Respiratory Review of 2017
TB/NTM

2017.4.15

대한결핵 및 호흡기학회 제 44차 워크샵
부산대학교병원 호흡기알레르기내과 목정하

Whole genome sequencing

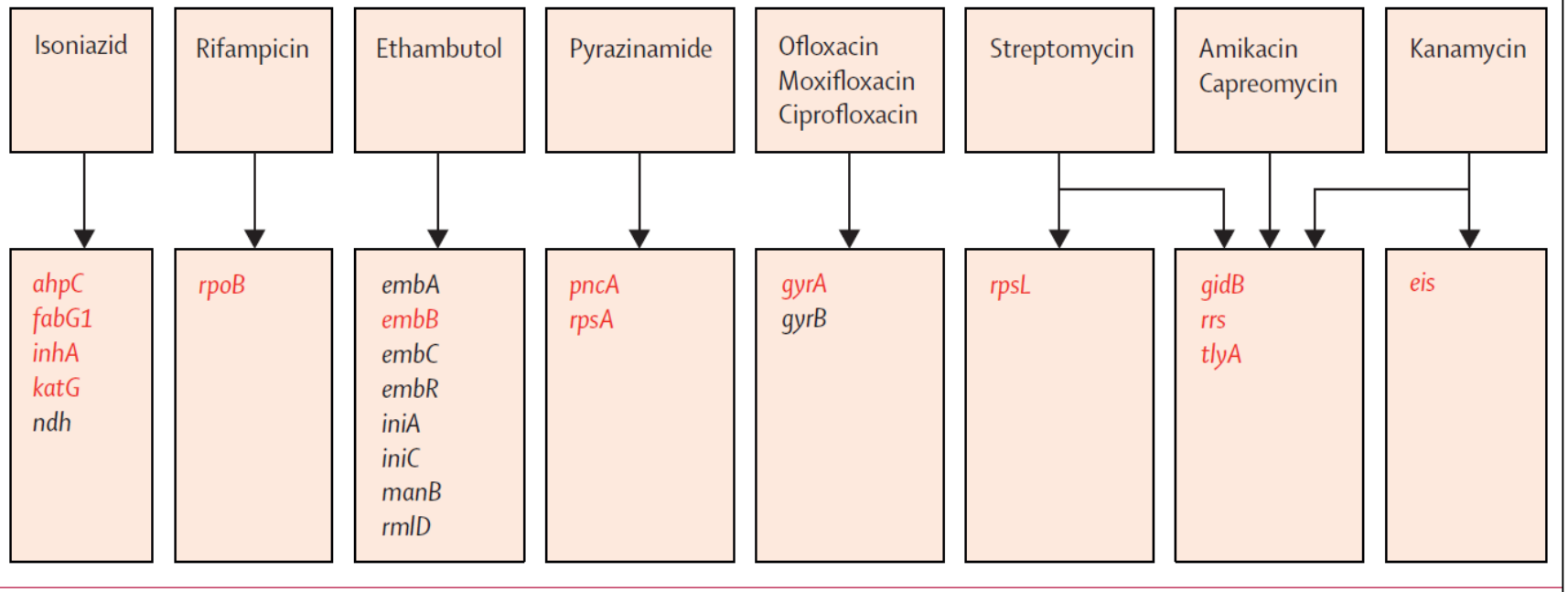


Figure 1: Candidate genes and mutations

Lancet Infect Dis 2015;15:1193-202.

	Phenotypically resistant						Phenotypically sensitive						All		Excluding uncharacterised		Uncharacterised
	Genotype					Total	Genotype					Total	Sensitivity	Specificity	Sensitivity	Specificity	
	R	R_x	S_0	S_B	U		R	R_x	S_0	S_B	U						
Isoniazid	305	5	18	1	35	364	19	0	1065	52	52	1188	85·2 (81·1–88·7)	98·4 (97·5–99·0)	94·2 (91·1–96·5)	98·3 (97·4–99·0)	5·6%
Rifampicin	263	12	8	1	16	300	9	1	1200	4	38	1252	91·7 (87·9–94·5)	99·2 (98·5–99·6)	96·8 (94·1–98·5)	99·2 (98·5–99·6)	3·5%
Ethambutol	152	6	7	1	26	192	62	5	1003	79	210	1359	82·3 (76·1–87·4)	95·1 (93·8–96·2)	95·2 (90·7–97·9)	94·2 (92·7–95·4)	15·2%
Pyrazinamide	31	12	27	5	104	179	2	0	1218	67	83	1370	24·0 (17·9–30·9)	99·9 (95·5–100·0)	57·3 (45·3–68·7)	99·8 (99·4–100·0)	12·1%
Streptomycin	278	6	6	9	49	348	10	1	970	34	189	1204	81·6 (77·1–85·5)	99·1 (98·4–99·5)	95·0 (91·9–97·2)	98·9 (98·1–99·4)	15·3%
Ofloxacin	2	3	4	2	0	11	0	0	489	134	38	661	45·5 (16·7–76·6)	100·0 (99·4–100·0)	45·5 (16·7–76·6)	100·0 (99·4–100·0)	5·7%
Amikacin	36	16	5	0	2	59	1	2	427	38	140	608	88·1 (77·1–95·1)	99·5 (98·6–99·9)	91·2 (80·7–97·1)	99·4 (98·1–99·9)	21·3%
Total	1067	60	75	19	232	1453	103	9	6372	408	750	7642	77·6 (75·3–79·7)	98·5 (98·2–98·8)	92·3 (90·7–93·7)	98·4 (98·1–98·7)	10·8%

Total sensitivity and specificity data are weighted means (95% CIs). We investigated each drug separately by comparing the phenotype for each across isolates with this data available. The unit of analysis was therefore not an isolate, but a phenotype. R=resistance-determining mutation. R_x=resistance determinant only as a mixed base call (heteroresistance). S_0=zero mutations present. S_B=only benign mutations present. U=uncharacterised mutations present in the absence of a resistance-determining mutation. Characterised mutations only exclude the U columns. To avoid double counting for several drugs from the same class, ofloxacin and amikacin were included as representatives of their antibiotic classes, because these had the most resistant phenotypes. Results for ciprofloxacin, moxifloxacin, kanamycin, and capreomycin are in the appendix.

Table: **Phenotypic predictions for the validation set**

Lancet Infect Dis 2015;15:1193-202.

Advantages of WGS

- Screening all resistance determinants
  - higher sensitivity than LPA alone (81.6% vs. 85.1%)

- Characterising mutations as benign
  (e.g., 83% of *rpoB* I491F – phenotypically susceptible)
  - information of which drugs to be given

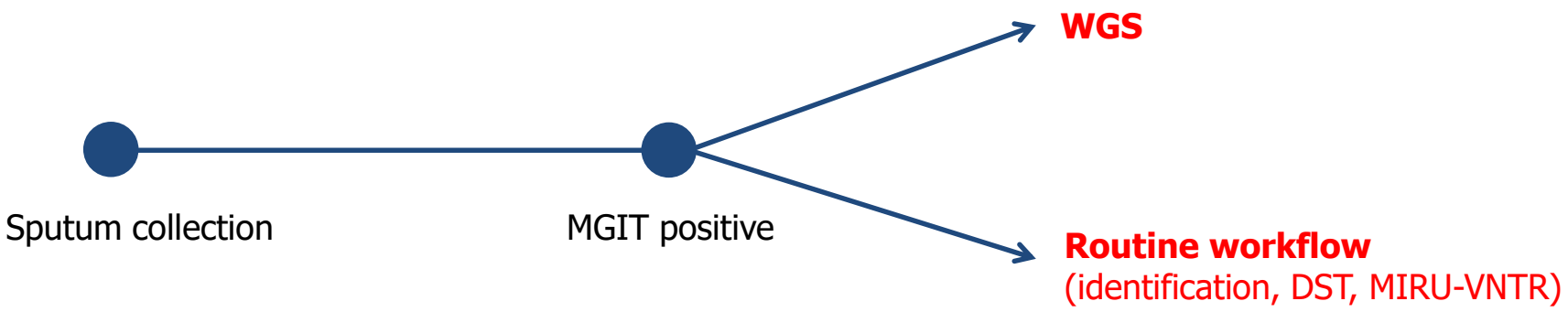
- DST for additional (novel) drugs at no additional cost
  - helpful when designing new treatment regimens

- Outbreak detection
  - potentially adding to local tuberculosis control

Rapid, comprehensive, and affordable mycobacterial diagnosis with whole-genome sequencing: a prospective study

Louise J Pankhurst, Carlos del Ojo Elias*, Antonina A Votintseva*, Timothy M Walker*, Kevin Cole, Jim Davies, Jilles M Fermont, Deborah M Gascoyne-Binzi, Thomas A Kohl, Clare Kong, Nadine Lemaitre, Stefan Niemann, John Paul, Thomas R Rogers, Emma Roycroft, E Grace Smith, Philip Supply, Patrick Tang, Mark H Wilcox, Sarah Wordsworth, David Wyllie, Li Xu, Derrick W Crook, for the COMPASS-TB Study Group†*

Lancet Respir Med 2016;4:49-58.



	n
Routine methods and WGS identification failed	9
Routine methods failed	2*
Identified by routine methods	345 (100%)
Concordant	322 (93%)
M tuberculosis complex	157 (46%)
M avium complex	71 (21%)
M abscessus complex	39 (11%)
M gordonae	18 (5%)
M xenopi	11 (3%)
M tuberculosis complex (BCG)	8 (2%)
M kansasii	6 (2%)
M malmoense	3 (1%)
M fortuitum	2 (1%)
M szulgai	2 (1%)
M tuberculosis complex (*M africanum*)	2 (1%)
M celatum	1 (<1%)
M lentiflavum	1 (<1%)
M tuberculosis complex and *M avium* complex	1 (<1%)
Part concordant	10 (3%)
WGS gained one species	5 (1%)†
WGS missed one species	3 (1%)‡
WGS identified related species	1 (<1%)§
WGS identified subspecies	1 (<1%)¶
Discordant	3 (1%)‖
WGS failed	10 (3%)

Table 1: **Concordance between single WGS and routine laboratory methods for mycobacterial speciation**

Sensitivity 95%
Specificity 98%

Lancet Respir Med 2016;4:49-58.

	DST successful: resistant				DST successful: sensitive				DST failed				DST not attempted			
	Resistant	Sensitive	Mixed*	Failed†	Resistant	Sensitive	Mixed*	Failed†	Resistant	Sensitive	Mixed*	Failed†‡	Resistant	Sensitive	Mixed*	Failed†
Total across drugs and drug classes§	40 (100%) /19 (100%)	7 (100%) /6 (100%)	1 (100%) /1 (100%)	0	1 (100%) /1 (100%)	618 (100%) /120 (100%)	5 (100%) /4 (100%)	31 (100%) /8 (100%)	0	1 (100%) /1 (100%)	0	4 (100%) /0	6 (100%) /4 (100%)	427 (100%) /118 (100%)	7 (100%) /6 (100%)	28 (100%) /10 (100%)
First-line drugs																
Isoniazid	13 (33%) /11 (56%)	2 (29%) /2 (33%)	1 (100%) /1 (100%)	0	0	143 (23%) /105 (88%)	0	7 (23%) /7 (88%)	0	1 (100%) /1 (100%)	0	1 (25%) /0	0	0	0	0
Rifampicin	5 (13%) /4 (21%)	1 (14%) /1 (17%)	0	0	0	148 (24%) /111 (93%)	4 (80%) /3 (75%)	9 (29%) /8 (100%)	0	0	0	1 (25%) /0	0	0	0	0
Ethambutol	5 (13%) /4 (21%)	1 (14%) /1 (17%)	0	0	1 (100%) /1 (100%)	153 (25%) /114 (95%)	0	7 (23%) /7 (88%)	0	0	0	1 (25%) /0	0	0	0	0
Pyrazinamide	8 (20%) /5 (26%)	1 (14%) /1 (17%)	0	0	0	149 (24%) /113 (94%)	1 (20%) /1 (25%)	8 (26%) /7 (88%)	0	0	0	1 (25%) /0	0	0	0	0
Second-line drugs																
Streptomycin	5 (13%) /3 (16%)	1 (14%) /1 (17%)	0	0	0	14 (2%) /12 (10%)	0	0	0	0	0	0	2 (33%) /1 (25%)	138 (32%) /103 (87%)	0	8 (29%) /7 (70%)
Fluoroquinolones	3 (8%) /3 (16%)	1 (14%) /1 (17%)	0	0	0	6 (1%) /5 (4%)	0	0	0	0	0	0	2 (33%) /2 (50%)	148 (35%) /109 (92%)	0	8 (29%) /7 (70%)
Aminoglycosides	1 (3%) /1 (5%)	0	0	0	0	5 (1%) /4 (3%)	0	0	0	0	0	0	2 (33%) /1 (25%)	141 (33%) /105 (89%)	7 (100%) /6 (100%)	12 (43%) /10 (100%)

Data are number of specimens (%)/number of patients (%). DST=drug susceptibility testing. *Resistant and sensitive. †Failed whole-genome sequencing prediction (insufficient sequencing data to predict drug resistance; each specimen sequenced only once). ‡There are zero patients because these samples have been removed during removal of duplicate specimens. §The numbers of patients do not add to the totals because patients can be counted in more than one category.

Table 2: Whole-genome sequencing resistance predictions for *Mycobacterium tuberculosis* complex specimens compared with phenotypic DST

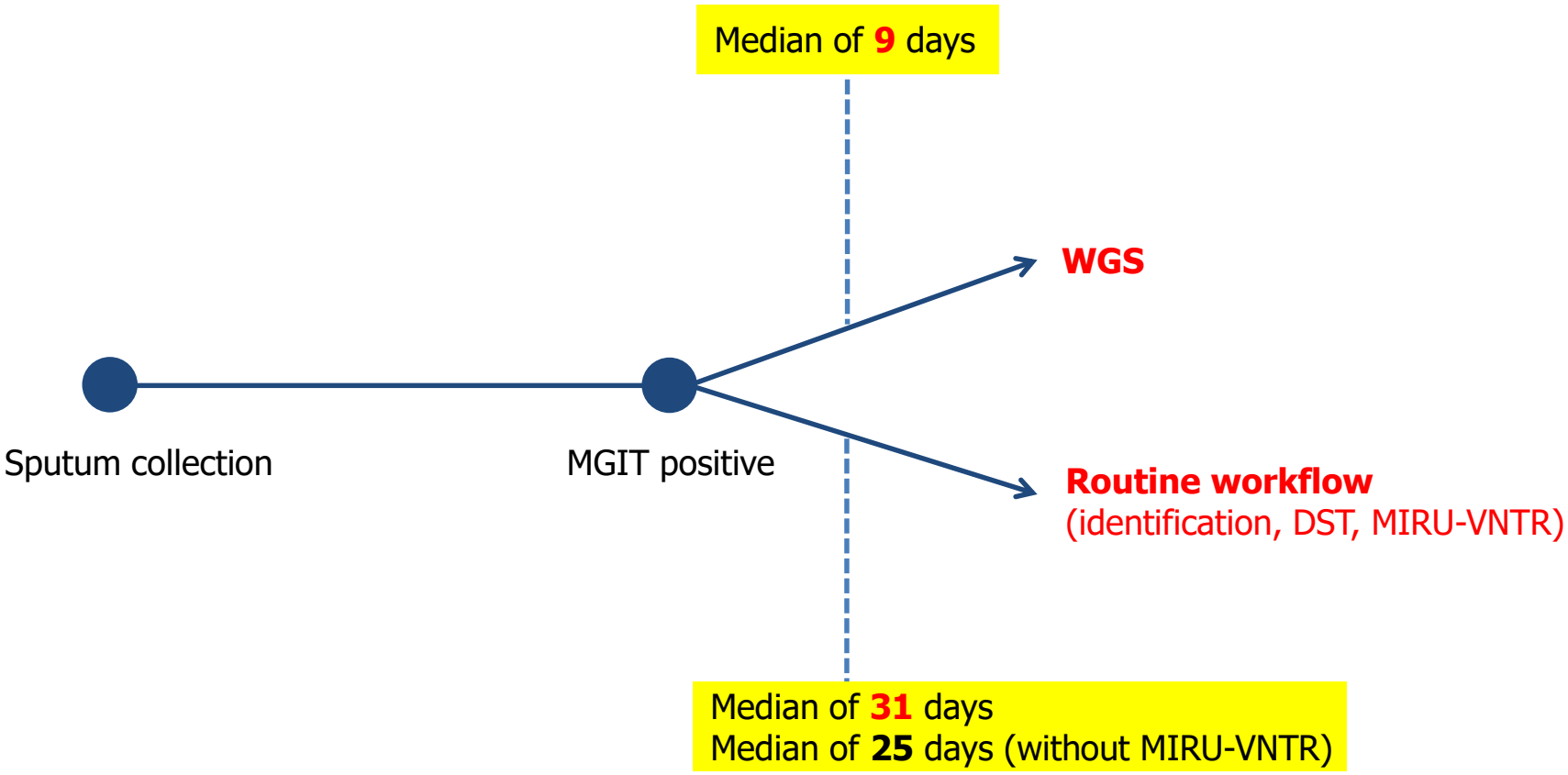
Lancet Respir Med 2016;4:49-58.

WGS predicted DST with **93%** accuracy.
(95% CI 91–95; 628 of 672 specimens; 168 MTBC specimens identified)

WGS linked 15 of 91 UK patients to an outbreak in 9 clusters.

WGS diagnosed a case of MDR-TB before routine diagnosis was completed.

Comparison of timeline

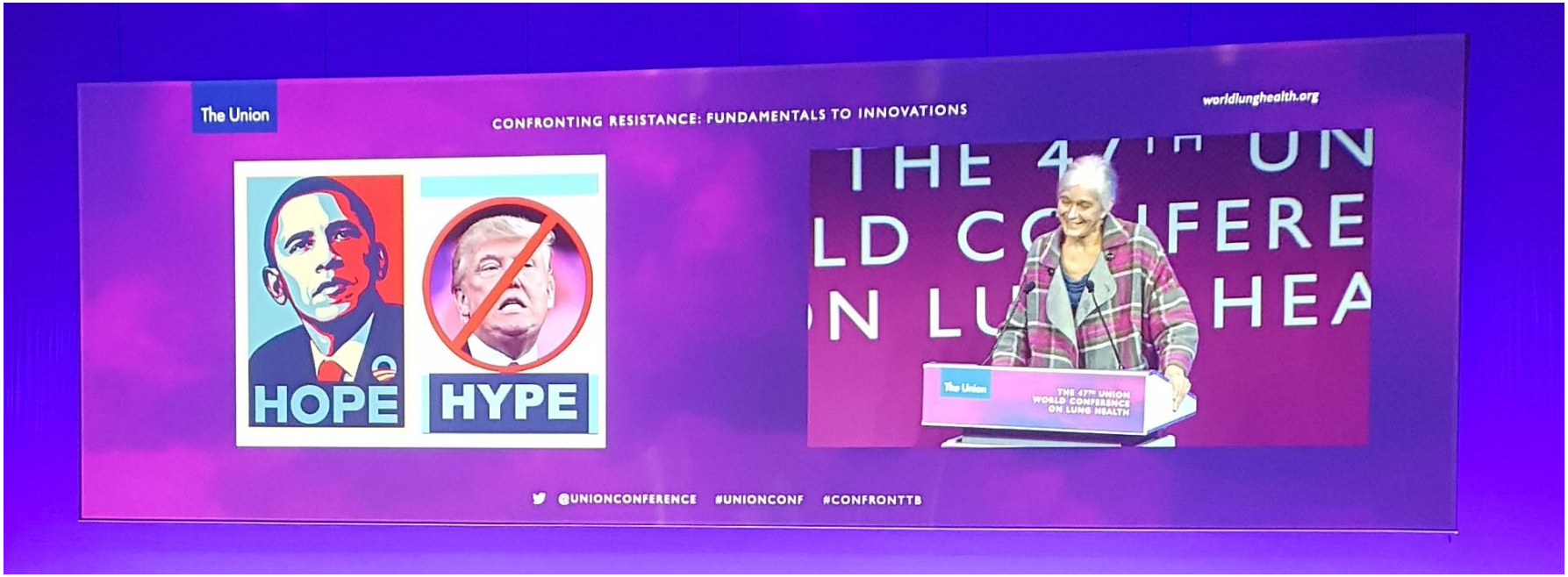


	Throughput in 2014 (n)*	Total per sample in 2014 (£)	10% fewer samples per year (£)	10% more samples per year (£)
WGS and routine clinical workflows				
MGIT culture	15 265	52·39	52·90	51·97
Cepheid Xpert MTB/RIF	617	99·66	102·35	97·44
WGS workflow only				
WGS	2207	118·55	120·16	117·26
Routine clinical workflows only				
Identification assays	2207	55·05	55·28	54·87
Hain MTBC	866	..	..	..
Hain CM/AS	1341	..	..	..
MIRU-VNTR	866	107·75	110·89	105·18
First-line DST	866	135·47	137·12	134·13
Limited second-line DST†	62	93·01	93·24	92·83
Second-line DST‡	62	101·27	104·24	98·86
WGS workflow scenarios				
MGIT culture and WGS	..	170·94	173·06	169·23
MGIT culture and WGS and first-line DST	..	306·41	310·18	303·36
MGIT culture and WGS and first-line DST and full second-line DST	..	500·68	507·66	495·05
Routine clinical workflow scenarios				
Culture and identification assays	..	107·44	108·18	106·84
Culture and identification assays and MIRU-VNTR and first-line DST	..	350·66	356·19	346·15
Culture and identification assays and MIRU-VNTR and first-line DST and full second-line DST	..	544·93	553·69	537·84
Total workflow costs				
WGS-based diagnostics	..	480·91	486·01	476·75
WGS-based diagnostics and first-line and full second-line DST	..	539·53	545·37	534·73
Routine clinical workflow-based diagnostics	..	518·31	524·00	513·64

Table 3: **Total cost per sample by process, accounting for error rates**

Lancet Respir Med 2016;4:49-58.

WGS, hope or hype?



The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2014;371.

REMoxTB	Control group	2HREZ / 4HR
	INH group	2HR**M**Z / 2HR**M**
	EMB group	2**M**REZ / 2**M**R

OFLOTUB	Control group	2HREZ / 4HR
	GFX group	2HR**G**Z / 2HR**G**

RIFAQUIN	Control group	2HREZ / 4HR
	4M group	2**M**REZ / 2**M + P** (twice weekly)
	6M group	2**M**REZ / 4**M + P** (once weekly)

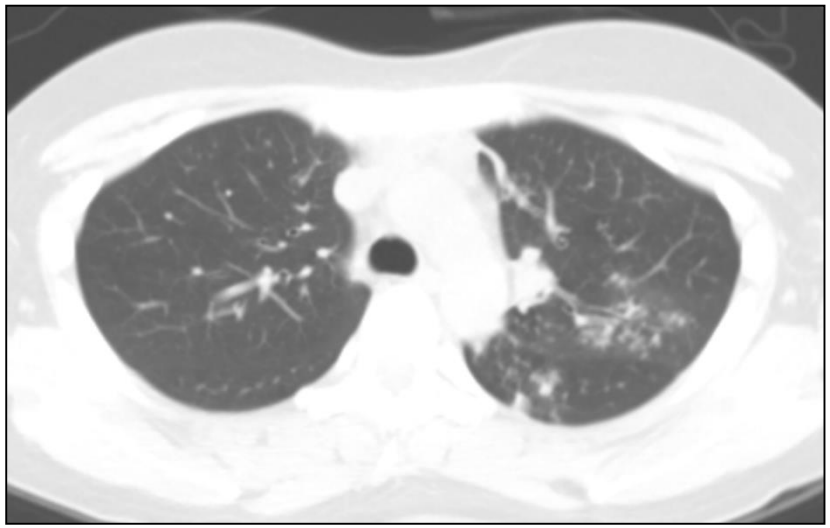
The Effectiveness and Safety of Fluoroquinolone-Containing Regimen as a First-Line Treatment for Drug-Sensitive Pulmonary Tuberculosis: A Systematic Review and Meta-Analysis

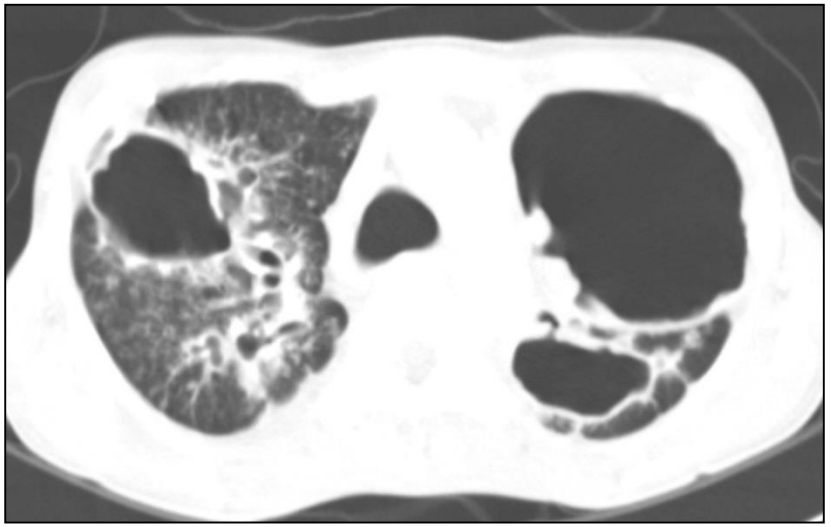
Hyun Woo Lee[1], Jung Kyu Lee[2], Eunyoung Kim[3], Jae-Joon Yim[1], Chang-Hoon Lee[1]*

PLoS One 2016;11:e0159827.

Results

Eleven RCTs that included 6,334 patients were selected. Fluoroquinolone-containing regimens had a higher rate of sputum culture conversion at 2 months of treatment (M-H fixed odds ratio [OR], 1.36; 95% confidence interval [CI], 1.20–1.54). However, the outcomes were less favorable (M-H fixed OR, 0.69; 95% CI, 0.59–0.82) and the associated total adverse events were more frequent (M-H fixed OR, 1.84; 95% CI, 1.46–2.31) in the fluoroquinolone-containing regimen group, without a significant heterogeneity according to treatment duration. Treatment with the fluoroquinolone-containing regimen for 4 months showed a higher relapse rate.





건강검진에서 발견, 무증상

AFB stain (-)

AFB culture : *M. tuberculosis*

DST : no resistance

2HREZ/4HR

VS

객혈로 내원

AFB stain : 4+

AFB culture : *M. tuberculosis*

DST : no resistance

2HREZ/4HR

Treatment of non-cavitary pulmonary tuberculosis with shortened fluoroquinolone-based regimens: a meta-analysis

N. Alipanah,* A. Cattamanchi,* R. Menzies,† P. C. Hopewell,* R. E. Chaisson,‡ P. Nahid*

INT J TUBERC LUNG DIS 2016;20:1522–8.

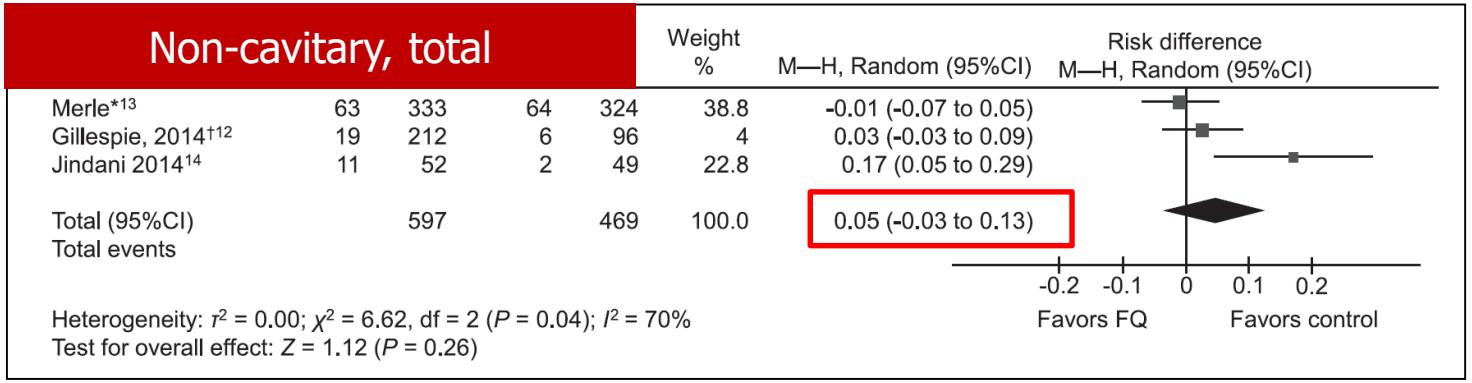
Author	Year	Location	Patients *n*	Intervention	Dosage mg	Follow-up months
Gillespie, REMoxTB[12]	2014	South Africa, India, Tanzania, Kenya, Thailand, Malaysia, Zambia, China, Mexico	1931	4MHRZ/2 placebo 4MRZE/2 placebo	MFX 400	18*
Jindani,† RIFAQUIN[14]	2014	South Africa, Zimbabwe, Botswana, Zambia	827	2MRZE/2M+P2xweekly	MFX 400, RPT 900	18*
				2MRZE/4M+P1xweekly	MFX 400, RPT 1200	
Merle, OFLOTUB[13]	2014	South Africa, Guinea, Senegal, Benin, Kenya	1692	2GHRZ/2GHR	GFX 400	24‡

Study	Patients *n*	Non-cavitary *n* (%)	Resistance* PZA *n* (%)	Resistance* FQ *n* (%)
Gillespie, REMoxTB[12]	1548	456 (29)	27 (2)	NA
Jindani, RIFAQUIN[14]	514	165 (32)	NA	NA
Merle, OFLOTUB[13]	1452	708 (49)	—	7 (2)‡

FQ- based regimen (n=597)
Standard regimen (n=469)

Rate of unfavorable outcomes

Non-cavitary, total



					Weight %	M—H, Random (95%CI)
Merle*[13]	63	333	64	324	38.8	-0.01 (-0.07 to 0.05)
Gillespie, 2014†[12]	19	212	6	96	4	0.03 (-0.03 to 0.09)
Jindani 2014[14]	11	52	2	49	22.8	0.17 (0.05 to 0.29)
Total (95%CI)		597		469	100.0	0.05 (-0.03 to 0.13)
Total events						

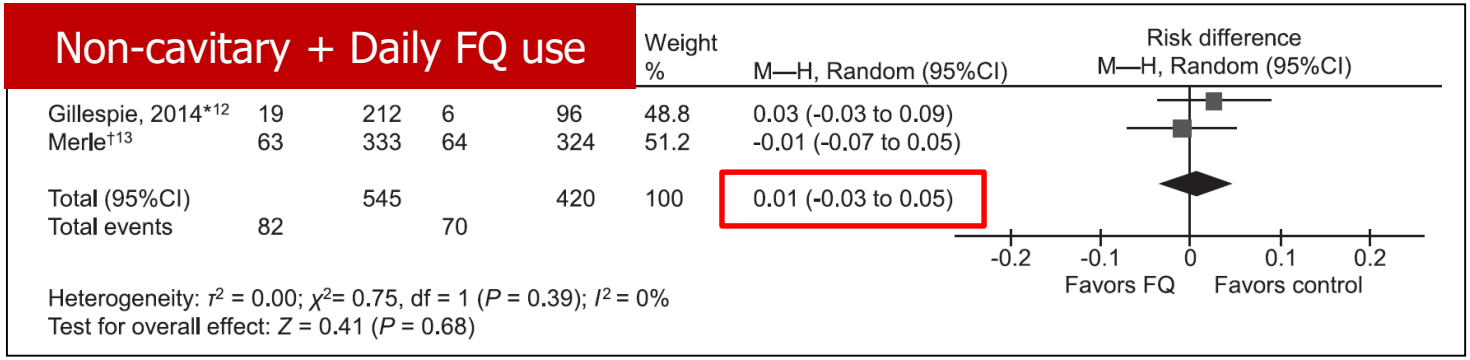
Risk difference M—H, Random (95%CI)

-0.2 -0.1 0 0.1 0.2

Favors FQ Favors control

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 6.62$, df = 2 ($P = 0.04$); $I^2 = 70\%$
Test for overall effect: $Z = 1.12$ ($P = 0.26$)

Non-cavitary + Daily FQ use



					Weight %	M—H, Random (95%CI)
Gillespie, 2014*[12]	19	212	6	96	48.8	0.03 (-0.03 to 0.09)
Merle†[13]	63	333	64	324	51.2	-0.01 (-0.07 to 0.05)
Total (95%CI)		545		420	100	0.01 (-0.03 to 0.05)
Total events	82		70			

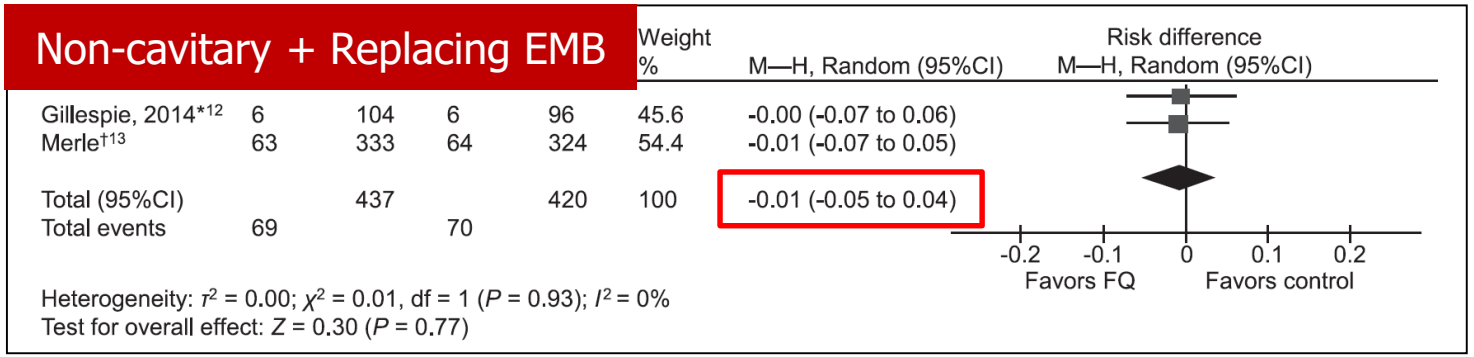
Risk difference M—H, Random (95%CI)

-0.2 -0.1 0 0.1 0.2

Favors FQ Favors control

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.75$, df = 1 ($P = 0.39$); $I^2 = 0\%$
Test for overall effect: $Z = 0.41$ ($P = 0.68$)

Non-cavitary + Replacing EMB



					Weight %	M—H, Random (95%CI)
Gillespie, 2014*[12]	6	104	6	96	45.6	-0.00 (-0.07 to 0.06)
Merle†[13]	63	333	64	324	54.4	-0.01 (-0.07 to 0.05)
Total (95%CI)		437		420	100	-0.01 (-0.05 to 0.04)
Total events	69		70			

Risk difference M—H, Random (95%CI)

-0.2 -0.1 0 0.1 0.2

Favors FQ Favors control

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.01$, df = 1 ($P = 0.93$); $I^2 = 0\%$
Test for overall effect: $Z = 0.30$ ($P = 0.77$)

INT J TUBERC LUNG DIS 2016;20:1522–8.

Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB

Simon Tiberi[1,30], Marie-Christine Payen[2,30], Giovanni Sotgiu[3,30], Lia D'Ambrosio[4,5,30], Valentina Alarcon Guizado[6], Jan Willem Alffenaar[7], Marcos Abdo Arbex[8,9], Jose A. Caminero[10,11], Rosella Centis[4], Saverio De Lorenzo[12], Mina Gaga[13], Gina Gualano[14], Aurora Jazmín Roby Arias[15], Anna Scardigli[11], Alena Skrahina[16], Ivan Solovic[17], Giorgia Sulis[18], Marina Tadolini[19], Onno W. Akkerman[20], Edith Alarcon Arrascue[11,21], Alena Aleska[22], Vera Avchinko[16], Eduardo Henrique Bonini[8,9], Félix Antonio Chong Marín[15], Lorena Collahuazo López[15], Gerard de Vries[23], Simone Dore[3], Heinke Kunst[24], Alberto Matteelli[18], Charalampos Moschos[13], Fabrizio Palmieri[14], Apostolos Papavasileiou[13], Antonio Spanevello[25,26], Dante Vargas Vasquez[27], Pietro Viggiani[12], Veronica White[28], Alimuddin Zumla[29] and Giovanni Battista Migliori[4]

Eur Respir J 2016;47:1235–43.

Patient`s characteristics

	Control (n=168)	Mpm/Clv (n=96)	*P*-value
Male	49.7%	56.3%	0.31
Age, years, median	32	34	0.79
HIV-positive	3.1%	9.0%	0.04
Bilateral disease + cavity	31.7%	53.8%	0.001
Smear-positive	63.0%	88.5%	< 0.0001
Culture-positive	98.7%	100.0%	0.53
Drug resistances, number, median	5	8	< 0.0001
XDR	6.0%	49.0%	< 0.0001
Linezolid use	24.5%	55.6%	< 0.0001
Delamanid use	0.0%	1.1%	0.40
Bedaquiline use	1.4%	9.5%	0.008
Surgical treatment	4.2%	15.2%	0.002
Mpm/Clv use, days, median		85	

Eur Respir J 2016;47:1235–43.

Outcomes and adverse events

	Control (n=168)	Mpm/Clv (n=96)	*P*-value
Sputum smear conversion	98.0%	94.8%	0.35
Sputum culture conversion	100.0%	94.8%	0.05
Time to culture conversion, days	42	44	0.81
Treatment success	68.5%	57.3%	0.07
AEs possibly d/t Mpm/Clv		6.5%	

Eur Respir J 2016;47:1235–43.

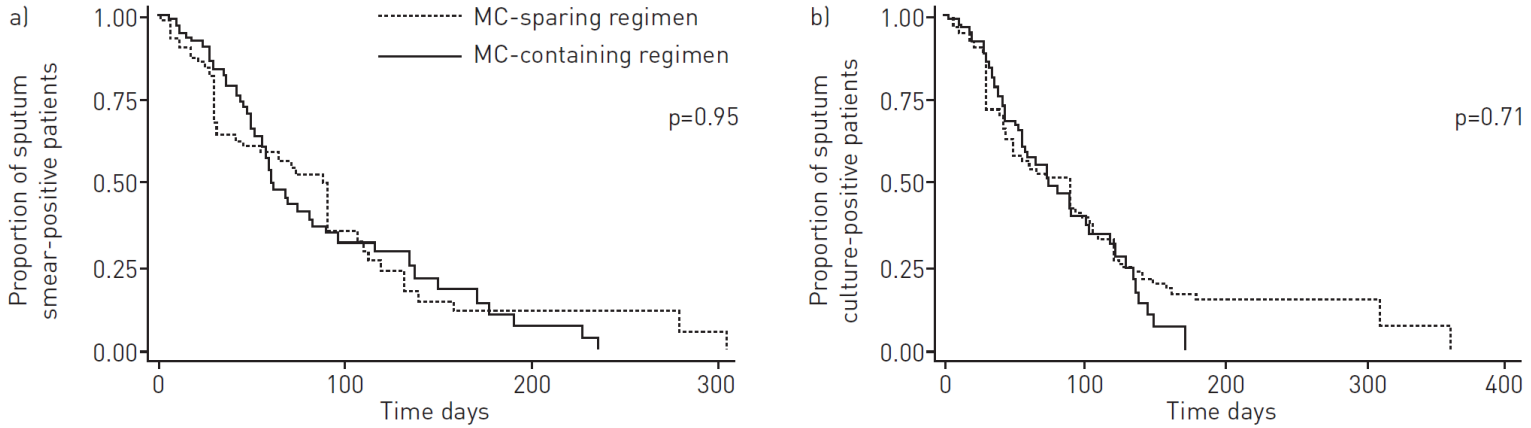


FIGURE 1 a) Sputum smear and b) culture conversion in multidrug- and extensively drug-resistant tuberculosis patients exposed and not exposed to meropenem/clavulanate (MC)-containing regimens.

Eur Respir J 2016;47:1235–43.

Patient`s characteristics

	Control (n=168)	Mpm/Clv (n=96)	*P*-value
Male	49.7%	56.3%	0.31
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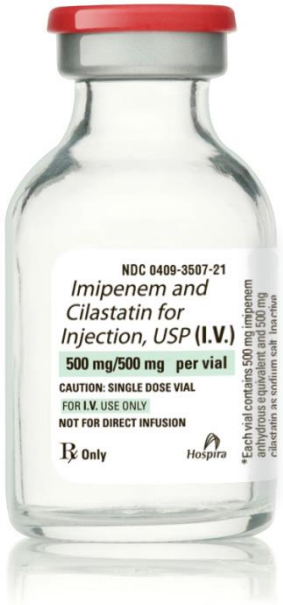
Eur Respir J 2016;47:1235–43.



Imipenem

bid ~ qid

Meropenem

bid ~ tid

Ertapenem

qd

Doripenem

bid ~ tid

Image from google.com

Pharmacokinetics of ertapenem in patients with multidrug-resistant tuberculosis

Sander P. van Rijn[1,7], Richard van Altena[2,7], Onno W. Akkerman[2], Dick van Soolingen[3,4], Tridia van der Laan[4], Wiel C.M. de Lange[2], Jos G.W. Kosterink[1,5], Tjip S. van der Werf[6] and Jan-Willem C. Alffenaar[1]

Eur Respir J 2016;47:1229-34.

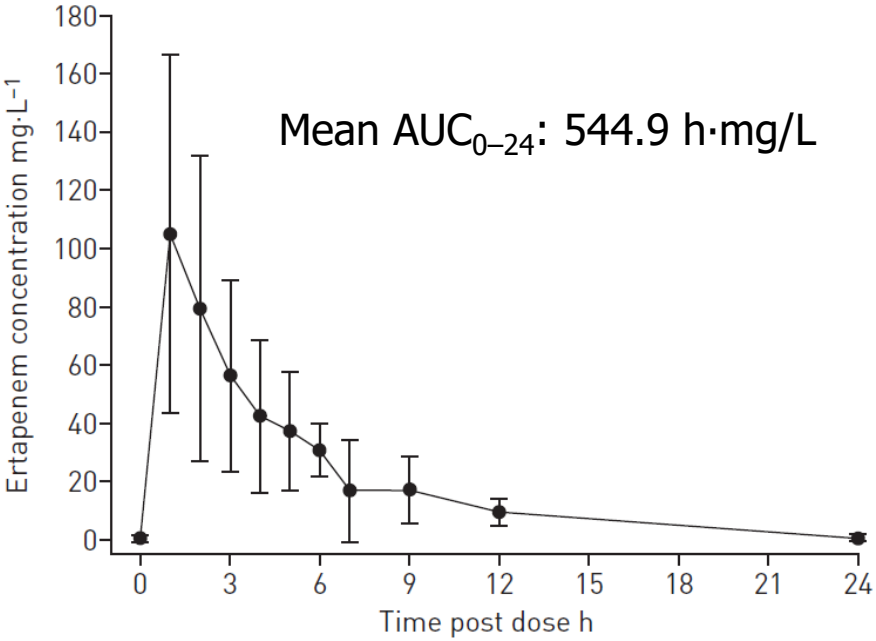
Methods

- Retrospective study
- MDR-TB patients with intolerance to SLD, XDR-TB
- Ertapenem 1g once daily
- Measurement : pharmacokinetics and safety profile

Clinical characteristics and treatment outcomes

	n=18
Age, years, mean	29
Male	44.4%
Duration of ertapenem, days, mean	77
Mfx / SLID / Lzd use	94.4% / 88.9% / 88.3%
Sputum culture conversion	100%
Cured	83.3%
Loss to follow-up	16.7%

Eur Respir J 2016;47:1229-34.



- **91.7%** (11 of 12) of patients exceeded 40% *t*free>MIC (0.25mg/L)
- **75.0%** (9 of 12) of patients exceeded 40% *t*free>MIC (0.5mg/L)

Adverse Events

Ertapenem discontinuation d/t adverse events (n=3)

- Allergic fever
- Elevated ALT (unrelated with ertapenem)
- Line sepsis (unrelated with ertapenem)

Surgery as an Adjunctive Treatment for Multidrug-Resistant Tuberculosis: An Individual Patient Data Metaanalysis

Gregory J. Fox,[1] Carole D. Mitnick,[2] Andrea Benedetti,[1] Edward D. Chan,[3] Mercedes Becerra,[2] Chen-Yuan Chiang,[4] Salmaan Keshavjee,[2] Won-Jung Koh,[5] Yuji Shiraishi,[6] Piret Viiklepp,[7] Jae-Joon Yim,[8] Geoffrey Pasvol,[9] Jerome Robert,[10] Tae Sun Shim,[11] Sonya S. Shin,[12] and Dick Menzies[1]; for the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB[a]

Clin Infect Dis 2016;62:887-95.

Patient`s Characteristics (simple pooled)

	Surgery (n=478)	NS1 (n=3760)	NS2 (n=2193)
Male	61.6%	69.8%	66.1%
Age, year, mean	37.0	39.4	37.6
Length of therapy, month, median	24.4	17.8	18.0
Extensive (smear + or cavity)	85.3%	76.3%	75.1%
XDR-TB	8.6%	5.1%	2.1%
Pneumonectomy	24.5%		
Partial lung resection	47.9%		
Lung resection, not specified	27.6%		
Surgery after culture conversion	58.7%		
Treatment success	69%	60%	51%
Treatment failure	10.3%	7.6%	12.0%
Death	8.4%	12.8%	13.9%
Loss to follow-up	11.7%	30.6%	22.4%

Clin Infect Dis 2016;62:887-95.

Factors associated with Tx success in surgery group

	Multivariable analysis OR (95% CI)
XDR-TB (vs not XDR)	0.4 (0.2 – 0.9)
4 effective drugs (vs 0-2) in cont. phase	3.4 (1.0 – 11.6)
Partial lung resection	3.3 (1.8 – 6.2)
Surgery after culture conversion	2.6 (0.9 – 7.1)

Clin Infect Dis 2016;62:887-95.

Table 5. Relationship Between Surgery and Treatment Success Compared With Death, Failure, or Relapse Using Multivariable and Propensity Score Matched Analyses to Adjust for Potential Confounding

Surgical Group	Unadjusted Estimate OR 95% CI	Adjusted Multivariable Estimate OR 95% CI	Adjusted Estimate Using Matching OR 95% CI	Measures of Heterogeneity[a] I^2_R
Group S vs group NS1				
Any lung resection surgery	1.3 (1.0–1.8)	1.1 (.8–1.5)	1.5 (.8–3.0)	*0.233*
Pneumonectomy	1.0 (.6–1.6)	1.1 (.6–1.9)	1.1 (.6–2.3)	*0.132*
Partial lung resection	**2.4 (1.5–3.7)**	**2.0 (1.2–3.3)**	**3.0 (1.5–5.9)**	*0.118*
Group S vs group NS2				
Any lung resection surgery	2.2 (1.0–4.5)	1.9 (.8–4.1)	1.4 (.4–4.8)	*0.000*
Pneumonectomy	1.2 (.2–2.7)	1.2 (.7–2.1)	0.7 (.1–3.0)	*0.000*
Partial lung resection	**3.7 (1.7–8.1)**	**3.2 (1.5–7.0)**	**2.0 (.4–9.5)**	*0.024*

Clin Infect Dis 2016;62:887-95.

Is bedaquiline as effective as fluoroquinolones in the treatment of multidrug-resistant tuberculosis?

Lorenzo Guglielmetti[1,2], Damien Le Dû[1], Nicolas Veziris[2,3], Eric Caumes[4], Dhiba Marigot-Outtandy[1,5], Yazdan Yazdanpanah[6], Jérôme Robert[2,3,7] and Mathilde Fréchet-Jachym[1,7] for the MDR-TB Management Group of the French National Reference Center for Mycobacteria and the Physicians of the French MDR-TB Cohort[8]

Eur Respir J 2016;48:582-4.

Methods

- Retrospective study
- MDR-TB patients in French referral TB center (2006-2014)

Bdq group : treated for ≥ 30 days with Bdq + not received Fq
(or received Fq while high-level Fq resistance)

Fq group : treated for ≥ 30 days with Fq + not received Bdq

- All patients received SLID and Lzd for ≥ 30 days
- 48% of patients had pre-XDR or XDR-TB

Clinical characteristics

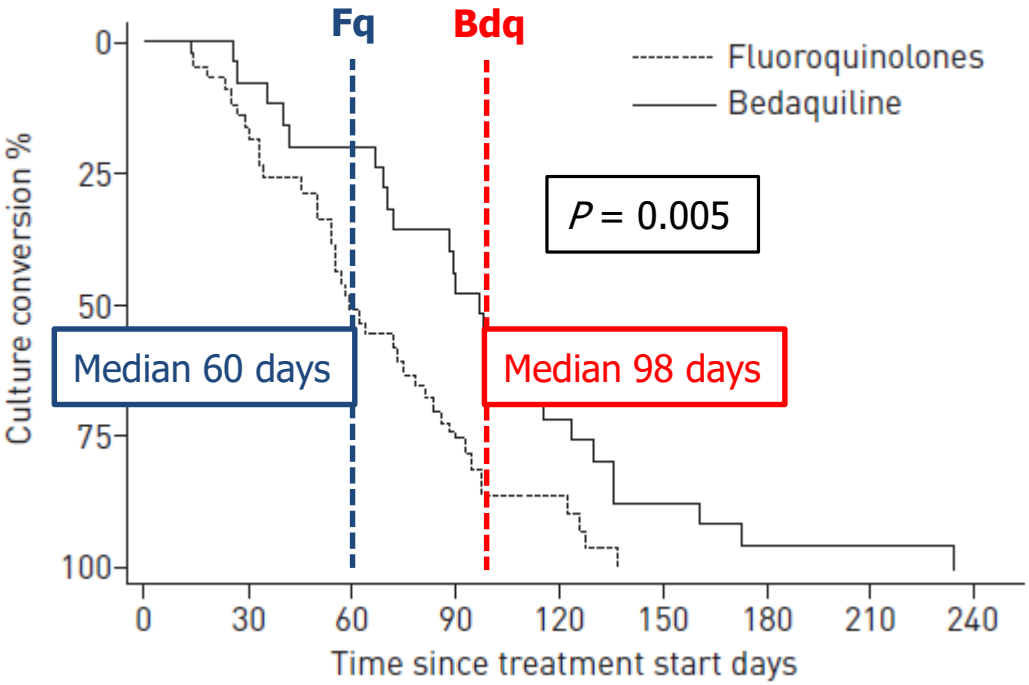
	Bdq group (n=25)	**Fq group** (n=42)	*P*-value
Male	96%	62%	0.001
Prior TB treatment	92%	55%	0.002
Bilateral disease	100%	76%	0.010
Susceptible drug in DST, median	5	8	< 0.001
Lung cavity			> 0.05
Sputum smear			> 0.05
Ethambutol use	28%	59%	0.022
Ethionamide use	20%	48%	0.036
Clofazimine use	32%	5%	0.004
Carbapenem/Clv use	48%	2%	< 0.001

Eur Respir J 2016;48:582-4.

Outcomes

	Bdq group (n=25)	Fq group (n=42)	*P*-value
3M culture conversion	44%	77%	0.02
6M culture conversion	96%	93%	> 0.05

Eur Respir J 2016;48:582-4.



Factors associated with faster TTC (multivariable analysis)

- Absence of lung cavities
- Negative sputum smear at treatment start
- Female sex
- Not associated with Fq use

Safety and efficacy of the C-Tb skin test to diagnose *Mycobacterium tuberculosis* infection, compared with an interferon γ release assay and the tuberculin skin test: a phase 3, double-blind, randomised, controlled trial

Morten Ruhwald, Henrik Aggerbeck, Rafael Vázquez Gallardo, Søren T Hoff, José I Villate, Bettine Borregaard, José A Martinez, Ingrid Kromann, Antón Penas, Luis L Anibarro, Maria Luiza de Souza-Galvão, Francisca Sánchez, Jose Ángel Rodrigo-Pendás, Antoni Noguera-Julian, Xavier Martínez-Lacasa, Maria Victoria Tuñez, Virginia Leiro Fernández, Joan P Millet, Antonio Moreno, Nazaret Cobos, José M Miró, Llanos Roldan, Angels Orcau, Peter Andersen, Joan A Caylá, the TESEC Working Group

Lancet Respir Med. 2017;5:259-68.

TST vs. IGRA

TST	IGRA
• Rich data and evidences • Cheap	• Specific • Single visit • No booster effect • Objective measure
• False positive (eg, BCG, NTM) • Subjective measure • Need return visit • Booster effect	• Expensive • Operator error (complex laboratory test)

Comparison of latent tuberculosis infection rate between contacts with active tuberculosis and non-contacts

Jung-Wan Yoo [a], Kyung-Wook Jo [b], Gu Young Park [c], Tae Sun Shim [b, *]

Respir Med. 2016;111:77-83.

A B S T R A C T

Background: Latent tuberculosis infection (LTBI) rate is usually high in contacts with infectious TB patients. In TB-prevalent country, however, background LTBI rate is already high in general population.
Aim: To compare the LTBI rate between controls and recognized close contacts.
Method: Between February 2010 and January 2014, 183 controls and 376 contacts with TB infection were enrolled. The tuberculin skin test (TST) and QuantiFERON®-TB Gold In-Tube (QFT-GIT) were used to diagnose LTBI.
Results: Higher TST positivity was found in the control group than in the contact group (37.7% *vs.* 29.9%, $P = 0.073$). The positive QFT-GIT rate was higher in contacts than in controls (32.6% *vs.* 24.1%, $P = 0.054$). A significantly higher positive QFT-GIT rate was found in contacts under 30 years of age than in controls (16.1% *vs.* 0%, $P = 0.005$).
Conclusion: In a TB-prevalent country, both TST and QFT-GIT were limited in the diagnosis of recent LTBI in adult contacts probably due to the high background LTBI rate. However, QFT-GIT seems to be better than TST in differentiating LTBI status in contacts younger than 30 year old.

Contact investigation of PNUH

Age group, years	**Contacts of TB** (n=188)	**Non-TB** (n=46)	*P*-value
18-39			
Positive TST	34%	14%	0.101
Positive T-spot.*TB*	29%	5%	0.031
40-59			
Positive TST	52%	18%	0.051
Positive T-spot.*TB*	52%	9%	0.009
≥ 60			
Positive TST	40%	57%	0.369
Positive T-spot.*TB*	55%	42%	0.554

Not published data

TST vs. IGRA

TST	IGRA
• Rich data and evidences • Cheap	• Specific • Single visit • No booster effect • Objective measure
• False positive (eg, BCG, NTM) • Subjective measure • Need return visit • Booster effect	• Expensive • Operator error (complex laboratory test)

Operational advantage

C-Tb skin test

(Recombinant ESAT-6 and CFP10)

High specificity

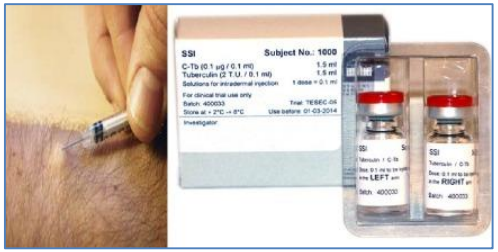


Image from google.com

	Negative controls (n=263)	Occasional contacts (n=299)	Close contacts (n=319)	Patients with tuberculosis (n=101)
C-Tb skin test				(p<0.0001)
Positive	9 (3%)	49 (16%)	136 (43%)	68 (67%)
Negative	253 (96%)	250 (84%)	180 (57%)	32 (32%)
Not done	1 (<0·5%)	0	0	1 (1%)
QuantiFERON-TB Gold In-Tube interferon γ release assay				
Positive	10 (4%)	57 (21%)	122 (42%)	82 (81%)
Negative	253 (96%)	227 (82%)	166 (57%)	19 (19%)
Indeterminate	0	2 (<1%)	2 (<1%)	0
Not done	0	13	26	0
Tuberculin skin test				
Positive	46 (22%)	80 (27%)	162 (51%)	90 (90%)
Negative	167 (78%)	219 (73%)	154 (49%)	10 (10%)
Not done	50 (19%)	0	0	1 (1%)

Table 2: Results by tuberculosis test

Concordance 94%

Lancet Respir Med. 2017;5:259-68.

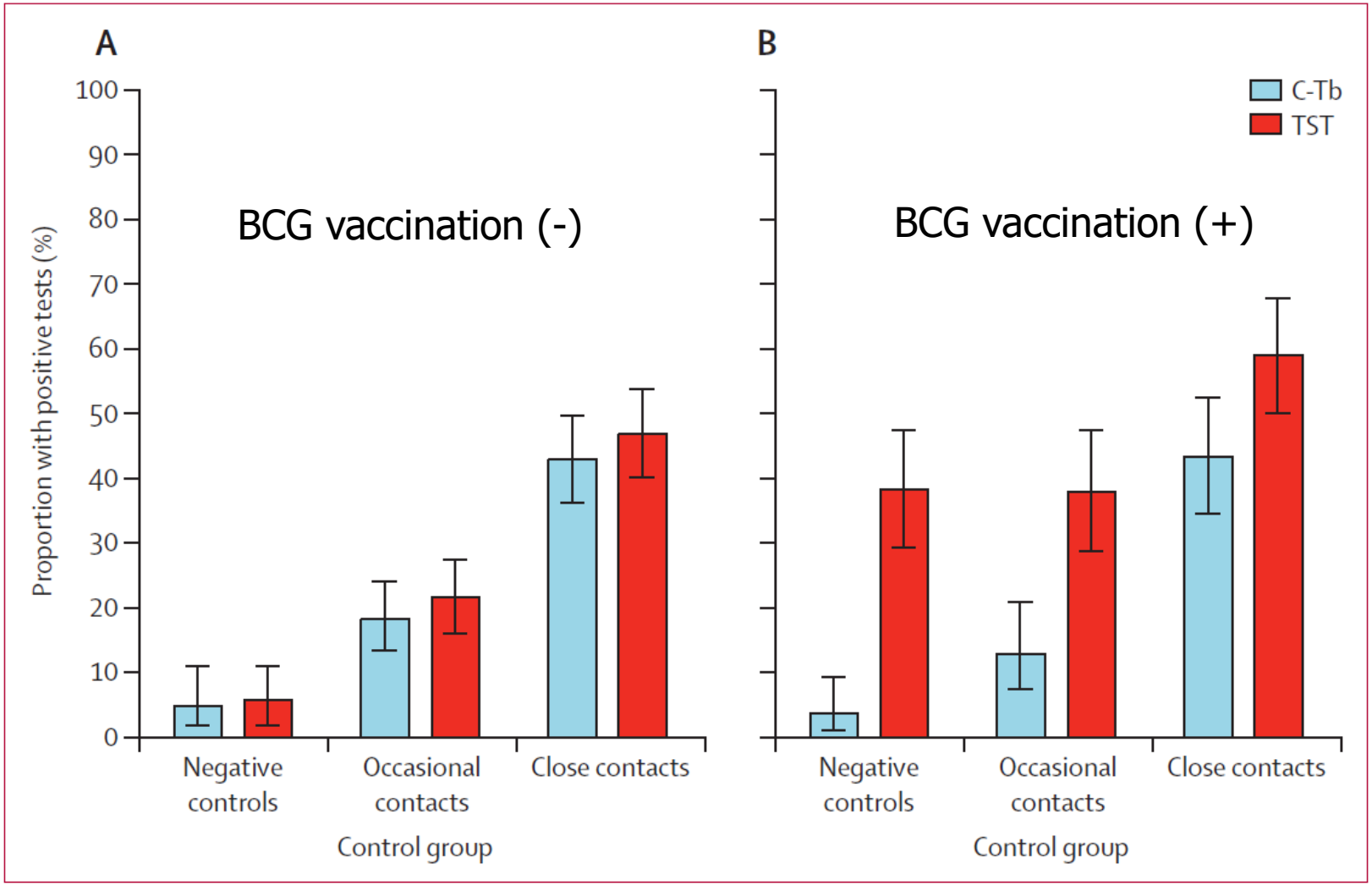


***Figure 3*: Association between positive skin test results and risk of infection in BCG vaccination status**

Lancet Respir Med. 2017;5:259-68.

Mycobacterial Characteristics and Treatment Outcomes in *Mycobacterium abscessus* Lung Disease

Won-Jung Koh,[1,a] Byeong-Ho Jeong,[1,a] Su-Young Kim,[1,a] Kyeongman Jeon,[1] Kyoung Un Park,[2] Byung Woo Jhun,[1] Hyun Lee,[1] Hye Yun Park,[1] Dae Hun Kim,[1] Hee Jae Huh,[3] Chang-Seok Ki,[3] Nam Yong Lee,[3] Hong Kwan Kim,[4] Yong Soo Choi,[4] Jhingook Kim,[4] Seung-Heon Lee,[5] Chang Ki Kim,[5] Sung Jae Shin,[6] Charles L. Daley,[7] Hojoong Kim,[1] and O. Jung Kwon[1]

Clin Infect Dis. 2017;64:309-16.

***M. abscessus* subspecies *abscessus* lung disease**

- Highly drug-resistant
  - Inducible macrolide resistance (*erm* gene (41))
  - Acquired macrolide resistance (*rrl* gene mutation)
- Sputum culture conversion rates : 25%-42%
- High recurrence rate

- **C28 sequevar**
  - *erm*(41) gene T28C
  - nonfuntional *erm*(41) gene → susceptible to clarithromycin

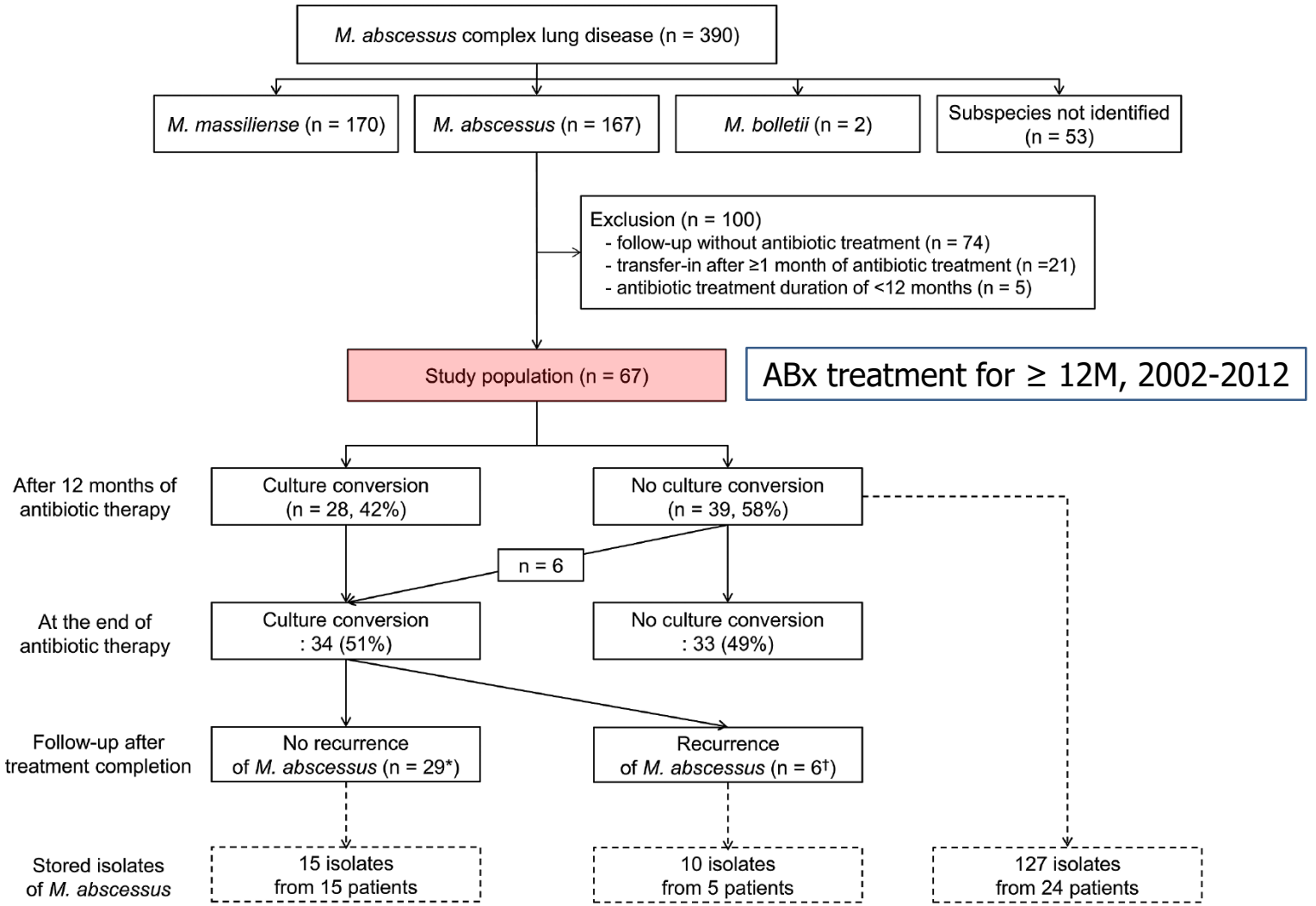


Figure 1. Study population. *, Mycobacterium avium complex lung disease developed in 9 patients (M. intracellulare in 6 and M. avium in 3) after the successful completion of treatment for M. abscessus lung disease. †, 1 patient had only 1 positive M. abscessus culture post-treatment.

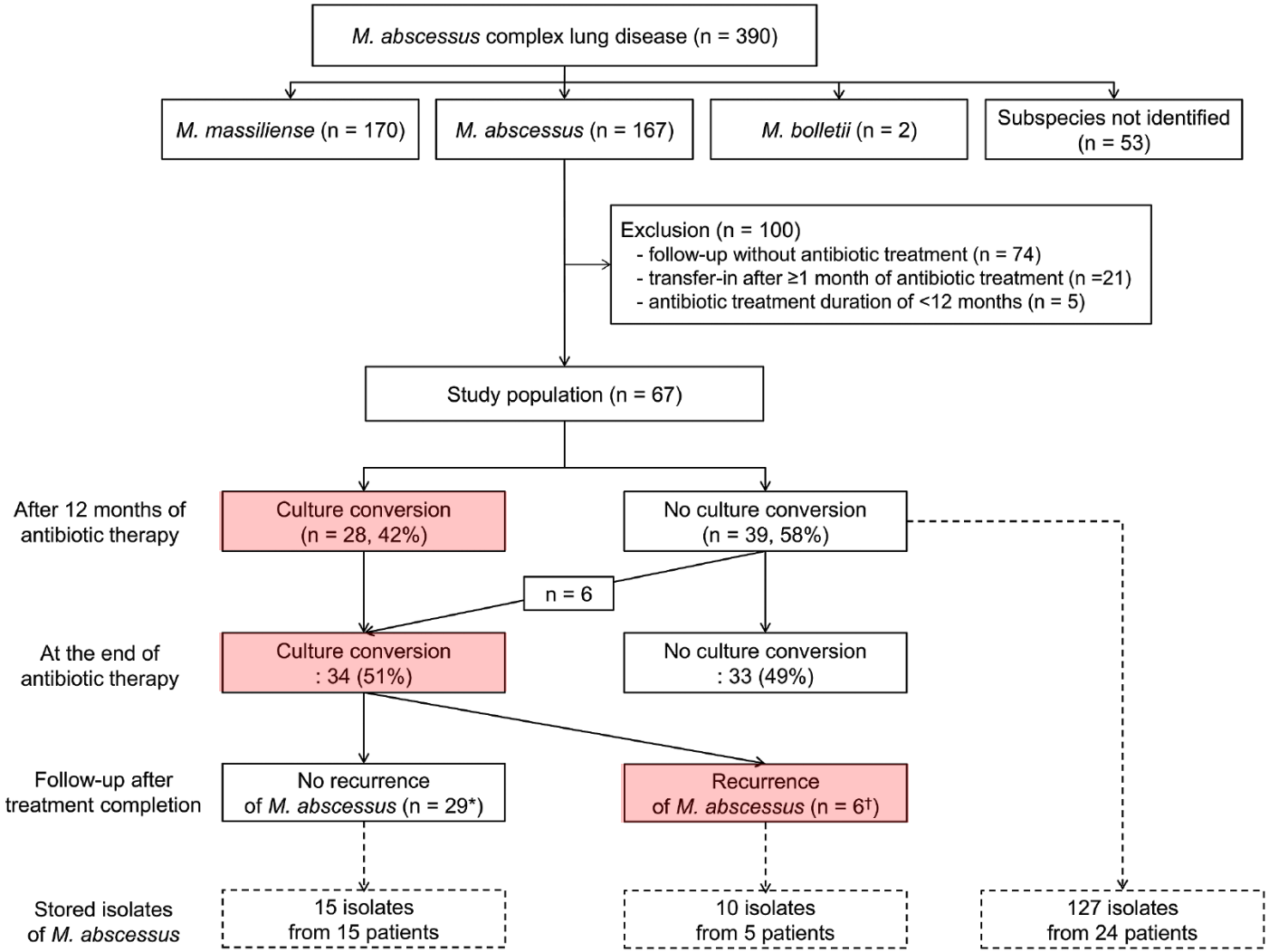


Figure 1. Study population. *, Mycobacterium avium complex lung disease developed in 9 patients (M. intracellulare in 6 and M. avium in 3) after the successful completion of treatment for M. abscessus lung disease. †, 1 patient had only 1 positive M. abscessus culture post-treatment.

Table 3. Comparison of the Mycobacterial Characteristics of Pretreatment *Mycobacterium abscessus* Isolates According to Treatment Outcomes

Mycobacterial Characteristics	Patients With Final Negative Conversion (n = 20)	Patients With Persistently Positive Cultures (n = 24)	*P* Value
Initial morphotype			
Smooth	9 (45)	2 (8)	.020
Mixed (smooth + rough)	4 (20)	8 (33)	
Rough	7 (35)	14 (58)	
Initial susceptibility to clarithromycin			
Susceptible	7 (35)	1 (4)	.015
Inducible resistance	13 (65)	23 (96)	
Resistant	0	0	
Initial 28th sequevar of *erm*(41)			
C28	6 (30)	1 (4)	.035
T28	14 (70)[a]	23 (96)	
Initial *rrl* mutation			

Data are presented as medians (interquartile ranges) or numbers (%).

[a] An isolate from 1 patient had a C19→T point mutation in the *erm*(41) gene, and this isolate was susceptible to clarithromycin [16].

Clin Infect Dis. 2017;64:309-16.

Genotypic analysis revealed that most episodes (22/24, 92%) of persistently positive cultures during antibiotic treatment and all cases of microbiologic recurrence after treatment completion were caused by different *M. abscessus* genotypes within a patient.

CONCLUSION

- Precise identification to the subspecies level and analysis of mycobacterial characteristics could help predict treatment outcomes in patients with *M. abscessus* lung disease.

- Treatment failures and recurrences are frequently associated with multiple genotypes, suggesting reinfection.

감사합니다