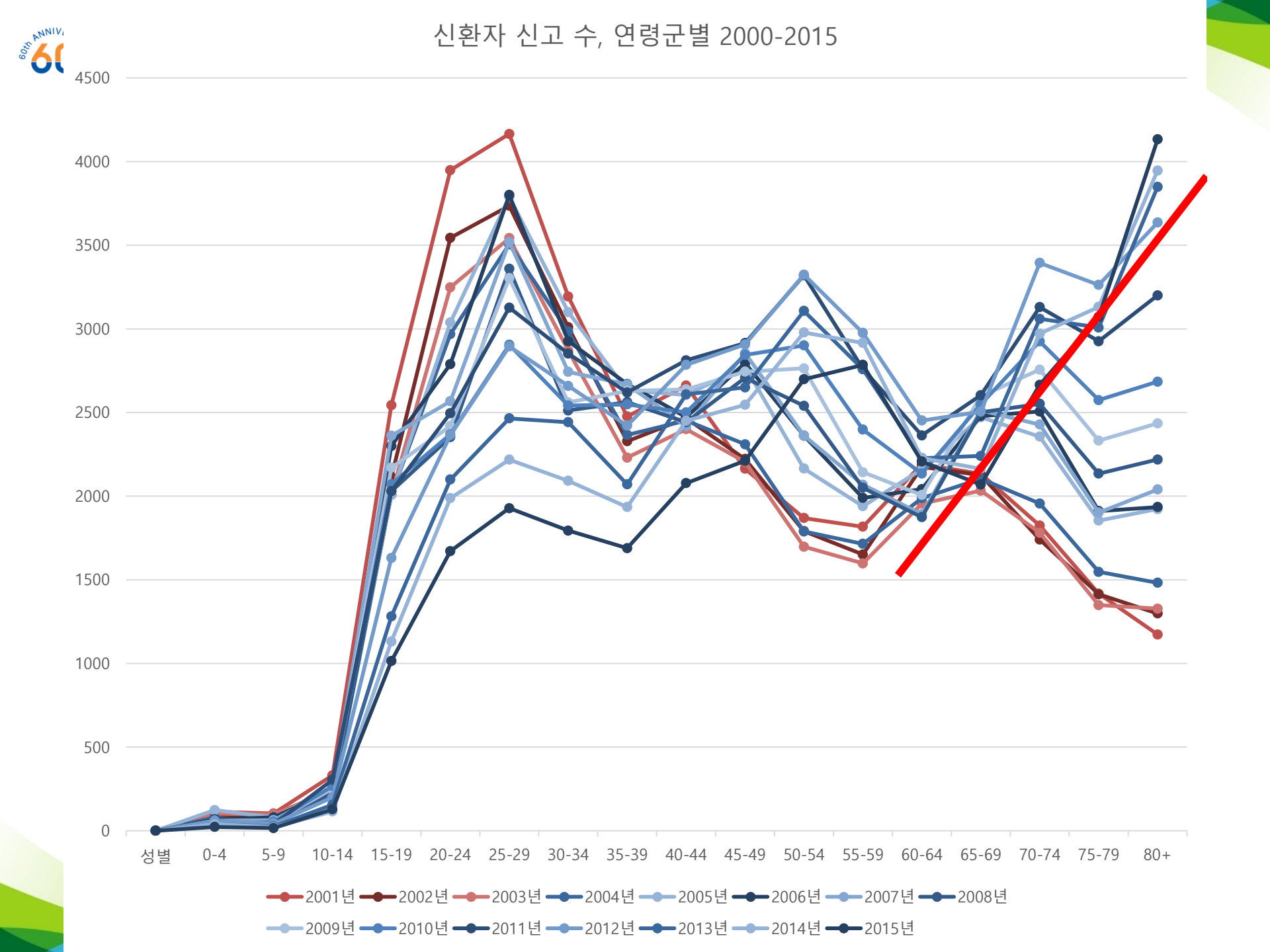
- Latent TB infection Treatment

- BCG vaccination

Prospects for TB elimination



Prospects for Tuberculosis Elimination. Annu. Rev. Public Health 2013; 34: 271-86


신환자 신고 수, 연령군별 2000-2015
4500
4000
3500
3000
2500
2000
1500
1000
500
0
성별
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
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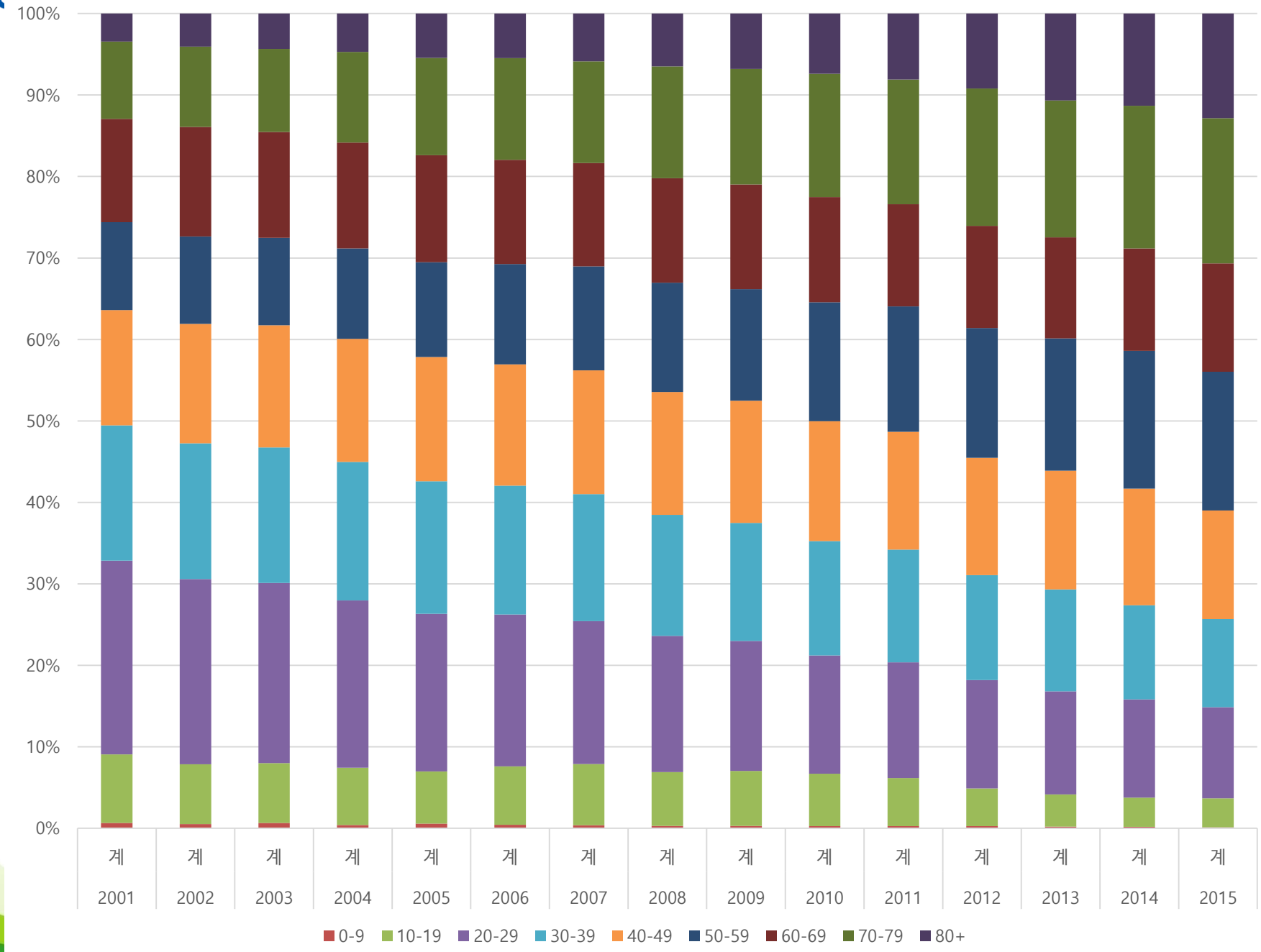
2015년


연령별 신고환자 수 비율(%),2001-2015
100%
90%
80%
70%
60%
50%
40%
30%
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10%
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계 2001
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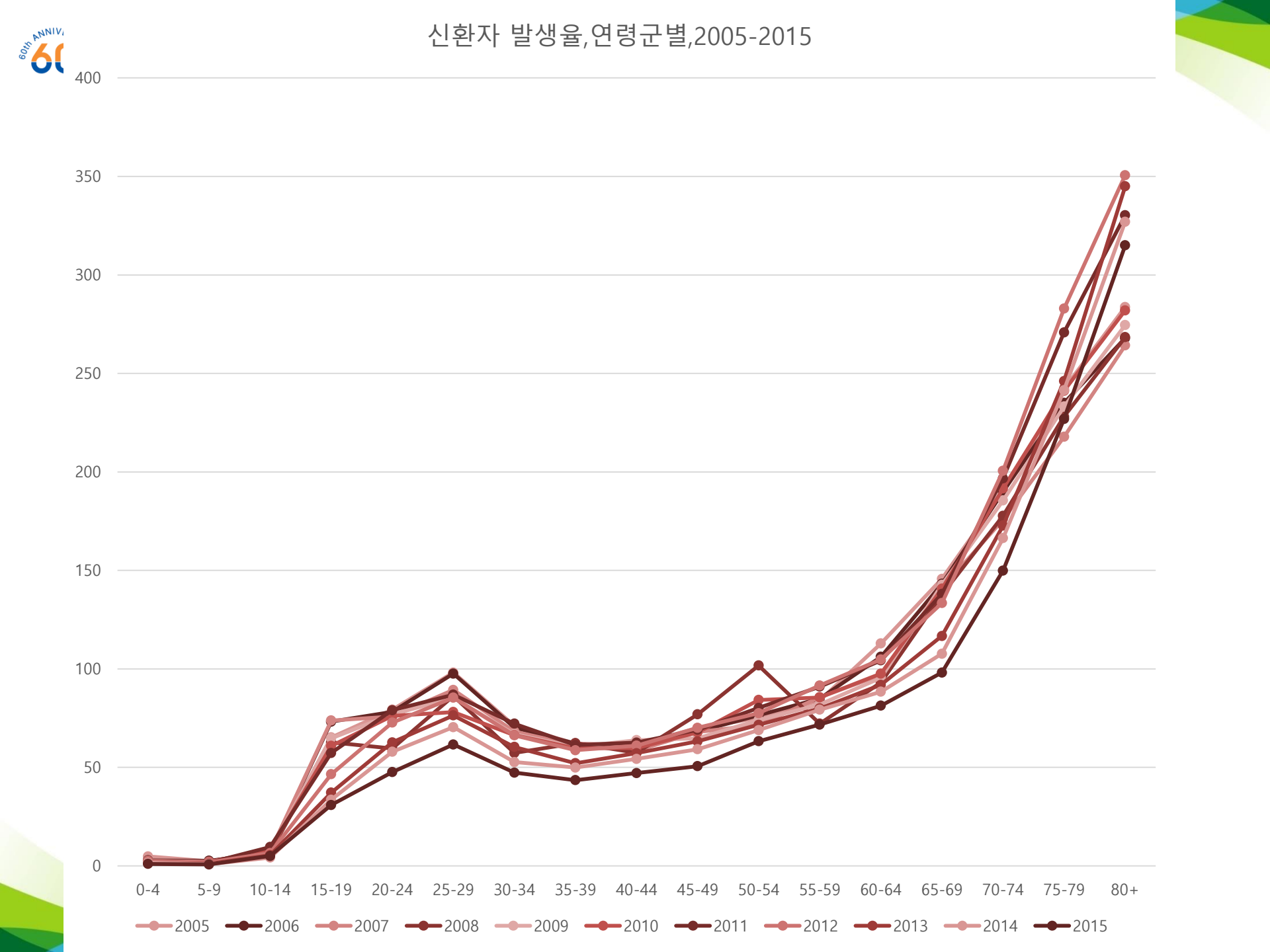
50-59
60-69
70-79
80+


신환자 발생율,연령군별,2005-2015
400
350
300
250
200
150
100
50
0
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80+
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

Contact investigation for tuberculosis: a systematic review and meta-analysis

Gregory J. Fox*, Simone E. Barry#, Warwick J. Britton#,¶ and Guy B. Marks*,+

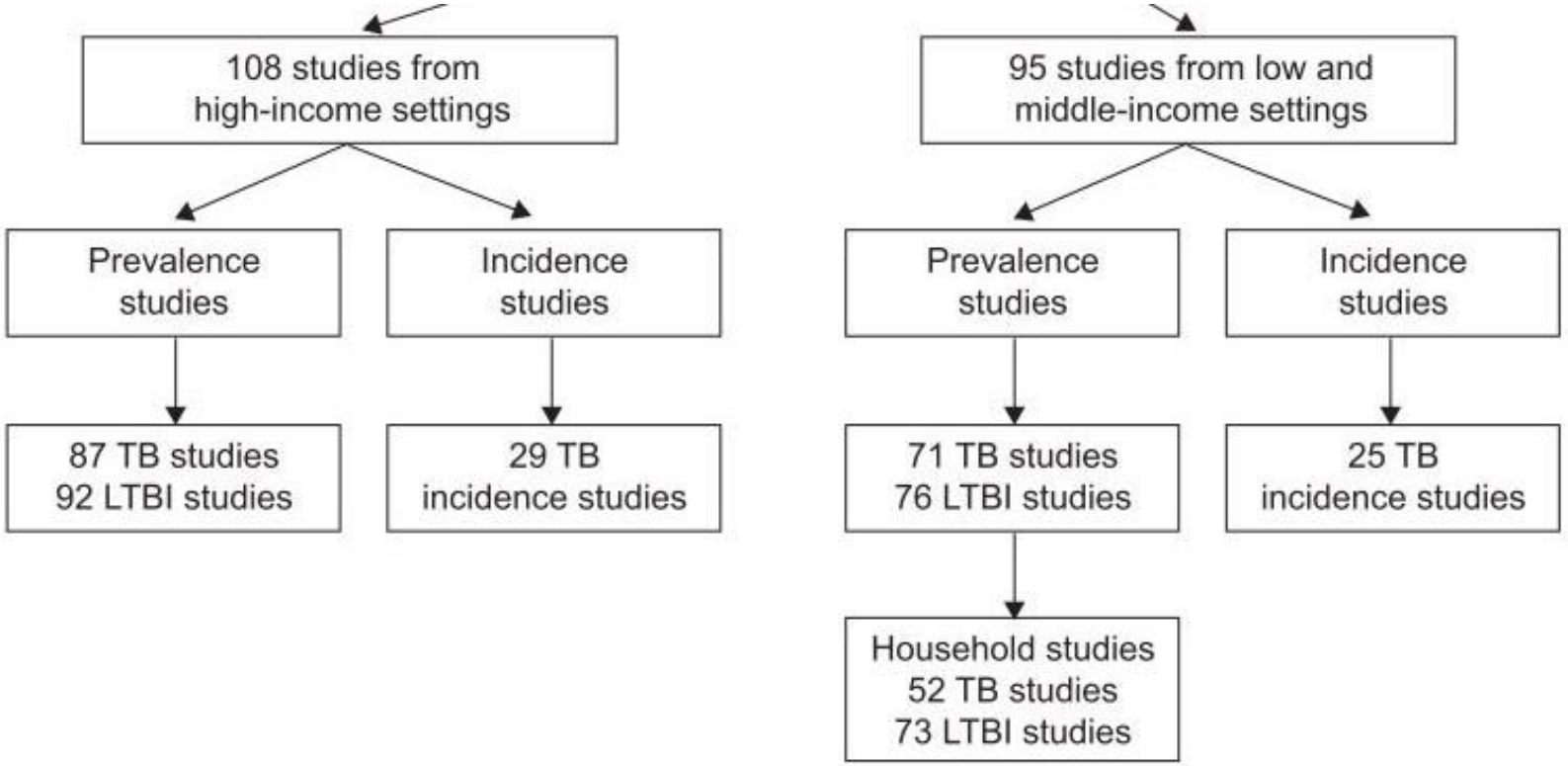


FIGURE 1. Flow diagram for study selection. TB: tuberculosis; LTBI: latent tuberculosis infection.

Eur Respir J 2013; 41: 140–156

접촉자중 잠복결핵감염 유병률

	Included Studies	Contacts with LTBI	Contacts screened	Proportion %
High Income				
All ages				
All	92	79511	284505	**28.1**
Index patient smear positive	34	25910	78784	34.8
Index patient XDR/MDR-TB	2	287	554	52.6
Household contacts	33	20960	67175	30.0
All close contacts	29	20213	68738	28.0
Causal contact only	7	28	5779	18.7
<= 5yrs	17	2093	6900	16.3
5-14 yrs	10	1407	4871	18.4
>= 15 yrs	8	6221	12633	41.9

Eur Respir J 2013; 41: 140–156

접촉자중 활동성 결핵 유병률

	Included Studies	Contacts with LTBI	Contacts screened	Proportion %
High Income				
All ages				
All	87	5058	308048	**1.4**
Index patient smear positive	27	1704	72936	3.3
Index patient XDR/MDR-TB	2	0	554	0.0
Household contacts	29	2047	56221	3.0
All close contacts	45	3053	127699	1.9
Causal contact only	9	73	15607	0.4
<= 5yrs	10	212	4057	4.7
5-14 yrs	9	253	5665	2.9
>= 15 yrs	9	507	17867	2.3

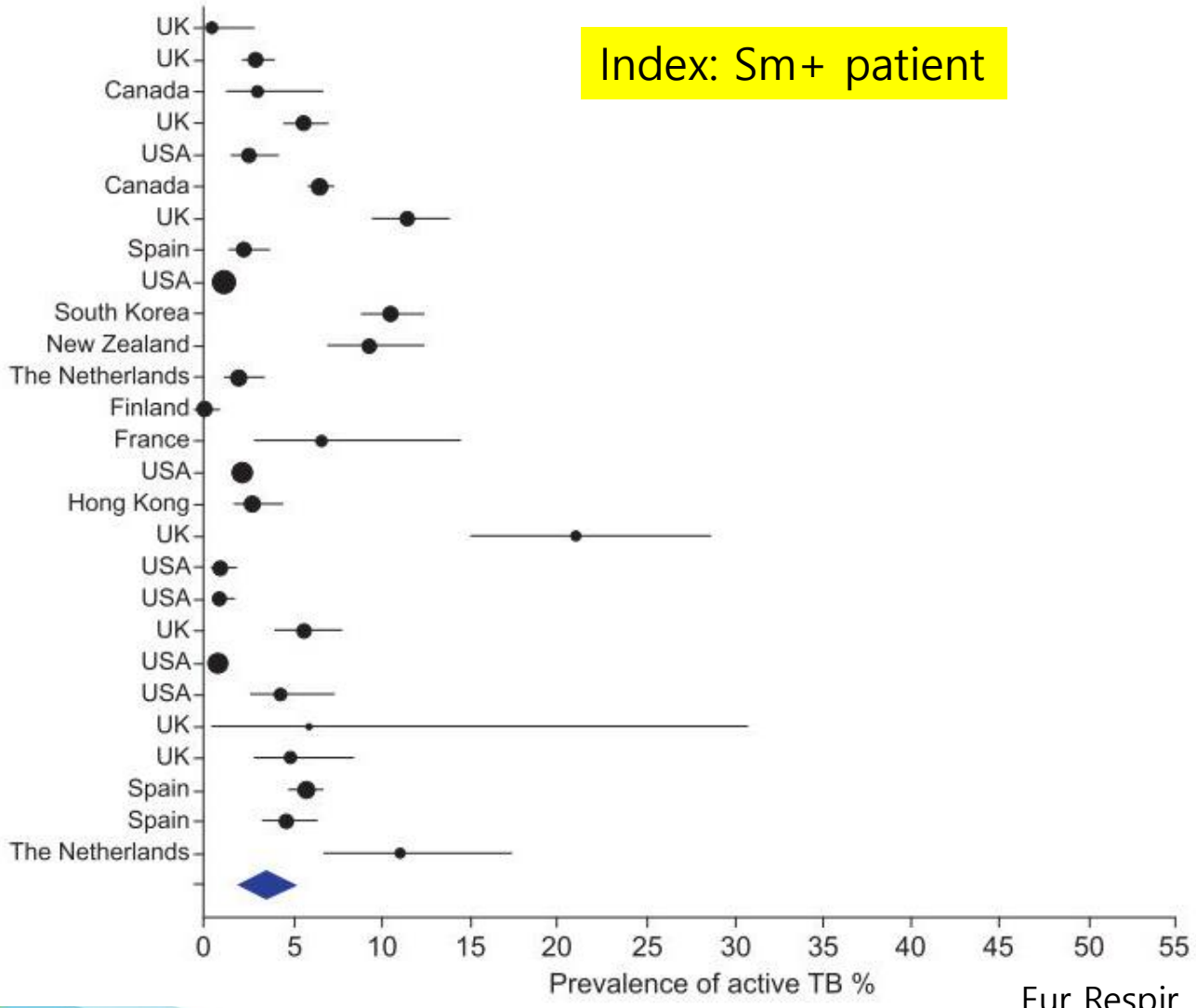
Eur Respir J 2013; 41: 140–156

접촉자중 미생물학적 확진 결핵 유병률

	Included Studies	Contacts with active TB	Contacts screened	Proportion %	95% CI
High Income					
All ages					
All	21	264	45897	**0.4**	0.2-0.7
Index patient smear positive	6	108	5970	0.7	0.3-1.9
Index patient XDR/MDR-TB	2	0	554	0.0	
Household contacts	14	116	5459	1.4	0.8-2.5
All close contacts		187	30269	0.40	0.2-0.9
Causal contact only	1	0	275	0.0	

Eur Respir J 2013; 41: 140–156

접촉자중 활동성 결핵 유병률

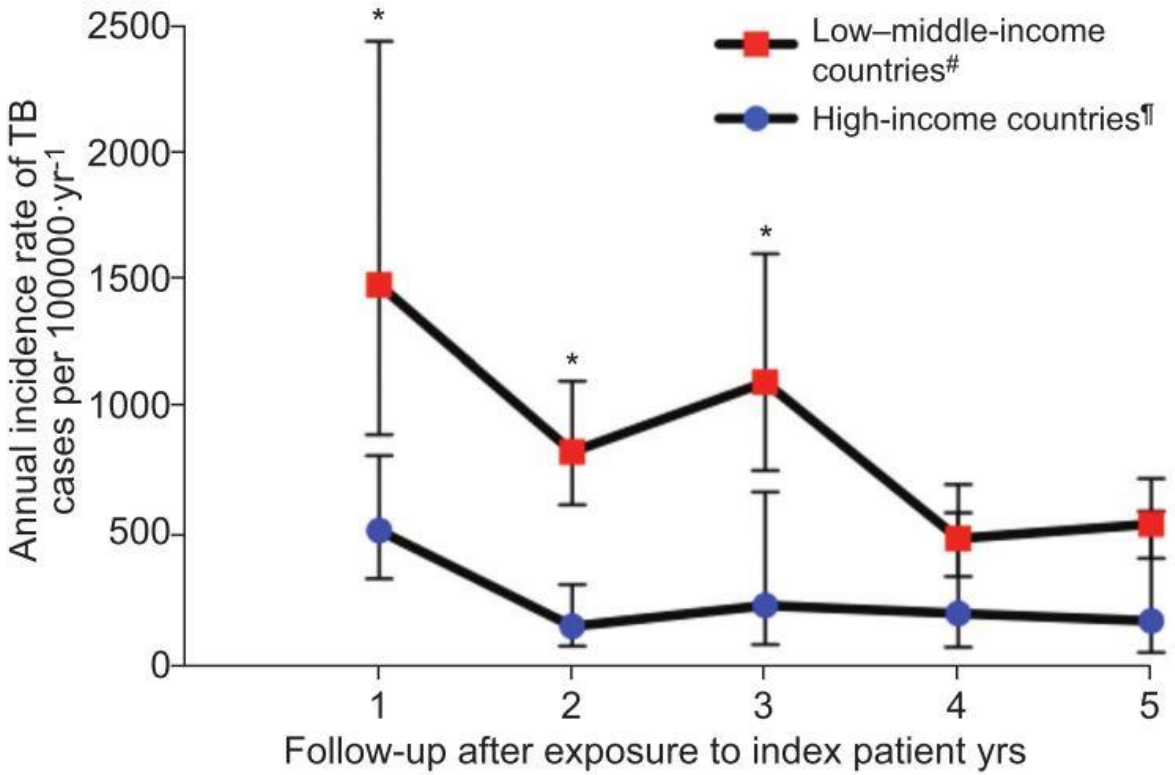


Index: Sm+ patient

Screened n	Proportion % (95% CI)
227	0.4 (0.0–2.8)
1582	2.9 (2.2–3.9)
200	3.0 (1.2–6.7)
1517	5.6 (4.5–6.9)
639	2.5 (1.5–4.1)
4355	6.5 (5.8–7.3)
873	11.5 (9.5–13.8)
723	2.2 (1.3–3.7)
33521	1.1 (1.0–1.2)
1223	10.5 (8.9–12.4)
461	9.3 (6.9–12.4)
715	2.0 (1.1–3.4)
609	0.0 (0.01–0.78)
91	6.6 (2.7–14.4)
6225	2.2 (1.8–2.6)
627	2.7 (1.6–4.4)
151	21.0 (15.0–28.5)
985	0.9 (0.5–1.8)
1096	0.9 (0.5–1.7)
647	5.6 (4.0–7.7)
11838	0.7 (0.6–0.9)
304	4.3 (2.4–7.4)
17	5.9 (0.3–30.8)
263	4.9 (2.7–8.5)
3071	5.7 (5.0–6.6)
823	4.6 (3.3–6.3)
153	11.1 (6.8–17.4)
72936	**3.3 (2.2–4.8)**

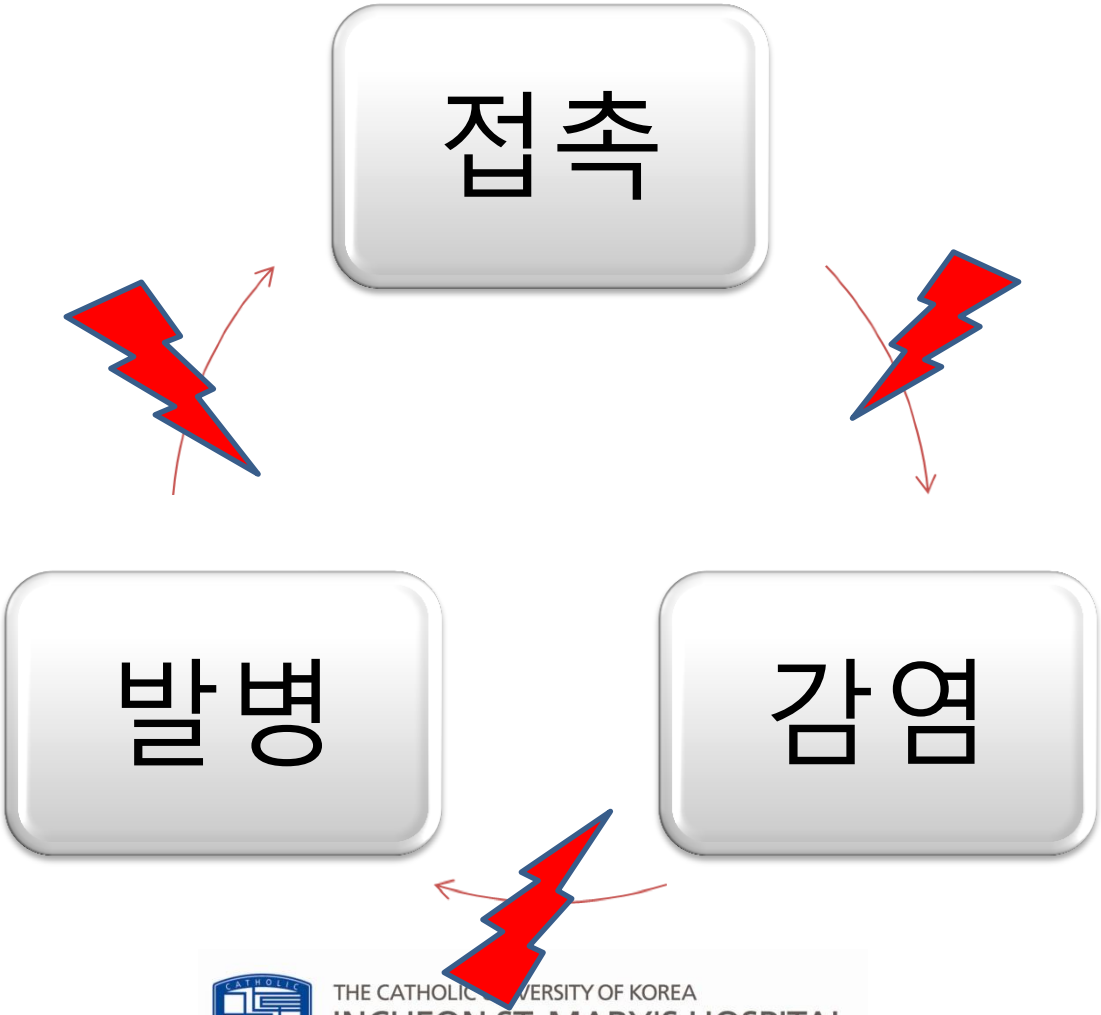
Eur Respir J 2013; 41: 140–156

Progression rate to active TB



Eur Respir J 2013; 41: 140–156

For TB elimiation



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Regimens for treatment of latent tuberculosis

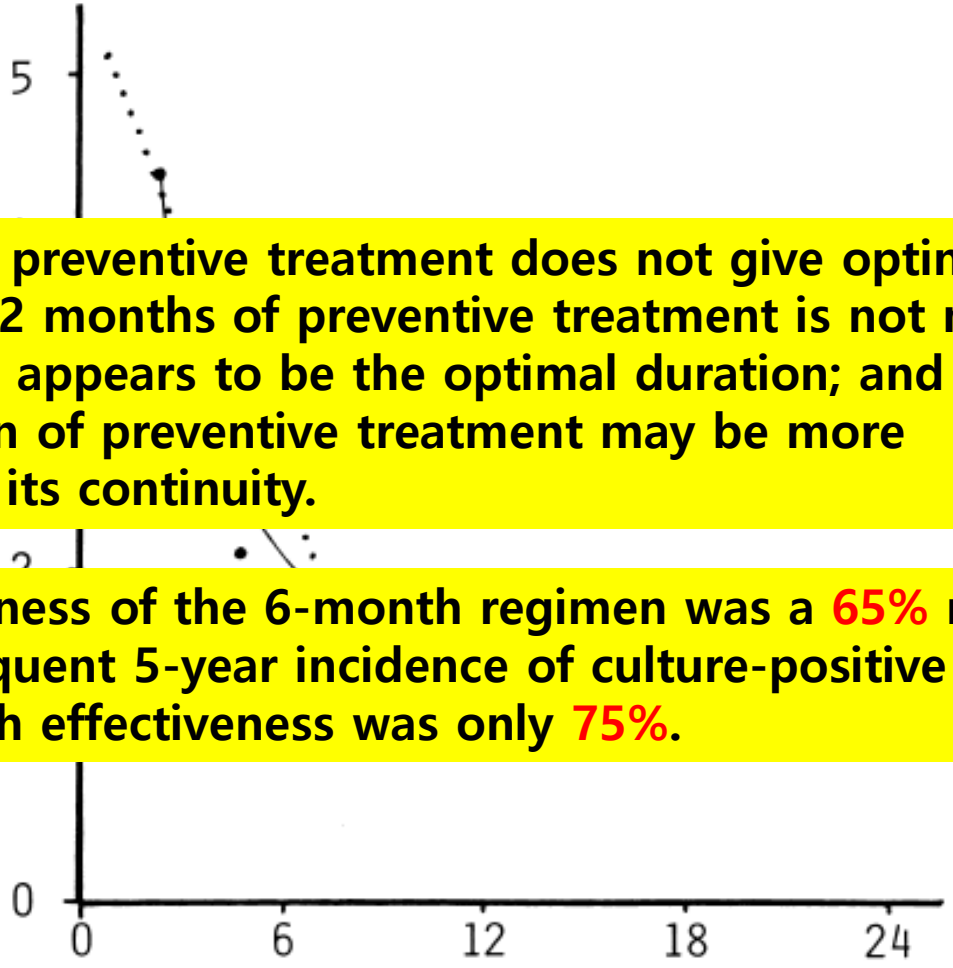
Drug regimen	Dose per body weight	Maximum dose
Daily Isoniazid alone for 6 or 9 months	Adults = 5 mg/kg Children = 10 mg/kg	300 mg
Daily Rifampicin alone for 3-4 months	Adults= 10 mg/kg Children = 10 mg/kg	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid Adults = 5 mg/kg Children = 10 mg/kg Rifampicin Adults and children = 10 mg/kg	Isoniazid = 300 mg Rifampicin= 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Adults and Children Isoniazid: 15 mg/kg Rifapentine (by body weight): 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–49.9 kg = 750 mg ≥50.0 kg = 900 mg	Isoniazid = 900 mg Rifapentine = 900 mg

From WHO

INH mono-therapy:

9H or 6H?

Duration?
How much INH is needed?



1) 6 months of preventive treatment does not give optimal protection;
2) More than 12 months of preventive treatment is not necessary;
3) 9–10 months appears to be the optimal duration; and
4) total duration of preventive treatment may be more important than its continuity.

1) The effectiveness of the 6-month regimen was a 65% reduction in the subsequent 5-year incidence of culture-positive tuberculosis
2) The 12-month effectiveness was only 75%.

INT J TUBERC LUNG DIS 3(10):847–850,1999

Isoniazid for preventing tuberculosis in non-HIV infected persons (Review)

- **Objectives:** 6H vs12 month course of INH for preventing TB at increased risk of developing active TB
- **Selecting Criteria:**

  Placebo control study, minimum of 2 years.
- **Main Results**

  1) Trial 17, 73,375 patients

  2) a relative risk (RR) of developing active TB of 0.40, (95% confidence interval CI 0.31 to 0.52), over two years or longer.

  3) There was **no significant difference between 6 and 12 month courses** (RR of 0.44, 95% CI 0.27 to 0.73 for six months, and 0.38, 95% CI 0.28 to 0.50 for 12 months).

  4) Preventive therapy reduced deaths from TB, but this effect was not seen for all cause mortality.

  5) INH was associated with hepatotoxicity in 0.36% of people on 6 months treatment & in 0.52% of people treated for 12 months.

Cochrane Database Syst Rev. 2000;(2):CD001363.

Merit & concern for INH mono-therapy

Merit

- Long experience
- Accepted effectiveness
- Low cost

Concern

- Long treatment duration
- Poor compliance
- Severe drug side events such as hepatoxicity

Hepatotoxicity Associated With Isoniazid Preventive Therapy

A 7-Year Survey From a Public Health Tuberculosis Clinic

- **Design:** Prospective cohort study
- **Duration:** from 1989 to 1995, **11,141** enrolled for LTBI Tx.
- **Results**: **11 pts**. Noted. **0.10%** of those starting, and **0.15%** of those completing

- **Definition of Hepatotoxicity-**

1) symptomatic 2) elevated enzyme over 5 times than normal 3) Sx improved after withdrawal INH and decision not to resume INH tx after the episode of hepatotoxicity resolved.

JAMA,MARCH 17,1999-VOL 281,No.11

Hepatotoxicity Associated With Isoniazid Preventive Therapy

A 7-Year Survey From a Public Health Tuberculosis Clinic

Table 3. Sex-, Age-, and Race/Ethnicity-Specific Rates of Hepatotoxicity in Persons Receiving Isoniazid Preventive Therapy, 1989-1995

	Cases of Hepatotoxicity, No.	Rate of Hepatotoxicity (Cases per 1000 Persons Starting Therapy)	χ^2 (*P* Value)	Adjusted Odds Ratio (95% Confidence Interval)
Total cohort (N = 11 141)*	11	1.0	. . .	. . .
Sex				
Males (n = 6066)	3	0.5	3.28 (.07)	1.0 (Reference)
Females (n = 5075)	8	1.6		3.30 (0.87-12.45)
Patient age, y				
0-14 (n = 1468)	0	. . .	5.22 (.02)†	. . .
15-34 (n = 7449)	6	0.8		1.0 (Reference)
35-64 (n = 1865)	4	2.1		3.17 (0.94-10.70)
≥65 (n = 359)	1	2.8		3.62 (0.43-30.42)
Race/ethnicity				
White (n = 1856)	4	2.2	3.08 (.08)	2.60 (0.75-8.95)
Nonwhite (n = 9285)‡	7	0.8		1.0 (Reference)
Asian (n = 5968)	5	0.8	. . .	. . .
Black (n = 1732)	2	1.2	. . .	. . .
Hispanic (n = 1050)	0	. . .	. . .	. . .
Other (n = 535)	0	. . .	. . .	. . .

JAMA,MARCH 17,1999-VOL 281,No.11

RIF mono-therapy:

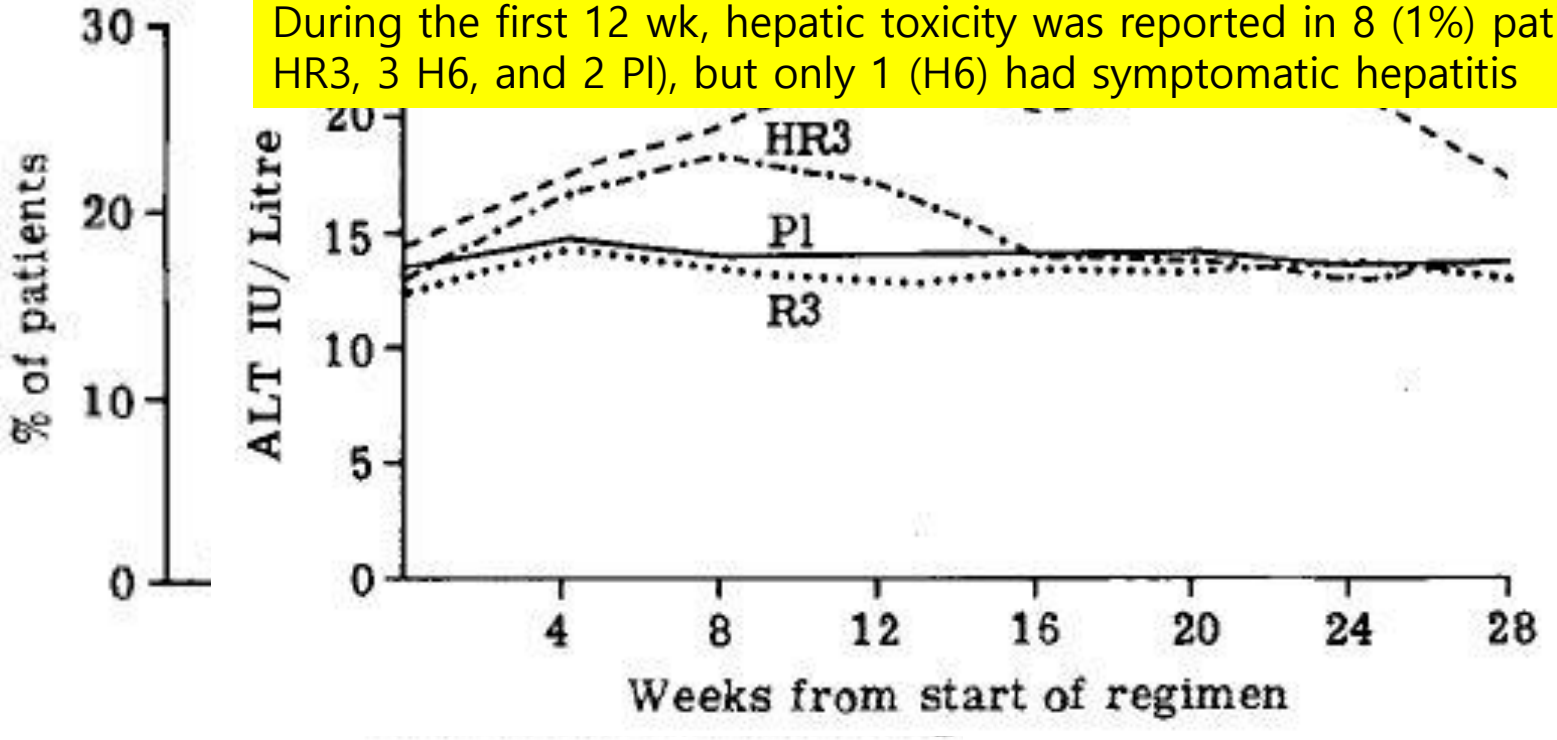
3~4R

A Double-blind Placebo-controlled Clinical Trial of Three Antituberculosis Chemoprophylaxis Regimens in Patients with Silicosis in Hong Kong

Double blind placebo-control study
Population: Silicosis subjects,679 men
Method:
Regimen: 3R, 3HR, 6H

Results
To active TB:
9%-2y, 15%-3yr, 20%- 4yr, **27%-**5yr in placebo
5%-2yr, 8%-3yr, 10%-4yr, **13%**-5yr in Tx. groups

During the first 12 wk, hepatic toxicity was reported in 8 (1%) patients (3 HR3, 3 H6, and 2 Pl), but only 1 (H6) had symptomatic hepatitis



AM REV RESPIR DIS 1992; 145:36-41

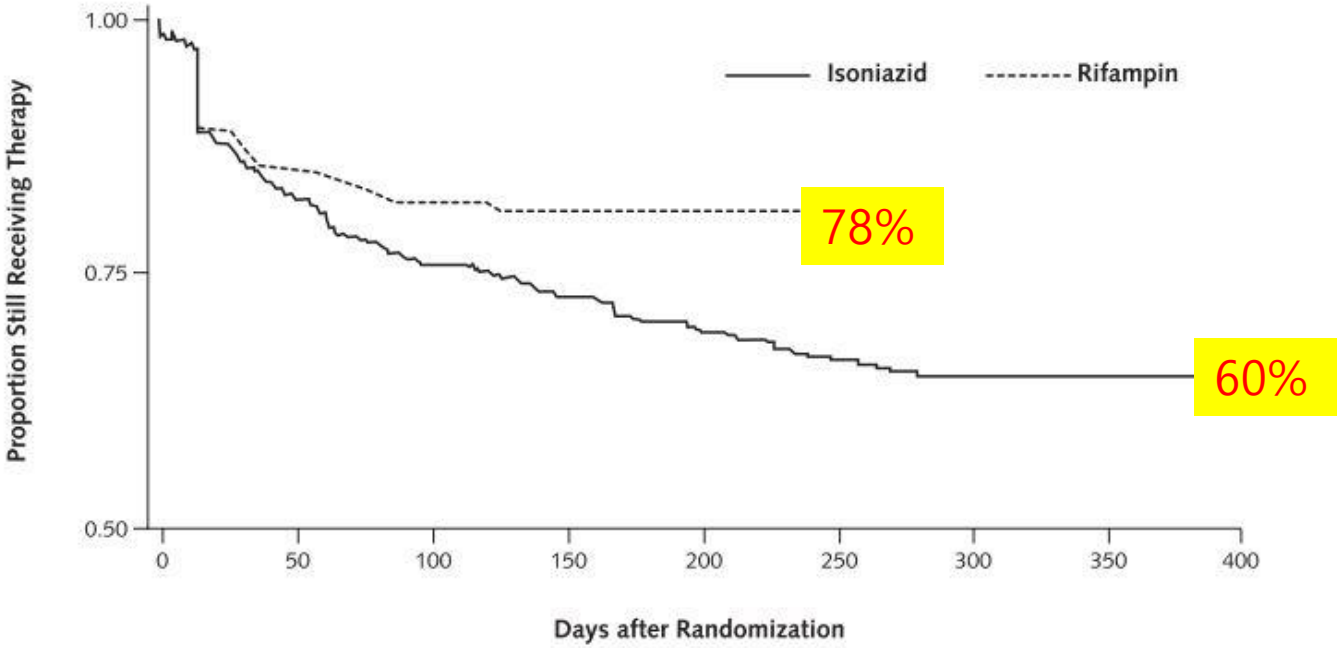
Annals of Internal Medicine | ARTICLE

Adverse Events with 4 Months of Rifampin Therapy or 9 Months of Isoniazid Therapy for Latent Tuberculosis Infection

A Randomized Trial

Dick Menzies, MD, MSc; Richard Long, MD; Anete Trajman, MD, PhD; Marie-Josée Dion, MSc; Jae Yang, MD; Hamdan Al Jahdali, MD; Ziad Memish, MD; Kamran Khan, MD, MPH; Michael Gardam, MD; Vernon Hoeppner, MD; Andrea Benedetti, PhD; and Kevin Schwartzman, MD, MPH

Figure 2. Interval from randomization to dropout or treatment completion.



events(Primary), 3 Adverse events and five enzyme and hematologic variables(2nd)

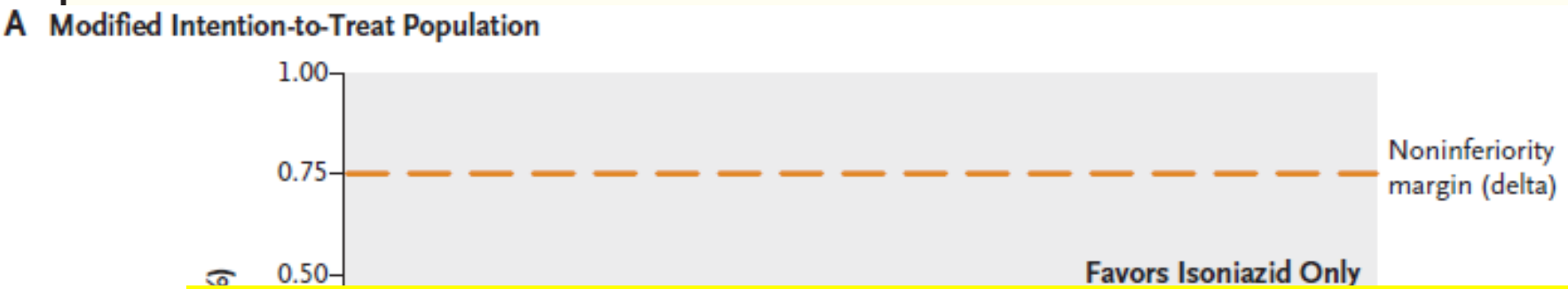
Ann Intern Med. 2008;149:689-697.

Table 2. **Final Outcomes of All Study Participants**

Variable	4 Months of Rifampin (n = 420), n (%)	9 Months of Isoniazid (n = 427), n (%)	Risk Difference (95% CI), %*
Completed therapy			
Subtotal	328 (78)	255 (60)	18 (12 to 24)
Had no symptoms or problems	180 (43)	119 (28)	15 (8 to 21)
Had symptoms but never stopped therapy	139 (33)	121 (28)	5 (−1 to 11)
Had symptoms, so physician stopped therapy; restarted and completed	9 (2)	15 (4)	−1 (−4 to 1)
Did not complete therapy (not protocol-adherent)			
Never started†	2 (0.4)	5 (1)	–
Started but no return visits (early patient default)	31 (7)	36 (8)	−1 (−4 to 3)
Had no symptoms or problems but did not complete (patient default)‡	18 (4)	44 (10)	−6 (−9 to −2)
Had symptoms, so physician did not stop therapy, but patient defaulted‡	17 (4)	47 (11)	−7 (−10 to −3)
Had symptoms, so physician stopped therapy; restarted, but patient defaulted later‡	0 (0)	1 (0.2)	–
Had problems, so physician stopped therapy permanently; physician default‡	9 (2)	16 (4)	−2 (−4 to 1)
Did not complete therapy (protocol-adherent)§			
Drug-related adverse events subtotal	16 (3.8)	24 (5.7)	−2 (−5 to 1)
Grade 3 or 4 adverse events			
Subtotal	7 (1.7)	17 (4.0)	−2 (−5 to −0.1)
Hepatotoxicity	3 (0.7)	16 (3.8)	−3 (−5 to −1)
Hematologic	2 (0.5)	1 (0.2)	–
Drug interaction	1 (0.2)	0 (0)	–
Rash	1 (0.2)	0 (0)	–
Grade 1 or 2 adverse events			
Subtotal	9 (2.2)	7 (1.7)	1 (−1 to 3)
Rash	8 (1.9)	5 (1.2)	1 (−1 to 3)
Gastrointestinal intolerance	1 (0.2)	2 (0.5)	–
Not related to study drug			
Death	0 (0)	1 (0.2)	–
Pregnancy	1 (0.2)	3 (0.7)	–

RPT&INH

The NEW ENGLAND



1. The completion rate was **82%** for the combination therapy group a nd **69%** for INH (p<0.01).
2. tuberculosis developed in 7 of 3986 subjects in the combination-therapy group (cumulative rate, **0.19%**) and in 15of 3745 subjects in the isoniazid-only group (cumulative rate, **0.43%**), for a difference of 0.24 percentage points
3. Rates of permanent drug discontinuation owing to an adverse event were 4.9% in the combination-therapy group and 3.7% in the isoniazid-only group (P=0.009)

3. Hepatoxicity was observed more frequently in the INH group than t he combination therapy group (2.7 versus 0.4 percent; p<0.001),
4. "hypersensitivity" was observed more frequently in the combination therapy group than the INH group (3.8 versus 0.5 percent; p<0.001).

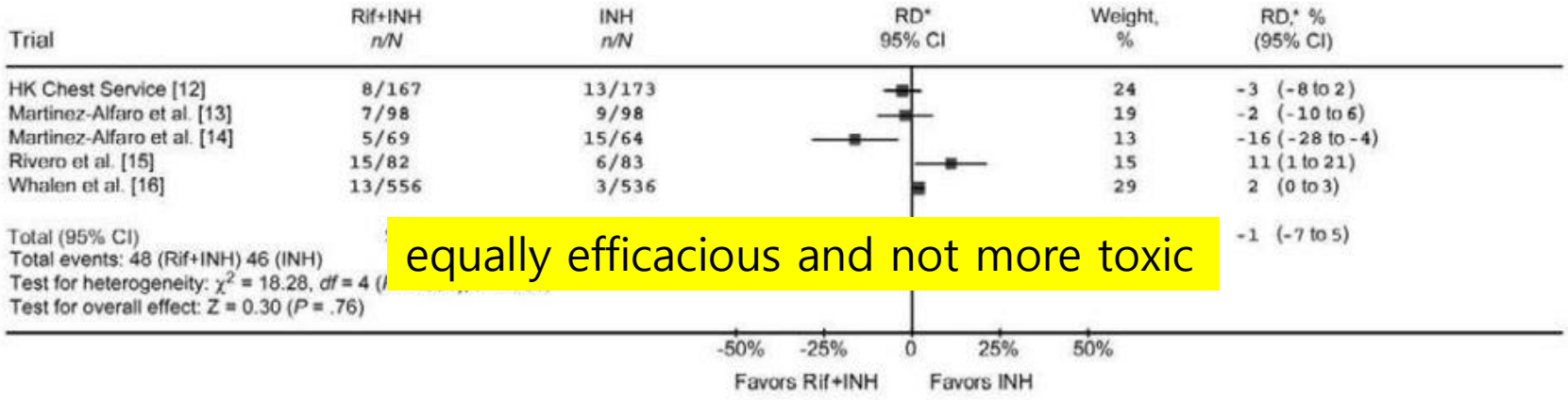
No. at Risk

Isoniazid only	3745	3644	3599	3555	3513	3484	3454	3405	3394	3310
Combination therapy	3986	3866	3827	3799	3783	3752	3726	3675	3661	3577

INH+RIF

Short-Course Therapy with Rifampin plus Isoniazid, Compared with Standard Therapy with Isoniazid, for Latent Tuberculosis Infection: A Meta-analysis

3HR vs 6~12H 비교연구
Median F/U: 13 ~17 mo



equally efficacious and not more toxic

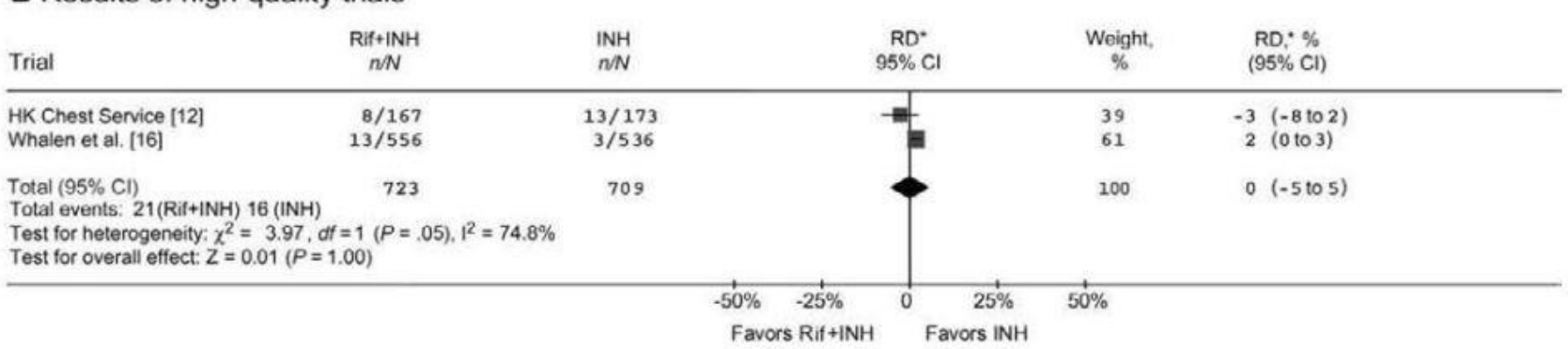


Figure 3. Pooled risk difference (RD) for development of severe adverse effects. HK, Hong Kong; I^2, percentage of total variation across the studies that is the result of heterogeneity rather than chance; INH, isoniazid; *n/N*, total no. of trial p… required drug discontinuation/total no. of trial participants who received the regimen specified; … overall result. *, RDs pooled using a random-effects model.

Clin Infect Dis. 2005;40(5):670

약제선정

Annals of Internal Medicine

Treatment of Latent Tuberculosis Infection

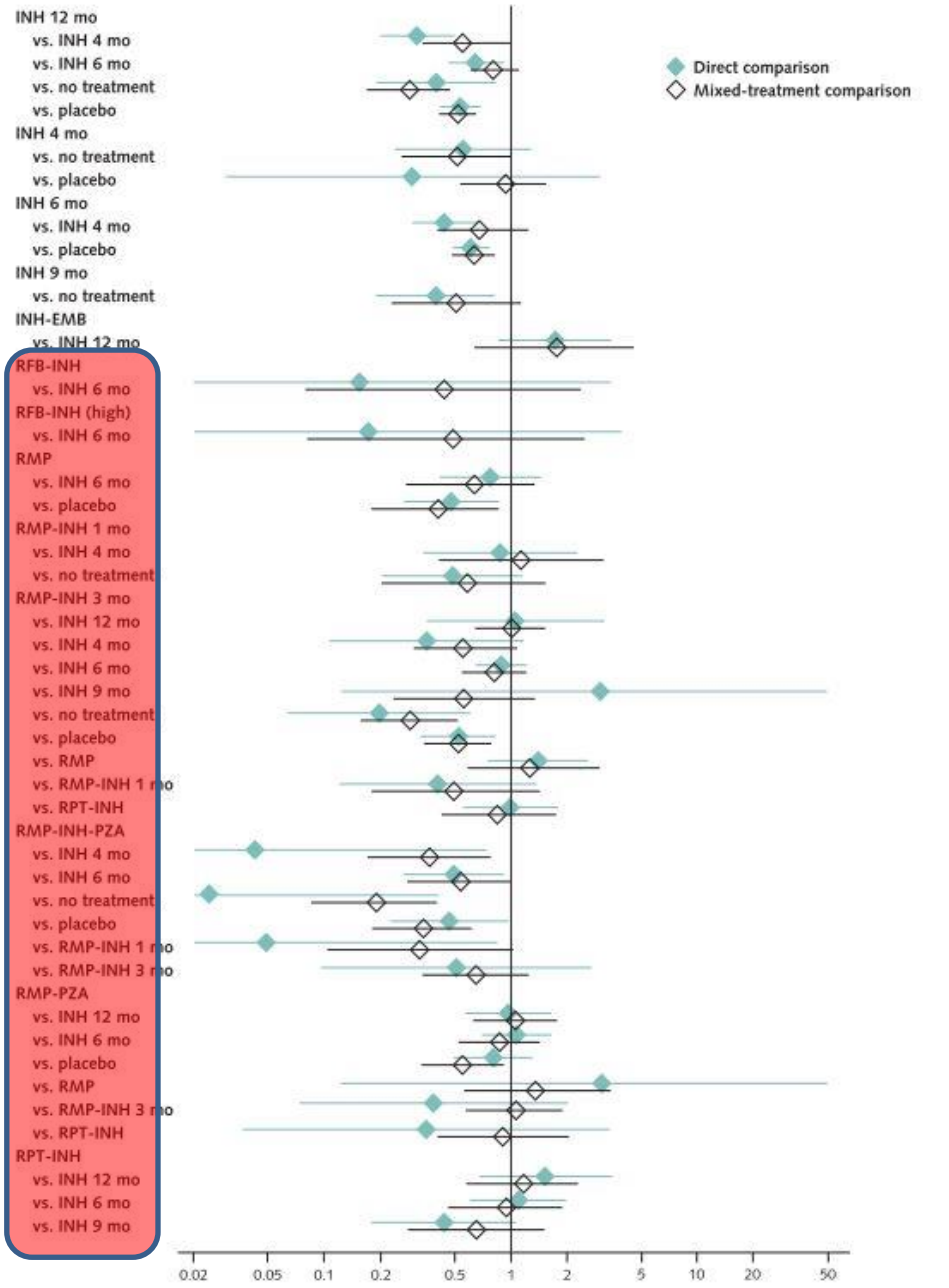
A Network Meta-analysis

Helen R. Stagg, PhD*; Dominik Zenner, MD*; Ross J. Harris, MSc; Laura Muñoz, MD; Marc C. Lipman, MD; and Ibrahim Abubakar, MBBS, PhD

Table 1. Odds Ratios for the Prevention of Active Tuberculosis, Derived From the Network Meta-analysis*

Regimen	Odds Ratio (95% Credible Interval)
No treatment	1.82 (1.05–3.05)
INH 3–4 mo	0.94 (0.53–1.56)
INH 6 mo	0.64 (0.48–0.83)
INH 9 mo	0.94 (0.40–2.10)
INH 12–72 mo	0.52 (0.41–0.66)
RFB-INH	0.28 (0.05–1.49)
RFB-INH (high)	0.31 (0.06–1.59)
RPT-INH	0.61 (0.29–1.22)
RMP	0.41 (0.18–0.86)
RMP-INH 1 mo	1.07 (0.36–2.79)
RMP-INH 3–4 mo	0.52 (0.34–0.79)
RMP-INH-PZA	0.34 (0.18–0.62)
RMP-PZA	0.55 (0.33–0.92)
INH-EMB	0.91 (0.32–2.42)

Figure 2. Comparison of odds ratios for active tuberculosis obtained from random-effects pairwise meta-analysis, with a corresponding estimate from the mixed treatment comparison model.



Treatment of Latent Tuberculosis Infection

A Network Meta-analysis

Table 3. Standard Random-Effects Meta-analysis for Hepatotoxicity*

Baseline	Treatment	Comparisons, n†	Odds Ratio (95% CI)	I^2, %	P Value	Publication Bias‡
INH 6 mo	RMP	1	0.03 (0.00–0.48)	–	–	–
INH 9 mo	RMP	3	0.17 (0.06–0.47)	0.0	0.982	–
INH 6 mo	RMP-INH 3–4 mo	4	0.89 (0.52–1.55)	0.0	0.921	–
INH 9 mo	RMP-INH 3–4 mo	1	0.73 (0.24–2.20)	–	–	–
INH 12–72 mo	RMP-INH 3–4 mo	2	0.20 (0.11–0.35)	0.0	0.452	–
RPT-INH	RMP-INH 3–4 mo	1	0.87 (0.43–1.78)	–	–	–
Placebo	RMP-INH-PZA	1	3.02 (0.12–74.31)	–	–	–
INH 6 mo	RMP-INH-PZA	1	3.49 (0.14–85.82)	–	–	–
RMP-INH 3–4 mo	RMP-INH-PZA	1	3.62 (0.15–89.01)	–	–	–
INH 6 mo	RMP-PZA	4	3.47 (1.46–8.25)	36.3	0.195	–
INH 12–72 mo	RMP-PZA	1	1.26 (0.58–2.70)	–	–	–
RPT-INH	RMP-PZA	1	7.98 (1.79–35.58)	–	–	–
RMP-INH 3–4 mo	RMP-PZA	1	1.79 (0.67–4.76)	–	–	–

1. various therapies containing rifamycins for 3 months or more were efficacious at preventing active TB, potentially more so than isoniazid alone.
2.Regimens containing rifamycins may be effective alternatives to isoniazid monotherapy.

순서

1. 국가결핵관리에서 잠복결핵감염치료의 중요성
2. 잠복결핵치료와 효과
3. 외국 진료지침의 소개
4. 국내 잠복결핵진단 및 치료 현황

Korean Guidelines(2014)

권고요약

- LTBI 치료를 결정하기 전에 반드시 활동성 결핵의 가능성을 배제하여야 한다.
- LTBI 표준치료는 이소니아지드(5 mg/kg/일, 최대 300 mg/일) 9개월 요법(9H)을 권고하나(IA), 리팜핀 4개월 요법(4R, IIB) 및 3개월 이소니아지드/리팜핀 요법(3HR, IIB)도 선택적으로 고려할 수 있다.
- 최근 전염성결핵 환자의 접촉자인 경우 약제 선택시 전염원(index case)의 약제감수성검사 결과를 참고한다.
- LTBI 치료 전 기저 혈액검사를 시행하고 간독성의 위험군에서는 규칙적으로 혈액검사를 시행한다(IIA).
- LTBI 치료 중 활동성 결핵이 발생하면 치료에 사용중인 약제를 포함하여 초치료 표준처방으로 치료를 시작한다(IIIA).

CDC(2013)

Table 2: Choosing the Most Effective LTBI Treatment Regimen

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)	9 months	Adult: 5 mg/kg Children: 10-20 mg/kg** Maximum dose: 300 mg	Daily	270
		Adult:15 mg/kg Children: 20-40 mg/kg** Maximum dose: 900 mg	Twice weekly†	76
	6 months	Adult: 5 mg/kg Children: Not recommended Maximum dose: 300 mg	Daily	180
		Adult: 15 mg/kg Children: Not recommended Maximum dose: 900 mg	Twice weekly†	52
Isoniazid (INH) and Rifapentine (RPT)	3 months	Adults and Children 12 years of age and over: **INH*:** 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum **RPT*:** 10.0–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg *≥50.0 kg* *900 mg maximum*	Once weekly†	12
Rifampin (RIF)	4 months	Adult: 10 mg/kg*** Maximum dose: 600 mg	Daily	120

WHO(2015)

Drug regimen	Dose per body weight	Maximum dose
Daily Isoniazid alone for 6 or 9 months	Adults = 5 mg/kg Children = 10 mg/kg	300 mg
Daily Rifampicin alone for 3-4 months	Adults= 10 mg/kg Children = 10 mg/kg	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid Adults = 5 mg/kg Children = 10 mg/kg Rifampicin Adults and children = 10 mg/kg	Isoniazid = 300 mg Rifampicin= 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Adults and Children Isoniazid: 15 mg/kg Rifapentine (by body weight): 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–49.9 kg = 750 mg ≥50.0 kg = 900 mg	Isoniazid = 900 mg Rifapentine = 900 mg

WHO(2015)

2.3. Treatment options for LTBI

The following treatment options are recommended for the treatment of LTBI: 6-month isoniazid, or 9-month isoniazid, or 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone. *(Strong recommendation, moderate to high quality of evidence)*

Remark: *There was consensus of the Panel on the equivalence of 6-month isoniazid, 9-month isoniazid, and 3-month rifapentine plus isoniazid. However, the Panel could not reach a consensus and voted on the equivalence of 3–4 months isoniazid plus rifampicin and 3–4 months rifampicin alone as alternative options to 6-month isoniazid. Sixty per cent of the Panel members voted for 4-month rifampicin alone as an equivalent option to 6-month isoniazid while 53% voted for 3–4 months isoniazid plus rifampicin as an equivalent option to 6-month isoniazid. Rifampicin- and rifapentine-containing regimens should be prescribed with caution to people living with HIV who are on antiretroviral treatment due to potential drug-to-drug interactions. See annex 3 for drug dosage.*

WHO(2015)

Table 2:
Regimens that showed significant efficacy when compared to placebo and profile of heptotoxicity

Comparator	Intervention	Development of incident TB		Hepatotoxicity	
		OR (95% CI)	Quality of evidence	OR (95% CI)	Quality of evidence
Placebo	Isoniazid 6 months	0.61 (0.48–0.77)	Low	0.99 (0.42–2.32)	Low
Placebo	Isoniazid 12–72 months	0.53 (0.41–0.69)	Low	0.59 (0.23–1.55)	Very low
Placebo	Rifampicin 3–4 months	0.48 (0.26–0.87)	Moderate	-	-
Placebo	Rifampicin and isoniazid 3–4 months	0.52 (0.33–0.84)	Low	-	-

WHO(2015)

Table 3:
Comparison of efficacy of 6-month isoniazid with other regimens for the development of incident TB and hepatotoxicity

Comparator	Intervention	Development of incident TB		Hepatotoxicity	
		OR (95% CI)	Quality of evidence	OR (95% CI)	Quality of evidence
Isoniazid 6-month	Rifampicin 3–4 months	0.78 (0.41–1.46)	Moderate	0.03 (0.00–0.48)	Low
Isoniazid 6-month	Rifampicin and isoniazid 3–4 months	0.89 (0.65–1.23)	Low	0.89 (0.52–1.55)	Very low
Isoniazid 6-month	3-month weekly rifapentine plus isoniazid*	1.09 (0.60–1.99)	Low	1.00 (0.50–1.99)	Low
Isoniazid 9-month	3-month weekly rifapentine plus isoniazid	0.44 (0.18–1.07)	Low	0.16 (0.10–0.27)	Moderate

NICE(2016)

118. For people, including those with HIV, aged younger than 65 years with evidence of latent TB who have been in close contact with people who have suspected infectious or confirmed active pulmonary or laryngeal drug-sensitive TB, offer either of the following drug treatments:

- 3 months of isoniazid (with pyridoxine) and rifampicin **or**

Evidence used in the original model suggested that people who develop active TB at an older age are more likely to die of it (Crofts et al. 2008). Consequently, the model reflects that people aged 51–65 are approximately 5½ times more likely to develop hepatotoxicity when receiving antituberculosis drugs than people aged less than 35. However, people aged 45–64 are also 4 times more likely to die of active TB, if they develop it, than people aged 15–44. This proved to be an important consideration in balancing the risks and benefits of treatment in people of different ages; it is not clear that previous analyses have adequately accounted for this trade-off.

transplant. **[new 2016]**

121. Clearly explain the risks and potential benefits of each treatment regimen. In discussion with the person, select a suitable regimen if they wish to proceed with preventive treatment. **[new 2016]**

NICE(2016)

Table 27: Numbers needed to treat to avert 1 death due to active TB, and numbers of patients needed to be treated to cause 1 death due to LTBI treatment in

Table 31: Treatment for latent TB infection: adherence (restricted subgroup) – rankings for each comparator

Table 33: Treatment for latent TB infection: hepatotoxicity (restricted subgroup) – rankings for each comparator

	Probability best	Median rank (95%CrI)
3HRp	0.477	2 (1, 4)
Placebo / no treatment	0.290	2 (1, 4)
3HR	0.187	3 (1, 6)
4R	0.045	4 (1, 5)
3H	0.002	5 (3, 5)
6H	0.000	6 (5, 7)
9-12H	0.000	7 (6, 8)
2RZ	0.000	8 (6, 8)
12H	0.004	10 (3, 10)

treatment

All estimates represent the median of 1000 probabilistic model simulations.

Pre-treatment monitoring

Korean Guidelines(2014)

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CDC

- Patients with underlying liver disease (eg, hepatitis C)
- Pregnant and postpartum women within three months of delivery
- Patients who consume alcohol regularly
- Patients on other medication(s) with potential hepatotoxicity

123. Offer adult testing for hepatitis B and C before starting treatment for latent TB. See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults. **[new 2016]**

124. Consider testing children and young people for hepatitis B and C before starting treatment for latent TB. See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults. **[new 2016]**

125. If a person also has severe liver disease, for example, Child-Pugh level B or C, work with a specialist multidisciplinary team with experience of managing TB and liver disease. **[new 2016]**

126. Manage treatment with caution, ensuring careful monitoring of liver function, in:

- people with non-severe liver disease
- people with abnormal liver function (including abnormal transaminase levels) before starting treatment for latent TB infection
- people who misuse alcohol or drugs. **[new 2016]**

127 Ensure people having treatment for latent TB who also have social risk factors, such as misusing alcohol or drugs or being homeless, are linked to support services. They should also have an assessment of social needs and stability, including potential barriers to adherence or treatment completion (see section 9). **[new 2016]**

128. People in the groups listed in recommendation 118 who do not have treatment for latent TB, as specified in recommendations 118, 120-1, 125-7, for any reason should be advised of the risks and symptoms of TB (on the basis of an individual risk assessment), usually in a standard letter of the type referred to as 'Inform and advise' information (see section 9.2). **[new 2016]**

Regimens for treatment of latent tuberculosis

	Korea(2014)	CDC(2013)	WHO(2015)	NICE(2016)
Isoniazid(INH) only	300 mg PO daily for 9 months (9H)(1A)	9HR(preferred for aged 2 to 11 years) or 6HR	6H or 9H	6H(+pyridoxine)
Rifampin	600* mg PO daily for 4 months (4R)(IIB)	Adult: 10 mg/kg Max: 600mg	3~4R	
Isoniazid & rifampin	300 mg PO daily for 3 months And 600 mg PO daily for 3 months(3HR)(IIB)	Not mentioned	3~4HR	3HR(+pyridoxine)
Isoniazid & rifapentine	Not mentioned	Isoniazid 15 mg/kg, 900 mg maximum Rifapentine(RPT) 10 to 14 kg: 300mg 14.1 to 25 kg: 450 mg 25.1 to 32 kg: 600 mg 32.1 to 49.9 kg: 750 mg >50 kg: 900 mg max. For 3 months given by DOT.	12 dose INH & RPT	

Treatment of drug-resistant LTBI

WHO 2015

2.4. Preventive treatment for contacts of MDR-TB cases

Serious limitations of the quality of evidence prevent drawing any recommendations on MDR-TB preventive therapy as a public health measure. Strict clinical observation and close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment for contacts with MDR-TB cases.

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Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009–2012

S. Bamrah[*], **R. Brostrom**[*,†], **F. Dorina**[‡], **L. Setik**[‡], **R. Song**[*,§], **L. M. Kawamura**[¶], **A. Heetderks**[*], and **S. Mase**[*]

in an observational cohort study in which 119 infected contacts received a 12-month fluoroquinolone-based regimen

Table 1

Treatment regimens for MDR LTBI, Chuuk, Federated States of Micronesia, 2009–2012[*]

Source patient isolate	MDR LTBI treatment regimen
M. tuberculosis resistant to INH, RMP and ETH	Adults aged >12 years: MFX 400 mg by mouth daily and EMB 15 mg/kg by mouth daily for 12 months Children aged 12 years: LVX 20 mg/kg by mouth daily and EMB 15 mg/kg by mouth daily for 12 months
M. tuberculosis resistant to INH, RMP, PZA, EMB and SM	Adults aged >12 years: MFX 400 mg by mouth daily for 12 months Children aged 12 years: LVX 20 mg/kg by mouth daily and ETH 20 mg/kg by mouth daily for 12 months

Int J Tuberc Lung Dis. 2014;18(8):912.

Treatment completion rate for MDR-TB contacts by age and regimen, Chuuk, Federated States of Micronesia 2009–2012

	Patients who started treatment *n*	Patients who completed treatment *n* (%)
Age, years		
<5	6	6 (100)
5–11	20	19 (95)
12–17	17	17 (100)
26–40	14	11 (73)
41–55	17	15 (88)
>55	13	11 (85)
Total	104	93 (89)
Treatment regimen		
MFX only	46	36 (83)
MFX + EMB	24	21 (88)
LVX only*	5	5 (100)
LVX + EMB	17	16 (94)
LVX + ETH	12	12 (100)
Total	104	93 (89)

Of the 104 who initiated treatment, 93 (89%) completed treatment,

Int J Tuberc Lung Dis. 2014;18(8):912.

순서

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4. 국내 잠복결핵감염진단 및 치료 현황

The results from report of national tuberculosis monitoring

잠복결핵지표	2013	2014	2015	2016
가족 접촉자 검진율, %	74.5	84.8	95.9	92.6
관리율, %	95.4	94.9	99.2	99.5
LTBI Tx 시작률, %		63.8	71.5	
LTBI Tx 완료율, %	61.2	85.2	85.6	

주요 지표 결과(2011~2014)

주요활동목표	평가지표	2011년	2012년	2013년	2014년	2015년 3Q~2016년2Q
활동성 결핵환자 조기 발견	**접촉자 검진 후 결핵의심 및 환자수 비율**	3.6%	2.7%	2.9%	3.02%	3.4%
	활동성 결핵환자 관리율*	87%	91.8%	98.8%	**99.6%**	
활동성 결핵환자 적정 관리율	도말양성 신환자의 치료 성공률	74.6%[1]	74.4%[1]	70.2% 전체치료성공 74.4%	75.5%	
	치료 중단율	3.6%	3.6%	4.6%	3.8%	
	치료 실패율	0.5%	0.2%	0.1%	0.1%	
	지침의거 초기 치료율		96.3%[2])	91.8%	92%	
	약제 감수성 검사 시행율	보고 없음	57%	72.6%	77.5%	
잠복결핵 유병률 감소	**접촉자 확인율**	NA	NA	NA	**NA**	**98.0%**
	접촉자 검진율	63.7%	57.4%	59.8%	**99.8%**	**84.5%**
	접촉률	0.75	1.0	1.42	**2.1**	**2.1**
	잠복결핵검진율,%	63.8%	57.3%	59.8%		**28.6**
	잠복결핵감염율	26.3%	26.8%	33.3%	**24.5%**	**28.7**
	잠복결핵치료시작율	21.7%	30.7%	17%	**18.2%**	**62.3**

Contact Investigation results from PPM data, 2015,3Q ~2016,2Q

지표	15-3Q	15-4Q	16-1Q	16-2Q
활동성결핵환자수	7611	7294	7316	7977
접촉자 검진 대상자	7954	7756	7521	7788
접촉자 검진수	6627	6328	6628	6616
접촉자 확인율,%	97.4	97.8	98.2	98.7
접촉자 검진율,%	79.6	78	85.9	82.4
결핵의심자	229	216	213	221
결핵의심 및 환자비율(%)	3.5	3.4	3.2	3.3

국가결핵관리사업 monitoring 지표 from TBnet

Contact Investigation results from PPM data, 2015,3Q ~2016,2Q

	15-3Q	15-4Q	16-1Q	16-2Q
결핵 의심자 수	229	216	213	221
Sm test No.	112	87	122	111
Sm test rate,%	48.9	40.3	57.3	50.2
Sm+ No.	12	7	15	8
Sm+ rate,%	10.7	8	12.3	7.2
Cx. test No.	86	80	101	88
Cx. test rate,%	37.6	37	47.4	39.8
Cx+ No.	12	12	10	8
Cx+ rate,%	14	15	9.9	9.1
가족 검진자 수, 명	5049	4711	4715	4203
Normal	4296 (85.1%)	4009 (85.1%)	3943 (83.6%)	3307 (78.7%)
Active TB	38 (0.8%)	38 (0.8%)	46 (1.0)	34 (0.8%)
LTBI	577 (11.4%)	516 (11.0%)	606 (12.9%)	732 (17.4%)
Other lung disease	132(2.6%)	148(3.1%)	120(2.5%)	130(3.1%)
Not indicated for LTBI screening	6(0.1%)	0	0	0
Suspected TB(active+other lung disease)	3.4%	3.9%	3.5%	3.9%
평균 가족수(=접촉률)	2.1	2.1	2.1	2

국가결핵관리사업 monitoring 지표 from TBnet

Contact Investigation results from PPM data, 2015,3Q ~2016,2Q,adult

잠복결핵지표	15-3Q	15-4Q	16-1Q	16-2Q
접촉자 검진율,%	79.6	78	85.9	82.4
LTBI검진율,%	23.5	24.5	28.2	38.4
잠복결핵감염률,%	17.3	15.2	14.7	21
잠복결핵감염치료시작률,%	64.6	67.6	59.1	57.7

국가결핵관리사업 monitoring 지표 from TBnet

결론

- TB elimiation 이라는 목표달성을 위해서는 지금보다 적극적인 잠복결핵감염 검사 및 치료가 필요하다.
- 잠복결핵감염 치료는 risk and benefit을 따져 치료를 대상을 선정해야 하며,
- 치료를 시작할 때도 환자의 위험요소- 연령, 간질환 등-를 고려하여 약제를 개별화하여 선택하여야 한다.
- 국내외 연구를 바탕으로 잠복결핵치료 대상장 및 약제 선택 등에 대한 구체적 진료치침의 개발이 필요하다.


감사합니다.