# RIFASHORT

## AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE 1200mg AND 1800mg RIFAMPICIN DAILY IN THE REDUCTION OF TREATMENT DURATION FOR PULMONARY TUBERCULOSIS FROM 6 MONTHS TO 4 MONTHS

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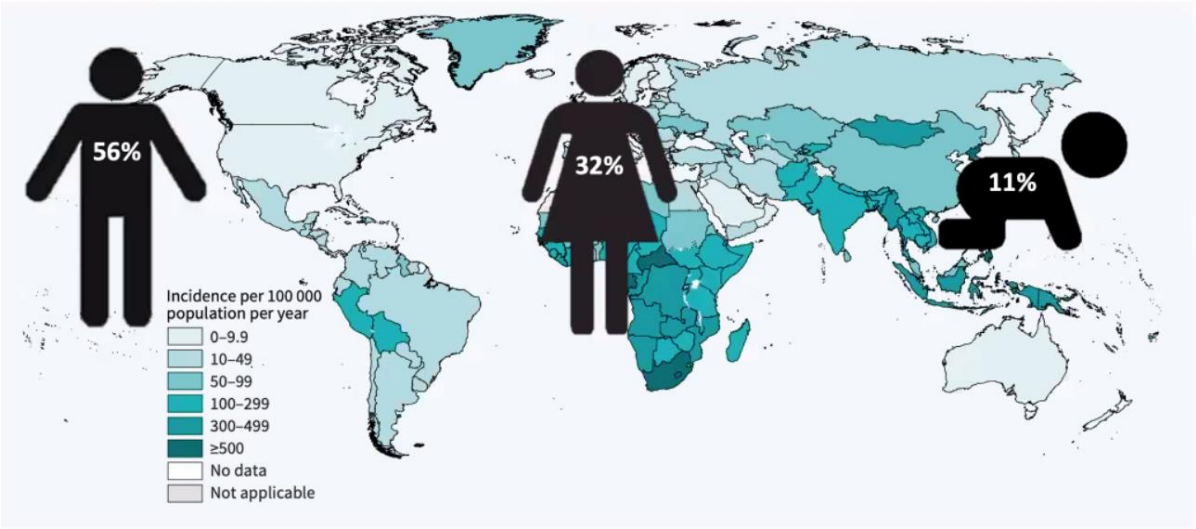
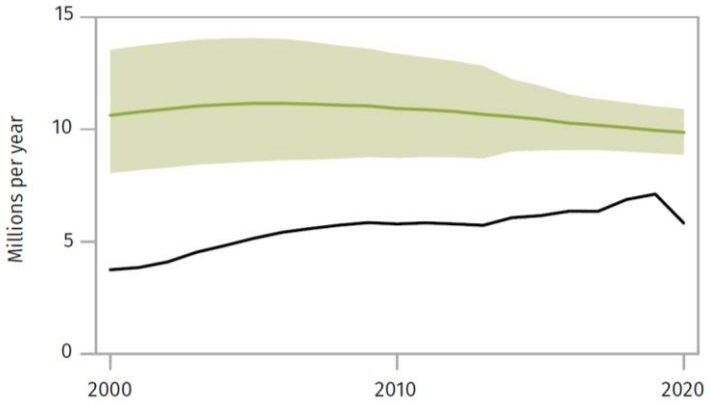
# Tuberculosis

- 10.6 million TB incident cases (2021)
  - **6.7% HIV infected: 710 000 cases**
- 1.4 million deaths in HIV-neg people
  - **+187 000 deaths among PLHIV**
- 3.6% MDR-TB (resistant to rifampicin and isoniazid)

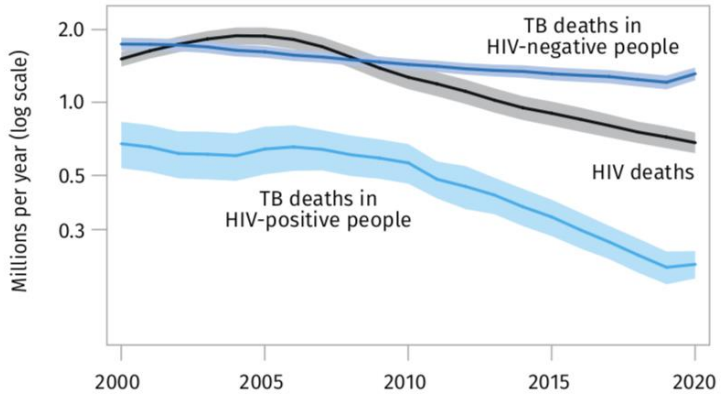


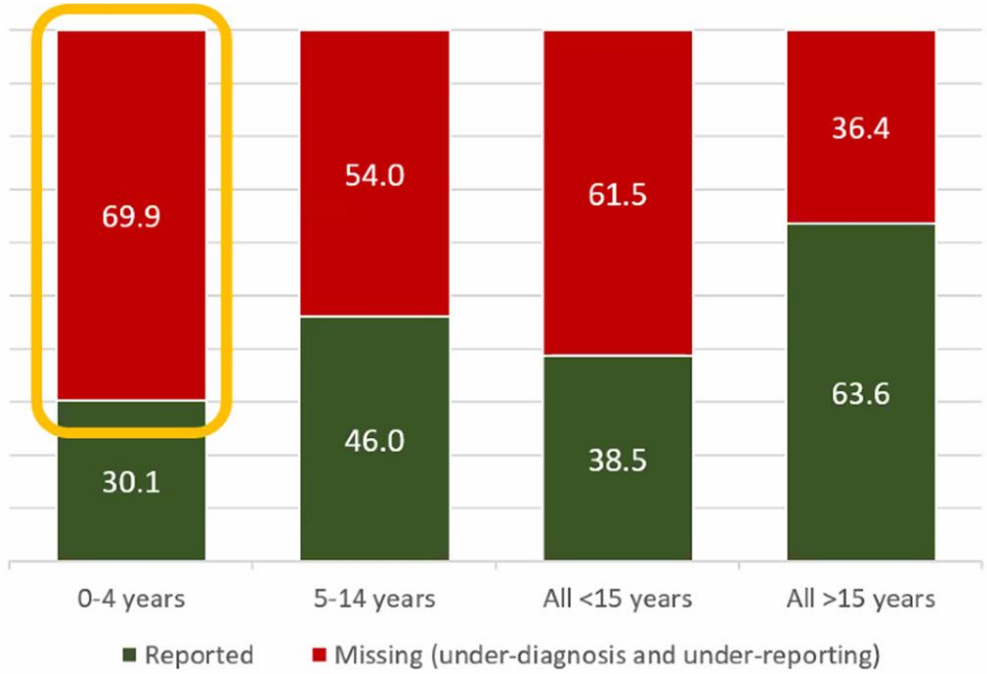

*WHO Global TB Report 2022*

**TB case notification**



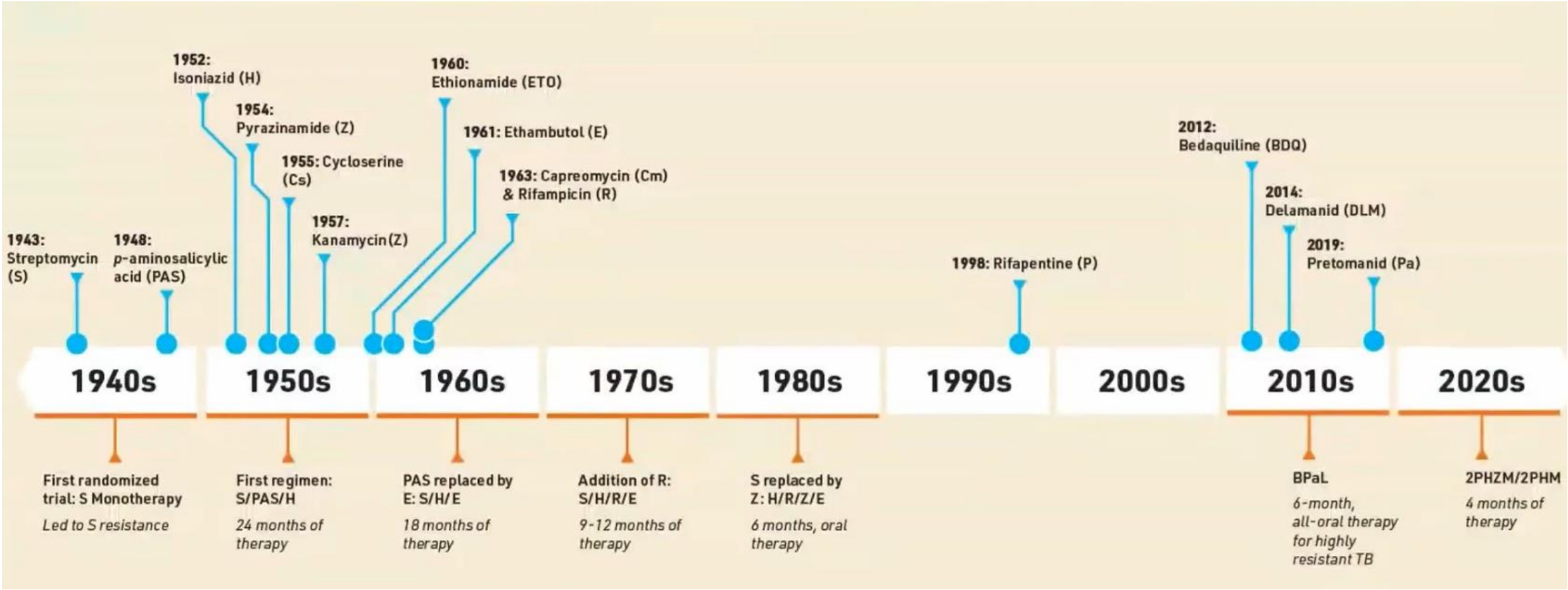

**Deaths**




WHO TB report 2022

# Antituberculosis treatment development



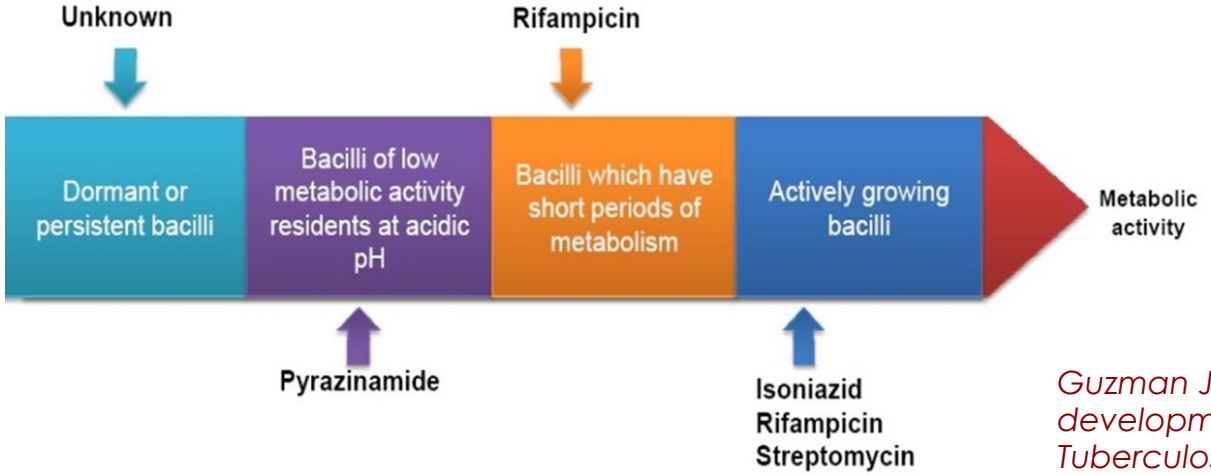

Source: TB alliance

# Standard of cares for drug-susceptible TB

- 2HRZ(E) 4RH
  - Isoniazid (H): 5mg/Kg
  - Rifampicin (R): 10mg/Kg
  - Pyrazinamide (Z): 35mg/Kg
  - Ethambutol (E): 20mg/Kg
- Treatment success worldwide 86% (WHO TB report 2022)
- Well tolerated globally : no specific monitoring
- Fixe dose combination: RHZE, RHE, RH
- Generic: 30€ for 6 months treatment
- Extension of treatment in some extra-pulmonary TB forms: meningitis, TB spondylodiscitis

# Shortening treatment duration drug susceptible TB

- Rationale for shortening treatment duration
  - Improve treatment adherence and reduce the risk of emergence of drug resistance
  - Reduce the duration of exposure to potential toxic drugs
  - Patient's benefit
- Limited efficacy of anti-TB drug on the intra-cellular (macrophages) stage of *Mycobacterium tuberculosis (MTB)*: latency
  - Drugs with potential good sterilising activity: R, Z, fluoroquinolones, nitroimidazole, diarylquinolines best sterilizing activity
  - Short treatment requires drugs with good sterilising activity




*Guzman JD, Montes-Rincon X, Ribon W. Research and development of New Drugs Against Tuberculosis. Tuberculosis. SBN 978-953-51-1049-1 2013*

# 1st option: substitution of E or H by fluoroquinolones to reduce duration to 4 months

- Four non-inferiority RCT
  - REMoxTB: 2HRZM 2MHR et 2MRZE 2RH
  - RIFAQUIN: 2MRZE $2(MP)_2$
  - OFLOTUB: 2HRZG 2HR
  - Velayutham: 3MHRZE, 2MHRZE 2MHR, 2MHRZE $2(MHR)_3$ et 2MHRZE $2(MHRE)_3$
- Non-inferiority not shown

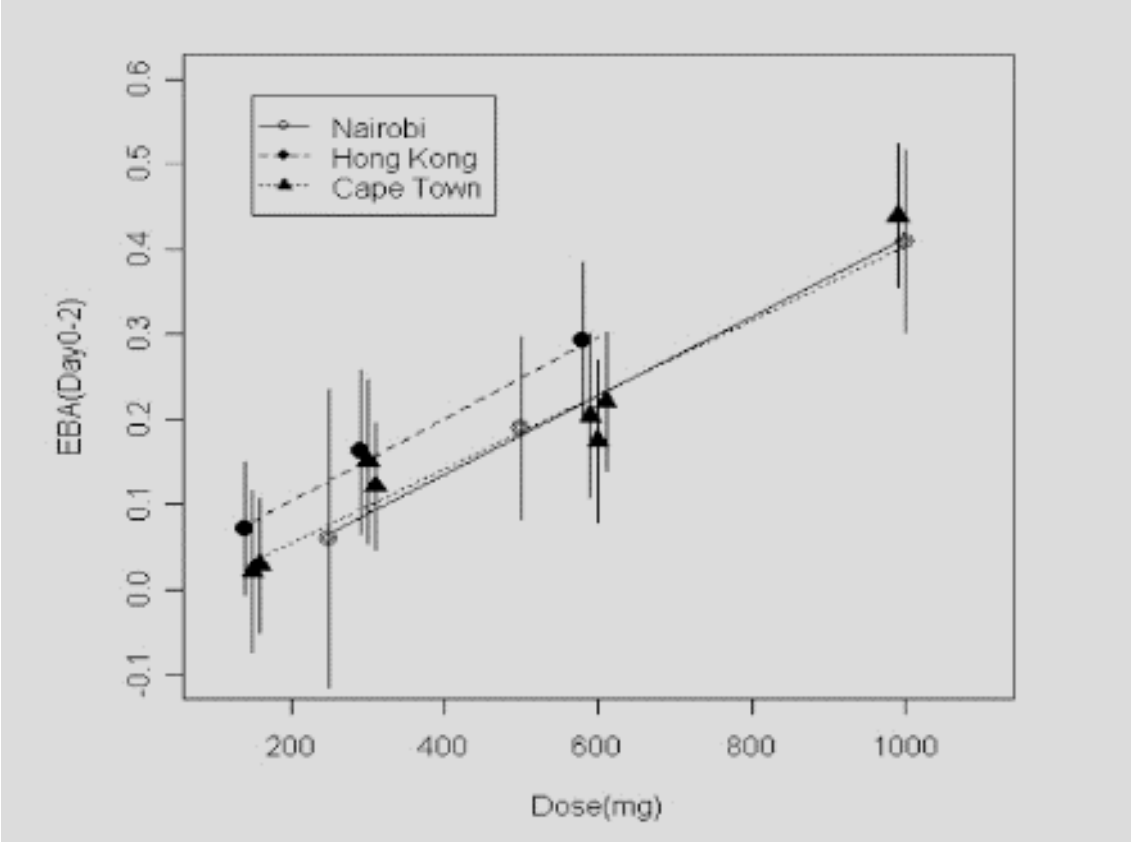
| | Pop | *Difference Experimental. Gr – Control. Gr (95%CI) | | | |
|---|---|---|---|---|---|
| **REMoxTB** | | 2HRZM 2MRH | | 2ERZM 2MRE | |
| | mITT | 6.1 (1.7 to **10.5**) | | 11.4 (6.7 to **16.1**) | |
| | PP | 7.7 (2.7 to **13.0**) | | 9.0 (3.8 to **14.2**) | |
| **RIFAQUIN** | | 2MRZE $2(MP)_2$ | | | |
| | mITT | 13.1 (5.6 to **19.4**) | | | |
| | PP | 13.6 (7.0 to **20.2**) | | | |
| **OFLOTUB** | | 2HRZG 2HR | | | |
| | mITT | 3.5 (-0.7 to **7.7**) | | | |
| | PP | 5.5 (1.6 to **9.4**) | | | |
| **Velayutham** | | 3MHRZE | 2MHRZE 2MHR | 2MHRZE $2(MHR)_3$ | 2MHRZE $2(MHRE)_3$ |
| | mITT | 14.9 (6.0 to **23.8**) | 0.4 (-3.6 to **4.5**) | 4.3 (-0.5 to **8.9**) | 1.9 (-2.5 to **6.4**) |
| | PP | 14.6 (5.6 to **23.7**) | 0.4 (-3.7 to **4.5**) | 3.9 (-0.8 to **8.6**) | 1.5 (-2.5 to **6.4**) |

*M: moxifloxacine; P: rifapentine; G: gatifloxacine*

Gillespie GH et al. N Engl J Med 2014, Jindani A et al. N Engl J Med 2014; Merle C et al. N Engl J Med 2014; Velayutham B et al. TMIH 2020; Grace AG et al. Cochrane Database of Systematic Reviews 2019

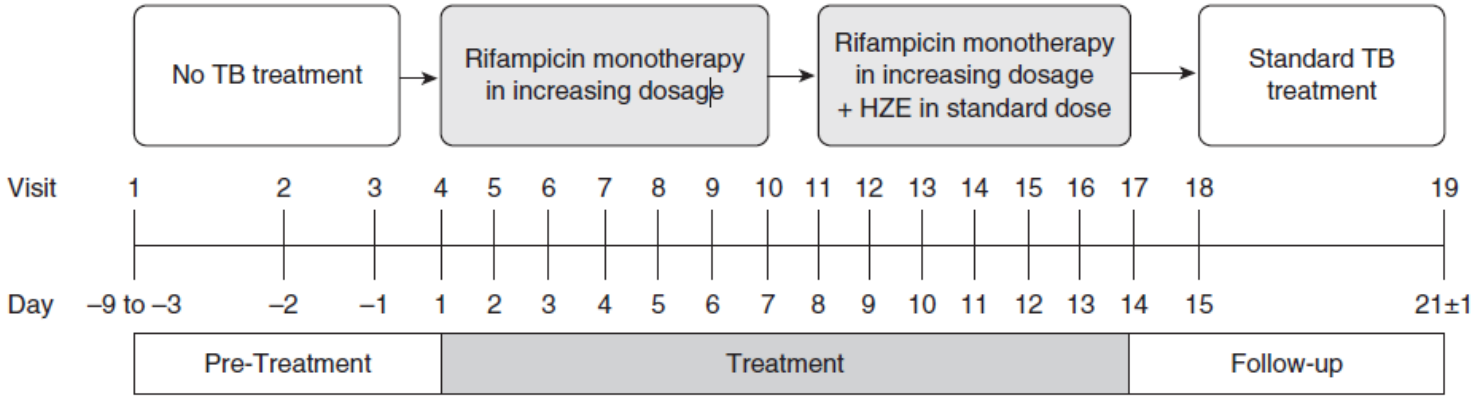
# 2nd option: increasing the sterilizing effect of R with the dose increase

- R inhibits bacterial DNA-dependent RNA polymerase thus inhibiting transcription to RNA
- R is highly bactericidal
- Linear increase of early bactericidal effect with higher R doses

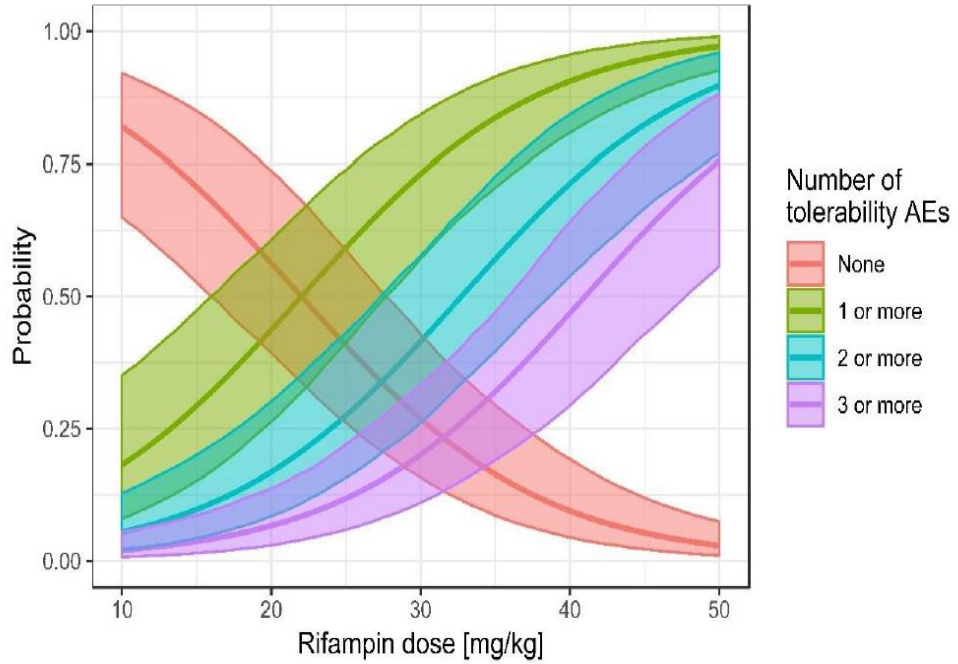


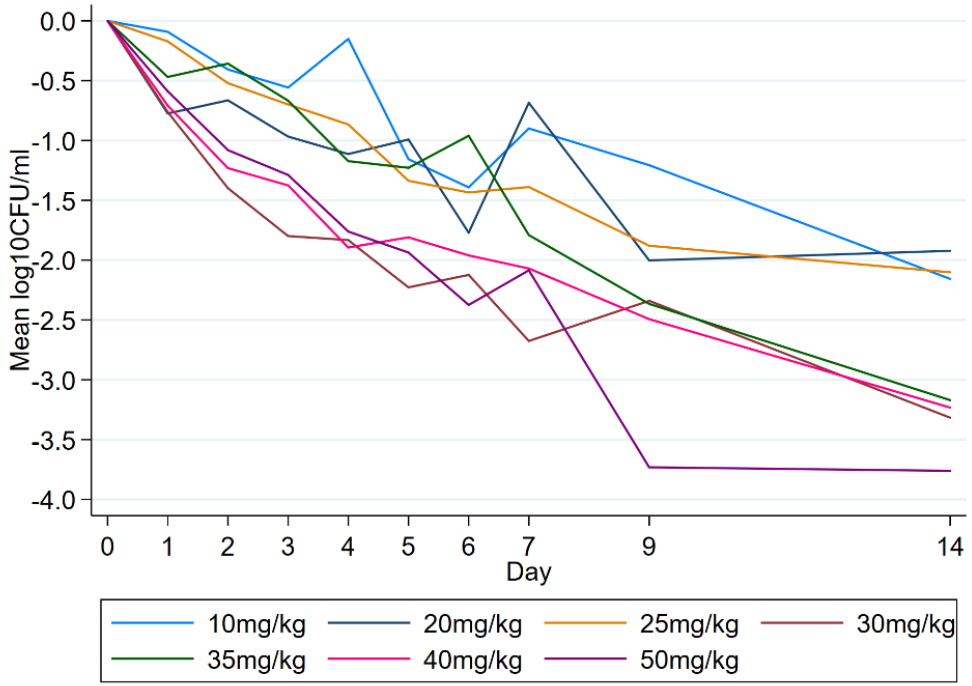

**Early bactericidal activity (EBA) related to R dose** *Diacon A.H, et al.2007*

# What is the maximum tolerable dose of rifampicin: **dose escalating phase 2a study**




**Maximum tolerable dose : 40 mg/Kg**




Boeree MJ, et al. Am J Respi Crit Care Med 2015; te Brake L et al. ERJ 2021

# Safety risk with the dose increase of R?

- Rifampicin used at high dose for treatment for other bacterial infection
- Rifatox study showed the safety of 15 and 20mg/Kg of rifampicin
- PanaCEA trial showed no increase in serious adverse events at R doses of R up to 35 mg/kg administered to HIV negative TB patients for 12 weeks(3 months)

Borere MJ et al. Lancet Infect Dis 2016
Jindani A et al. 2016; 20: 832-8

# RIFASHORT phase 3 trial

## Objectives

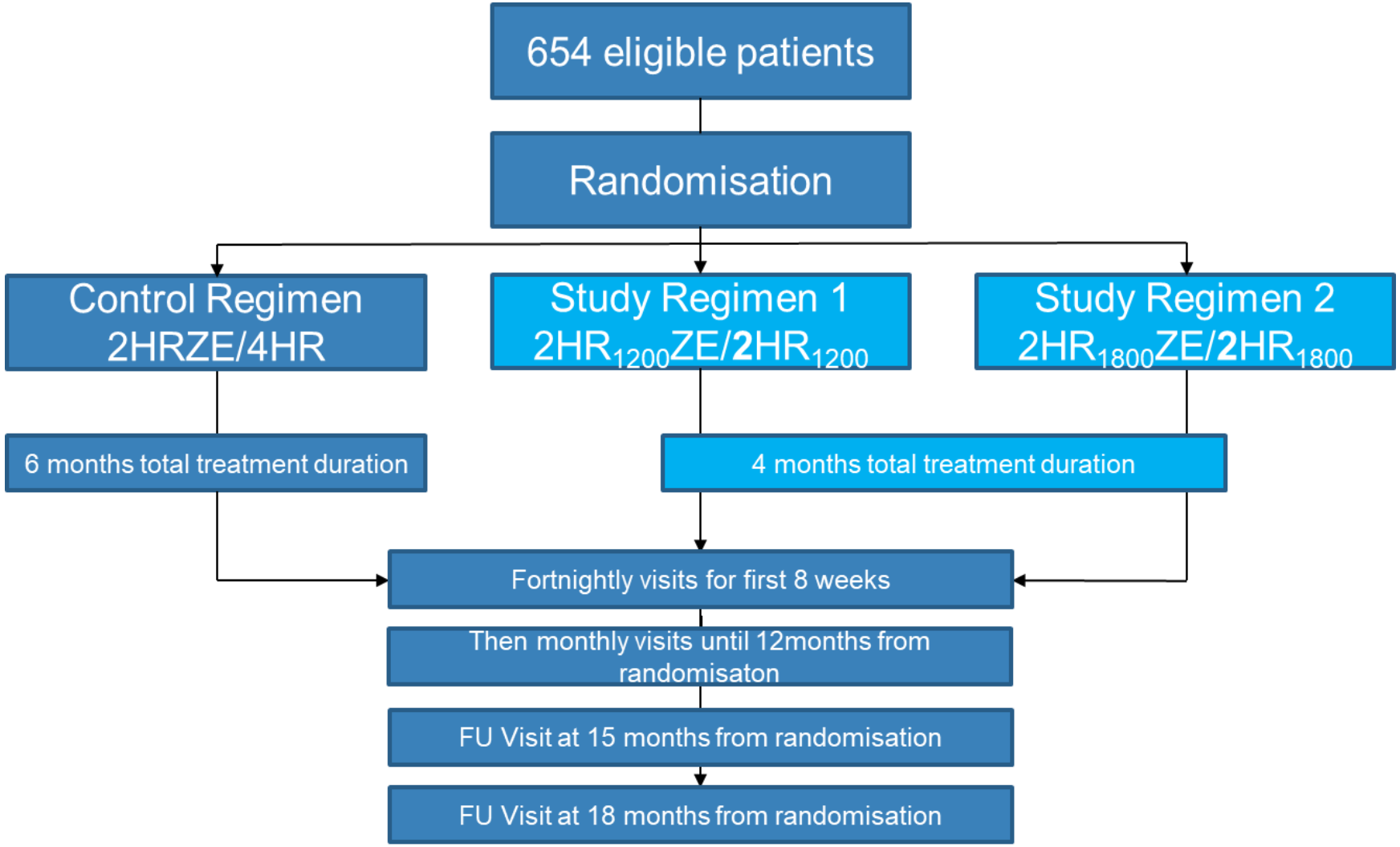
- To determine whether an increase in the daily dose of rifampicin from the current WHO recommended dose **to 1200mg or 1800mg** would result in more rapid sterilisation of the lungs and allow a reduction of treatment **duration to 4 months**
- To assess whether the increased doses will result in an increase in **severe (grade 3 or 4)** adverse events and/or any **serious adverse events**

## Outcomes

- Efficacy: **combined unfavourable endpoint measured 18 months from randomisation** (failure, TB recurrence and death)
- Safety: occurrence of **grade 3 or 4 adverse events** at any time during treatment

# Design

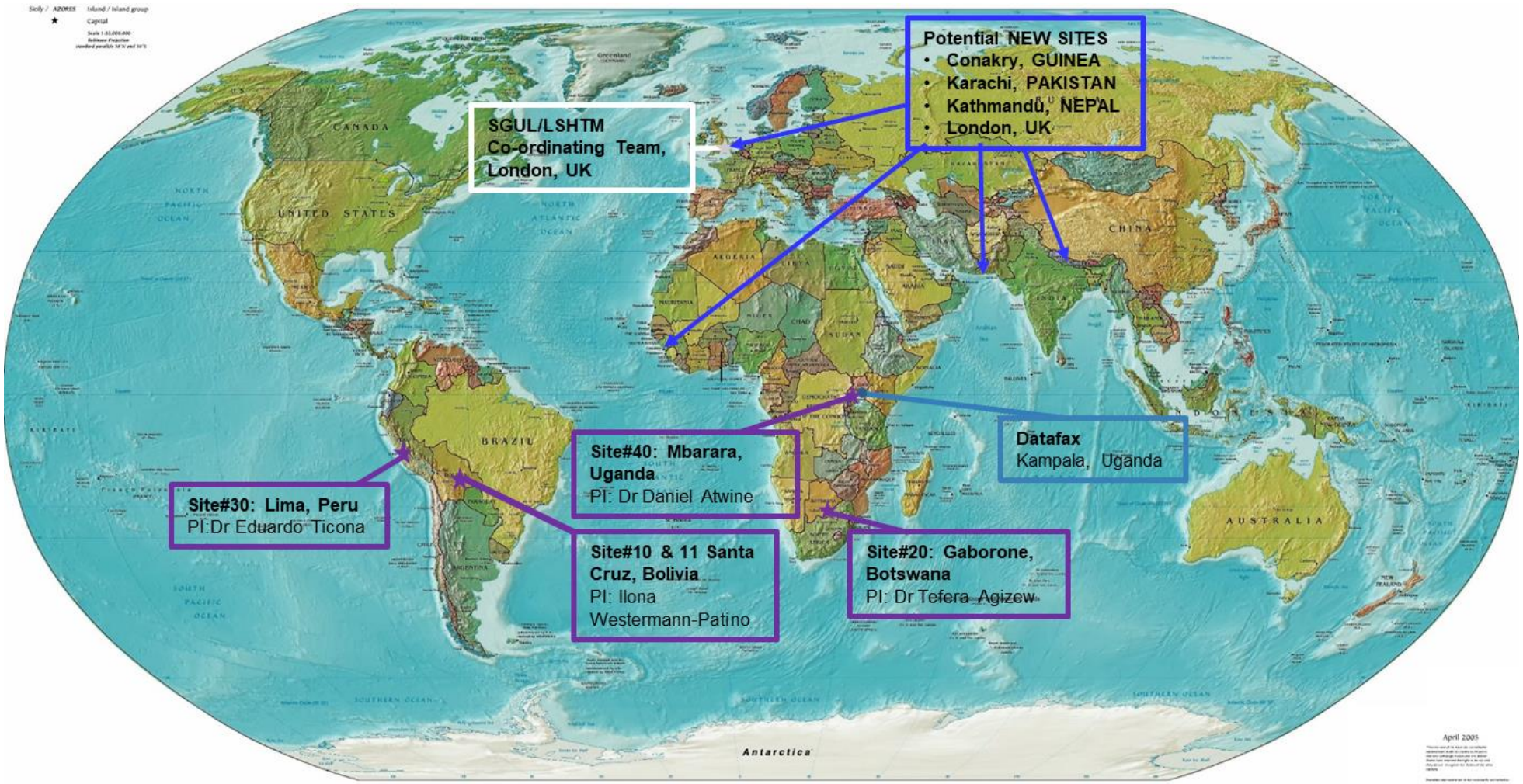
Phase **3 non-inferiority open label** parallel randomized controlled trial



# International trial

Coordination: St Georges University London, UK

Sites: Lima, Peru; Santa Cruz Bolivia, Mbarara, Uganda; Conakry, Guinea, Kathmandu, Nepal, Karachi, Pakistan



# Eligibility criteria

## Inclusion

- Newly diagnosed, smear microscopy or Xpert positive, pulmonary tuberculosis
- ≤ **one week** of previous TB treatment
- ≥ 18 years old
- Consent  to participation
- Stable home address
- Pre-menopausal or of a child-bearing age women with non hormonal contraception

## Exclusion

- R resistance by Xpert MTB/RIF or culture (late exclusions)
- TB meningitis or extra-pulmonary TB
- Pregnancy/breast feeding
- Uncooperative behaviour
- History of seizures
- Contraindication to study drugs
- HIV infected
- Grade 4 blood disorder, Hb <7d/dL
- Peripheral neuritis
- Pre-existing liver disease
- ALT> 5 times ULN

# Treatment and handling of changes in its administration

- Fixed dose combination tablets are weight banded as per WHO guidelines
- Additional rifampicin tablets are given to make up to fixed dose of 1200mg or 1800mg
- Pyridoxine supplement given with every dose
- Adherence
  - Every dose is expected to be DOT
  - Domiciliary  treatment monitor (DTM) training
  - Treatment card review is performed each time the DTM or patient collects the medication
  - Pill count
  - Adherence questionnaire

**4FDC**

Ethambutol (275mg)

Isoniazid (75mg)

Rifampicin (150mg)

Pyrazinamide (400mg)

**2FDC**

Rifampicin (150mg)

Isoniazid (75mg)

# Schedule of events

| Visit # | Weeks from enrolment | Consent | Home details | Clinical details | Chest X-ray | Blood and urine tests* | Progress report (including AE review) | Sputum for microscopy &culture (no. of specimens) | Susceptibility test (INH and Rif) |
|---|---|---|---|---|---|---|---|---|---|
| **0** | Screening | √ | √ | √ | | FBC, ALT, bilirubin, creatinine, HIV, HbA1c pregnancy | | 1 and 1 for Xpert MTB/RIF | √ **(dst if culture +ve)** |
| **1** | Enrolment | √ | √ | √ | √ | Hep B and C | √ | 1 | √**(dst if culture +ve)** |
| **2** | 2 weeks | | | | | ALT only | √ | 0 | **N/A** |
| **3** | 4 weeks | | | | | √ ALT & FBC | √ | 0 | **N/A** |
| **3.5** | 6 weeks | | | | | √ ALT & FBC | √ | 0 | **N/A** |
| **4** | 8 weeks | | | | | √ ALT & FBC | √ | 2 | √**(dst if culture +ve)** |
| **5** | 12 weeks | | | | | √ ALT & FBC | √ | 2 | √**(dst if culture +ve)** |
| **6** | 16 weeks | | | | | √ ALT & FBC | √ | 2 | √**(dst if culture +ve)** |
| **7** | 20 weeks | | | | | √ ALT & FBC | √ | 2§ /1# | √**(dst if culture +ve)** |
| **8** | 24 weeks | | | | | √§ ALT & FBC | √ | 2§ / 1# | √**(dst if culture +ve)** |
| **9** | 28 weeks | | | | | √§ ALT & FBC | √ | 1 | √**(dst if culture +ve)** |
| **10** | 32 weeks | | | | | | √ | 1 | √**(dst if culture +ve)** |
| **11** | 36 weeks | | | | | | √ | 1 | √**(dst if culture +ve)** |
| **12** | 40 weeks | | | | | | √ | 1 | √**(dst if culture +ve)** |
| **13** | 44 weeks | | | | | | √ | 1 | √**(dst if culture +ve)** |
| **14** | 48 weeks | | | | | | √ | 1 | √**(dst if culture +ve)** |
| **15** | 60 weeks | | | | | | √ | 2 | √**(dst if culture +ve)** |
| **16** | **72 weeks** | | | | | | √ | **2** | √**(dst if culture +ve)** |

# Sample size

- 7 % unfavorable outcome in the control regimen
- 90% power to test the hypothesis that SR2 was noninferior to control, with a noninferiority margin of 8%
- one-sided significance level of 0.05
- 525 participants
- 20% inflation to take into account late exclusions or unassessable because of drug resistance or loss to follow-up = **654 participants**

# Study profile

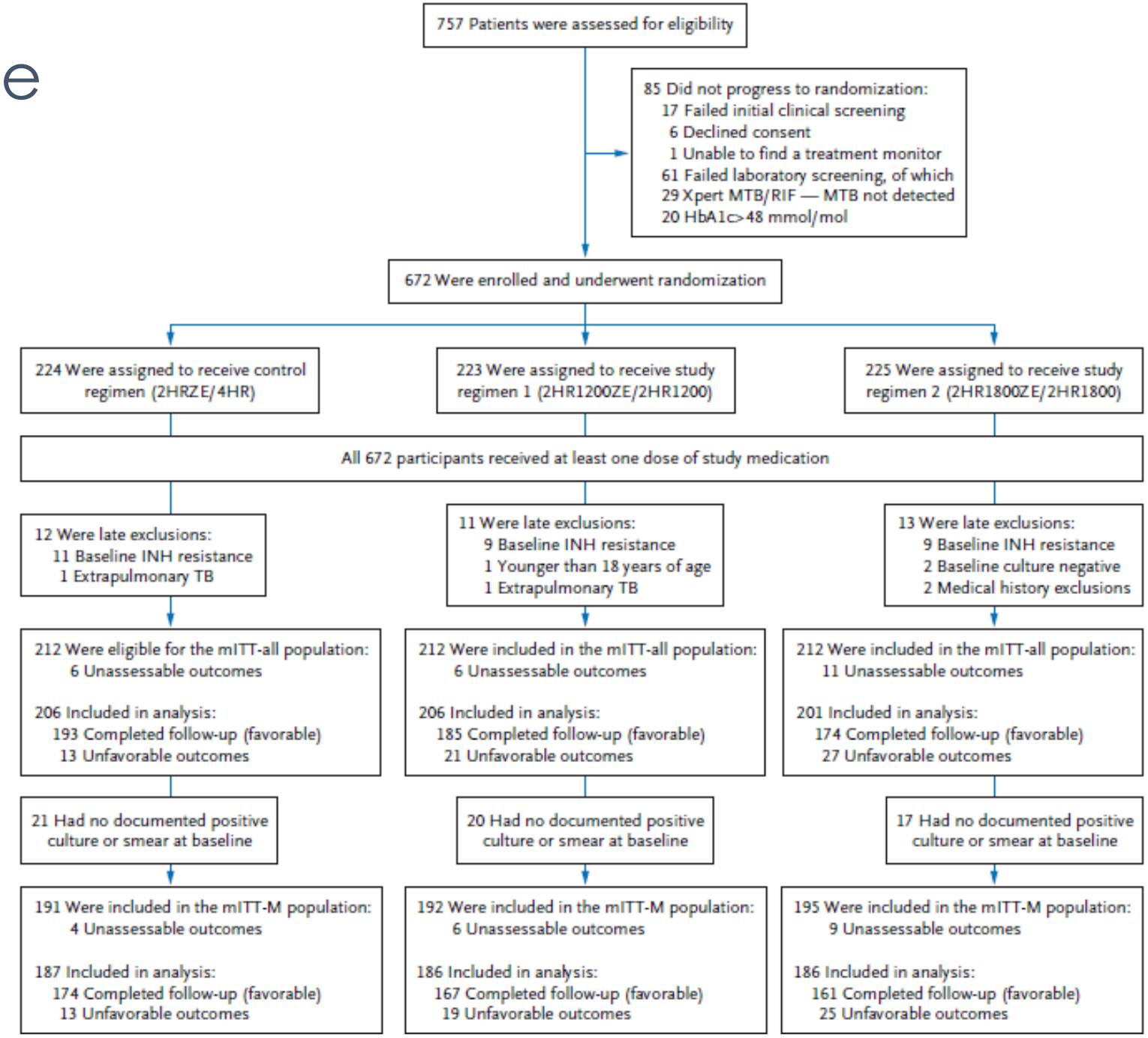
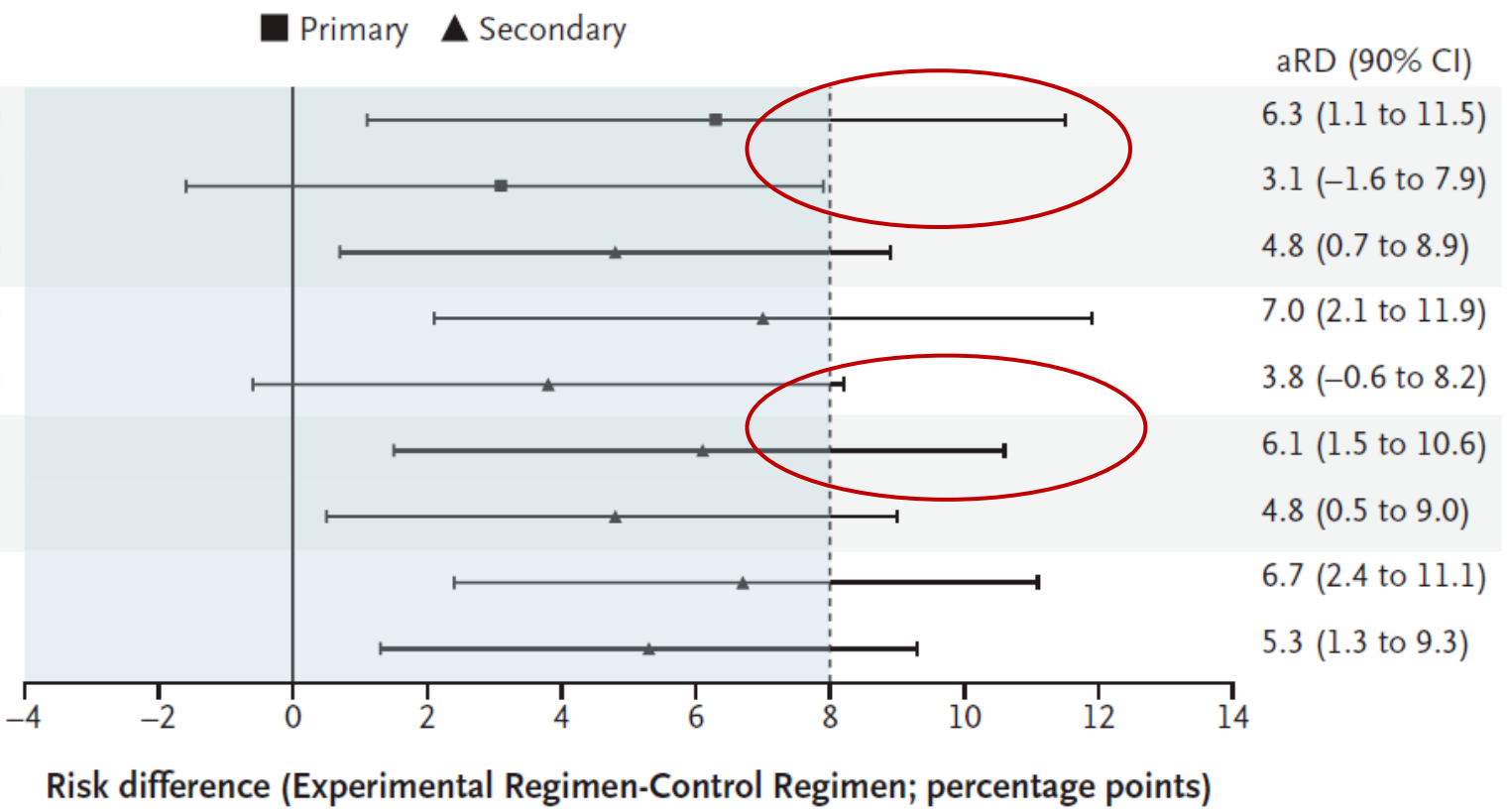


Table 1. Baseline Characteristics of the Participants (Modified Intention-to-Treat Microscopy Positive Population).*

| Characteristic | Control (n=191) | Study Regimen 1 (n=192) | Study Regimen 2 (n=195) |
|---|---|---|---|
| Age, yr — median (IQR) | 29.0 (23.0–38.0) | 29.0 (22.0–36.0) | 28.0 (23.0–43.0) |
| Age, yr — no. (%) | | | |
| 18–24 | 57 (29.8) | 64 (33.3) | 72 (36.9) |
| 25–34 | 73 (38.2) | 69 (35.9) | 53 (27.2) |
| >34 | 61 (31.9) | 59 (30.7) | 70 (35.9) |
| Weight, kg — median (IQR) | 52.2 (47.0–57.7) | 51.9 (46.8–58.1) | 52.6 (48.0–58.0) |
| BMI — median (IQR) | 18.4 (16.9–20.2) | 18.6 (16.9–20.8) | 18.8 (17.0–21.0) |
| Female sex — no. (%) | 54 (28.3) | 41 (21.4) | 49 (25.1) |
| Ethnicity — no. (%) | | | |
| African | 136 (71.2) | 133 (69.3) | 134 (68.7) |
| Hispanic | 1 (0.5) | 2 (1.0) | 1 (0.5) |
| Mixed | 32 (16.8) | 34 (17.7) | 36 (18.5) |
| Indigenous (South American) | 1 (0.5) | 1 (0.5) | 0 (0.0) |
| Asian | 21 (11.0) | 22 (11.5) | 24 (12.3) |
| Smoking status — no. (%) | | | |
| Current | 47 (24.6) | 33 (17.2) | 36 (18.5) |
| Former | 15 (7.9) | 15 (7.8) | 17 (8.7) |
| Never | 129 (67.5) | 144 (75.0) | 142 (72.8) |
| CXR cavitation — no. (%) | | | |
| Unreadable/unknown | 0 | 1 (0.5) | 1 (0.5) |
| Yes | 165 (86.4) | 174 (90.6) | 174 (89.2) |
| No | 26 (13.6) | 17 (8.9) | 20 (10.3) |
| CXR grading — no. (%) | | | |
| Unreadable/unknown | 3 (1.6) | 1 (0.5) | 3 (1.5) |
| Normal or minimal disease | 3 (1.6) | 4 (2.1) | 4 (2.1) |
| Moderately advanced disease | 86 (45.0) | 88 (45.8) | 85 (43.6) |
| Far advanced disease | 99 (51.8) | 99 (51.6) | 103 (52.8) |
| Sputum smear grading — no. (%) | | | |
| + or scanty | 68 (35.6) | 77 (40.1) | 81 (41.5) |
| ++ | 52 (27.2) | 41 (21.4) | 49 (25.1) |
| +++ | 71 (37.2) | 74 (38.5) | 65 (33.3) |

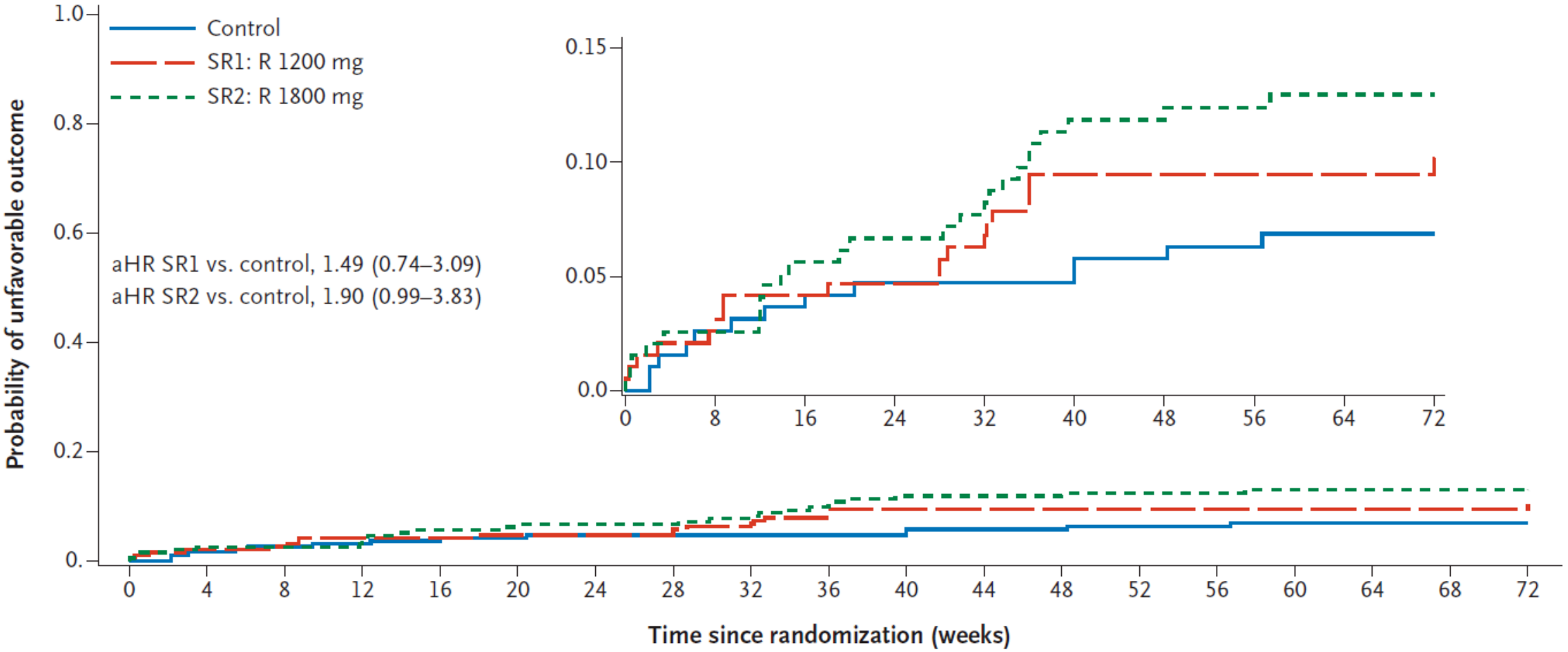
# Primary efficacy results

| Study population | Study regimen | % Unfavorable | Control | aRD (90% CI) |
|---|---|---|---|---|
| mITT-M | SR2 (R 1800 mg) | 13.4 (25/186) | 7.0 (13/187) | 6.3 (1.1 to 11.5) |
| | SR1 (R 1200 mg) | 10.2 (19/186) | 7.0 (13/187) | 3.1 (–1.6 to 7.9) |
| | SR1 + SR2 | 11.8 (44/372) | 7.0 (13/187) | 4.8 (0.7 to 8.9) |
| mITT-All | SR2 | 13.4 (27/201) | 6.3 (13/206) | 7.0 (2.1 to 11.9) |
| | SR1 | 10.2 (21/206) | 6.3 (13/206) | 3.8 (–0.6 to 8.2) |
| PP-M | SR2 | 10.6 (19/180) | 4.4 (8/182) | 6.1 (1.5 to 10.6) |
| | SR1 | 9.3 (17/182) | 4.4 (8/182) | 4.8 (0.5 to 9.0) |
| PP-All | SR2 | 10.8 (21/195) | 4.0 (8/201) | 6.7 (2.4 to 11.1) |
| | SR1 | 9.4 (19/202) | 4.0 (8/201) | 5.3 (1.3 to 9.3) |




Jindani A et al. Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis. N Eng J Med Evidence. 2023

# Probability of unfavourable outcome




Jindani A et al. Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis. N Eng J Med Evidence. 2023

**Table 3. Laboratory-Defined and Clinical Adverse Events According to Treatment Group.***

| Participants Experiencing | Control (n=224) | Study Regimen 1 (n=223) | Study Regimen 2 (n=225) |
|---|---|---|---|
| Primary safety outcome | | | |
| Grade 3 or 4 adverse event — no. (%) | 9 (4.0) | 10 (4.5) | 10 (4.4) |
| Percentage point difference from control (95% CI) | | 0.5 (–3.3 to 4.2) | 0.4 (–3.3 to 4.2) |
| Secondary safety outcome | | | |
| Grade 1–4 adverse event — no. (%) | 120 (53.6) | 109 (48.9) | 115 (51.1) |
| Percentage point difference from control (95% CI) | | –4.7 (–13.9 to 4.6) | –2.5 (–11.7 to 6.8) |
| Other safety outcomes — no. (%) | | | |
| Serious adverse event | 3 (1.3) | 3 (1.3) | 3 (1.3) |
| Notifiable adverse event | 10 (4.5) | 13 (5.8) | 13 (5.8) |
| Notifiable adverse event, excluding pregnancy | 6 (2.7) | 11 (4.9) | 13 (5.8) |
| Death | 5 (2.2) | 8 (3.6) | 3 (1.3) |
| Hepatotoxicity outcomes | | | |
| ALT>180 U/l (5×ULN, grade 3) — no. (%) | 3 (1.3) | 7 (3.1) | 7 (3.1) |
| ALT>360 U/l (10×ULN, grade 4) — no. (%) | 2 (0.9) | 1 (0.4) | 4 (1.8) |
| Grade 3/4 ALT results, U/l — median (IQR; max) | 387 (237–511; 511) | 212 (189–350; 449) | 377 (332–450; 942) |
| Total bilirubin >3 mg/dl (2.6×ULN, grade 3) — no. (%) | 1 (0.4) | 1 (0.4) | 6 (2.7) |
| Total bilirubin >6 mg/dl (5×ULN, grade 4) — no. (%) | 1 (0.4) | 0 | 3 (1.3) |
| Grade 3/4 total bilirubin results, mg/dl — median (IQR; max) | 12.1 | 3.2 | 5.4 (4.1–9.4; 29.5) |
| Satisfies Hy's law (ALT>3×ULN and total bilirubin >2×ULN) — no. (%) | 0 | 1 (0.4) | 2† (0.9) |

# Conclusion

*Four-month high-dose rifampicin regimens did not have dose-limiting toxicities or side effects but failed to meet noninferiority criteria compared with the standard 6-month control regimen for treatment of pulmonary tuberculosis.*

# Points de discussion

- Non-infériorité et choix de la marge de non-infériorité

  8%: trop bas? 12% dans les essais thérapeutiques VIH et TB résistante
- Critère d'évaluation principale
  - Guérison sans récidive à 1 an:  long, cher
  - Critère composite
  - Pas de bon biomarqueur de la guérison
- Perspectives pour réduire la durée du traitement
  - Nécessité d'introduire des nouvelles molécules
    - Moxifloxacine et rifapentine: essai phase 3 avec non-infériorité d'un régime de 4 mois (cf diapo)
    - 2 mois avec bedaquiline et linézolide: essai TRUNCATE TB (cf diapo)
    - Faut-il utiliser les médicaments clés du traitement de la TB MDR dans un conetxe limité d'alternatives thérapeutiques
  - Traitement individualisé (cf diapo)
    - Traitement court pour des formes peu sévères/avancées
    - Traitement long pour des formes plus avancées
  - Prendre en compte le fait que la majorité des patients vivent dans les pays à ressources limitées

    Traitement standardisé et approche simplifié

# Diapos supplémentaires

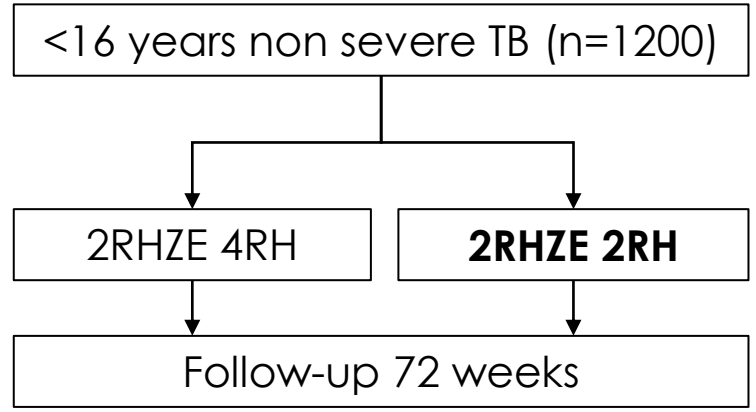
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

# Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

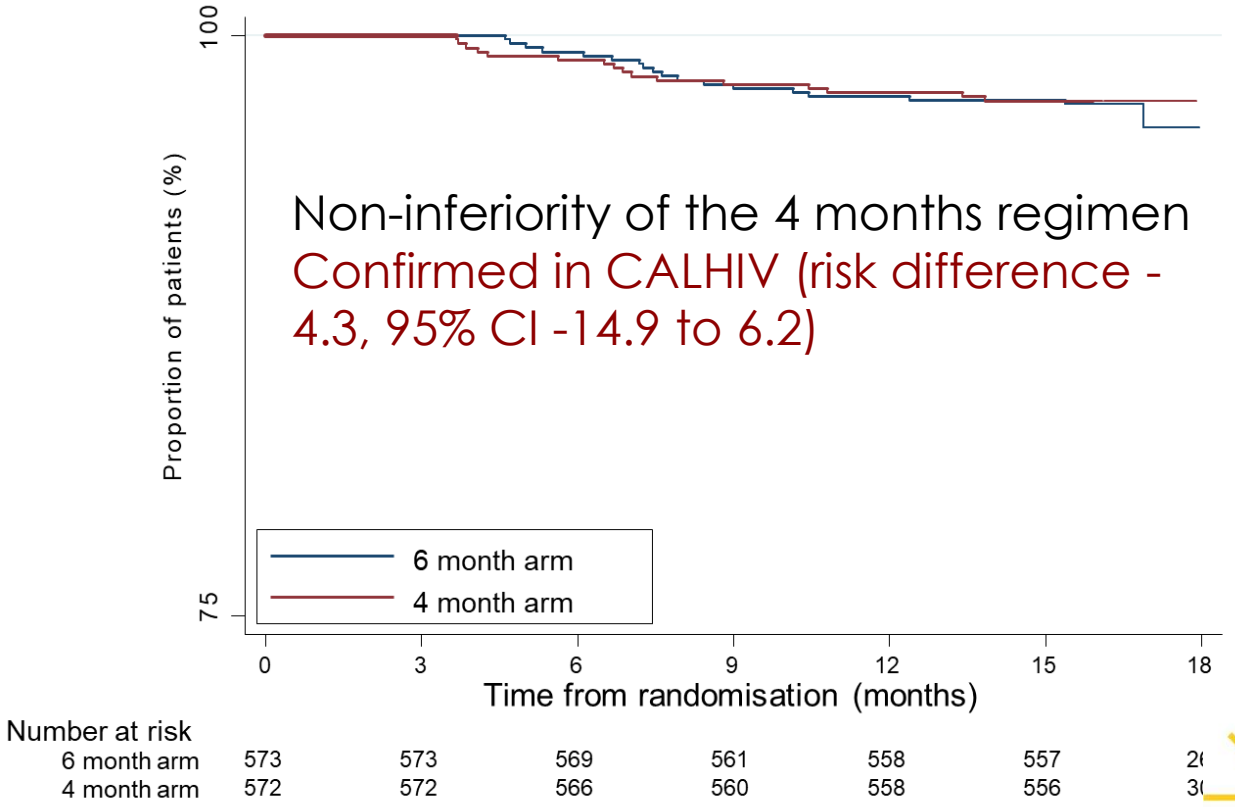
A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

Non-severe TB
- Pulmonary TB
  - ≤ 1 lobe without cavity
  - No bronchial obstruction
  - No complicated pleural effusion
  - No miliiary
- Peripheral adenopathy
- Sputum smear-negative




## Phase 3 non-inferiority trial

| | 4 months N=602 | 6 months N=602 |
|---|---|---|
| Age (years), median | 3.4 | 3.5 |
| Girls, n (%) | 297 (49) | 286 (48) |
| HIV-positive, n (%) | 65 (11) | 62 (10) |
| Clinical presentation, n(%)<br>Pulmonary<br>Pulmonary & adenopathy<br>Adenopathy<br>Other | <br>398 (66)<br>182 (30)<br>19 (3)<br>3 (1) | <br>406 (67)<br>171 (28)<br>21 (3)<br>4 (1) |
| Confirmed TB, n(%) | 85 (14) | 80 (13) |




Non-inferiority of the 4 months regimen
Confirmed in CALHIV (risk difference -4.3, 95% CI -14.9 to 6.2)

SHINE

# TRUNCATE TB

- Multi-arm, multi-stage non-inferiority trial to compare 4 months regimens with standard regimen
- Two months regimen with rescue therapy with 2HRZE 4HR in case of relapse during 2 months f-up
  - HZE + R35mg/Kg + linezolid (L) 600
  - HZE + R35mg/Kg + clofazimine 200mg*
  - HZE + P1200 + L600 + levofloxacin 100mg*
  - HZE + L600 + bedaquiline 400mg 2 weeks and 200mg 3 weeks

**Interrupted by the trial steering committee to reach sample size to allow NI evaluation in 2 arms*

**Table 2. Primary Efficacy Outcome.***

| Outcome | Standard Treatment (N=181) | Strategy with Rifampin–Linezolid (N=184) | Strategy with Rifampin–Linezolid vs. Standard Treatment Adjusted Difference (97.5% CI)† | Strategy with Bedaquiline–Linezolid (N=189) | Strategy with Bedaquiline–Linezolid vs. Standard Treatment Adjusted Difference (97.5% CI)† |
|---|---|---|---|---|---|
| **Intention-to-treat population‡** | | | | | |
| Primary outcome: composite of death, ongoing treatment, or active disease at wk 96 — no. (%)§ | 7 (3.9) | 21 (11.4) | 7.4 (1.7 to 13.2) | 11 (5.8) | 0.8 (–3.4 to 5.1) |
| **Per-protocol population‡‡** | | | | | |
| Primary outcome — no./total no. (%) | 6/177 (3.4) | 17/160 (10.6) | 6.9 (0.9 to 12.8) | 9/176 (5.1) | 0.9 (–3.3 to 5.1) |

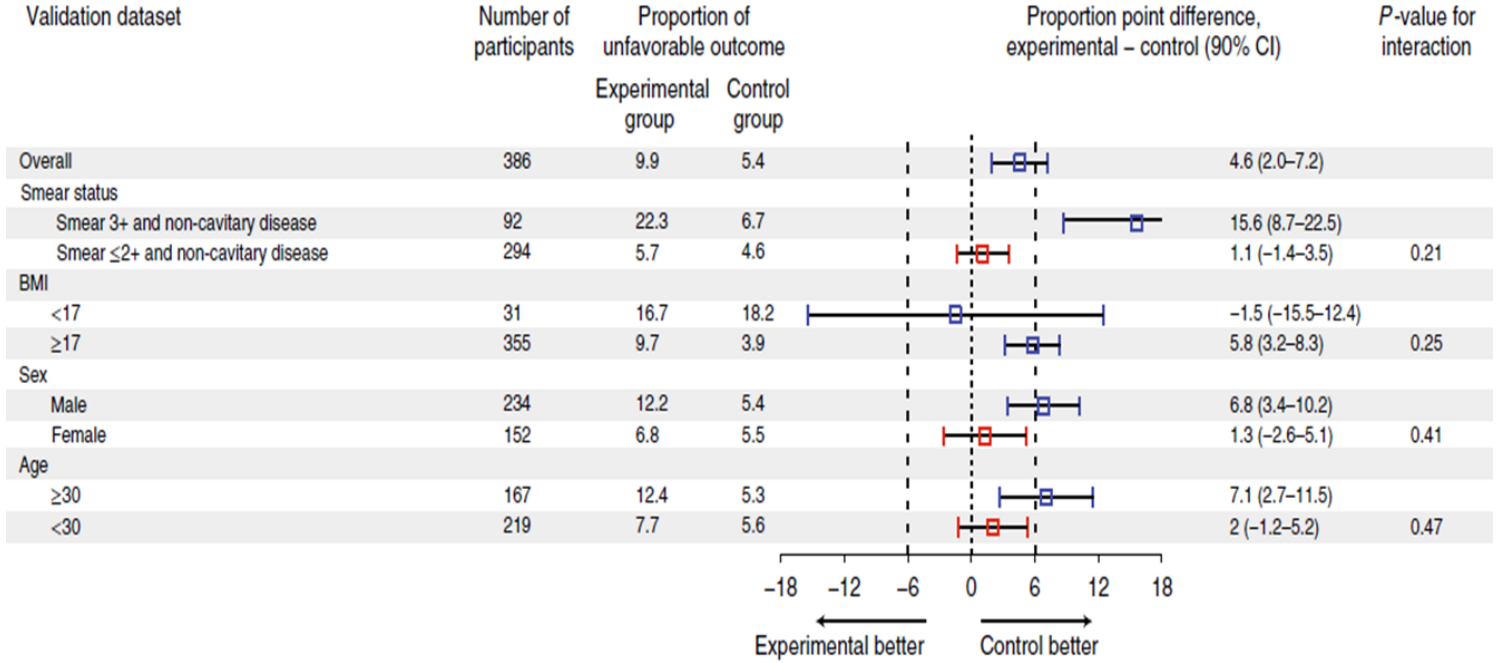
No difference of adverse events grade 3 and 4

*Paton NI et al. N Eng J Med 2023*

# « Stratified medicine approach »

- Limitations of the « One-size-fits-all » approach
  - Majority of patients do not need 6 months therapy
  - 6 months therapy not enough in patients with severe forms of TB, HIV infected, low BMI
- Efficacy is the greatest determinant of impact compared to a novel shorter regimen: increase efficacy from 94% to 99% reduce mortality by 6%
- Stratified medicine approach
  - Type/duration of treatment based on baseline markers of poor outcomes
  - Treatment extension according to on-treatment outcome parameters

Review of the efficacy of the fluoroquinolone trials according to predictors of poor outcomes



| Validation dataset | Number of participants | Proportion of unfavorable outcome | | Proportion point difference, experimental – control (90% CI) | *P*-value for interaction |
|---|---|---|---|---|---|
| | | Experimental group | Control group | | |
| Overall | 386 | 9.9 | 5.4 | 4.6 (2.0–7.2) | |
| Smear status | | | | | |
| Smear 3+ and non-cavitary disease | 92 | 22.3 | 6.7 | 15.6 (8.7–22.5) | |
| Smear ≤2+ and non-cavitary disease | 294 | 5.7 | 4.6 | 1.1 (−1.4–3.5) | 0.21 |
| BMI | | | | | |
| <17 | 31 | 16.7 | 18.2 | −1.5 (−15.5–12.4) | |
| ≥17 | 355 | 9.7 | 3.9 | 5.8 (3.2–8.3) | 0.25 |
| Sex | | | | | |
| Male | 234 | 12.2 | 5.4 | 6.8 (3.4–10.2) | |
| Female | 152 | 6.8 | 5.5 | 1.3 (−2.6–5.1) | 0.41 |
| Age | | | | | |
| ≥30 | 167 | 12.4 | 5.3 | 7.1 (2.7–11.5) | |
| <30 | 219 | 7.7 | 5.6 | 2 (−1.2–5.2) | 0.47 |



*Imperial MZ et al. Nature Medicine 2018*
*Kendall EM et al. PLoS Med 2017.*


merci
thank you
obrigado
gracias
danke
go raibh maith agat
спасибо
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mochchakkeram
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