Online Supplement to:

"Effectiveness and safety of standardized shorter MDR-TB regimens: IPD and aggregate data meta-analyses"

Search strategy for published studies *see Bastos, M et al. [9].*

Medline search

MDR or XDR

1. exp multidrug resistant tuberculosis/ or exp extensively drug resistant tuberculosis/
2. (multidrug resistant tuberculosis or extensive* drug resistant tuberculosis or MDR-TB or XDR-TB).ti,ab,kw.
3. (tuberc* and (MDR or XDR or drug resistan* or multidrug resistan* or multi drug resistan* or poly drug resistan* or extensive* drug resistan*)).ti,ab,kw.

Drugs

4. exp Fluoroquinolones/ or exp Quinolones/ or exp Levofloxacin/ or (fluoroquinolone* or quinolone* or levofloxacin or Levaquin or moxifloxacin or Avelox).ti,ab,kw.
5. exp Kanamycin/ or exp Amikacin/ or exp Capreomycin/ or exp Aminoglycosides/ or (Kanamycin or Amikacin or Capreomycin or (tuberc* and injectable*)).ti,ab,kw.
6. exp Pyrazinamide/ or exp Ethambutol/ or exp Cycloserine/ or exp Ethionamide/ or exp Prothionamide/ or (Pyrazinamide or Ethambutol or para-aminosalicylic acid or Cycloserine or Ethionamide or Prothionamide).ti,ab,kw.
7. high dose.ti,ab,kw. and ((INH or isoniazid).ti,ab,kw. or exp isoniazid/)

Efficacy

8. exp Treatment Outcome/ or exp Prognosis/ or exp Death/ or exp Mortality/ or exp Treatment Failure/ or exp Survival/ or exp Recurrence/ or exp Patient Dropouts/ or exp Patient Compliance/
9. (Treatment Outcome* or Prognosis or Death or Mortality or Treatment Failure or drug treatment failure or failure or Survival or Recurrence or relapse or Patient Dropout* or dropout or non-compliance or compliance or efficacy or effective* or cure or success* or default or adheren* or conversion* or microbiologic conversion or smear conversion or culture conversion or sputum conversion).ti,ab,kw.

Toxicity

10. exp Treatment Outcome/ or exp Prognosis/ or exp Death/ or exp Mortality/ or exp Treatment Failure/ or exp Survival/ or exp Recurrence/ or exp Toxicity Tests/ or exp Drug Tolerance/ or exp "Drug-Related Side Effects and Adverse Reactions"/
11. (Treatment outcome* or Prognosis or Death or Mortality or Treatment Failure or drug treatment failure or failure or Survival or Recurrence or relapse or Toxicity Test* or toxicity or Drug Tolerance or toler* or intolerance or Side Effect* or Adverse Drug Reaction* or adverse drug event* or adverse event* or adverse reaction* or safe* or drug safety).ti,ab,kw.

New drugs

12. (Bedaquiline or TMC-207 or delamanid or OPC-67683).ti,ab,kw.

Final steps

13. 1 or 2 or 3
14. 4 or 5 or 6 or 7
15. 8 or 9
16. 10 or 11
17. 13 and 14 and 15
18. 13 and 14 and 16
19. 12 and 13 and 15
20. 12 and 13 and 16
21. limit 17 to (humans and yr="2009 -Current")
22. limit 18 to (humans and yr="2009 -Current")
23. limit 19 to (humans and yr="2012 -Current")
24. limit 20 to (humans and yr="2012 -Current")
25. 21 or 22
26. 23 or 24
27. 25 or 26

(EmBase and the Cochrane Library were searched using the same strategy)

Figure S1. PRISMA diagram of study selections.

Adapted from Bastos, M et al. (ref 9)

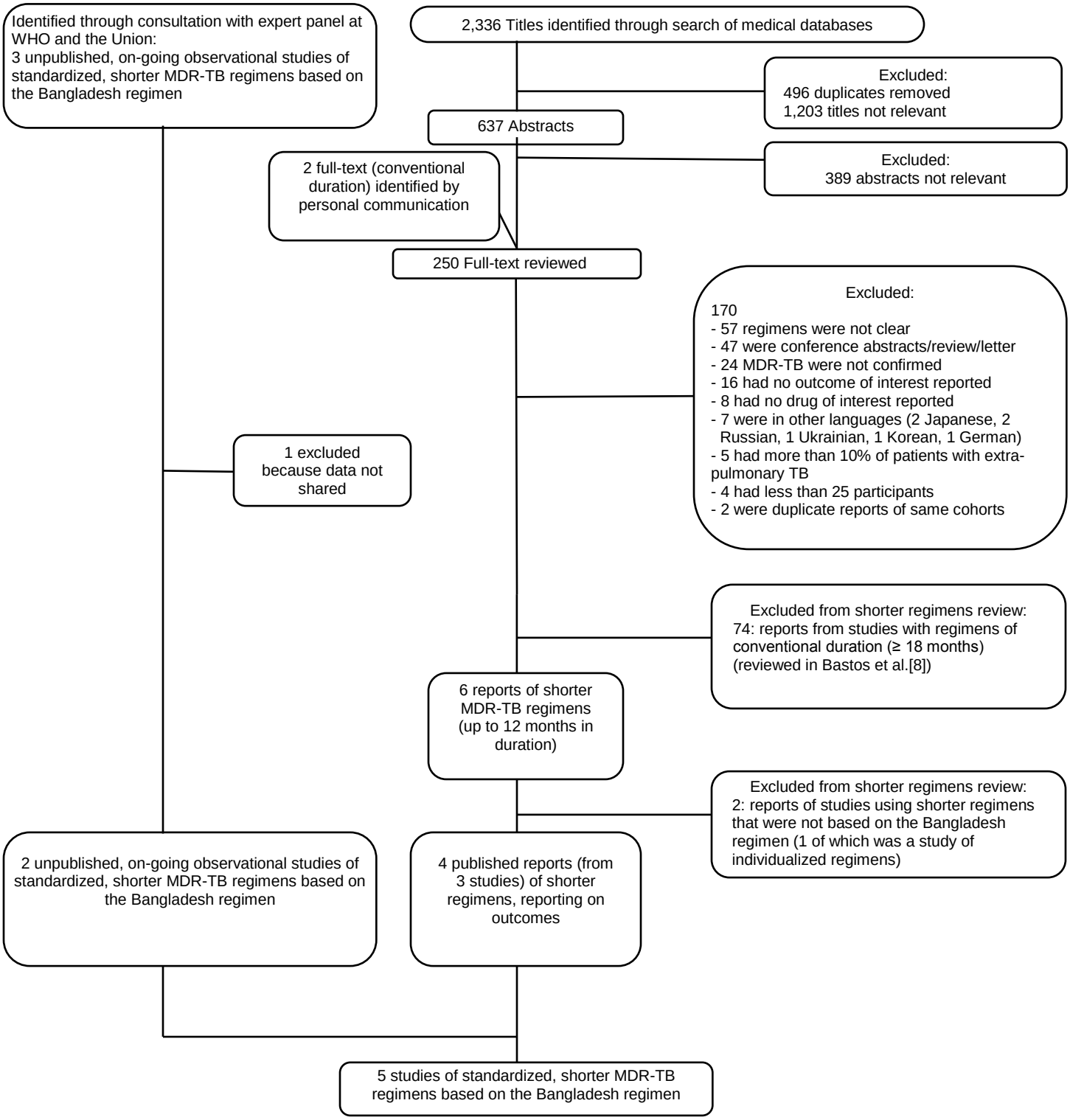

Table S1. Individual studies' eligibility/inclusion/exclusion criteria

a) Eligibility/inclusion criteria

Cohort	Inclusion criteria – as reported in publications or protocols
Bangladesh	All patients with confirmed or highly-likely MDR-TB detected in the Damien Foundation Project area in Bangladesh and complying with protocol-defined conditions (agreement to be hospitalized during intensive phase) were eligible for study enrolment if they took at least 1 day of the assigned treatment regimen and provided written consent
Niger	Presumptive or confirmed MDR-TB
Cameroon	Confirmed MDR-TB *and* No previous treatment with second-line drugs (or < 1 month of exposure) *and* Agreed to 4 months of hospitalization in the Centre Jamot in Yaounde´ or in Dibamba Catholic Health Centre, Douala *and* Agreed to receiving DOT through-out treatment *and* Signed consent form
Uzbekistan	Eligible for enrollment if: No previous treatment with second-line drugs (or < 1 month of exposure) *and*: New presumptively diagnosed MDR TB patients (adults and children) with Xpert® MTB/RIF or Hain MTBDR, or confirmed with Hain MTBDR plus on positive cultures if initial molecular tests negative or confirmed from MGIT culture/DST if initial molecular tests negative; Children (<14 yo) suspected of MDR TB without bacteriological confirmation but documented as a close contact of a confirmed MDR TB patient; AND Informed consent to participate in the study signed by the patient or the responsible caretaker for patients <16 years old (as per national legislation).
Swaziland	New presumptively diagnosed MDR TB patients (adults and children) with Xpert® MTB/RIF or confirmed from MGIT culture/DST if initial Xpert® MTB/RIF negative; Children (<14 yo) suspected of MDR TB without bacteriological confirmation but documented as a close contact of a MDR TB confirmed patient; AND Informed consent to participate in the study signed by the patient or the responsible caretaker for patients <16 years old (as per national legislation). Of note, patients with a history of prior treatment with second line anti-TB drugs will be included. Patients with documentation of resistance to Ofloxacin (and not to Amikacin/Kanamycin) will be included in the regimen. Preconditions before initiation of treatment with the study regimen: 1. Live or be willing to spend the entire treatment course in Manzini-region/Swaziland 2. No exclusion criteria; 3. Completion of baseline tests; 4. Completion of one preliminary adherence counseling session including appointment of a treatment supporter

b) Exclusion criteria

Cohort	Exclusion criteria – as reported in publications or protocols
Bangladesh	*Ineligible:* Refusal to be hospitalized Advanced liver disease Cardio-respiratory insufficiency *Excluded from analysis:* 1) history of Previous treatment with second-line drugs (≥ 1 month of exposure); or 2) culture identified only environmental mycobacteria and *Mycobacterium tuberculosis* was never isolated; or 3) the Antwerp laboratory failed to confirm rifampin- plus isoniazid-resistant TB (i.e., MDR-

	TB).
Niger	*Ineligible:* Previous treatment with second-line drugs (≥ 1 month of exposure) Diabetes Pregnancy Severe liver disease *Excluded from analysis:* No laboratory confirmation of MDR-TB (excluded from analysis)
Cameroon	*Ineligible*: Pregnancy Very poor clinical condition Known hypersensitivity to any of the study drugs
Uzbekistan	*Ineligible:* Baseline contraindications to any medications of the study regimen medications, where benefits of the regimen do not outweigh the risks as judged by treating physician; Severe renal insufficiency with estimated creatinine clearance of <30 ml/min at baseline (calculated with Cockcroft-Gault formula); Patients with extrapulmonary TB only (without involvement of lung parenchyma) Patients with documented ofloxacin resistance Patients with XDR TB (additional resistance to second line drugs kanamycin (or capreomycin) AND ofloxacin); Patients with resistance to both Km and Cm. Critically ill and in the judgement of the treating physician unlikely to survive more than 1 week (these patients may still be commenced on standard MDR TB treatment according to the Karakalpakstan comprehensive TB treatment guidelines) Has one or more of the following risk factors for QTc prolongation: A confirmed prolongation of QTc interval (Fridericia formula), e.g., repeated demonstration of QTcF (Fridericia correction) interval > 500 ms in the screening ECG (i.e., retesting to reassess eligibility will be allowed once using an unscheduled visit during the screening phase) *Excluded from analysis:* All patients commenced on the 9 month regimen and thereafter with full DST found to be either: Non MDR TB (eg drug sensitive, mono or poly drug resistant TB) or resistance to Ofloxacin (with or without injectable resistance) with MGIT culture and FLD/SLD-DST or Showing resistance to both kanamycin and capreomycin. In case of resistance only to kanamycin the regimen will be continued with the use of capreomycin at the same dose as kanamycin and this adjustment of regimen will not be considered as a change of regimen and therefore will not be a cause of withdrawal.
Swaziland	*Exclusion criteria at baseline:* Baseline contraindications to any medications of the study regimen medications, where benefits of the regimen do not outweigh the risks as judged by treating physician; Severe renal insufficiency with Creatinine clearance of <30 ml/min at baseline (calculated with Cockcroft-Gault formula); Patient with probable or proven involvement of meninges and bones will be excluded from the study because of the different complexity of their management; Patients with documented XDR TB (additional resistance to SLD Kanamycin/Amikacin AND Ofloxacin/Moxifloxacin); Resistance to Km/Am and Cm. Resistance to Mfx. Patients with prior documented ECG abnormality such as confirmed prolongation of QTc interval.

Table S2. Individual studies' bacteriologic outcome definitions

a) Cure

Cohort	Cure: bacteriologic criteria
Bangladesh	Completed treatment and ≥ 5 negative cultures following the last positive culture over at least 12 months of follow-up (including the follow-up period)
Niger	Completed treatment with ≥ 5 consecutive negative cultures during the final 8 months of treatment Note: 1 positive culture permitted if followed by ≥ 4 negative cultures
Cameroon	Completed treatment with ≥ 5 consecutive negative cultures
Uzbekistan	Completed treatment with ≥ 4 negative cultures within final 5 months of treatment Note: 1 positive culture permitted if followed by ≥ 3 negative cultures in the final 3 months of treatment
Swaziland	Completed treatment with ≥ 5 consecutive negative cultures Note: 1 positive culture permitted if followed by ≥ 3 negative cultures

b) Failure

Cohort	Failure: bacteriologic criteria
Bangladesh	≥ 1 positive culture during treatment after ≥ 150 days; *or* death or default with bacteriological evidence of active TB after the first 2 months of treatment
Niger	≥ 2/5 cultures positive in the final 8 months of treatment; *or* 1/3 final cultures positive
Cameroon	≥ 1 positive culture at 5 months or later; *or* bacteriological reversion to positive after conversion (unless isolated positive culture, see Note); *or* evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs Note: a positive culture in the continuation phase that occurred after conversion with two negative cultures, and that was followed by ≥ 2 negative cultures and no positive cultures was not classified as failure
Uzbekistan	Patient fails to show culture negative by the end of month 5 of prolonged intensive phase; *or* ≥ 2 cultures positive during the continuation phase; *or* 1 culture positive during the last 3 months of treatment; *or* amplification of resistance with either ofloxacin, capreomycin, or kanamycin resistance
Swaziland	Fails to show culture negative by the end of month 6 of a prolonged intensive phase; *or* ≥ 2 cultures positive during the continuation phase; *or* 1 culture positive during the last 3 months of treatment

c) Treatment completion

Cohort	Treatment completion
Bangladesh	Completion of treatment with documented bacteriological conversion status persisting up to the end of treatment, but < 5 negative cultures or, 12 months of observation after the last positive culture
Niger	Completion of treatment with documented bacteriological conversion but not meeting criteria for cure
Cameroon	Completion of treatment without meeting the definition for cure or treatment failure due to missing culture results.
Uzbekistan	Completed treatment with < 5 cultures performed in final 5 months of treatment, or bacteriological conversion persisting through the end of treatment with < 5 negative cultures. Note: Categorization as "Treatment completed" restricted to participants in whom culture results unavailable due to inability to produce sputum, all other participants classified as "Other" (e.g. if insufficient number of cultures due to contamination, or other "programmatic" reasons).
Swaziland	Completed treatment with < 5 cultures performed in final 5 months of treatment, or bacteriological conversion persisting through the end of treatment with < 5 negative cultures. Note: Categorization as "Treatment completed" restricted to participants in whom culture results unavailable due to inability to produce sputum, all other participants classified as "Other" (e.g. if insufficient number of cultures due to contamination, or other "programmatic" reasons).

d) Loss to follow-up

Cohort	Loss to follow-up
Bangladesh	Interruption of treatment for ≥ 2 months not meeting the criteria for prior failure
Niger	Interruption of treatment for ≥ 2 consecutive months without medical approval
Cameroon	Interruption of treatment for ≥ 2 consecutive months
Uzbekistan	Interruption of treatment for ≥ 2 consecutive months without medical approval and not meeting criteria for failure
Swaziland	Interruption of treatment for ≥ 2 consecutive months without medical approval and not meeting criteria for failure

e) Relapse

Cohort	Relapse
Bangladesh	≥ 1 positive culture during 24 months of post-treatment follow-up, unless due to re-infection (strain genotypically different from the initial isolate)
Niger	≥ 1 positive culture during 24 months of post-treatment follow-up
Cameroon	Not reported. Participants followed for up to 12 months post-treatment.
Uzbekistan	≥ 1 specimen taken during the 12-month follow-up period bacteriologically positive MDR TB by culture and DST
Swaziland	≥ 1 specimen taken during the 12-month follow-up period bacteriologically positive MDR TB by culture and DST, of the same strain found in initial diagnosis, proven by molecular techniques

Table S3. Relapse

	Country, (years of enrollment)				
	Bangladesh, (2005-2011)	**Niger, (2008-2010)**	**Cameroon, (2008-2011)**	**Uzbekistan, (2013-2015)**	**Swaziland, (2014-2016)**
Duration of post treatment follow-up	2 years	2 years	1 year	1 year	1 year
Number eligible for relapse (cure or treatment completion)	418	58	134	46	17
Year 1 post-treatment					
Number evaluated for relapse	397	51	117	44	15
Culture-confirmed relapse	2	0	0	1	1
Year 2 post-treatment					
Number evaluated for relapse	384	49	*Not applicable*	*Not applicable*	*Not applicable*
Culture-confirmed relapse	1	0	*Not applicable*	*Not applicable*	*Not applicable*

Table S4. Between-study within-stratum heterogeneity estimates for treatment failure/relapse vs. success.

Variable	Events/Patients (%)	*Between study heterogeneity (95%CI)*
Age		
< median	15/256 (5.9%)	0.6 (0 – 7.1)
≥ median (31 years old)	6/242 (2.5%)	**2.2 (0.2 - 25)**
Gender		
Female	11/165 (6.7%)	0 (0 - 2.7)
Male	10/333 (3%)	**2 (0.4 - 20.4)**
HIV status		
Positive	1/12 (8.3%)	Not applicable*
Negative or unknown	20/486 (4.1%)	**1.2 (0.2 - 11.8)**
Sputum smear		
Smear-positive	16/441 (3.6%)	**1.1 (0.2 - 11.2)**
Smear-negative	5/53 (9.4%)	0.1 (0 - 16.7)
Chest X-Ray		
Cavitary disease	6/102 (5.9%)	0.2 (0 - 10.2)
Non-cavitary	11/374 (2.9%)	**1.2 (0.1 - 23.8)**
Timing of culture conversion		
Did not convert by month 2	15/113 (13.3%)	0.4 (0 - 5.4)
Converted by month 2	6/356 (1.7%)	**1.5 (0.1 - 17.2)**
Fluoroquinolone used		
Moxifloxacin	12/74 (16.2%)	**3.7 (0.7 - 38.2)**
Gatifloxacin	9/424 (2.1%)	Not applicable*
Fluoroquinolone resistance		
Resistant	9/56 (16.1%)	0 (0 - 157.2)
Susceptible	11/417 (2.6%)	**3.7 (0.7 - 38.2)**
Second line injectable resistance		
Resistant	1/11 (9.1%)	Not applicable*
Susceptible	17/457 (3.7%)	**1.1 (0.2 - 11.3)**
Pyrazinamide resistance		
Resistant	15/124 (12.1%)	0.1 (0 - 2.9)
Susceptible	2/135 (1.5%)	1.7 (0 - 47)
Ethambutol resistance		
Resistant	19/312 (6.1%)	1.2 (0.2 - 11.7)
Susceptible	0/163 (0%)	Could not compute
Prothionamide resistance		
Resistant	2/76 (2.6%)	1.1 (0 - 45.6)
Susceptible	9/339 (2.7%)	0 (0 - 4.5)

*Not applicable as only 1 study within the stratum. Between study heterogeneity quantified as the variance of the random effects parameter, and is considered significant if the confidence interval does not contain 0.