# TB/NTM

2018-4-14

연세 의대 내과학교실
강영애

# Tuberculosis

## Global Burden of TB

- Estimated 10.4 million in 2016
  - 140 / 100,000 population
  - 6.3 million new cases reported
  - 3.6 million bacteriologically confirmed
- Estimated RR/ MDR TB : 600,000 new cases
  - Estimated 4.1% (2.8-5.3) of new cases, 19% (9.8-27) of previously treated cases
  - 153,119 RR/MDR cases were notified (26%)

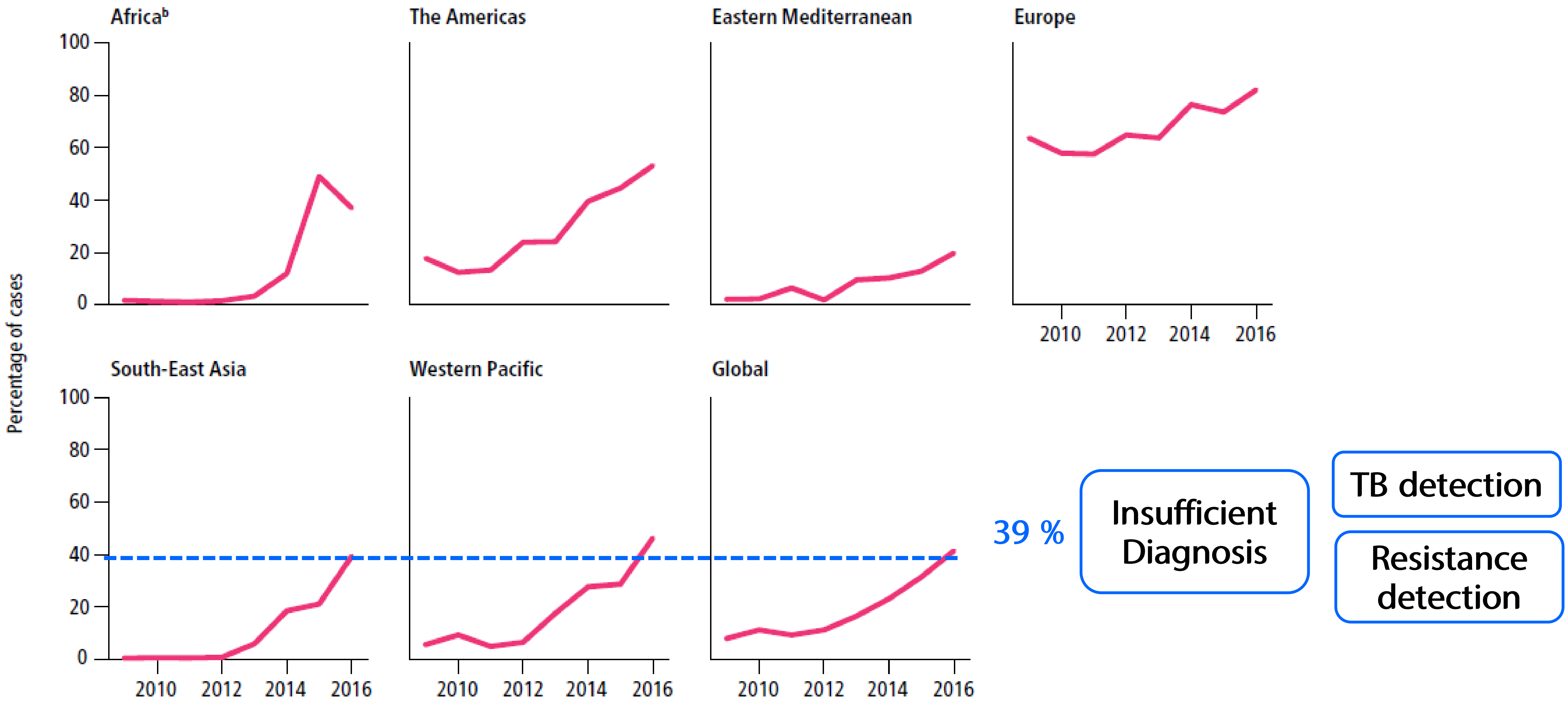
## TB burden in Korea

- 39,245 cases notified in 2016
  - 76.8 /100,000 population
  - 30,892 new cases
- 852 MDR-TB new cases notified
- 59 XDR-TB new cases notified
- Percentage of TB cases with MDR/RR-TB: 2016 survey (WHO report )
  - New cases : 3.4 % (3.1-3.7)
  - Previously treated : 11% (9.4-12)

WHO TB report 2017

결핵 환자 신고 연보 2016

## Percentage of bacteriologically confirmed TB cases tested for RR-TB, globally and for WHO regions, 2009–2016[a]

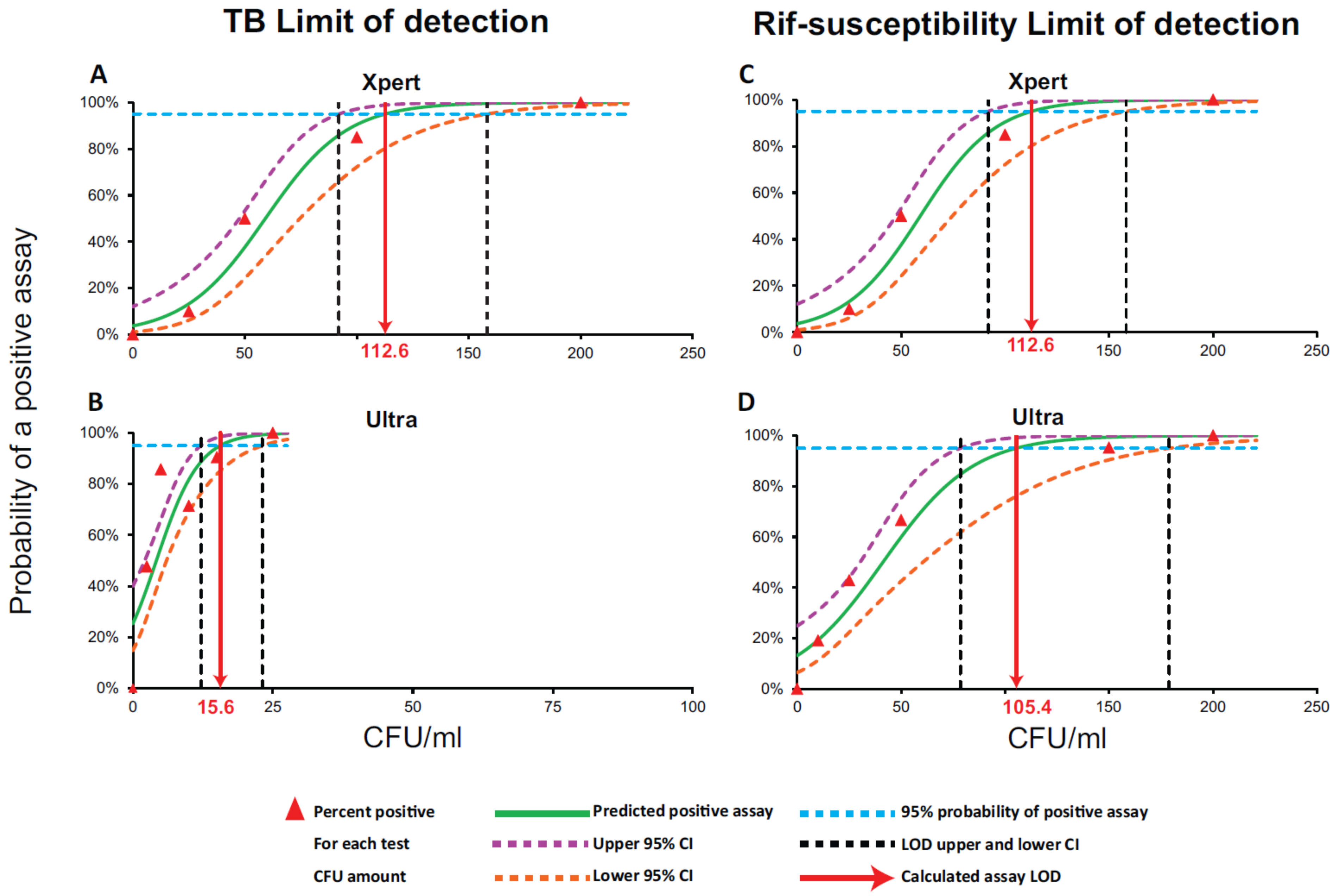



WHO TB report 2017

# Xpert MTB/RIF vs Xpert MTB/RIF Ultra

- For better TB detection
  - 1) inclusion of two new PCR assays that targets tow different multi-copy genes, IS6110, IS1081
  - 2) conversion of the rpoB and IS6110 assays into fully nested PCRs
  - 3) use of a larger PCR tube (25 -> 50ul PCR tube)
- To improve the accuracy of rifampicin resistance detection
  - Incorporates melting temperature-based analysis instead of real-time PCR

Mbio 2017;8:e00812



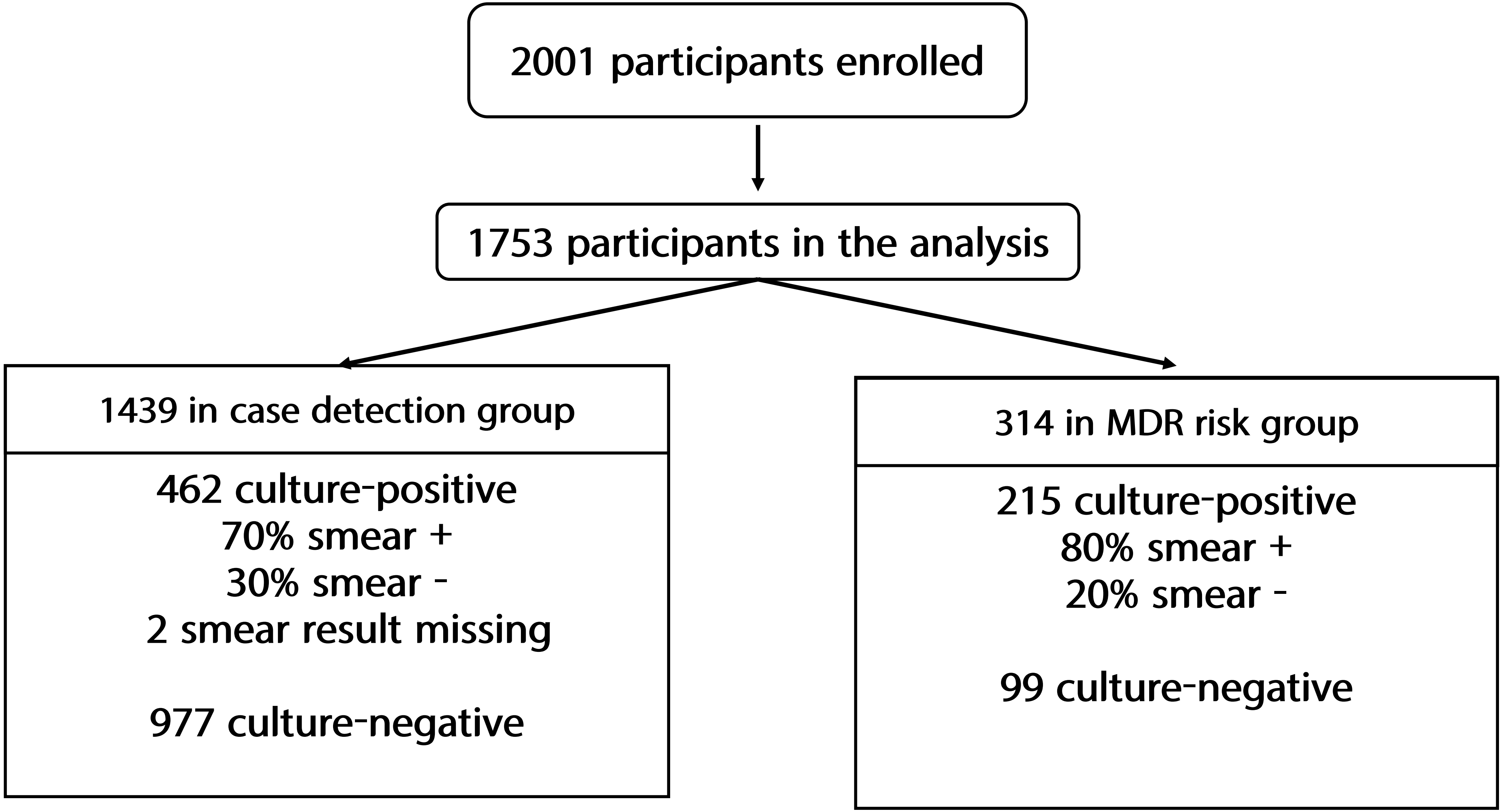

Mbio 2017;8:e00812

# Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study

*Susan E Dorman*, Samuel G Schumacher*, David Alland, Pamela Nabeta, Derek T Armstrong, Bonnie King, Sandra L Hall, Soumitesh Chakravorty, Daniela M Cirillo, Nestani Tukvadze, Nino Bablishvili, Wendy Stevens, Lesley Scott, Camilla Rodrigues, Mubin I Kazi, Moses Joloba, Lydia Nakiyingi, Mark P Nicol, Yonas Ghebrekristos, Irene Anyango, Wilfred Murithi, Reynaldo Dietze, Renata Lyrio Peres, Alena Skrahina, Vera Auchynka, Kamal Kishore Chopra, Mahmud Hanif, Xin Liu, Xing Yuan, Catharina C Boehme, Jerrold J Ellner, Claudia M Denkinger, on behalf of the study team†*

- Prospective, multicenter, diagnostic accuracy study
- Investigational assay : Xpert MTB/RIF Ultra (Xpert Ultra)
    - To improve sensitivity, two different multicopy amplification targets (IS6110 and IS1081), uses improved assay chemistry and cartilage design
- Population
    - Adult, pulmonary TB
    - Multinational (South Africa, Uganda, Kenya, India, China, Georgia, Belarus, and Brazil)
    - Case detection group, multidrug-resistant risk group
- Primary outcome
    - To estimate and compare sensitivity of Xpert Ultra with that of Xpert for detection of smear-negative TB and RR
    - To estimate and compare  Xpert Ultra and Xpert specificities for detection of RR

Lancet Infect Dis 2018;18:76




Lancet Infect Dis 2018;18:76

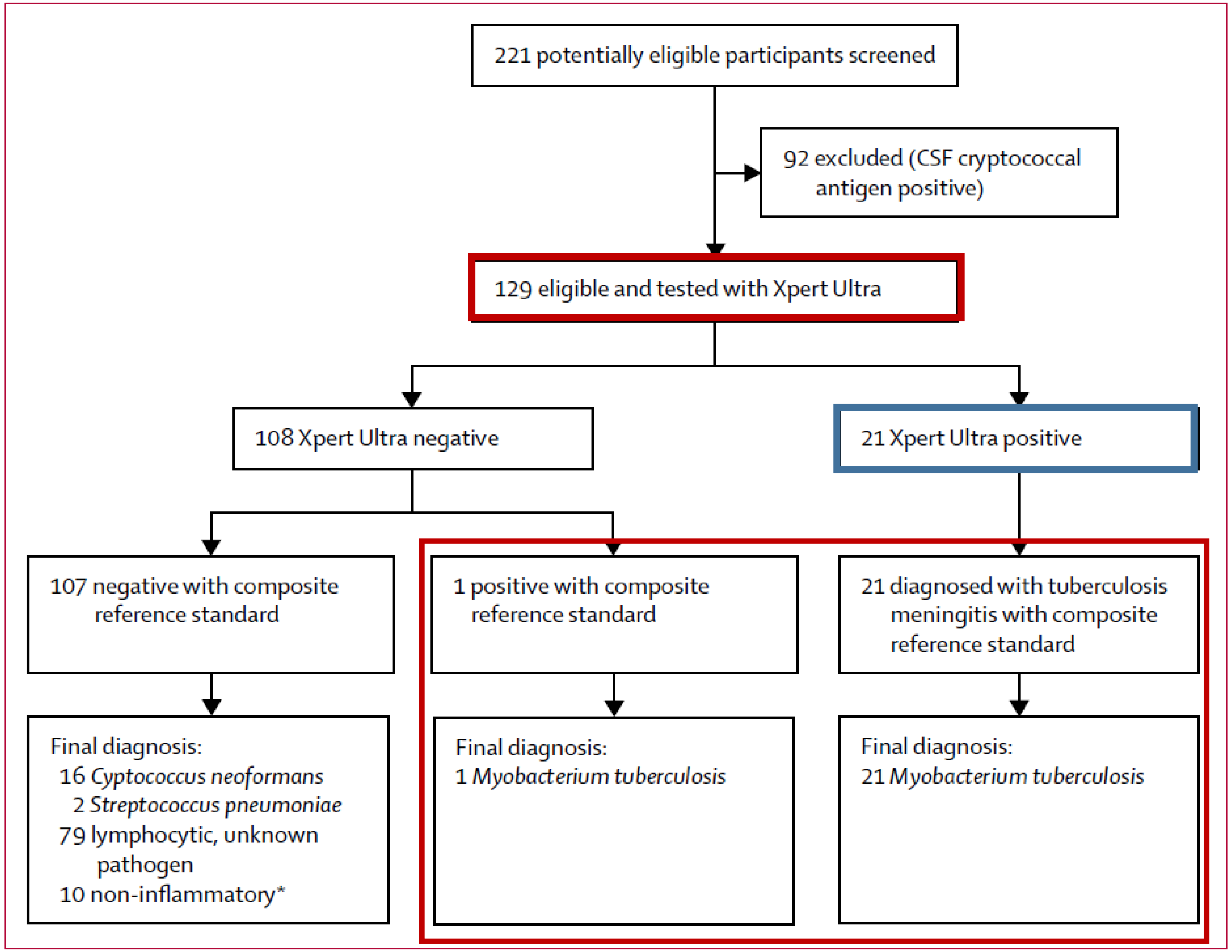
# Xpert MTB/RIF vs Xpert MTB/RIF Ultra

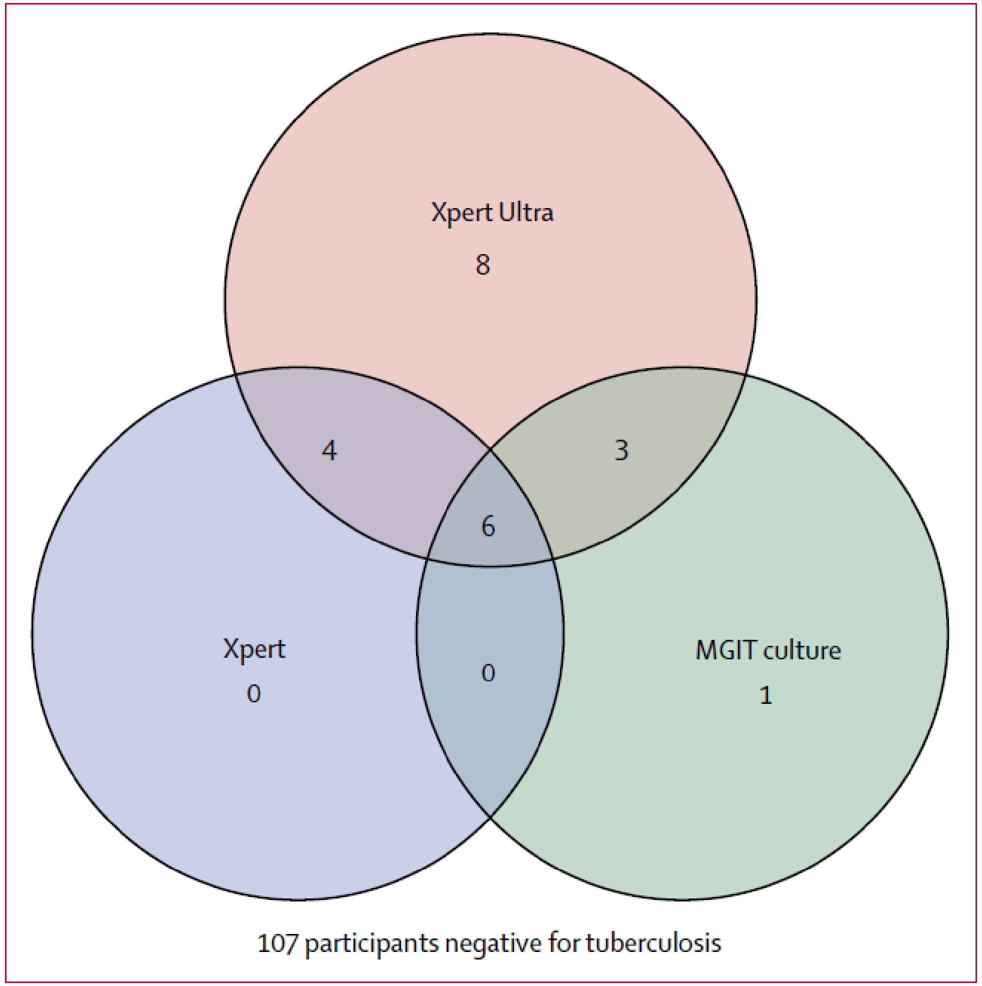
| | Tuberculosis detection | | | | Detection of Rifampicin resistance | |
|---|---|---|---|---|---|---|
| | Sensitivity all culture + | Sensitivity smear - | Sensitivity HIV+ | Specificity | Sensitivity | Specificity |
| Xpert | 83 % | 46% | 77% | 98% | 95% | 98% |
| | (79-86) | (37-55) | (68-84) | (97-99) | (91-98) | (95-99) |
| Xpert Ultra | 88% | 63% | 90% | 96% | 95% | 98% |
| | (85-91) | (54-71) | (83-95) | (94-97) | (91-98) | (97-99) |
| Difference (Ultra-Xpert) | 5.4% | 17% | 13% | -2.7% | -0.6% | 0.3% |
| | 3.3-8.0 | 10-24 | 6.4-21 | -3.9 - -1.7 | -3.2 – 1.6 | -0.7-1.5 |
| Non-inferiority margin | Not predefined | -7% | Not predefined | Not predefined | -3% | -3% |

Lancet Infect Dis 2018;18:76

# Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study

*Nathan C Bahr, Edwin Nuwagira, Emily E Evans, Fiona V Cresswell, Philip V Bystrom, Adolf Byamukama, Sarah C Bridge, Ananta S Bangdiwala, David B Meya, Claudia M Denkinger, Conrad Muzoora, David R Boulware, on behalf of the ASTRO-CM Trial Team*



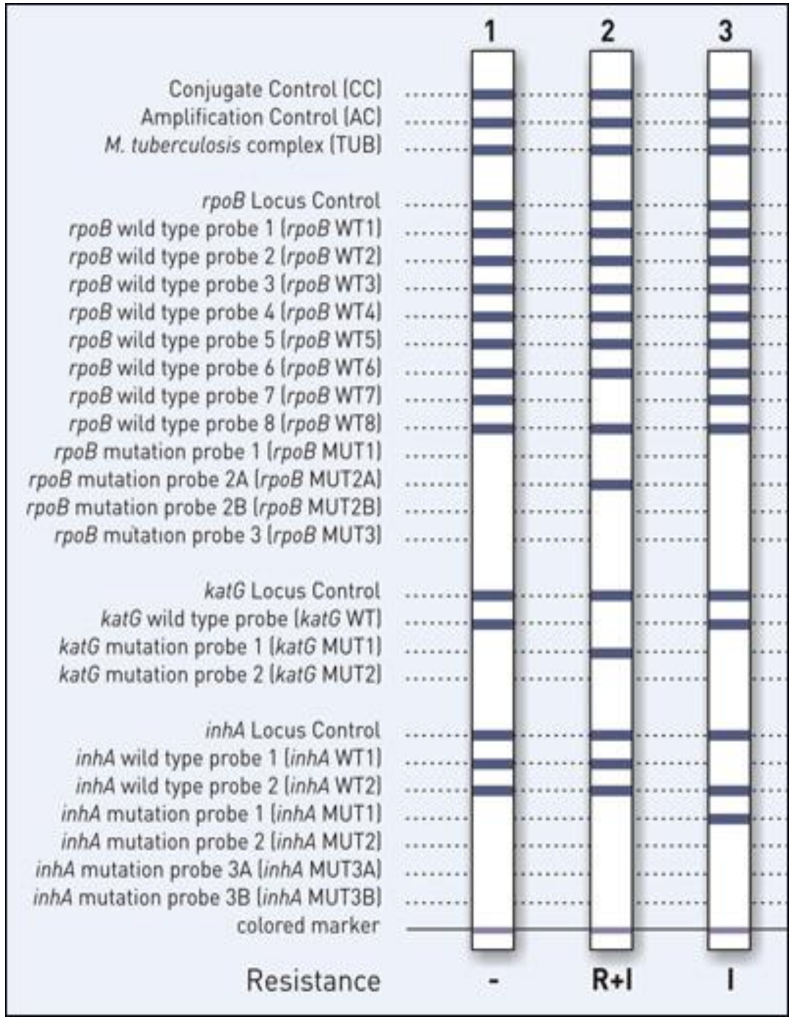




Lancet Infect Dis 2018;18:68

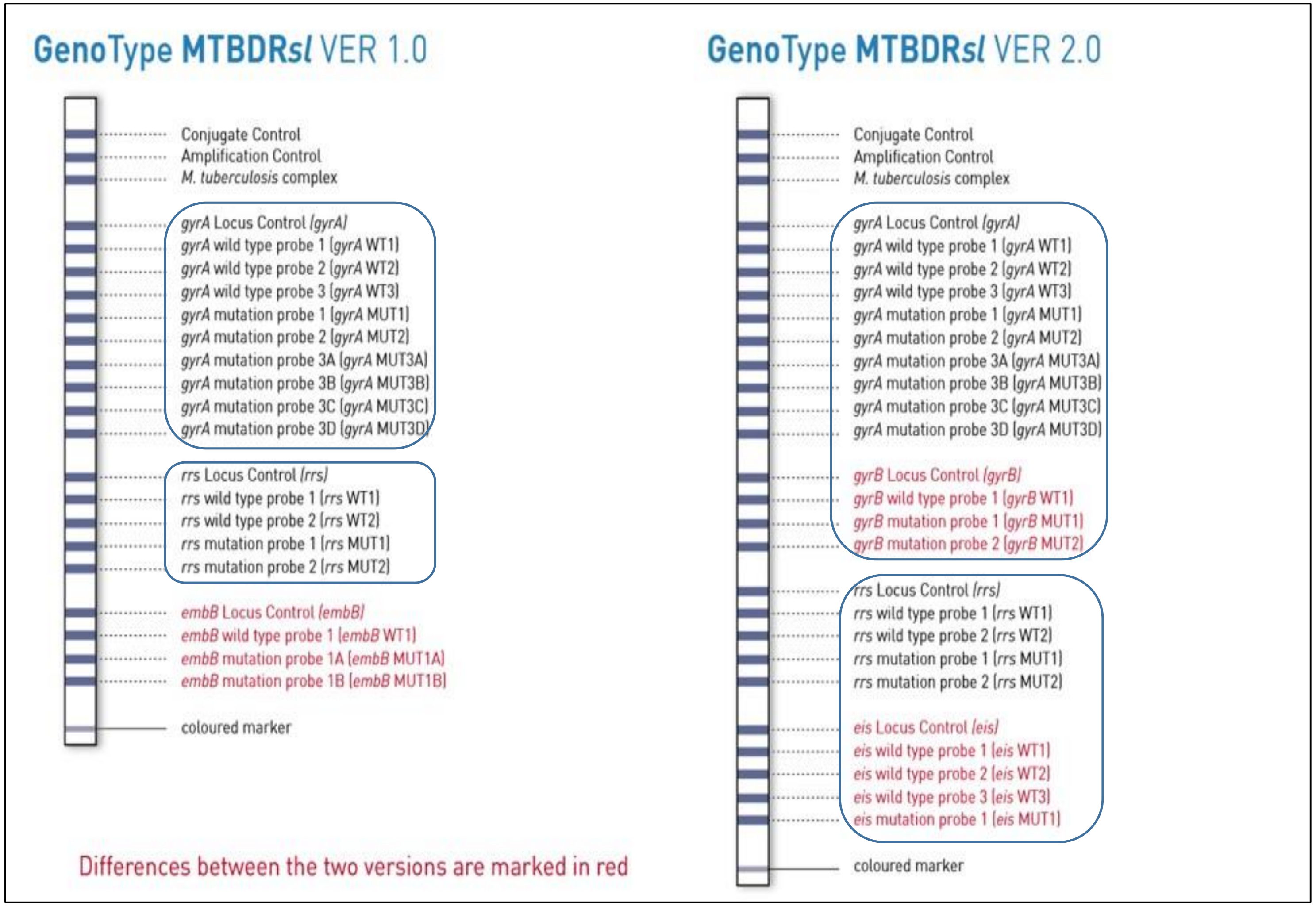
# WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF

- The current WHO recommendations for the use of Xpert MTB/RIF also apply to the use of Ultra as the initial diagnostic test for all adults and children with signs and symptoms of TB and in the testing of selected extrapulmonary specimens (CSF, lymph nodes and tissue specimens).

# Rapid molecular test_line probe assay




MTB DR assay




MTB DR*sl* assay

# MTBDRsl assay in RR/MDR TB detection

| | | Sensitivity | Specificity |
|---|---|---|---|
| FQ | Direct (sputum) | 0.86 (0.75-0.93) | 0.99 (0.97-0.99) |
| | Indirect (culture) | 0.86 (0.79-0.90) | 0.99 (0.97-0.99) |
| SLID | Direct (sputum) | 0.87 (0.38-0.99) | 0.99 (0.94-1.00) |
| | Indirect (culture) | 0.77 (0.63-0.86) | 0.99 (0.97-1.00) |
| XDR | Direct (sputum) | 0.69 (0.39-0.89) | 0.99 (0.95-0.99) |
| | Indirect (culture) | 0.69 (0.39-0.89) | 0.99 (0.95-0.99) |

WHO Policy Guidance 2016

# WHO policy recommendation

**1) For patients with confirmed rifampicin-resistant TB or MDR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones**

- (Conditional recommendation; moderate certainty in the evidence for test accuracy for direct testing of sputum specimens; low certainty in the evidence for test accuracy for indirect testing of *Mycobacterium tuberculosis* cultures).

**2) For patients with confirmed rifampicin-resistant TB or MDR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to the second-line injectable drugs**

- (Conditional recommendation; low certainty in the evidence for test accuracy for direct testing of sputum specimens; very low certainty in the evidence for test accuracy for indirect testing of *Mycobacterium tuberculosis* cultures).

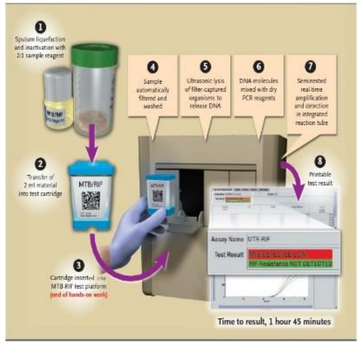
WHO Policy Guidance 2016

# Performance of the GenoType MTBDR*sl* assay for the detection second-line anti-TB drug resistance

| | Sensitivity | Specificity | Accuracy | K value |
|---|---|---|---|---|
| Sputum (n=23) | | | | |
| Any FQs | 85.7 (42.1-99.6) | 81.3 (54.4-96.0) | 82.6 (61.2-95.0) | 0.620 (0.289-0.950) |
| Any SLIDs | 100 (19.4-100) | 95 (75.1-99.9) | 95.7 (78.1-99.9) | 0.832 (0.515-1.149) |
| Culture (n=84) | | | | |
| Any FQs | 88 (68.8-97.5) | 98.3 (90.9-100) | 95.2 (88.3-98.7) | 0.883 (0.772-0.995) |
| Any SLIDs | 86.7 (59.5-98.3) | 100 (92.3-100) | 97.6 (91.7-99.7) | 0.914 (0.798-1.031) |
| Total (n=107) | | | | |
| Any FQs | 87.5 (71.0-96.5) | 94.7 (86.9-98.5) | 92.5 (85.8-96.7) | 0.822 (0.703-0.940) |
| Any SLIDs | 88.9 (65.3-98.6) | 98.9 (93.9-100) | 97.2 (92.0-99.4) | 0.898 (0.784-1.012) |

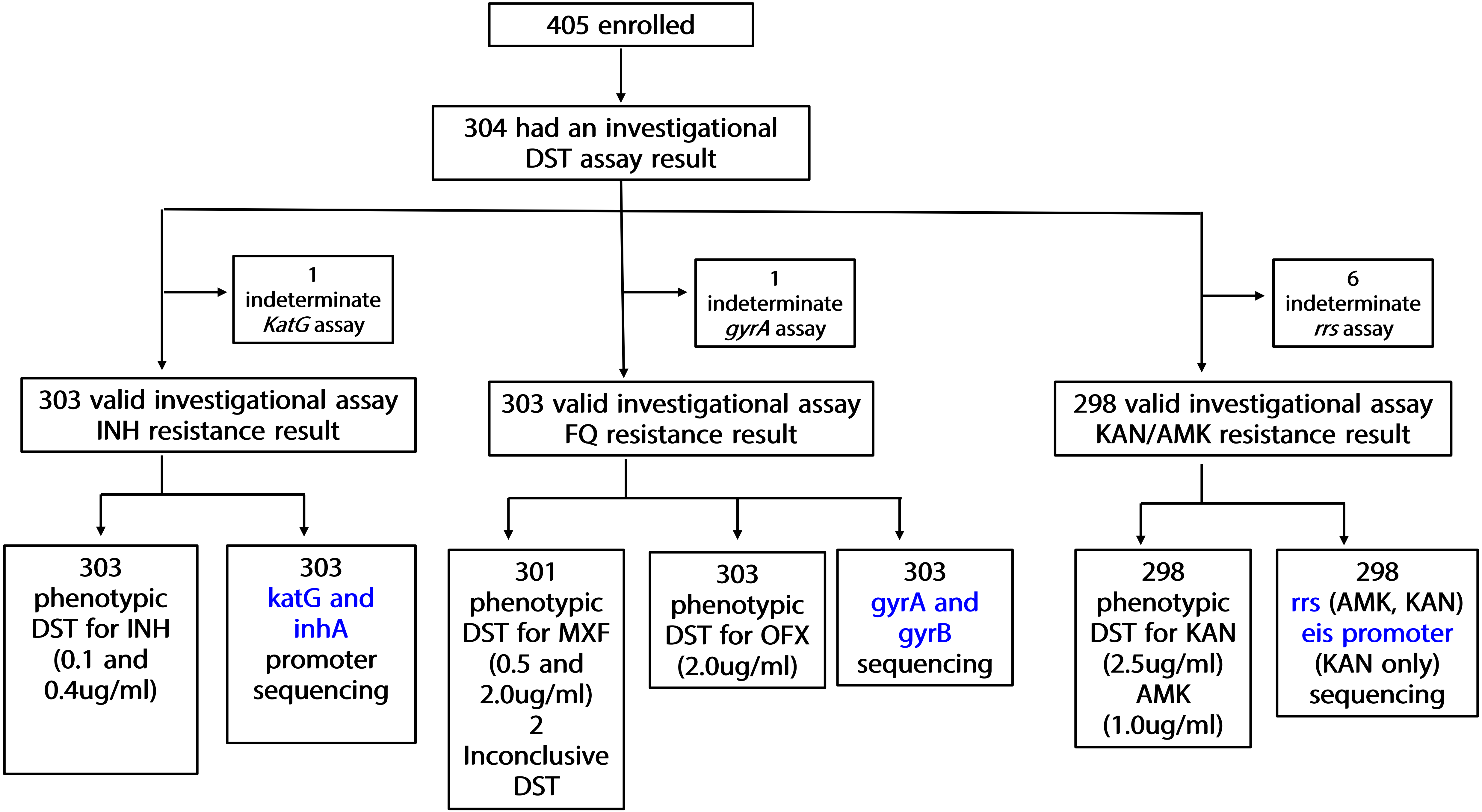
J Infect Chemother 2017;23:820

# Xpert MTB/RIF and INH/FQ/SLID



- Blinded, multicenter, prospective diagnostic accuracy study.
- Investigational assay
  - Automated, cartilage-based molecular assay for the detection of resistanc to FQ, AG, INH
  - INH (KatG, inhA), FQ (gyrA, gyrB), KM/AMK (rrs,eis promoter regions)
- Population
  - China, South Korea
  - Case-detection group
  - Drug-resistance – risk group
- Primary outcome
  - To determine the sensitivity and specificity of the investigational assay for the detection of MTB with resistance to isoniazid, moxifloxacin, ofloxacin, amikacin, kanamycin
  - Reference standard : phenotypic DST (liquid), DNA sequencing of the genes katG, gyrA, gyrB, rrs, eis and inhA promoter

N Eng J Med 2017;377:1043


405 enrolled
304 had an investigational DST assay result
1 indeterminate KatG assay
1 indeterminate gyrA assay
6 indeterminate rrs assay
303 valid investigational assay INH resistance result
303 valid investigational assay FQ resistance result
298 valid investigational assay KAN/AMK resistance result
303 phenotypic DST for INH (0.1 and 0.4ug/ml)
303 katG and inhA promoter sequencing
301 phenotypic DST for MXF (0.5 and 2.0ug/ml) 2 Inconclusive DST
303 phenotypic DST for OFX (2.0ug/ml)
303 gyrA and gyrB sequencing
298 phenotypic DST for KAN (2.5ug/ml) AMK (1.0ug/ml)
298 rrs (AMK, KAN) eis promoter (KAN only) sequencing

# Sensitivity and Specificity of the Investigational Assay, with Phenotypic Drug-Susceptibility Testing

| Drug | Sensitivity | | Specificity | |
|---|---|---|---|---|
| | No. / total No. | % (95% CI) | No. / total No. | % (95% CI) |
| Isoniazid | 150 / 180 | 83.3 (77.1-88.5) | 122/123 | 99.2 (95.6–100.0) |
| Ofloxacin | 84 / 95 | 88.4 (80.2–94.1) | 201/208 | 96.6 (93.2–98.6) |
| Moxifloxacin (0.5ug/ml) | 78 / 89 | 87.6 (79.0–93.7) | 200/212 | 94.3 (90.3–97.0) |
| Moxifloxacin (2.0ug/ml) | 51 / 53 | 96.2 (87.0–99.5) | 210/250 | 84.0 (78.9–88.3) |
| Kanamycin | 35 / 49 | 71.4 (56.7–83.4) | 245/249 | 98.4 (96.0–99.6) |
| Amikacin | 29 / 41 | 70.7 (54.5–83.9) | 256/257 | 99.6 (97.9–100.0) |

N Eng J Med 2017:377:1043

DR-TB STAT

**Phase III Clinical Trial Results at the 48th Union World Conference on Lung Health: Implications for the Field[1]**

## Phase III drug- resistant TB trial

- Stage 1 of the STREAM trial
- Otsuka 213 delamanid trial

# Phase III trial in MDR TB

| STREAM stage 1 | Otsuka 213 Delamanid trial |
|---|---|
| Randomized, non-inferiority trial | Randomized, placebo-controlled, double-blind, placebo-controlled superiority trial |
| 9mo shorter regimen vs conventional regimen | OBR+ delamanid vs OBR |
| Favorable outcome at 132wks after randomization | Time to sputum culture conversion over 6 months |
| Sites | Sites |
| Ethiopia (2), South Africa (3), Vietnam, Mongolia | Estonia, Latvia, Lithuania, Moldova, Peru, the Philippines, and South Africa |
| 424 patients enrolled | 511patients enrolled |
| 282 in 9mo shorter regimen vs 142 in control | 341 in delamanid vs 170 in control |
| Enrollment closed : June 2015 | 327 eligible for the efficacy analysis |
| Results expected : 2018 | |

| STREAM 1 | 9 months<br>Study arm (N ) | Conventional<br>Control (N ) |
|---|---|---|
| Favorable | 78.1% (164) | 80.6% (87) |
| Unfavorable | 21.9% (46) | 19.4% (21) |
| Deaths in people with HIV | 18% | 7% |

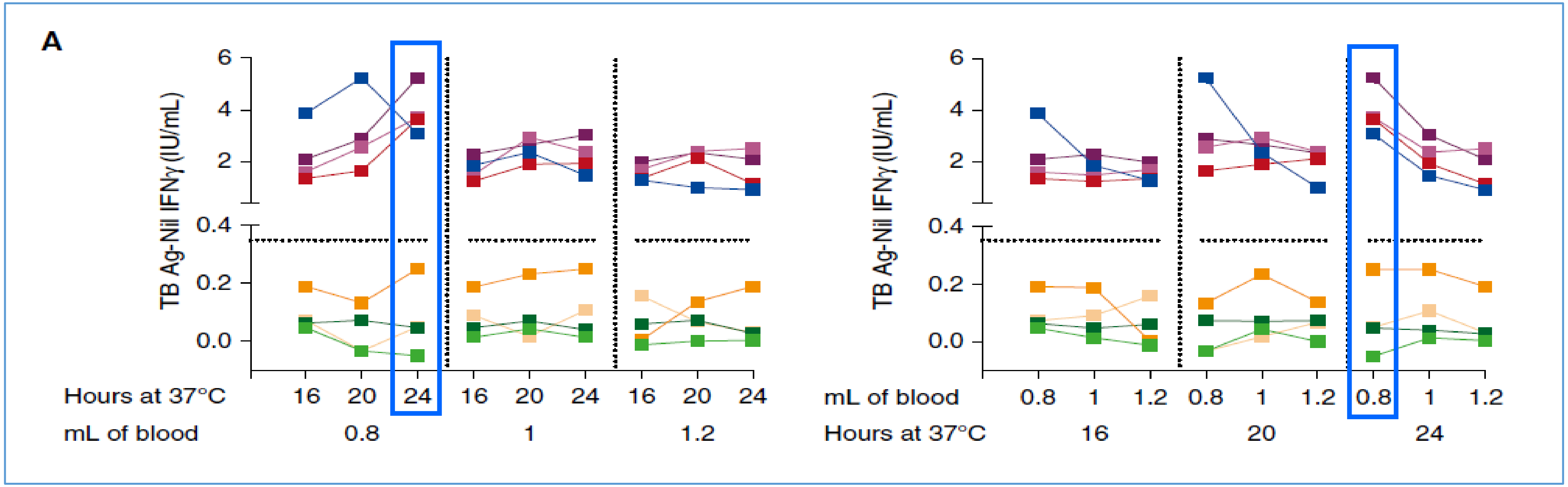
| C213* | Delamanid Study arm<br>(n=341) | Control (N=170) |
|---|---|---|
| Treatment success, 30mo | 77.1% | 77.6% |
| **All cause mortality** | **5.3%** | **4.7%** |
| **Culture conversion, 6mo** | **87.6%** | **86.1%** |
| The delamanid arm achieved culture conversion on average 6 to 13 days earlier (p=0.056) | | |
| | FQ resistance 7.1%, XDR 4.4% | FQ resistance 4.0%, XDR 2.0% |

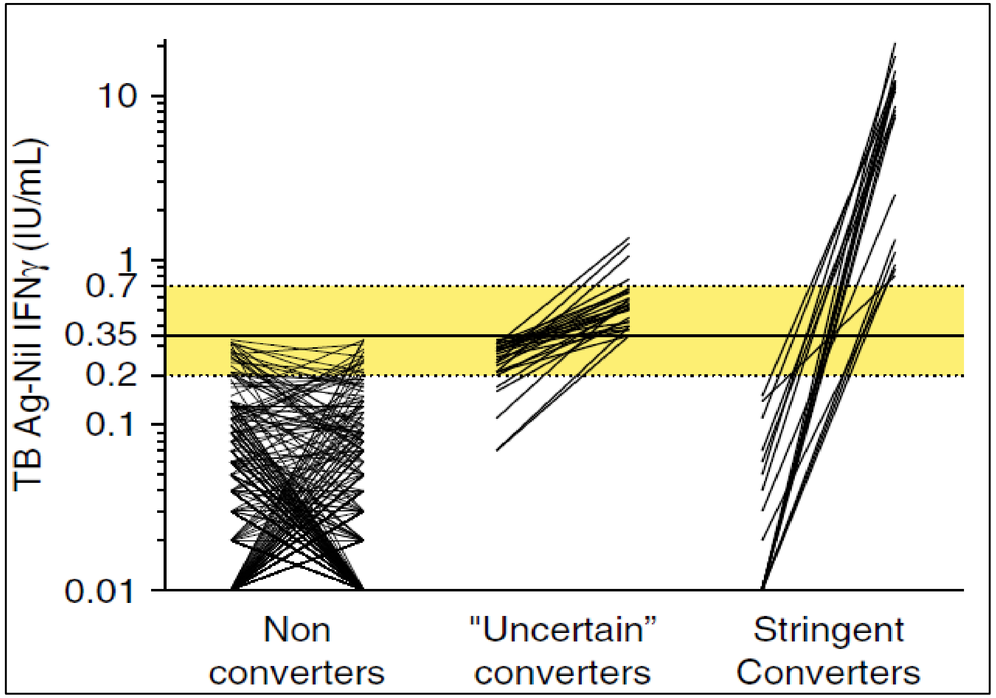
# ORIGINAL ARTICLE

## Optimization and Interpretation of Serial QuantiFERON Testing to Measure Acquisition of *Mycobacterium tuberculosis* Infection

Am J Respir Crit Care Med 2017;196:638

- Objective
  - To improve the consistency of serial QuantiFERON-TB testing algorithms and provide a data-driven definition of conversion
- Population
  - Healthy adolescents cohort recruited at the South African Tuberculosis Vaccine Initiative (SATVI) in South Africa

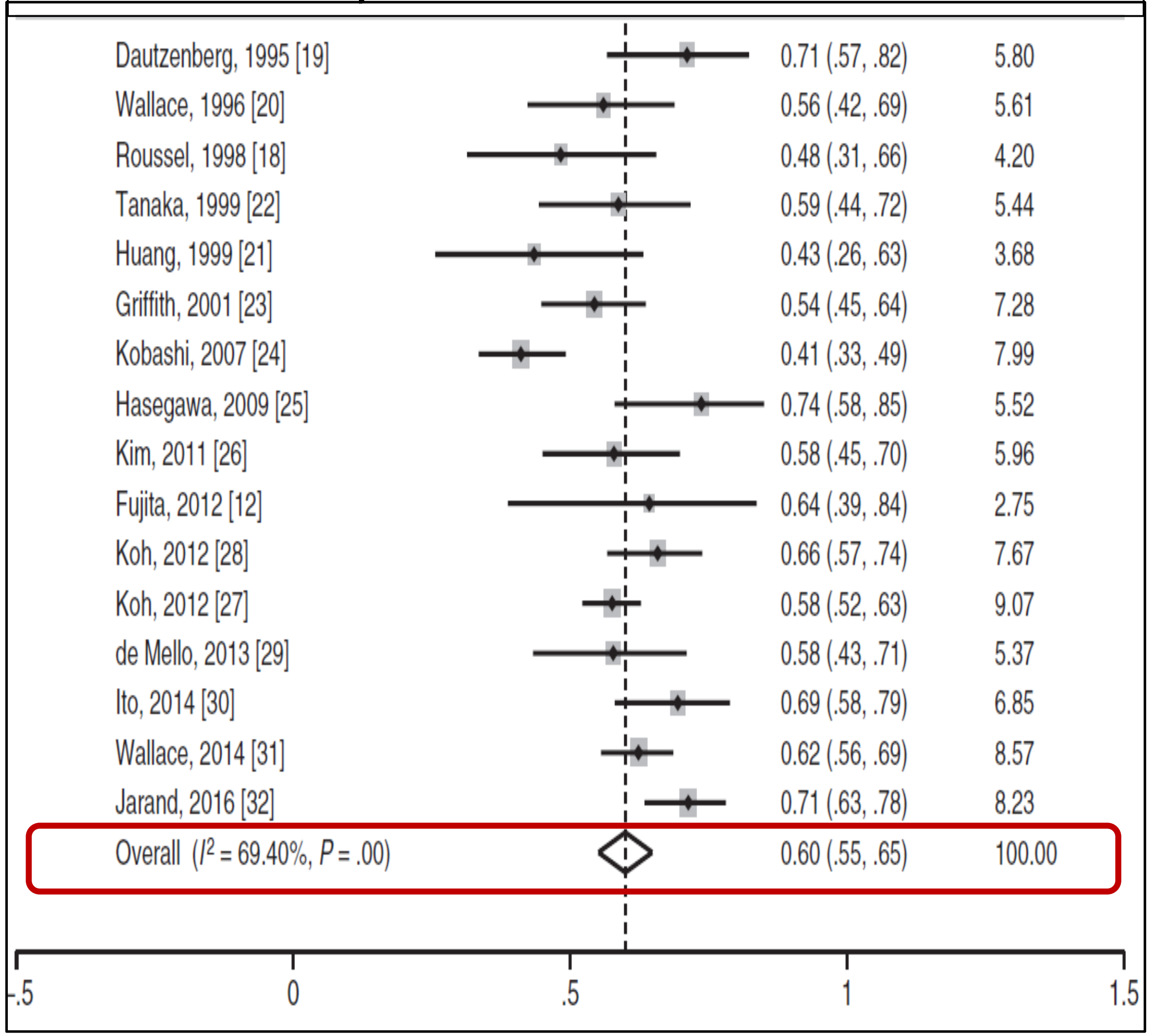





| QFT class | TB cases | n | Observation years | Incidence (cases/100PY) | IRR | 95% CI |
|---|---|---|---|---|---|---|
| Stringent non-converters | 2 | 648 | 1,289.79 | 0.16 (0.02-0.56) | reference | reference |
| Stringent persistent positives | 19 | 989 | 1,953.07 | 0.97 (0.59-1.52) | 6.27 | 1.51-55.55 |
| Stringent converters | 14 | 485 | 874.3 | 1.60 (0.88-2.69) | 10.33 | 2.37-93.62 |
| “Uncertain” converters | 3 | 310 | 453.3 | 0.66 (0.14-1.95) | 4.27 | 0.49-51.10 |

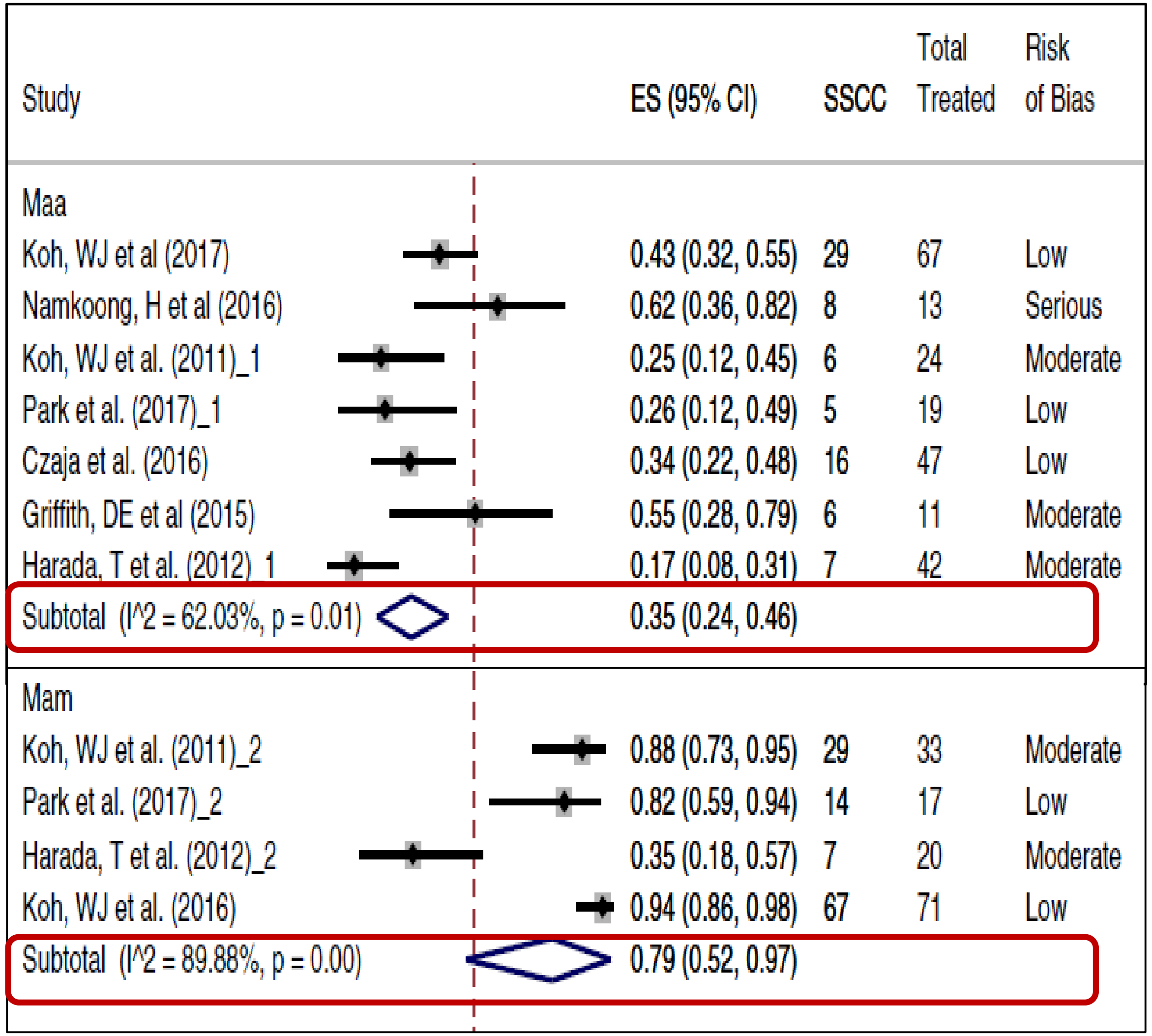
Am J Respir Crit Care Med 2017;196:638

## Treatment Outcomes of Mycobacterium avium Complex
## Lung Disease: A Systematic Review and Meta-analysis
## 16 studies, 1462 patients




Clin Infec Dis 2017;65:1077

## Meta-analyses of the Effect of Chemotherapy on Pulmonary Mycobacterium abscessus
## 19 studies, 508 patients Maa. 204 patients Mam




Antimicrob Agents Chemother 2017;61:e01206

ORIGINAL ARTICLE

# Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease

Kenneth N. Olivier[1], David E. Griffith[2], Gina Eagle[3], John P. McGinnis II[3], Liza Micioni[3], Keith Liu[3], Charles L. Daley[4], Kevin L. Winthrop[5], Stephen Ruoss[6], Doreen J. Addrizzo-Harris[7], Patrick A. Flume[8], Daniel Dorgan[9], Matthias Salathe[10], Barbara A. Brown-Elliott[2], Renu Gupta[3,11], and Richard J. Wallace, Jr.[2]

[1]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; [2]The University of Texas Health Science Center at Tyler, Tyler, Texas; [3]Insmed Incorporated, Bridgewater, New Jersey; [4]National Jewish Health, Denver, Colorado; [5]Oregon Health & Science University, Portland, Oregon; [6]Stanford University School of Medicine, Stanford, California; [7]New York University School of Medicine, New York, New York; [8]Medical University of South Carolina, Charleston, South Carolina; [9]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [10]Leonard M. Miller School of Medicine, University of Miami, Miami, Florida; and [11]Global Biopharma, Moorestown, New Jersey

ORCID ID: 0000-0001-8200-255X (K.N.O.).

Am J Respir Crit Care Med 2017;195:814

- Randomized, double-blind phase II study, North America
- Blind phase
  - Study arm : Liposomal amikacin inhalation 590mg qd + multidrug regimen for 84days (12w)
  - Control arm : placebo inhalation + multidrug regimen for 84days (12w)
- Open-label phase
  - liposomal amikacin inhalation for additional 84 days for both group
- Primary outcome
  - change from baseline to Day 84 on a semi-quantitative mycobacterial growth scale
- Subjects
  - NTM lung disease :MAC or M.abscessus
  - Received ongoing ATS/IDSA guidelines–based multidrug treatment for at least 6mo
  - Persistently positive cultures

Am J Respir Crit Care Med 2017;195:814

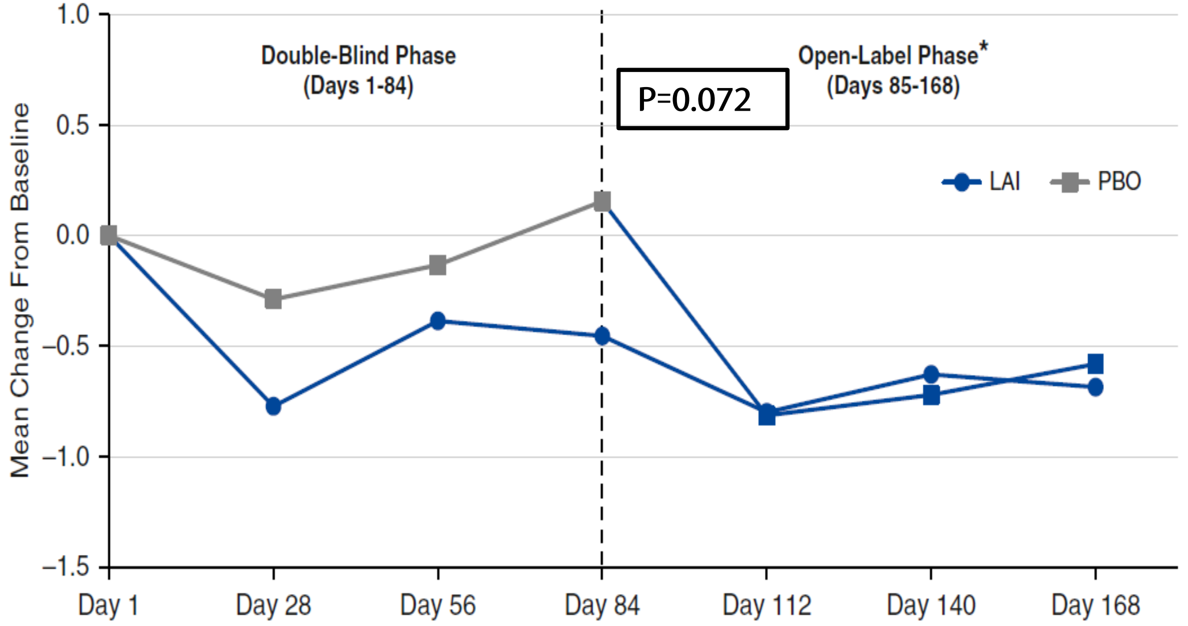
## Baseline Demographics and Characteristics

| | LAI (n = 44) | Placebo (n = 45) |
|---|---|---|
| Age, mean (SD) | 58.0 (16.61) | 59.1 (15.20) |
| Female sex | 38 (86.4) | 40 (88.9) |
| BMI,mean (SD) | 21.76 (2.705) | 22.10 (3.941) |
| Mycobacterium avium complex | 29 (65.9) | 28 (62.2) |
| Mycobacterium abscessus | 15 (34.1) | 17 (37.8) |
| CF | 8 (18.2) | 9 (20.0) |
| Mycobacterial load, n (%) | | |
| Culture negative | 3 (6.8) | 3 (6.7) |
| Growth in liquid medium | 3 (6.8) | 3 (6.7) |
| 1–49 colonies | 17 (38.6) | 10 (22.2) |
| 1+ | 2(4.5) | 4 (8.9) |
| 2+ | 2 (4.5) | 2 (4.4) |
| 3+ | 3 (6.8) | 4 (8.9) |
| 4+ | 14 (31.8) | 19 (42.2) |
| Cavitary disease | 33 (75.0) | 35 77.8) |
| Macrolide resistant | 8 (18.0) | 15 (33.3) |
| Amikacin mutation positive | 2 (4.5) | 6 (13.3) |

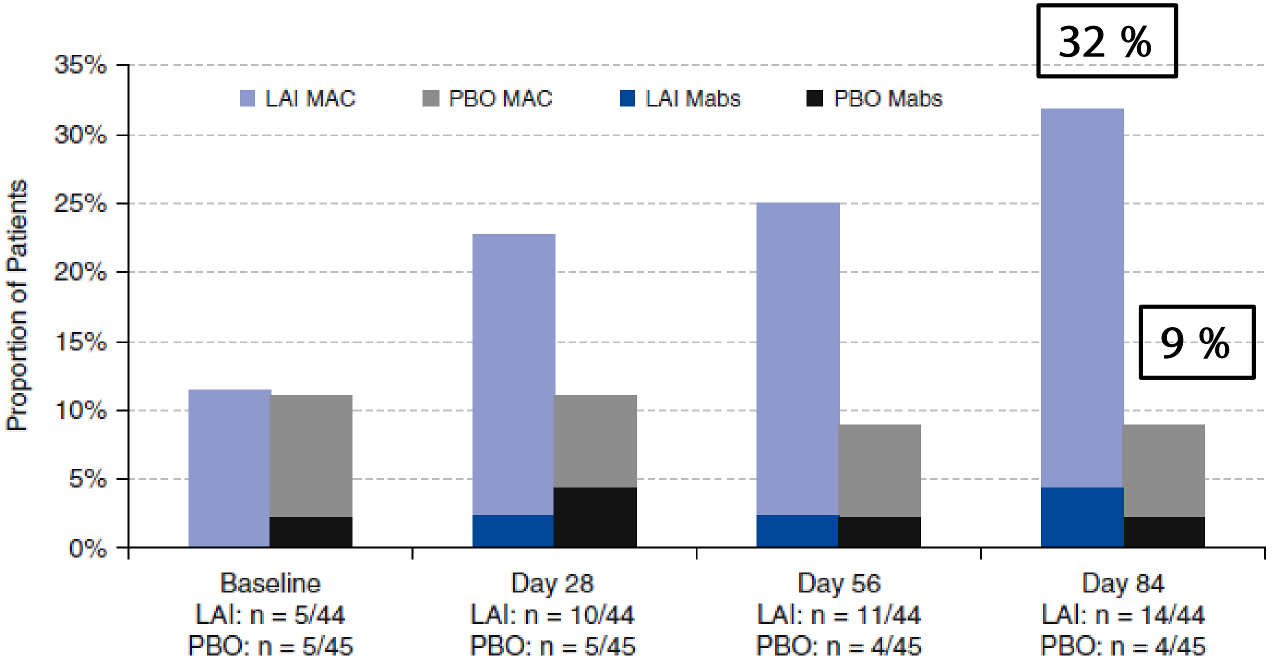
## Treatment-Emergent Adverse Events during double-blind phase

| | LAI (n = 44) | Placebo (n = 45) |
|---|---|---|
| Patients with TEAEs | 41 (93.2) | 40 (88.9) |
| Number of TAEs | 240 | 140 |
| Dysphonia | 43.2% | 8.9% |
| Bronchiectasis exacerbation | 38.6% | 20.0% |
| Cough | 31.8% | 13.3% |
| Oropharyngeal pain | 20.5% | 2.2% |
| wheezing | 9.1% | 2.2% |
| Serious TAE | 8 (18.2) | 4 (8.9) |
| Not serious TAE | 33 (75.0) | 36 (80.0) |
| Relationship to study drug | | |
| Related | 32 (72.7) | 17 (37.8) |
| Not related | 9 (20.5) | 23 (51.1) |
| Patients with audio-vestibular TEAEs | 5 (11.4) | 5 (11.1) |
| Patients with renal TEAEs | 1 (2.3) | 0 |
| Patients with TEAEs leading to study drug discontinuation, | 7 (15.9) | 0 |

Mean change from baseline on the semi-quantitative scale (SQS) for mycobacterial culture growth through the end of the open-label phase




Proportion of patients with negative sputum cultures for nontuberculous mycobacteria in the double-blind phase



# Safety and Effectiveness of Clofazimine for Primary and Refractory Nontuberculous Mycobacterial Infection

*Stacey L. Martiniano, MD; Brandie D. Wagner, PhD; Adrah Levin, MPH; Jerry A. Nick, MD; Scott D. Sagel, MD, PhD; and Charles L. Daley, MD*

Chest 2017;152:800

# Clofazimine-Containing Regimen for the Treatment of *Mycobacterium abscessus* Lung Disease

Bumhee Yang,[a] Byung Woo Jhun,[a,b] Seong Mi Moon,[a] Hyun Lee,[a] Hye Yun Park,[a] Kyeongman Jeon,[a] Dae Hun Kim,[a] Su-Young Kim,[a] Sung Jae Shin,[c] Charles L. Daley,[d] Won-Jung Koh[a]

Antimicrob Agents Chemother 2017;61:e02052-16

# Observational cohort in CF and non-CF patients with pulmonary and extrapulmonary NTM infection , 2006-2014, US, multicenter

| | All patients (n=112) | Culture conversion (n=33) |
|---|---|---|
| Age, median (range), y | 62 (11-83) | 67 (13-82) |
| Female sex | 83 (74%) | 27 (82%) |
| CF | 24 ( | 11 (33%) |
| Pulmonary | 99 (88%) | |
| NTM species | | |
| MAC | 41 (37%) | 11 (33%) |
| Mycobacterium abscessus complex | 54 (48%) | 18 (55%) |
| 2 NTM species | 15 (17%) | 4 (12%) |
| Unidentified | 1 (1%) | |
| First line treatment | 25 (22%) | 4 (12%) |
| Failed previous treatment | 87 (78%) | 29 (88%) |

Culture Conversion in pulmonary disease Tolerating Clofazimine for at Least 6 Months
N=74 , culture conversion = 33 (45%)

Discontinuation of clofazimine d/t ADR, 16 (14%)

| ADR | All patients (n=112) |
|---|---|
| Skin discoloration | 68 (61) |
| Dry skin | 33 (29) |
| Sun hypersensitivity | 18 (16) |
| Nausea | 37 (33) |
| Diarrhea | 28 (25) |
| Abdominal pain | 25 (22) |
| Anorexia | 21 (19) |
| Vomiting | 18 (16) |
| Fatigue | 34 (30) |
| Dizziness | 22 (20) |
| Neuralgia | 19 (17) |

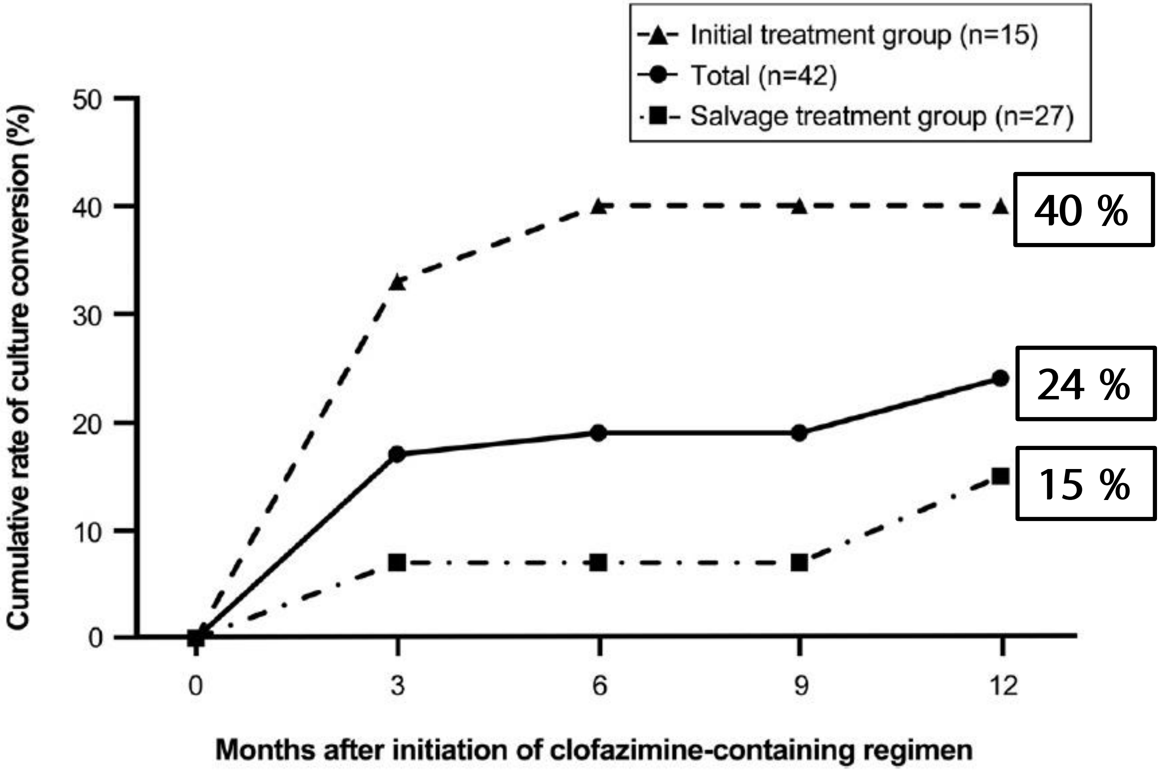
Chest 2017;152:800

# Clofazimine-containing regimen for the treatment of M.abscessus lung disease

## Retrospective observational cohort study, 2013-2015, N=42, Korea, single center

| Clinical characteristic | Value (*n* = 42) |
|---|---|
| Median age (yr) (IQR) | 60 (53–69) |
| No. (%) of female patients | 33 (79) |
| Median body mass index ($kg/m^2$) (IQR) | 20 (18–22) |
| No. (%) of nonsmokers | 33 (79) |
| No. (%) of patients with radiographic type | |
| Nodular bronchiectatic form | 36 (86) |
| With cavity | 19 |
| Without cavity | 17 |
| Fibrocavitary form | 6 (14) |
| No. (%) of patients with positive sputum AFB smear | 29 (69) |
| No. (%) of patients in initial treatment group | 15 (36) |
| No. (%) of patients in salvage treatment group | 27 (64) |

| Parameter | Value ($n$ = 42) |
|---|---|
| No. (%) of patients with symptomatic improvement | 34 (81) |
| No. (%) of patients with radiologic improvement | 13 (31) |
| Microbiologic improvement | |
| No. (%) of patients with sputum culture conversion | 10 (24)[a] |
| Median time to negative culture conversion (wk) (IQR) | 5.0 (4.6–28.9) |




Discontinuation of clofazimine 18 (43%), after 24.4 w
Dose reduction of clofazimine 5 ( 12%),after 26 w

| Adverse effect | No. (%) of patients<br>Total ($n$ = 23) |
|---|---|
| Gastrointestinal disturbance | 12 (52) |
| Skin color change | 9 (39) |
| Dizziness | 1 (4) |
| Others | 1 (4) |

Antimicrob Agents Chemother 2017;61:e02052-16

# Treatment outcome definitions in nontuberculous mycobacterial pulmonary disease: an NTM-NET consensus statement

Jakko van Ingen[1], Timothy Aksamit[2], Claire Andrejak[3,4], Erik C. Böttger[5], Emmanuelle Cambau[6], Charles L. Daley[7], David E. Griffith[8], Lorenzo Guglielmetti[9,10], Steven M. Holland[11], Gwen A. Huitt[7], Won-Jung Koh[12], Christoph Lange[13,14,15,16], Philip Leitman[17], Theodore K. Marras[18], Kozo Morimoto[19], Kenneth N. Olivier[20], Miguel Santin[21], Jason E. Stout[22], Rachel Thomson[23,24], Enrico Tortoli[25], Richard J. Wallace Jr[26], Kevin L. Winthrop[27] and Dirk Wagner[28] for NTM-NET

Eur Respir J 2018;51:1800170

| Outcome | Definition |
|---|---|
| Culture conversion | at least three consecutive negative mycobacterial cultures from respiratory samples, collected at least 4 weeks apart, during antimycobacterial treatment |
| Microbiological cure | multiple consecutive negative but no positive cultures with the causative species from respiratory samples after culture conversion and until the end of antimycobacterial treatment |
| Clinical cure | Patient-reported and/or objective improvement of symptoms during antimycobacterial treatment, sustained until at least the end of treatment, but no cultures available to prove culture conversion or microbiological cure |
| Treatment failure | The re-emergence of multiple positive cultures or persistence of positive cultures with the causative species from respiratory samples after $\geqslant$ 12 months of antimycobacterial treatment, while the patient is still on treatment |
| Recurrence | The re-emergence of at least two positive cultures with the causative species from respiratory samples after cessation of antimycobacterial treatment |
| Relapse | The emergence of at least two positive cultures with the same strain of the causative species after the end of treatment |
| Reinfection | The emergence of at least two positive cultures with a different strain of the causative species or a strain of a different species after the initiation of the treatment episode |

# 감사합니다.