New TB drugs for the treatment of children and adolescents with rifampicin-resistant TB in Mumbai, India

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SUMMARY

SETTING: Médecins Sans Frontières (MSF) clinic in Mumbai, India.
OBJECTIVE: To determine the final treatment outcomes, culture conversion and adverse events (AEs) during treatment among children and adolescents (0–19 years) with rifampicin-resistant tuberculosis (RR-TB) who received ambulatory injectable-free treatment, including bedaquiline (BDQ) and/or delamanid (DLM) during September 2014–January 2020.

DESIGN: This was a retrospective cohort study based on review of routinely collected programme data.

RESULTS: Twenty-four patients were included; the median age was 15.5 years (min-max 3–19) and 15 (63%) were females. None were HIV-coinfected. All had fluoroquinolone resistance. Twelve received treatment, including BDQ and DLM, 11 received DLM and one BDQ. The median exposure to BDQ (n = 13) and DLM (n = 23) was 82 (IQR 80–93) and 82 (IQR 77–96) weeks, respectively. Seventeen (94%) patients with positive culture at baseline (n = 18) had negative culture during treatment; median time for culture-conversion was 7 weeks (IQR 5–11). Twenty-three (96%) had successful treatment outcomes: cured (n = 16) or completed treatment (n = 7); one died. Eleven (46%) had 17 episodes of AEs. Two of 12 serious AEs were associated with new drugs (QTcF >500 ms).

CONCLUSION: Based on one of the largest global cohorts of children and adolescents to receive new TB drugs, this study has shown that injectable-free regimens containing BDQ and/or DLM on ambulatory basis were effective and well-tolerated among children and adolescents and should be made routinely accessible to these vulnerable groups.

KEY WORDS: paediatrics; gastric lavage; sputum induction; Xpert; extrapulmonary; new drugs

CHILDREN CONTRIBUTED TO 11% of 10 million global burden of TB cases in 2018.1 Although an estimated 33 000 children become sick with rifampicin (RIF) resistant TB (RR-TB; defined as TB resistant to RIF and isoniazid [INH]) every year, there is a wide gap between diagnosis and treatment initiation.2 Treatment outcomes have been reported to be better in children with RR-TB than in adults;3,4 however, the inclusion of children in many therapeutics advances, including access to the newer TB drugs bedaquiline (BDQ) and delamanid (DLM), have been delayed.5

In 2018, the WHO recommended the use of BDQ for children 6 years and above, while DLM use in children has been extended to ages 3–6 years (compared to earlier age group of 6–17 years).6,7 In 2019, Borisov et al. presented the first global report on active TB drug safety monitoring and management (aDSM), including the new TB drugs. According to the report, the proportion of patients reporting serious adverse events (SAEs) related to BDQ and DLM was respectively 1% and 0.8%, although information on children and adolescents was limited.8 Studies across the globe have reported on safety of new drugs (BDQ and DLM) in treatment for children and adolescents with complex resistance TB profiles on compassionate use;2,7–11 however, children still have limited access to these new TB drugs.2 The adverse events (AEs) associated with injectables in RR-TB treatment are well-known.12 The WHO has therefore emphasised that children should be treated with all-oral regimens, which requires the inclusion of new TB drugs (BDQ, DLM) in treatment regimen for children and adolescents.6,13

A systematic review by D’Ambrosio et al. in 2017 highlighted the paucity of documentation on new anti-TB drugs used for treatment in children.14 Although early evidence on the combined use of
BDQ and DLM has been documented, the lack of information on children and adolescents has been confirmed in the systematic review by Pontali et al.\textsuperscript{15} Studies from India have reported about the need of new TB drugs for early and effective cure for children,\textsuperscript{16} but the evidence on safety and efficacy of treatment regimen including BDQ and DLM in children and adolescents is low in country.

In India, the Médecins Sans Frontières (MSF), at its independent clinic in Mumbai, has been providing drug-resistant TB (DR-TB) treatment including new TB drugs (BDQ and/or DLM) to children and adolescents with complex TB resistance profiles such as pre-extensively drug-resistant TB (pre-XDR-TB; defined as TB resistant to RIF, INH and second-line injectables or fluoroquinolones [FQs]) and XDR-TB, defined as TB resistant to RIF, INH, second-line injectables and FQs since 2015. The current study aimed to determine the final treatment outcomes, interim culture conversion or radiological/clinical status during treatment and AEs (including QT interval measures with Fridericia’s correction [QTcF >500 ms]) during treatment.

**METHODS**

**Study design**

This was a retrospective cohort study based on a review of routinely collected programme data.

**Setting**

**DR-TB Programme in Médecins Sans Frontières clinic**

The study was conducted in the MSF clinic in Mumbai—a known RR-TB hotspot in India. The clinic provides free-of-cost treatment to patients with DR-TB and HIV since 2007, with a multi-disciplinary team of doctors, nurses, psychologist, psychiatrist, counsellors, social workers and peer educators (cured patients who provide peer-support to patients on treatment by sharing their treatment experience with patients and handling frequently asked questions by patients and families).\textsuperscript{17} All patients are treated under ambulatory care. The programme follows national and international guidelines for DR-TB diagnosis and treatment.

The clinic offers DR-TB treatment to patients with complex TB resistance profiles, referred from private/public institutions, who fail to respond to standard DR-TB treatment. The referred patients are re-evaluated at the MSF clinic and undergo drug susceptibility testing (DST) using Xpert® MTB/Rif (Cepheid, Sunnyvale, CA, USA), line-probe assay and phenotypic DST. Sputum induction and gastric lavage are carried out as diagnostic procedures in children not expectorating spontaneously. Patients are referred to a nearby hospital for biopsy in case of presumptive extra-pulmonary TB (EPTB). Treatment regimens are individualised based on results received. Counsellors and community health workers provide treatment literacy (drug dosage, mode of administration, AEs) and treatment adherence support to the patients and families before treatment initiation and during treatment. The clinical and laboratory information are maintained in patient files and recorded in an electronic database.

The treatment is administered for at least 18 months, as recommended by the WHO, and extended if needed based on clinical and bacteriological response. Patients are routinely monitored using growth charts (weight/height), laboratory investigations, culture follow-up, chest X-ray and electrocardiography (ECG). Chest X-rays were read by two independent experts. In case of discrepancies, the case is discussed by the technical experts in the DR-TB committee meeting and discrepancies are resolved by consensus. Every month routine laboratory evaluation and cultures are performed for monitoring of patients during treatment. A reminder call is made to the patient 1 day prior about their clinic appointment. At each follow-up, the samples are collected for culture from the patient, and patients are clinically evaluated for AE. All AE episodes are clinically managed (either by lowering the dose or intermittently discontinuing the likely associated drug). AE of each patient is categorised and reported by the clinical team during the routine monitoring process at the MSF Clinic. All AEs are reported to the MSF Pharmacovigilance (PV) Unit based in Geneva, Switzerland. The PV team reviews the categorisation of AE and confirms the AE categories. The PV team reverts back to the clinical team for any clarification of the AEs and ensures follow-up of the AEs to assign outcomes. Post-treatment follow-up visits are conducted every 3–6 months for 1 year after treatment completion to monitor for relapse/reinfection.

**DR-TB treatment regimens including new drugs for children and adolescents in India**

Although the WHO issued an interim guideline in 2016 for the use of DLM in children aged 6–17 years,\textsuperscript{7} it is still under process of approval by regulatory authorities, including in India. The recent guidelines on the programmatic management of DR-TB (PMDT) in India mentions the use of BDQ for DR-TB treatment in patients aged ≥18 years under routine programme settings,\textsuperscript{18} while DLM could be considered for children and adolescents aged 6–17 years. The use of BDQ in those aged 6–17 years and DLM in children aged 3–5 years could be considered after approval from the Drug Controller General of India (DCGI). Access to these new TB drugs in the country is restricted to children/adolescents with severe or complicated RR-TB with additional resistance to other drugs, especially FQs. The injectable-free RR-TB treatment would only be accessible to all
children/adolescents with RR-TB once India starts following the new WHO guidelines.

The MSF Clinic has been providing these new TB drugs to DR-TB patients with limited treatment options to design effective treatment regimens since 2015.19

Study population and participants
All children and adolescents (age 0–19 years at the time of RR-TB treatment initiation) who initiated treatment including new drugs (BDQ and/or DLM for at least 1 month during treatment) in the MSF programme between September 2014 and June 2018 and achieved end of treatment outcome (September 2014–January 2020) were included in the study.

Operational definitions
Household contact
Household contacts were permanent members of the household living (at least 1 month) with the patients suffering from DR-TB and receiving treatment.

Concomitant administration of BDQ and DLM
Some patients received DR-TB treatment regimen containing concomitant BDQ and DLM for at least 1 month during treatment.

Treatment outcomes
Standard definitions for treatment outcomes as per India PMDT guidelines were followed. According to the guidelines, “cure” was defined as “A microbiologically confirmed multidrug-resistant/RR-TB patient who has completed treatment without evidence of failure and three or more consecutive cultures taken at least 1 month apart, from 8 months onwards, are negative, including culture at the end of treatment.”18

Culture conversion
The patient is considered to have culture-converted when two consecutive cultures taken at least 30 days apart are found to be negative.18

Adverse event
Standard definitions of AE, including grading (1–4), were used.20 In our study, SAEs included other SAEs (that need hospitalisation) in addition to Grade 3 and 4 AEs.

Data management and analysis
Data (including patient characteristics, baseline culture and DST reports, treatment regimen, follow-up culture results, AE, treatment outcome records) stored in the MSF TB programme databases (electronic medical records portal, Bahmni)21 were exported into and analysed using STATA v15 (StataCorp, College Station, TX, USA). Median (min-max) and proportions were used to describe the demographic and clinical characteristics. Numbers and proportions were used to summarise the analytic output (treatment outcomes, episodes of AE). Kaplan–Meier curve was used to describe the time to culture conversion after treatment initiation.

Ethics approval
The study received ethics approval from the Institutional Review Board, Tata Institute of Social Sciences, Mumbai, India. As the study met the criteria for a posteriori analysis of routinely collected clinical data, it did not require MSF Ethics Review Board full review. The study was conducted with the permission of the Medical Director, MSF Operational Centre Brussels, Belgium.

RESULTS
Demographic and clinical characteristics
Of 24 patients who received treatment, 14 (58%) were adolescents aged 15–19 years (Table 1). The median age of patients was 15.5 years (min-max 3–19); 15 (63%) were females. None were HIV-coinfected. Twenty patients had pulmonary TB. The site of involvement of the four patients with extrapulmonary TB was the lymph nodes. All patients had FQ resistance: eight had pre-XDR-TB while 16 had XDR-TB. Fifteen (63%) were retreatment cases, of whom eight patients had previously

| Characteristic | n (%) |
|---------------|-------|
| Total         | 24 (100) |
| Age group, years |       |
| 0–4           | 2 (8)  |
| 5–9           | 4 (17) |
| 10–14         | 4 (17) |
| 15–19         | 14 (58) |
| Age, years, median [min–max] | 15.5 [3–19] |
| Sex           |       |
| Male          | 9 (37) |
| Female        | 15 (63) |
| Negative HIV status | 24 (100) |
| TB site       |       |
| Pulmonary     | 20 (83) |
| Extra-pulmonary | 4 (17)  |
| Previous episode of TB |       |
| Yes           | 15 (63) |
| No            | 9 (37) |
| TB resistance profile |       |
| Pre-XDR-TB (resistance to RIF, INH and FQ) | 8 (33) |
| XDR-TB        | 16 (67) |
| New TB drugs received |       |
| BDQ only      | 1 (4)  |
| DLM only      | 11 (46) |
| DLM and BDQ   | 12 (50) |

RR-TB = rif-resistant TB; MSF = Médecins Sans Frontières; XDR-TB = extensively drug-resistant TB; RIF = rifampicin; INH = isoniazid; FQ = fluoroquinolone; BDQ = bedaquiline; DLM = delamanid.
been treated with second-line TB drugs. Four patients were household contacts of three patients with RR-TB who received treatment from MSF Clinic. The proportion of patients with resistance to individual TB drugs is shown in Figure 1.

**Treatment regimen and duration**

Twelve patients received a treatment regimen containing both BDQ and DLM, while 11 received DLM and one patient received BDQ containing treatment. All 12 patients received concomitant administration of BDQ and DLM during the treatment. Of the 12, three patients received a second drug after a short delay (within 1–4 months) due to limited access (two received BDQ after DLM, one received DLM after BDQ); however, no deterioration in clinical condition was reported due to the delay in administering the second drug. The median duration of treatment was 89 weeks (interquartile range [IQR] 85–98). Clofazamine, linezolid, imipenem, amoxycillin/clavunate, along with the new TB drugs, were common drugs included in the regimen (non-tabulated). The median exposure to individual BDQ ($n = 13$) and DLM ($n = 23$) during treatment was respectively 82 (IQR 80–93) weeks and 82 (IQR 77–96) weeks; the median duration of co-administration of BDQ and DLM in patients ($n = 12$) was 82 weeks (IQR 79–89).

**Culture conversion during treatment**

Of 24 patients, 18 (75%) had positive culture reports for TB at baseline: 17 (94% of 18) had negative culture reports and 1 died before culture conversion. The median time to culture conversion was 7 weeks (IQR 5–11). Figure 2 shows the Kaplan–Meier curve of time to culture conversion after treatment initiation.

**Adverse events**

During the treatment, 11 patients had a total of 17 episodes of AEs (Table 2). Of the 12 SAE episodes, only two were associated with the new drugs (QTcF > 500 ms): one in patient receiving BDQ and DLM, and one in a patient receiving DLM only. In these two episodes, BDQ administration was interrupted for 10 days due to SAE in the patient; DLM was not interrupted in any of the patients. None of the patients were advised permanent treatment discontinuation.

**Final treatment outcome**

All 24 patients had recorded final treatment outcomes: 23 (96%) had successful treatment outcomes—cured ($n = 16$) and completed treatment ($n = 7$); one patient died at Month 18 of treatment due to progressive deterioration of clinical condition from advanced TB.

**DISCUSSION**

This is one of the largest cohorts of children and adolescents globally treated with new TB drugs (BDQ and/or DLM), including half receiving BDQ and DLM concomitantly. This is also the first study from India to report on treatment outcomes in children and adolescents with RR-TB receiving injectable-free regimen containing the new TB drugs on an ambulatory basis in a high RR-TB prevalence setting. More than 95% patients had successful final treatment outcomes. About half of the cohort had one or more than one episode of AEs during treatment.

We believe the study provides important insights for policy and practice related to the new TB drugs for DR-TB treatment in children and adolescents. First, the high proportion of successful treatment
outcome looks promising and shows the effectiveness of the new TB drugs among children and adolescents. Studies have reported promising safety and efficacy results in adults receiving the new TB drugs;19,22,23 however, few reports have been published to date on early experiences of the new TB drugs in children and adolescents.9,10,24 Our study findings thus add evidence in support of the use of injectable-free regimens involving new TB drugs in children and adolescents11,22,25 and highlights their contribution in achieving successful treatment outcomes. Some clinical trials are ongoing.

### Table 2 Adverse events among children and adolescents during RR-TB treatment at the MSF Clinic, Mumbai, India, September 2014–January 2020

| Adverse event grade* | Categories | Episodes | Likely associated with only BDQ/DLM† | Likely associated with other TB drug(s)† |
|----------------------|------------|----------|-------------------------------------|----------------------------------------|
| Grade 4              | QTC prolongation (>500 ms) | 2 | BDQ and DLM (n = 1) | — |
|                      | Electrolyte imbalance (Mg²⁺, i.e., hypomagnesaemia) | 1 | Not associated | CPM |
|                      | Increased hepatic enzymes | 1 | Not associated | Not associated (hepatitis A) |
| Grade 3              | Electrolyte imbalance (K⁺, i.e., hypokalemia) | 1 | Not associated | CPM |
|                      | Sepsis/infection | 3 | Not associated | Not associated (Port-a-cath, n = 3) |
|                      | Anaemia | 2 | Not associated | LZD (n = 2) |
|                      | Complaints of anger | 1 | Not associated | CS |
|                      | Optic neuritis | 1 | Not associated | LZD |
| Grade 2              | Electrolyte imbalance (Mg²⁺) | 1 | Not associated | Not associated |
|                      | Hypoaalbuminaemia | 1 | Not associated | Not associated |
|                      | QTC prolongation (481–500 ms) | 1 | BDQ and DLM | — |
| Grade 1              | Electrolyte imbalance (Ca²⁺, i.e., hypocalcaemia) | 1 | Not associated | CPM |
|                      | Increased hepatic enzymes | 1 | Not associated | PZA, ETH, MFX* |
| Total                |             | 17 |                               |                                      |

* Grading of adverse event based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events: Grade 1 = transient or mild discomfort (<48 h); no medical intervention/therapy required; Grade 2 = mild to moderate limitation in activity, some assistance may be needed, no or minimal medical intervention/therapy required; Grade 3 = marked limitation in activity, some assistance usually required, medical intervention/therapy required, hospitalisation possible; Grade 4 = extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable.

† Adverse events mentioned as ‘Not associated’ were not associated with BDQ, DLM or other TB drug(s) but due to advanced diseased condition of the patient or due to port-a-cath infection.

RR-TB = RR-resistant TB; MSF = Médecins Sans Frontières; BDQ = bedaquiline; DLM = delamanid; Mg = magnesium; CPM = capreomycin; K = potassium; LZD = linezolid; CS = cycloserine; Ca = calcium; PZA = pyrazinamide; ETH = ethionamide; MFX* = high-dose moxifloxacin.
on safety, efficacy and pharmacokinetics of new TB drugs for children and adolescents (for BDQ, Janssen C211, IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) 2005-DAIDS ID 11884; for DLM, Otsuka 232, Otsuka 233, IMPAACT 2005-DAIDS ID 20721).26,27 Since results of many clinical trials are pending, more field-based studies are required to increase the evidence on new TB drugs.

Second, although 11 patients had 17 episodes of AEs during treatment, only two episodes of SAEs were related to the new TB drugs. None of the SAEs led to permanent cessation of treatment. This is in line with findings of other studies reporting reassuring safety results on the use of the new TB drugs in adults19 and adolescents.10,11 The safety results of our study could help national TB programmes (NTPs) in designing injectable-free treatment regimens containing new TB drugs for children and adolescents with RR-TB.12,28 In line with WHO recommendations, India’s NTP is required to provide new TB drugs to children and adolescents under the routine programme.

Third, in our cohort, the proportion of children less than 10 years old was low, at 25%. This can be explained by the known challenges in diagnosing TB in younger children, and highlights the need for better diagnostic tools.29,30 Although the MSF Clinic provides treatment to patients referred from public/private healthcare institutions, we believe that the availability and accessibility of newer techniques such as Xpert evaluation of stools and easier techniques of gastric lavage, sputum induction would be helpful in early DR-TB diagnosis. In addition, sensitisation of healthcare professionals is needed for the early identification of TB signs and symptoms in children and their referral for diagnosis.

Fourth, about two thirds of the patients had a previous episode of TB, half of whom had received treatment with second-line drugs in the past. This is alarming, as it indicates relapses from previous TB treatment (ineffective/failed or incomplete due to poor adherence) and/or extremely high TB transmission rates at community level. Most of the patients in the clinic resided in the urban slums of Mumbai, a known hotspot of complex RR-TB. In addition to effective drugs, the provision of tailored adherence counselling to children, adolescents and their family members31 could assist in better treatment outcomes and limit the transmission of disease in these communities.

The study had a few strengths. As the patients were from Mumbai, a known RR-TB hotspot in India, findings may be extrapolated to other high TB burden urban settings worldwide. The study provides a detailed report of AEs during treatment, often missed in routine TB programmes.

The study had several limitations. As it was based on a retrospective review of clinical data, there could be instances of missing data, including reports on AEs, which might have led to an underestimation of the proportion of AEs. As none of the patients were HIV-coinfected, the study results may not apply to children and adolescents with HIV-DR-TB co-infection. The study results may not be generalised to the population of Mumbai, as patients were referred from healthcare institutions for treatment. All patients in the cohort had bacteriological confirmation of TB, which is uncommon in paediatric patients worldwide.

In conclusion, treatment with injectable-free regimens containing new TB drugs (BDQ and/or DLM) on an ambulatory basis was effective and well-tolerated by children and adolescents with RR-TB. Thus, TB programmes should prioritise access and provision of BDQ and DLM for these vulnerable populations in routine programme settings.

Acknowledgements

The authors would like to thank patients with DR-TB and their families, and health care providers and project team involved in providing care to patients with DR-TB for their time and efforts; and N Lachenal and S Coutisson of the MSF pharmacovigilance team for their support in AE monitoring.

Conflicts of interest: none declared.

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**CONTEXTE :** Centres de santé de Médecins Sans Frontières (MSF) à Mumbai, Inde.

**OBJECTIF :** Déterminer les résultats finaux du traitement; la conversion de culture; et les effets secondaires (AEs) du traitement parmi les enfants et les adolescents (0–19 ans) atteints de la TB résistante à la rifampicine (RR-TB) qui ont reçu un traitement ambulatoire sans médicaments injectables incluant la bedaquiline (BDQ) et/ou le delamanide (DLM) de septembre 2014 à janvier 2020.

**SCHEMA :** Etude rétrospective de cohorte basée sur la revue des données de programme recueillies en routine.

**RÉSULTATS :** Vingt-quatre patients ont été inclus; l’âge médian a été de 15,5 (min-max 3–19) ans et 15 (63%) ont été des filles. Aucun n’était co-infecté par le VIH. Tous étaient résistants à la fluoroquinolone. Douze ont reçu un traitement incluant BDQ et DLM, 11 ont reçu DLM seul et 1 a reçu BDQ seule. L’exposition médiane à la BDQ (n = 13) et au DLM (n = 23) a été de 82 (IQR 80–93) et 82 (IQR 77–96) semaines, respectivement. Dix-sept (94%) patients ayant une culture positive au départ (n = 18) ont eu une culture négative au cours du traitement ; le délai médian de conversion de culture a été de 7 semaines (IQR 5–11). Vingt-trois patients (96%) ont eu un bon résultat de traitement ; guéris (n = 16) et traitement achevé (n = 7) ; un patient est décédé. Onze patients (46%) ont eu 17 épisodes d’effets indésirables (AE). Deux des 12 AE graves ont été associés avec les nouveaux médicaments (QTcF > 500 ms).

**CONCLUSION :** Cette étude, basée sur une des plus vastes cohortes mondiales d’enfants et d’adolescents recevant des nouveaux médicaments TB, a montré que des protocoles sans médicaments injectables contenant de la BDQ et/ou du DLM en ambulatoire avaient été efficaces et bien tolérés chez les enfants et les adolescents et devraient être accessibles en routine à ces groupes vulnérables.

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**RESUMEN**

**MARCO DE REFERENCIA :** Un consultorio de Médicos Sin Fronteras (MSF) de Mumbai, en la India.

**OBJETIVO :** Determinar los desenlaces terapéuticos finales, la conversión del cultivo y las reacciones adversas (AE) durante el tratamiento de los niños y los adolescentes (0–19 años) con TB resistente a rifampicina (TB-RR), que recibieron un tratamiento sin inyectables, que comportaba bedaquilina (BDQ), delamanide (DLM) o ambos, de septiembre del 2014 a enero del 2020.

**MÉTODO :** Fue este un estudio de cohortes retrospectivo a partir del análisis de los datos corrientes del programa.

**RESULTADOS :** Se incluyeron 24 pacientes; la mediana de la edad fue 15,5 años (de 3 a 19 años) and 15 eran de sexo femenino (63%). Ningún paciente presentaba coinfección por el VIH. Todos tenían resistencia a la fluoroquinolona. Doce pacientes recibieron tratamiento que incluya BDQ y DLM, 11 recibieron DLM y uno BDQ. La mediana (IQR) de la exposición a BDQ (n = 13) y DLM (n = 23) fue 82 (IQR 80–93) y 82 (IQR 77–96), respectivamente. Diez y siete (94%) pacientes con cultivo positivo inicial (n = 18) alcanzaron un cultivo negativo durante el tratamiento; la mediana del lapso hasta la conversión del cultivo fue 7 semanas (IQR 5–11). Veintitrés pacientes (96%) lograron desenlaces terapéuticos favorables (16 curados y 7 completaron el tratamiento) y un paciente falleció. Once casos (46%) presentaron 17 episodios de efectos adversos (AE). Dos de las 12 AE graves se asociaron con fármacos nuevos (intervalo QT, con corrección de Fridericia > 500 ms).

**CONCLUSIÓN :** El presente estudio, basado en una de las cohortes más extensas de niños y adolescentes del mundo tratados con nuevos fármacos contra la TB, mostró que las pautas terapéuticas sin inyectables, que consisten en BDQ, DLM o ambos, en un marco ambulatorio de tratamiento fueron eficaces y bien toleradas por los niños y los adolescentes y se deberían poner al alcance para el tratamiento corriente de estos grupos vulnerables.