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# Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report

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**Previous evidence on adverse events is available from single studies. This global project (658 patients from 26 countries) demonstrates aDSM is feasible and serious adverse events of recommended drugs are reasonably low (overall 57 out of 504, 11.3%).** http://bit.ly/2kzvbqe

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ABSTRACT The World Health Organization (WHO) recommends that countries implement pharmacovigilance and collect information on active drug safety monitoring (aDSM) and management of adverse events.

The aim of this prospective study was to evaluate the frequency and severity of adverse events to anti-tuberculosis (TB) drugs in a cohort of consecutive TB patients treated with new (*i.e.* bedaquiline, delamanid) and repurposed (*i.e.* clofazimine, linezolid) drugs, based on the WHO aDSM project. Adverse events were collected prospectively after attribution to a specific drug together with demographic, bacteriological, radiological and clinical information at diagnosis and during therapy. This interim analysis included patients who completed or were still on treatment at time of data collection.

Globally, 45 centres from 26 countries/regions reported 658 patients (68.7% male, 4.4% HIV co-infected) treated as follows: 87.7% with bedaquiline, 18.4% with delamanid (6.1% with both), 81.5% with linezolid and 32.4% with clofazimine. Overall, 504 adverse event episodes were reported: 447 (88.7%) were classified as minor (grade 1–2) and 57 (11.3%) as serious (grade 3–5). The majority of the 57 serious adverse events reported by 55 patients (51 out of 57, 89.5%) ultimately resolved. Among patients reporting serious adverse events, some drugs held responsible were discontinued: bedaquiline in 0.35% (two out of 577), delamanid in 0.8% (one out of 121), linezolid in 1.9% (10 out of 536) and clofazimine in 1.4% (three out of 213) of patients. Serious adverse events were reported in 6.9% (nine out of 131) of patients treated with amikacin, 0.4% (one out of 221) with ethionamide/prothionamide, 2.8% (15 out of 536) with linezolid and 1.8% (eight out of 498) with cycloserine/terizidone.

The aDSM study provided valuable information, but implementation needs scaling-up to support patient-centred care.

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## Introduction

With >558 000 patients estimated by the World Health Organization (WHO) in 2017 [1], rifampicin- and multidrug-resistant tuberculosis (MDR-TB) are a clinical and public health priority [1, 2]. From the public health perspective, it is imperative to prevent the selection of drug-resistant strains of *Mycobacterium tuberculosis* by effective treatment of drug-susceptible TB patients and to reduce the transmission of drug-resistant strains by diagnosing and treating them rapidly and effectively [3]. The clinical management of MDR- and extensively drug-resistant (XDR)-TB is expensive and medically challenging: clinicians are left with fewer effective drugs, which in turn cause more frequent serious adverse events than those used for the treatment of drug-susceptible TB [1, 2, 4, 5]. Since the implementation of a global approach to treat MDR-TB with second-line drugs (known as the "DOTS Plus" strategy) [4], monitoring, recording and reporting of adverse events have become more important.

In recent years, new (*i.e.* delamanid and bedaquiline) and repurposed anti-TB drugs have been introduced in the treatment of MDR-TB [2]. Bedaquiline was recently included in the new WHO MDR-TB classification [6, 7] as a priority drug (group A) following growing evidence of efficacy and tolerability [8–14]. Delamanid is in the WHO group C (add-on agents) [6], with a promising safety profile [15–18].

The repurposed anti-TB drugs [6, 19] linezolid [20, 21] and fluoroquinolones [19] have been included in group A, clofazimine in group B [22] and imipenem/meropenem in group C [23–25], based mainly on effectiveness studies, toxicity and programmatic considerations.

Although more evidence is becoming available from trials and observational studies on anti-TB drug toxicity, global active TB drug safety monitoring and management of adverse events (aDSM) information on the following is still missing: 1) new drugs; 2) linezolid and clofazimine; 3) drug combinations including drugs such as bedaquiline, delamanid, clofazimine and fluoroquinolones which increase the QT interval in the electrocardiogram (with possible life-threatening arrhythmias) [26, 27]; d) amikacin (group C, and other second-line-injectable drugs), cycloserine/terizidone (group B), ethionamide/prothionamide, para-aminosalicylic acid (PAS), ethambutol, pyrazinamide (group C) and high dose-isoniazid [6, 19].

The WHO recommends pharmacovigilance and aDSM, inviting national TB programmes to implement "active and systematic clinical and laboratory assessment of patients on treatment with new TB medicines, or novel MDR-TB regimens in order to detect and report potential or confirmed drug toxicities" [28–30].

As of today, no global study has reported adverse events of anti-TB drugs based on a prospective aDSM approach including patients treated with the new drugs bedaquiline and delamanid and repurposed drugs such as linezolid and clofazimine.

This approach has been possible through the Global Tuberculosis Network [31], which recently reported the study design of the first aDSM project originally involving 27 countries [30].

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The aim of the present register-based study was to prospectively evaluate the frequency and severity of adverse events due to anti-TB drugs in a cohort of consecutive TB patients treated with new and repurposed drugs in 26 countries following the principles and methods of the WHO aDSM project [28–30, 32]. We summarise the findings of an interim analysis of patients who completed or were still on treatment at the time of data collection.

## Methods

### Study design

A pilot study was implemented in 2015 to assess feasibility and utility of the project as well as to pretest the data flow and analysis. The coordinating centre's ethics committee approved the study on July 11, 2017. The study was proposed to the clinical centres or national TB programmes participating in the network. Each centre or country signed a confidentiality and data-sharing agreement with the coordinating centre and obtained local ethics committee clearance or had a waiver indicating no requirement for ethical approval due to the local regulations.

Starting from July 2017 and after the participating centres signed up to the project, all consecutive patients (including children and adolescents) undergoing treatment with bedaquiline and/or delamanid were enrolled based on their drug exposure [30]. No specific exclusion criteria were adopted for patient selection. Mexico, Paraguay, Spain, Slovakia and Sudan started reporting when the first case in the country initiated anti-TB treatment with bedaquiline and/or delamanid.

The adverse events of any drug involved in the treatment regimen were prospectively collected, ensuring a probabilistic mechanism of causality assignment (*e.g.* attribution of the adverse event to a specific drug based on its evidence-based profile). Each clinical unit participating in the study had a consilium-like mechanism for the management of the adverse events [5]. All adverse events and the proposed attribution to one or more specific drugs were revised by the international coordination team and discussed with the reporting clinicians. The scientific evidence available during the study period drove the attribution of an adverse event to a specific drug based on a probability method. Any discrepancy was resolved by consensus. We contacted investigators to ensure accuracy after recoding and validation of the dataset before final analysis. The datasets reported by clinical centres and national TB programmes were updated twice a year. The present manuscript reports the results of the interim analysis conducted on the data reported up to August 28, 2019.

### Variables and definitions

The data were obtained *via* a collection form in an electronic format based on the WHO-recommended template, although additional clinical details were requested [30]. Annual data collection occurs twice and is based on the information provided by the clinical files of the recruited clinical centres.

The information collected included anonymised patients' demographic data, bacteriological, radiological and clinical status at diagnosis, and data on treatment safety during therapy.

According to the WHO aDSM project, serious adverse events include death or a life-threatening event, hospitalisation or prolongation of hospitalisation, persistent or significant disability, or congenital anomaly. Serious adverse events included grade 3–5 adverse events (grade 3: serious; grade 4: life-threatening; grade 5: death) [13, 28, 32]. Minor adverse events included those of grade 1 (mild) and grade 2 (moderate) [13, 28, 32].

Whenever an adverse event occurred, the clinicians reported it using a form summarising the adverse event details, including the grade, the drug(s) responsible (with details on the dosage and the accompanying medications), the examinations performed, the actions taken, the duration and the outcome of the event (recovered/resolved, recovering/resolving, with sequelae, not recovered/resolved, died, unknown).

All case definitions (*e.g.* MDR-TB, new case, retreatment case, *etc.*) were derived from WHO documents [1, 6, 7].

The study coverage (annex 1; number of patients treated with new drugs reported/number of patients estimated) was defined in any country in agreement with the investigators and the national TB programme authorities [10].

### Data analysis

A descriptive analysis was performed on the patients evaluated in the cohort. The analysis was stratified by geographical area (*e.g.* Europe *versus* non-Europe, where Europe refers to WHO European region and non-Europe to WHO regions other than Europe), sex, risk factors (*e.g.* HIV sero-status, diabetes) and adverse event severity.

Qualitative and quantitative variables were summarised using absolute frequency, percentage median (interquartile ranges (IQR)) and mean±SD. Chi-squared or Fisher exact tests were used to compare qualitative variables, and the t-test or Mann–Whitney test was used to statistically compare quantitative variables.

Adverse events were analysed both "per drug" (proportion of patients treated with a given drug who experienced an adverse event attributed to this drug) and by groups (organ/system) of adverse events according to a format allowing international comparisons [13].

The map in figure 1 was created using the ggplot2 and rworldmap packages in R version 3.5.1 [10, 33].

## Results

Overall, 45 centres from 26 countries/regions in all continents reported 658 patients as of August 28, 2019 (figure 1, annexes 1–3).

Argentina, Australia (Victoria State), Brazil, Bulgaria, Chile, China (Zhejiang Province), Greece, Lithuania, Mexico, the Netherlands, Niger, Paraguay, Portugal, Russian Federation (Moscow and Arkhangelsk Oblasts), Slovakia, Spain, Sudan, Sweden and Switzerland (Vaud county) reported 100% of the patients treated with new drugs in the country/region, while Belarus, Belgium, India, Italy, Latvia, Peru and the United Kingdom reported a proportion of national patients ranging from 15% to 80% (annex 1).

Demographic, epidemiological and clinical characteristics of the patients are summarised in table 1 (stratified by geographical area, Europe *versus* other than Europe). The adverse events per drug in cases who completed or were still under treatment are summarised in tables 2 and 3 (for each drug: number of patients with adverse events/number of patients treated with the drug) and in annex 3. The serious cardiological adverse events are summarised in table 4 (serious QT prolongation and serious arrhythmia) and the minor ones in annex 4. A summary of serious adverse events per organ/system is summarised in figure 2 and per drug in annex 5. The interval between drug administration and adverse event occurrence, according to the treatment outcome at the study data collection, is summarised in annex 6.
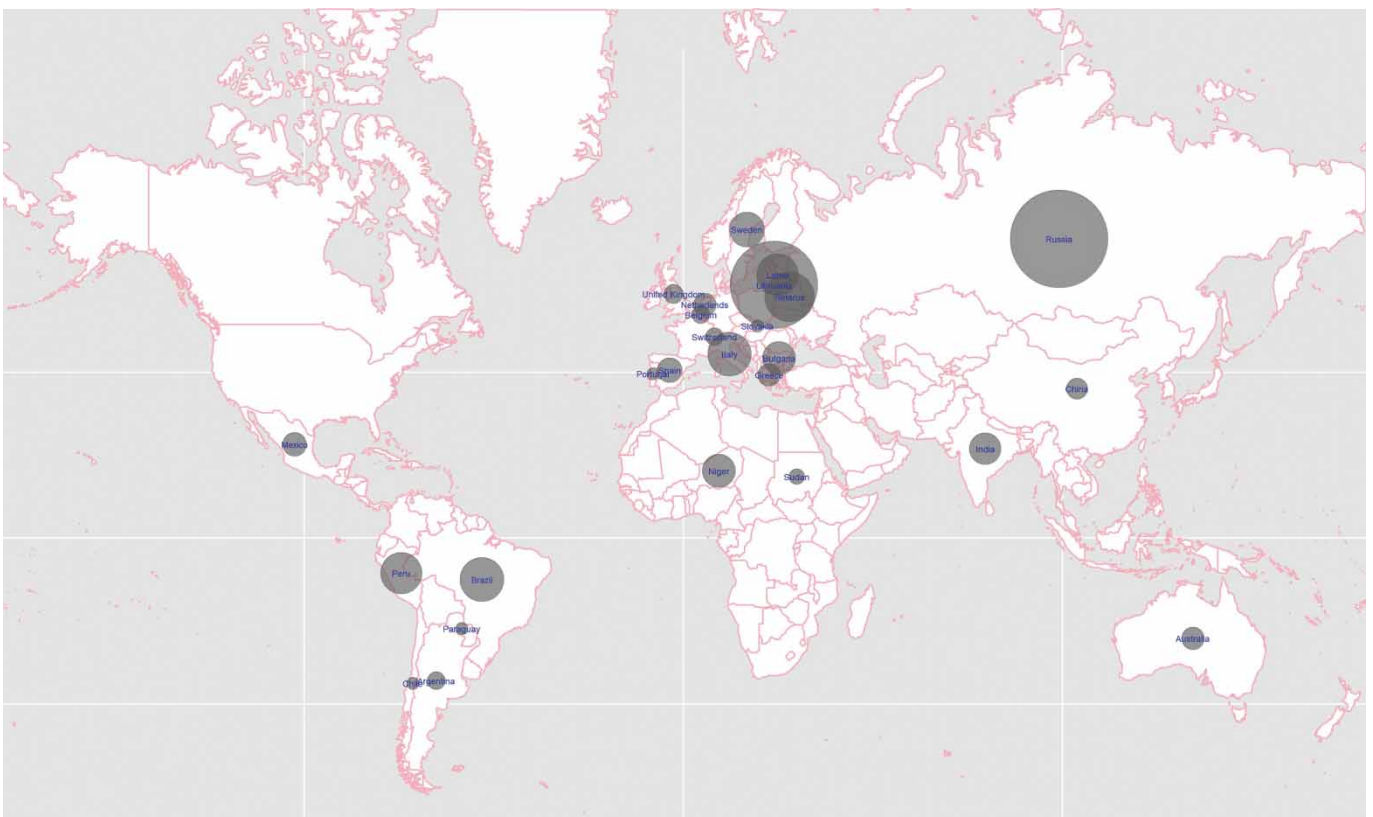


FIGURE 1 Global distribution of the clinical centres participating in the study. The size of the grey dots reflects the number of patients reported.

TABLE 1 Descriptive analysis of the characteristics of 658 tuberculosis (TB) patients by area of origin (Europe *versus* other settings)

| | Total | Geographic area of origin | | p-value[#] |
| --- | --- | --- | --- | --- |
| | | Non-European | European | |
| Subjects | 658 | 120 | 538 | |
| Male | 452/658 (68.7) | 80/120 (66.7) | 372/538 (69.1) | 0.60 |
| Age years | 42 (33–53) | 40.5 (30–54) | 42.5 (34–53) | 0.25 |
| Body weight kg | 60 (53–70) | 54.7 (49.0–61.5) | 62 (54–71) | <0.0001 |
| Height cm | 173 (165–178) | 167 (160–174) | 174 (168–178) | <0.0001 |
| Migrant | 85/656 (13.0) | 8/120 (6.79) | 77/536 (14.4) | 0.02 |
| Pregnant | 5/347 (1.4) | 2/72 (2.8) | 3/275 (1.1) | 0.28 |
| Breastfeeding female | 2/326 (0.6) | 2/66 (3.0) | 0/260 (0.0) | 0.04 |
| Thyroid disease | 9/568 (1.6) | 4/120 (3.3) | 5/448 (1.1) | 0.10 |
| Patients with previous ECG abnormalities | 68/545 (12.5) | 6/120 (5.0) | 62/425 (14.6) | 0.004 |
| Alcohol abuser | 148/657 (22.5) | 11/119 (9.2) | 137/538 (25.5) | <0.0001 |
| Drug abuser | 41/658 (6.2) | 6/120 (5.0) | 35/538 (6.5) | 0.54 |
| Methadone user | 7/561 (1.3) | 0/120 (0.0) | 7/441 (1.6) | 0.36 |
| Patients with diabetes mellitus | 63/651 (9.7) | 19/120 (15.8) | 44/531 (8.3) | 0.02 |
| People living with HIV | 29/655 (4.4) | 0/120 (0.0) | 29/535 (5.4) | <0.0001 |
| CD4 counts cells·mm$^{-3}$ | 94 (30–212) | | 94 (30–212) | |
| Patients on ART | 27/29 (93.1) | 0/60 (0.0) | 27/145 (18.6) | <0.0001 |
| Previous anti-TB treatment | 439/658 (66.7) | 109/120 (90.8) | 330/538 (61.3) | <0.0001 |
| Surgical therapy | 77/647 (11.9) | 6/120 (5.0) | 71/527 (13.5) | 0.01 |
| Pulmonary TB | 648/658 (7.1) | 119/120 (99.2) | 529/538 (98.3) | 0.50 |
| Extrapulmonary TB | 47/658 (7.1) | 2/120 (1.7) | 45/538 (8.4) | 0.006 |
| Sputum smear positive | 451/657 (68.7) | 116/120 (96.7) | 335/537 (62.4) | <0.0001 |
| Culture positive | 590/657 (89.8) | 118/120 (98.3) | 472/537 (87.9) | 0.001 |

Data are presented as n, n/N (%) or median (interquartile range), unless otherwise stated. ART: antiretroviral therapy. [#]: non-European *versus* European.

Out of 658 patients, 577 (87.7%) were treated with bedaquiline (which was co-administered with delamanid, in combination or sequentially, in 40 patients) and 121 (18.4%) with delamanid: 161 (24.5%) had TB caused by MDR-TB or rifampicin-resistant strains of *M. tuberculosis*, 224 (34%) pre-XDR strains (125 MDR-TB with additional resistance to a fluoroquinolone and 99 to an injectable drug), 245 (38.6%) XDR-TB strains, while 19 (2.9%) presented different other resistances explaining the prescription of new drugs (including three pan-susceptible TB patients: two with serious adverse events to first-line drugs and one per clinical decision) (annex 2).

Most patients were male (n=452, 68.7%) and the median (IQR) age was 42 (33–53) years. There were 85 (13.0%) migrants. HIV co-infection was reported in 29 (4.4%) out of 653 patients (three unknown status) with median (IQR) CD4 cell counts of 94 (30–212) cells·mm$^{-3}$. The majority (n=27, 93.1%) received antiretroviral therapy. A total of 47 (7.2%) individuals were lost to follow-up.

Pulmonary TB was diagnosed in 648 (98.5%) out of 658 patients, with 37 having involvement of both pulmonary and extrapulmonary sites and 10 with isolated extrapulmonary disease (n=4 lymph node, n=3 gastrointestinal, n=2 pleural, n=1 testicular and n=1 psoas abscess).

The percentages of sputum smear- and culture-positive patients at diagnosis were 68.7% (451 out of 657) and 89.8% (590 out of 657), respectively; the remaining patients had a positive molecular test or were treated based on the resistance profile of the index case (n=5), adverse events (n=2) and clinical decision (n=1) (annex 2).

The mean±SD number of drugs to which *M. tuberculosis* was resistant was 6.2±2.5. Overall, 439 (66.7%) out of 658 patients had been treated previously for TB.

The overall prevalence of drug resistance, related to the national drug resistance prevalence and sample size, was as follows: streptomycin n=415 (86.3%), pyrazinamide n=368 (77.0%), ethambutol n=476 (75.1%), fluoroquinolones n=385 (61.9%), ethionamide/prothionamide n=285 (60.8%), kanamycin n=315 (52.9%), capreomycin n=180 (31.0%), amikacin n=171 (30.3%), PAS n=86 (23.1%), cycloserine/terizidone n=25 (7.9%) and linezolid n=12 (4.7%).

TABLE 2 Serious (grade 3–5) and minor (grade 1–2) adverse events per drug in the overall cohort (658 tuberculosis (TB) patients)

| | Total adverse events[#] | | Patients with serious adverse events[¶] | | Patients with minor adverse events | |
|---|---|---|---|---|---|---|
| | n[+] (%) | 95% CI | n[+] (%) | 95% CI | n[+] (%) | 95% CI |
| Subjects n | | | 52 | | 343 | |
| Capreomycin | 52/187 (27.8) | 21.4–34.2 | 5/187 (2.7) | 0.4–5.0 | 47/187 (25.1) | 18.9–31.3 |
| Amikacin | 30/131 (22.9) | 15.7–30.1 | 9/131 (6.9) | 2.6–11.2 | 21/131 (16.0) | 9.7–22.3 |
| Ethionamide/prothionamide | 39/221 (17.6) | 12.6–22.6 | 1/221 (0.4) | −0.4–1.2 | 38/221 (17.2) | 12.2–22.2 |
| Pyrazinamide | 32/236 (13.6) | 9.2–18.0 | 1/236 (1.7) | 0.0–3.4 | 31/236 (13.1) | 8.8–17.4 |
| Delamanid | 16/121 (13.2) | 7.2–19.2 | 1/121 (0.8) | −0.8–2.4 | 15/121 (12.4) | 6.5–18.3 |
| Linezolid | 69/536 (12.9) | 10.1–15.7 | 15/536 (2.8) | 1.4–4.2 | 54/536 (10.1) | 7.6–12.7 |
| Bedaquiline | 64/577 (11.1) | 8.5–13.7 | 6/577 (1.0) | 0.2–1.8 | 58/577 (10.1) | 7.6–12.6 |
| PAS | 24/215 (11.2) | 7.0–15.4 | 1/215 (0.5) | −0.4–1.4 | 23/215 (10.7) | 6.6–14.8 |
| Clofazimine | 15/213 (7.0) | 3.6–10.4 | 3/213 (1.4) | −0.2–3.0 | 12/213 (5.6) | 2.5–8.7 |
| Cycloserine/terizidone | 30/498 (6.0) | 3.9–8.1 | 8/498 (1.8) | 0.5–2.7 | 22/498 (4.4) | 2.6–6.2 |
| Levofloxacin | 14/241 (5.8) | 2.9–8.8 | 0/241 (0.0) | | 14/241 (5.8) | 2.9–8.8 |
| Clarithromycin | 1/21 (4.8) | −4.3–13.9 | 1/21 (4.8) | −4.3–13.9 | 0/21 (0.0) | |
| Moxifloxacin | 9/240 (3.8) | 1.4–6.2 | 1/240 (0.4) | −0.4–1.2 | 8/240 (3.3) | 1.0–5.6 |

PAS: para-aminosalicylic acid. [#]: cumulative frequency of adverse events occurred in patients treated with anti-TB drugs; [¶]: in addition, three patients with serious adverse events due to all anti-TB drugs administered (n=2 gastrointestinal, n=1 renal problem; table 4); [+]: numerator is the number of patients who had at least an adverse event with the drug and denominator is the total number of patients treated with the drug: patients with adverse event per drug/number of patients treated with the drug (some patients may have had more than one adverse event per drug; table 4).

Treatment regimens included, in addition to bedaquiline and/or delamanid, linezolid (81.5%), moxifloxacin (37.1%), levofloxacin (36.6%), clofazimine (32.4%), capreomycin (28.4%), amikacin (19.9%) and carbapenems (11.2%).

The median (IQR) range of the administrative delay in procuring bedaquiline was 0 (0–11) days.

TABLE 3 Serious (grade 3–5) and minor (grade 1–2) adverse events per drug in 233 tuberculosis (TB) patients who completed treatment

| | Total adverse events | | Severe adverse events | | Minor adverse events | |
|---|---|---|---|---|---|---|
| | n[#] (%) | 95% CI | n (%) | 95% CI | n (%) | 95% CI |
| Subjects n | | | 20 | | 176 | |
| Capreomycin | 27/80 (33.8) | 23.4–44.2 | 2/80 (2.5) | −0.9–5.9 | 26/80 (32.5) | 22.2–42.8 |
| Amikacin | 12/42 (28.6) | 14.9–42.3 | 3/42 (7.1) | −0.7–14.9 | 11/42 (26.2) | 19.9–39.5 |
| Ethionamide/prothionamide | 20/71 (28.2) | 17.7–38.7 | 1/71 (1.4) | −1.3–4.1 | 19/71 (26.8) | 16.5–37.1 |
| Pyrazinamide | 14/106 (13.2) | 6.8–19.6 | 1/106 (0.9) | −0.9–2.7 | 12/106 (11.3) | 5.3–17.3 |
| Delamanid | 10/43 (23.3) | 10.7–35.9 | 1/43 (2.3) | −2.2–6.8 | 9/43 (20.9) | 8.8–33.1 |
| Linezolid | 30/185 (16.2) | 10.8–21.5 | 5/185 (2.7) | 0.4–5.0 | 27/185 (14.6) | 9.5–19.7 |
| Bedaquiline | 34/205 (16.6) | 11.5–21.7 | 2/205 (1.0) | −0.4–2.4 | 32/205 (15.6) | 10.6–20.6 |
| PAS | 11/102 (10.8) | 4.8–16.8 | 0/102 (0.0) | | 11/102 (10.8) | 4.8–16.8 |
| Clofazimine | 9/71 (12.7) | 5.0–20.5 | 1/71 (1.4) | −1.3–4.1 | 8/71 (11.3) | 3.9–18.7 |
| Cycloserine/terizidone | 14/178 (7.9) | 3.9–11.9 | 3/178 (1.7) | −0.2–3.6 | 11/178 (6.2) | 2.7–9.7 |
| Levofloxacin | 6/88 (6.8) | 1.5–12.1 | 0/88 (0.0) | | 6/88 (6.8) | 1.5–12.1 |
| Clarithromycin | 1/9 (11.1) | −9.4–31.6 | 1/9 (11.1) | −9.4–31.6 | 0/9 (0.0) | |
| Moxifloxacin | 9/87 (10.3) | 3.9–16.7 | 0/87 (0.0) | | 4/87 (4.6) | 0.2–9.0 |

PAS: para-aminosalicylic acid. [#]: numerator is the number of patients who had at least an adverse event with the drug and denominator is the total number of patients treated with the drug: patients with adverse event per drug/number of patients treated with the drug (some patients may have had more than one adverse event per drug; table 4).

**TABLE 4** Summary of nine serious cardiological adverse events which occurred in nine patients out of 658 in the cohort

| | Country | Age | Sex | Drug considered responsible | Current prescribed regimen | Treatment outcome | Baseline QTc value msec | QTcF$_{max}$ prolongation reached msec | Episode(s) n | Drug permanently interrupted | If yes, after how many days | Total drug exposure days | Drug restarted | Outcome: adverse event resolved/ resolving |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **QT prolongation** | Italy | 41 | Male | Bdq | Z, Cfz, Lzd, Trd, Merop, Clav, Bdq | Still on treatment | 454 | 480 | 1 | Yes | 190 | 190 | No | Resolved |
| | Italy | 32 | Female | Cfz | Cfz, PAS, Trd, Amk, Bdq, Lzd | Still on treatment | 454 | 500 | 1 | Yes | 23 | 23 | No | Resolved |
| | Italy | 50 | Male | Cfz | Mxf, Lzd, Trd, Cfz, Amk, Bdq | Still on treatment | 465 | 566 | 1 | Yes | 204 | 204 | No | Resolved |
| | Lithuania | 35 | Female | Mfx[#,¶] | Dlm, Lfx, Mfx, Cm, Lzd | Still on treatment | 352 | 618 | 1 | Yes | 11 | 11 | No | Resolved |
| | Russia | 71 | Female | Bdq | Bdq, Lzd, Lfx, Cs, Azitro, Cm | Cured | 354 | 556 | 1 | No | | 266 | Yes | Resolving |
| | Russia | 55 | Female | Bdq | Bdq, Lzd, Lfx, Cs, Azitro, Z | Cured | 341 | 527 | 1 | No | | 233 | Yes | Resolving |
| | Russia | 73 | Female | Bdq | Bdq, Lfx, Cs, Cm, PAS | Still on treatment | 338 | 521 | 1 | Yes | 84 | 84 | No | Resolved[§] Resolving |
| | Sweden | 33 | Female | PAS[+] | Bdq, Lfx, Cs, Z, E, Lzd, Cfz[§] | Still on treatment | 438 | 530 | 1 | Yes | 17 | 17 | No | Resolved |
| **VES-bigeminy arrhythmia** | Sweden | 59 | Male | Dlm | Bdq, Cfz, Lfx, Lzd, Dlm | Cured | 393 | 420 | 1 | Yes | 4 | 4 | No | Resolved |

QTc: corrected QT interval; QTcF: QT Fridericia-corrected QT interval; QT prolongation: an electrical disturbance visible on the ECG, measuring the delayed ventricular repolarisation, when the heart muscle takes longer than normal to recharge between beats; VES: ventricular extrasystole; Bdq: bedaquiline; Z: pyrazinamide; Cfz: clofazimine; Lzd: linezolid; Trd: terizidone; Merop: meropenem; Clav: clavulanic acid; PAS: para-aminosalicylic acid; Amk: amikacin; Mfx: moxifloxacin; Cm: capreomycin; Lfx: levofloxacin; Cs: cycloserine; Azitro: azitromycin; E: ethambutol; Dlm: delamanid. [#]: Mfx was co-administered with delamanid; delamanid was well tolerated, with no adverse event reported; [¶]: Mfx was withdrawn after 231 days in a patient with Wolff–Parkinson–White syndrome: it was not considered as adverse event; [+]: PAS was responsible for diarrhoea, increased magnesium level and QT prolongation (which normalised after stopping the drug); [§]: after 2 months of treatment during pregnancy, linezolid and clofazimine were added after delivery.
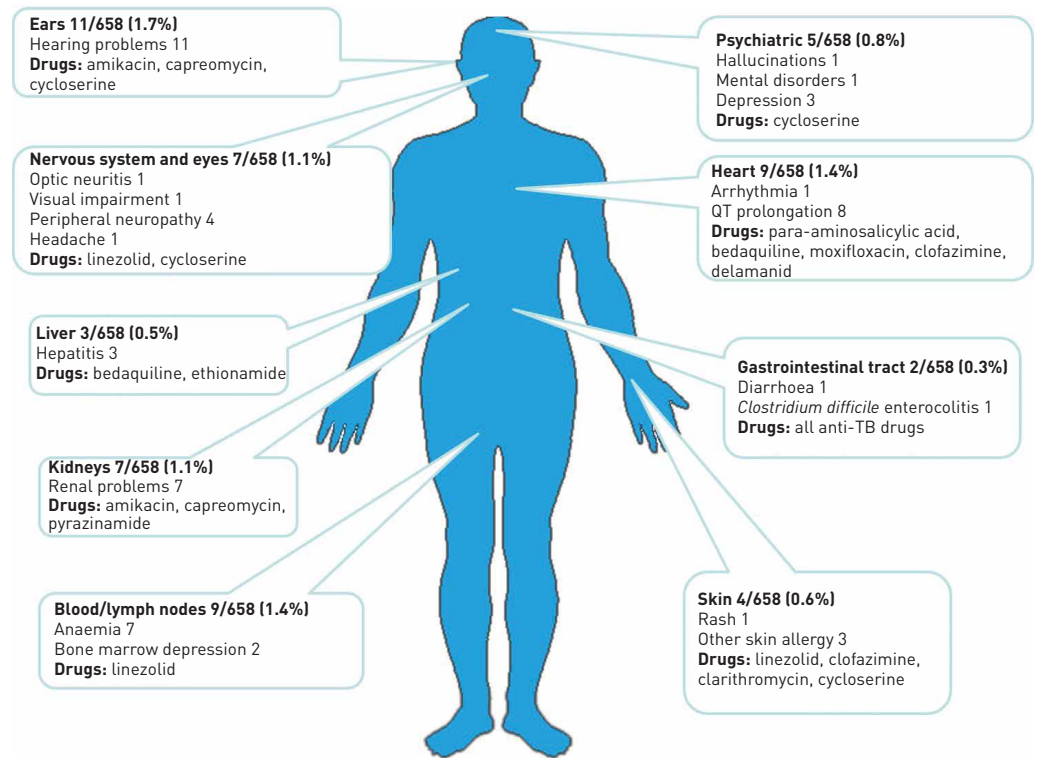
**Ears 11/658 (1.7%)**
Hearing problems 11
**Drugs:** amikacin, capreomycin, cycloserine

**Psychiatric 5/658 (0.8%)**
Hallucinations 1
Mental disorders 1
Depression 3
**Drugs:** cycloserine

**Nervous system and eyes 7/658 (1.1%)**
Optic neuritis 1
Visual impairment 1
Peripheral neuropathy 4
Headache 1
**Drugs:** linezolid, cycloserine

**Heart 9/658 (1.4%)**
Arrhythmia 1
QT prolongation 8
**Drugs:** para-aminosalicylic acid, bedaquiline, moxifloxacin, clofazimine, delamanid

**Liver 3/658 (0.5%)**
Hepatitis 3
**Drugs:** bedaquiline, ethionamide

**Gastrointestinal tract 2/658 (0.3%)**
Diarrhoea 1
*Clostridium difficile* enterocolitis 1
**Drugs:** all anti-TB drugs

**Kidneys 7/658 (1.1%)**
Renal problems 7
**Drugs:** amikacin, capreomycin, pyrazinamide

**Blood/lymph nodes 9/658 (1.4%)**
Anaemia 7
Bone marrow depression 2
**Drugs:** linezolid

**Skin 4/658 (0.6%)**
Rash 1
Other skin allergy 3
**Drugs:** linezolid, clofazimine, clarithromycin, cycloserine

FIGURE 2 Summary of the distribution of 57 serious adverse events by organ/system.

Patients were exposed to bedaquiline for a median (IQR) of 170 (99–239) days, and to delamanid for 168 (145.5–182) days. Adjuvant surgical therapy and subsequent pulmonary rehabilitation were performed in 77 (11.9%) patients.

The median (IQR) treatment duration in the cohort was 385 (231–545) days, including 233 (35.9%) patients who completed treatment and 369 (56.7%) who were still on treatment (150 (44.2%) out of 339 having had 6 months of bedaquiline and 49 (67.1%) out of 73 of delamanid) as of August 28, 2019.

### Adverse events
Overall, 504 adverse event episodes were reported by clinical centres of which 447 (88.7%) were classified as minor (grade 1–2) and 57 (11.3%) were classified as serious (grade 3–5) (annex 5).

### Serious adverse events
Overall, 57 (11.3%) serious adverse events were reported by 55 patients for different organs/systems (table 2 and 3, annex 5), all resolved/resolving except six (10.5%) as follows: n=2 gastrointestinal, n=7 nervous system, n=4 skin, n=11 hearing, n=5 psychiatric, n=9 blood, n=9 cardiac, n=3 hepatic and n=7 renal (annex 3).

The overall proportion of patients reporting serious adverse events related to linezolid, clofazimine, bedaquiline and delamanid in patients treated with these medicines was 2.8% (15 out of 536), 1.4% (three out of 213), 1.0% (six out of 577) and 0.8% (one out of 121), respectively (table 2). Among patients who completed treatment the proportion of serious adverse events was (nonsignificantly) higher (table 3).

Clinicians reported to have notified the adverse events to the health authorities in their countries as follows: 3 (52.6%) out of 57 serious and 19 (4.3%) out of 447 minor adverse events.

### Cardiological adverse events
Overall, 17 (2.6%) out of 658 patients experienced a Fridericia-corrected QT prolongation (QTcF) ⩾500 msec. Among them, 16 received bedaquiline (six with serious and 10 with minor adverse events; two of them with co-administered delamanid). In a single case, treated with delamanid alone, a serious adverse event was reported and attributed to moxifloxacin (table 4).

A QTcF interval prolongation causing serious cardiological adverse events was reported by eight patients only (table 4); the drug responsible was bedaquiline in four patients, clofazimine in two patients, moxifloxacin and PAS in one patient, while in another patient it was due to a non-TB drug (amitriptyline, data not shown). No deaths were recorded. Out of those who received bedaquiline, the drug was withdrawn only in two patients reporting serious adverse events (two (0.35%) out of 577), while in two patients the QT normalised after interrupting the concomitant administration of clofazimine. All serious QT-related adverse events resolved/are resolving.

A single patient had one minor adverse event related to QTcF prolongation requiring withdrawal of the drug (moxifloxacin replaced by levofloxacin) (annex 4).

Overall, 32 patients experienced minor adverse events related to QT prolongation, the majority due to bedaquiline (n=28, 87.5%) and fluoroquinolones (n=3, 9.3%) (annex 4).

A single patient discontinued delamanid after experiencing a serious adverse event (ventricular bigeminy arrhythmia appearing 4 days into treatment) (table 4).

## Discussion

The aim of the present study was to prospectively evaluate the frequency and severity of adverse events due to anti-TB drugs in a cohort of consecutive patients following the principles and methods of the WHO aDSM project.

The project worked as a "register" according to the WHO proposal to national programmes, aimed at promoting regular monitoring of adverse events, as well as collecting and reporting information on bacteriological status at diagnosis, during and at the end of treatment with final outcomes [7, 29, 30]. WHO recommends that countries use their existing surveillance methodology (electronic registers or existing electronic medical record systems) to extract the data and use them for clinical and public health purposes [29].

National TB programmes face difficulties in implementing aDSM and contributing to the global database. While the amount and type of information to collect is known and there is a sufficient burden of patients to satisfy the need to establish a routine adverse event recording and reporting system, the existing surveillance systems are currently not equipped to collect and analyse relevant variables.

The present project represents the first effort to document the feasibility of the aDSM approach and to collect quality scientific evidence on the adverse events in patients treated with new and repurposed drugs in "field conditions" in countries from all continents. The available scientific evidence on the safety and tolerability profile of anti-TB drugs can be retrieved from single observational and experimental studies. This project provides an international assessment following a register-based methodology.

A first important finding of the study is that when treatment regimens including bedaquiline and delamanid are used, the overall proportion of adverse events is reasonably low (8.7% of patients with serious adverse events (grade 3 and 4, no grade 5 adverse events)).

Notably, the injectables (and ethionamide) are the drugs causing more adverse events (table 2 and 3). With the new WHO all-oral approach [6, 7] and the availability of new drugs, capreomycin will no longer be used, and amikacin as well as ethionamide/prothionamide (and PAS) will be used less. In contrast, linezolid will be used increasingly, and being a drug with frequent and serious adverse events [20] there is a need to balance efficacy and toxicity [34]. Therapeutic drug monitoring may help achieve a therapeutic target of area under the curve/minimal inhibitory concentration >119 [35] while keeping trough concentrations low enough to prevent toxicity [36].

A second important outcome of this study is the possibility to carefully analyse the adverse events caused by bedaquiline and delamanid and by repurposed drugs. While overall 11.1% of the patients had adverse events to bedaquiline and 13.2% to delamanid (table 2), the serious adverse events due to these drugs were few, with only two patients discontinuing bedaquiline (0.35%) and one discontinuing delamanid (0.8%) because of cardiological adverse events [14, 37].

The proportion of patients reporting serious adverse events related to linezolid- and clofazimine-treated patients was 3% and 1.4%, respectively (annex 3).

Overall, 5.8% of the patients experienced an adverse event with levofloxacin and 3.8% with moxifloxacin, while only two patients had serious adverse events with moxifloxacin at the normal dose. None of the 12 patients treated with high-dose isoniazid and high-dose moxifloxacin reported adverse events.

Worryingly, an important proportion of adverse events identified by care providers were not reported to health authorities at the national level. We speculate that the explanations for the adverse event

under-reporting include lack of awareness, the administrative burden (need to report to the country and to the aDSM system and to the drug manufacturer with different forms and multiple steps), confidentiality issues, the involvement of different sectors (public and private, prisons, *etc.*) and the fear of blame.

Furthermore, there were a few discrepancies on grading of the adverse event "QTc prolongation". In four patients the adverse events were initially categorised as minor, even though they had resulted in the withdrawal of the offending drug. In agreement with the treating physician these adverse events were reclassified as serious. Asymptomatic conditions such as QTc prolongation need clear and well publicised criteria for accurate grading. QTc interval monitoring is usually performed in MDR-TB patients exposed to bedaquiline and delamanid in the WHO European region; although rare fatal events have been recorded, the ECG is a cost-effective preventive intervention for those at risk of developing cardiological adverse events [38].

To avoid premature discontinuation of potent drugs, available national and or international expert panels could be consulted for guidance [5, 31]. Medical conditions which can significantly increase the probability of a cardiological adverse event in MDR-TB patients (*i.e.* hypokalaemia and AIDS) should be monitored carefully [39].

When compared with the recent individual data meta-analysis performed in five cohorts (Armenia, Georgia, South Africa, France and Janssen Therapeutic cohort) on 537 patients treated with bedaquiline under compassionate use [13], the proportion of adverse events seems rather consistent with those found in our study. For example, 4.9% of patients suffered cardiac adverse events in the five-cohort study similar to the 5.5% in our study (denominator: patients treated with bedaquiline). Similarly, the proportion of interruptions of bedaquiline treatment in our study due to QTcF increase (0.35%) is consistent with that described in a recent systematic review of the literature (0.68%) [26].

The study has several strengths, including the number of countries participating [26] and a large sample size (to our knowledge one of the largest multinational cohorts of MDR-TB patients treated with bedaquiline- and/or delamanid-containing regimens based on WHO aDSM protocol), the prospective design and the accuracy of the information collected in countries with different epidemiological and economic backgrounds. Last, but not least, the majority of countries/states/regions (21 out of 26) provided data on all the consecutive patients treated with bedaquiline and delamanid during the study period.

A limitation is represented by the use of a consensus-based process to attribute adverse events to a specific drug, which included the local expert panel and the aDSM International Group panel. The scientific evidence on the safety and tolerability profile of a single drug or of a pharmacological combination was the driver adopted to identify the drug responsible of an adverse event; the probability of proving a causal relationship in specific patients, where the scientific evidence is poor, is very low. Further studies focused on the anti-TB drugs' safety, based on the re-challenge methodology (*i.e.* drug administration after interruption following the occurrence of an adverse event) could help elucidate the adverse event profile of the anti-TB drugs. Furthermore, only a few centres carried out therapeutic drug monitoring to assess the relationship between adverse events and drug exposure (dosage and frequency of administration). Moreover, no variables related to concomitant medications, which could affect drug exposure, were recorded, with HIV therapy in patients with HIV infection the only exception. It was not possible to use approaches like the Naranjo score or the Yale algorithm [40, 41]. A second limitation is that few paediatric patients (four individuals aged <18 years) and people living with HIV (n=29, 4.4%) were included in the cohort to allow specific subanalyses.

The psychological role played by providing information on the risk of treatment failure following drug withdrawal, as well as potential biased communication with migrants and the clinical setting (*e.g.* ambulatory care), could have affected the patients' tolerability profile and the reporting of adverse events. Unfortunately, we did not collect any variables which could evaluate those important features.

Furthermore, we evaluated the occurrence of adverse events in both individuals completing their regimen and still on treatment, for whom the cumulative drug toxicity (*e.g.* from linezolid) may be underestimated. Among patients who completed treatment, where the cumulative toxicity can be adequately assessed, the proportion of adverse events was (nonsignificantly) higher.

We did not collect any genetic/pharmacogenomic data, which could increase the risk of some adverse events. Future studies are needed to better clarify the role played by host and environmental characteristics in the occurrence of adverse events.

Finally, as the majority of countries started their aDSM project with this study, preselection or under-notification of adverse events (particularly minor ones and those not related to the new drugs) cannot be excluded. The under-reporting in a real-world setting can be a key issue in estimating the safety profile of a drug/pharmacological regimen. Healthcare workers and patients should be aware of the

importance of reporting the occurrence of adverse events to better understand the pharmacological safety and the benefit/risk ratio of a prescription. A classification bias of some adverse events should be considered: although all clinical centres enrolled in the project followed the WHO protocol on adverse events' reporting, local audits aimed at assessing the implementation of the standard operating procedures (*e.g.* regular audiometry) were not carried out because of financial constraints.

Unfortunately, several countries (in America, Asia and sub-Saharan Africa) declined when asked to participate, in view of the voluntary basis of the study perceived as "difficult" or "time-consuming" without provision for additional resources. For this reason, and because of the different entry time in the study (which works as a "register"), the study does not allow us to evaluate the prevalence of drug resistance in the different settings. There is an urgent need to overcome the administrative burden involved in reporting adverse event by easy-to-use e-forms that can be automatically compiled from medical records.

The study will continue to evaluate early and final treatment outcomes as periodic updates occur and the "cohort" is therefore a "living" one. This cohort allows evaluation of novel treatments and combinations in a relatively short time-frame; particularly important given the substantial variation in international practice and guidelines recommending person-centred therapy for MDR-TB [42, 43].

This approach will allow the participating countries to evaluate the "quality" of their treatment services and minimise the risk of post-treatment sequelae responsible of functional damage and impaired quality of life [44–46].

In conclusion, the study results confirm that aDSM for patients undergoing anti-TB regimens with new drugs is feasible. Furthermore, the study reaffirms the relative safety of new drugs recommended by the new WHO guidelines, as the occurrence of serious adverse events in this large cohort of patients from 26 countries was observed in <10% of patients. Greater adoption of the recommended aDSM at a local, national and international level is possible by improving the quality of the process (*i.e.* standardised, active and regular recording and reporting based on shared standard operating procedures).

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