# MSF IN KARAKALPAKSTAN

## IMPROVING CARE FOR PEOPLE THROUGH HIGH IMPACT RESEARCH

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MEDECINS SANS FRONTIERES

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## IMPROVING CARE FOR PEOPLE THROUGH HIGH IMPACT RESEARCH

MEDECINS SANS FRONTIERES

For nearly three decades, Médecins Sans Frontières/Doctors Without Borders (MSF) has worked in close partnership with the Ministry of Health (MoH) of Uzbekistan to transform tuberculosis (TB) care in the Republic of Karakalpakstan in the west of the country. Together, MSF and the MoH have responded to the critical need for improved TB diagnosis, treatment, and care through the implementation of the Nukus TB Project.

MSF began its work in Karakalpakstan in 1998 trying to assess the impact of the Aral Sea environmental disaster on human health to help the people who live in the area cope with their environment. MSF has combined a direct medical programme to improve the health of the population while analysing and sharing findings to gain a better understanding of the relationship between the environmental disaster and human health outcomes.

Into this context, the introduction of the World Health Organization's (WHO) recommended Directly Observed Therapy, Short Course (DOTS) strategy for tuberculosis control with an assured drug supply, standardised regimens, and its effect on the political commitment afforded to tuberculosis, offered the opportunity to quell the high incidence of TB. MSF, in close cooperation with the Ministry of Health, has worked since 1998 to expand this treatment programme first initiated by the WHO in Muynak throughout the whole of Karakalpakstan. In the early 2000s, MSF and the MoH began investigating the region's drug resistance profile, leading to the launch of a drug-resistant TB programme in 2003. To meet the needs of patients with multidrug-resistant TB (MDR-TB), MSF renovated the TB Hospital Number 2.

One of MSF's key innovations was the introduction and piloting of outpatient care, which evolved into a fully integrated ambulatory treatment model. This shift significantly increased the number of patients who could be treated by removing the limitations imposed by hospital bed capacity.

By 2010, the project had expanded into a comprehensive, person-centred care model accessible in all districts of Karakalpakstan. This included the introduction of rapid drug resistance testing, along with expanded ambulatory and home-based care options. MSF also provided psychosocial, psychological, and adherence support to patients and their families, helping them manage treatment side effects and the social impact of the disease.

As part of its commitment to advancing best practices in TB care, MSF supported the national rollout of the WHO's 2016 TB treatment guidelines starting in 2017, including the shorter-course regimen. MSF also helped implement the 2019 WHO guidelines across all 16 rayons of Karakalpakstan. To enhance diagnostic capacity, MSF established a state-of-the-art mycobacteriology lab in Nukus—now the most advanced facility of its kind in Central Asia—offering comprehensive TB and MDR-TB testing alongside high-quality clinical laboratory services.

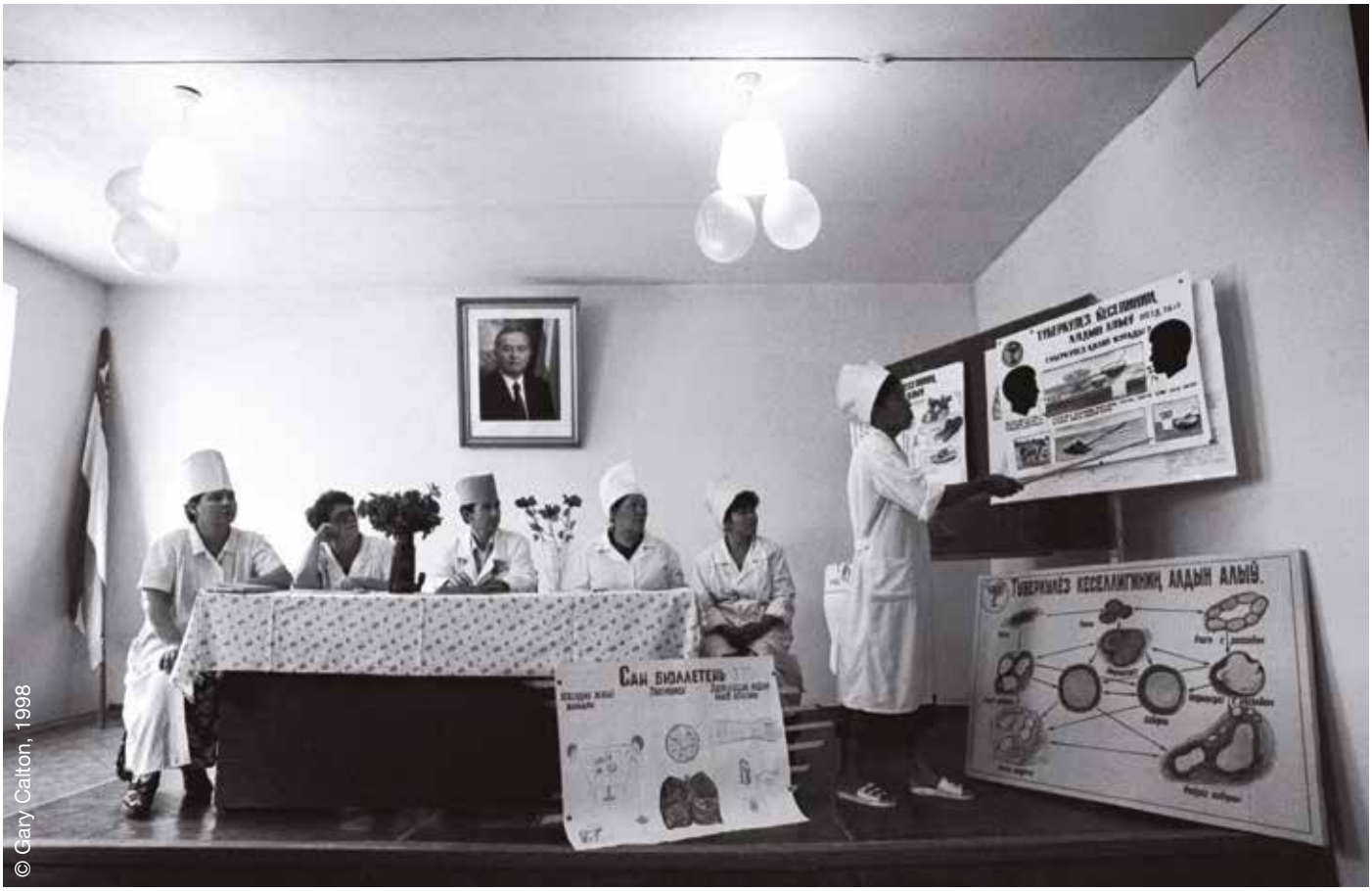
In 2017, Nukus became one of the sites for the TB-PRACTECAL clinical trial, a multi-site phase II/III study sponsored by MSF to test a shorter, all-oral treatment regimen for MDR-TB. The trial demonstrated that the new regimen was faster (six months), more effective, and had fewer side effects than the global standard. These groundbreaking results influenced the World Health Organization's 2022 guidelines, in which the new regimen was adopted as a priority recommendation.

Building on this success, MSF and the MoH launched the SMARRTT (Six-Month All-Oral Regimens for Rifampicin-Resistant Tuberculosis) operational research project in 2022. This initiative aimed to extend the benefits of the new regimen to a wider patient population, and MSF worked with national partners to roll it out across Uzbekistan.

Through its longstanding presence in Uzbekistan, MSF has contributed significantly to both the national and global fight against TB by promoting a person-centred model of care, strengthening local healthcare systems through capacity building, and investing in innovative research and development.

## Activity summary:

From 1998 to 2003, MSF in Karakalpakstan, Uzbekistan, expanded WHO's DOTS programme to combat the high TB prevalence by training local healthcare workers, supplying drugs, and upgrading laboratories in high-prevalence areas like Nukus and Muynak, in collaboration with the MoH. By 2003, MSF shifted focus to drug-resistant TB (DR TB), introducing longer treatment regimens to tackle the growing challenge of multidrug-resistant strains.



| Year/Month | Article | Journal | Citations | QR Code |
|---|---|---|---|---|
| 2000 Dec | **Dispatches from abroad: aground in a sea of TB** | Canadian Medical Association Journal | 4 | |
| 2001 Jun | **Acting on an environmental health disaster: the case of the Aral Sea** | Environmental Health Perspectives | 175 | |
| 2002 | **Perceived Health and Psychosocial Well-Being in the Aral Sea Area** | Toxic Turmoil (Book) | 2 | |
| 2003 Feb | **Impacts of an environmental disaster on psychosocial health and well-being in Karakalpakstan** | Social Science & Medicine | 116 | |
| 2003 Mar | **To treat or not to treat? Implementation of DOTS in Central Asia** | The Lancet | 12 | |
| 2003 Mar | **Safe water for the Aral Sea Area \| European Journal of Public Health** | European Journal of Public Health | 20 | |
| 2003 Jun | **The dynamics and characteristics of aeolian dust in dryland Central Asia: possible impacts on human exposure and respiratory health in the Aral Sea basin** | The Geographical Journal | 167 | |
| 2003 Aug | **Assessment of dietary exposure to some persistent organic pollutants in the Republic of Karakalpakstan of Uzbekistan** | Environmental Health Perspectives | 88 | |

# Acting on an environmental health disaster: the case of the Aral Sea

The Aral Sea area in Central Asia has been encountering one of the world's greatest environmental disasters for more than 15 years. During that time, despite many assessments and millions of dollars spent by large, multinational organizations, little has changed. The 5 million people living in this neglected and virtually unknown part of the world are suffering not only from an environmental catastrophe that has no easy solutions but also from a litany of health problems. The region is often dismissed as a chronic problem where nothing positive can be achieved. Within this complicated context, Medecins Sans Frontieres, winner of the Nobel Peace Prize in 1999, is actively trying to assess the impact of the environmental disaster on human health to help the people who live in the Aral Sea area cope with their environment. Medecins Sans Frontieres has combined a direct medical program to improve the health of the population while conducting operational research to gain a better understanding of the relationship between the environmental disaster and human health outcomes. In this paper we explore the health situation of the region and the broader policy context in which it is situated, and present some ideas that could potentially be applied to many other places in the world that are caught up in environmental and human health disasters.

## Impact on policy and guidelines

Cited in major international policy reports on environmental health and climate adaptation:

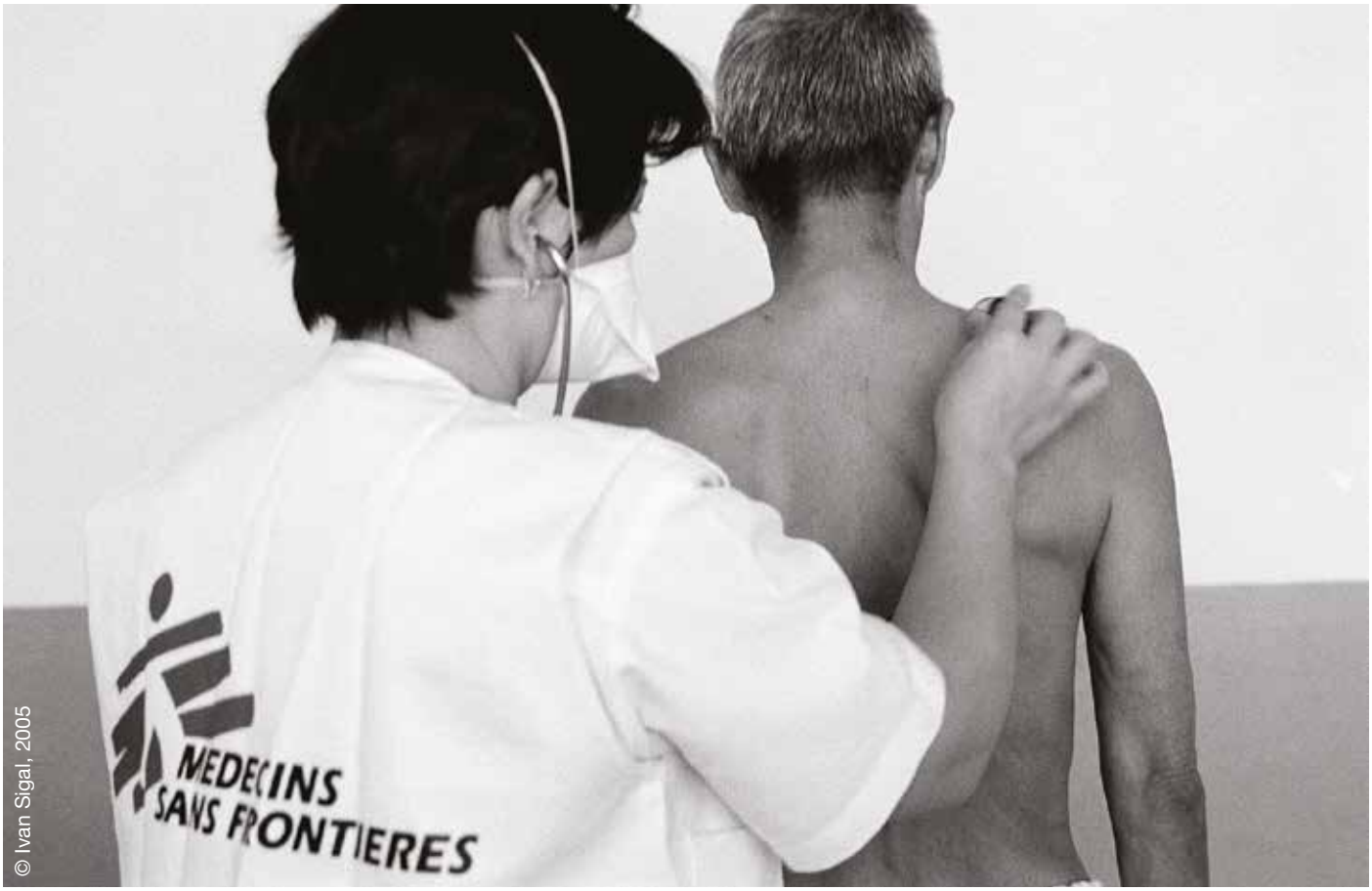
- Informed the WHO report *The precautionary principle: protecting public health, the environment and the future of our children*, advocating for evidence-based environmental protection.
- Referenced by the Intergovernmental Panel on Climate Change (IPCC) report *Managing the risks of extreme events and disasters to advance climate change adaptation*, linking climate change with extreme weather and climate events, the impacts of such events, and the strategies to manage the risks.
- Cited by the Asian Development Bank in *Addressing climate change and migration in Asia and the Pacific*, contributing to understanding the potential impacts of climate change on migration in Asia and the Pacific.

## Humanitarian focus

Humanitarian crises come in all shapes and sizes. MSF's decision to establish operations in Karakalpakstan, Uzbekistan, underscores MSF's humanitarian commitment and ambition to address complex and multifaceted crises; those that may fall outside of the conventional conception of a humanitarian setting. The people from and in this region face significant health challenges, including the environmental fallout from the Aral Sea disaster and a high prevalence of multidrug-resistant tuberculosis (MDR-TB). By combining medical interventions with research into environmental health impacts, MSF indicated its commitment, and ability, to tackling neglected diseases and crises exacerbated by systemic and environmental factors, ensuring vulnerable populations receive the care they sorely miss.

## Activity summary:

From 2003 to 2008, MSF and MoH shifted from implementing WHO's DOTS programme to launching a DOTS-Plus pilot programme, focused on diagnosing and treating multidrug-resistant tuberculosis (MDR-TB) with individualised second-line drug regimens, in collaboration with the MoH. By 2007, MSF began integrating drug-susceptible and drug-resistant TB management, scaling up outpatient care and collaborating with partners like the Global Fund to supply second-line drugs.



| Year/Month | Article | Journal | Citations | QR Code |
|---|---|---|---|---|
| 2003 Nov | **Effect of multidrug resistance on global tuberculosis control** | The Lancet | 23 | |
| 2004 May | **Multidrug-resistant Tuberculosis in Central Asia** | Emerging Infectious Diseases | 113 | |
| 2005 Oct | **Does one size fit all? Drug resistance and standard treatments: results of six tuberculosis programmes in former Soviet countries** | IJTLD | 45 | |
| 2005 Nov | **The Beijing genotype and drug resistant tuberculosis in the Aral Sea region of Central Asia** | Respiratory Research | 172 | |
| 2006 Oct | **Tuberculosis Recurrence and Mortality after Successful Treatment: Impact of Drug Resistance** | PLOS Medicine | 224 | |
| 2007 Jun | **Risk of Acquired Drug Resistance during Short-Course Directly Observed Treatment of Tuberculosis in an Area with High Levels of Drug Resistance** | Clinical Infectious Diseases | 110 | |
| 2007 Nov | **Multidrug-Resistant Tuberculosis Treatment Outcomes in Karakalpakstan, Uzbekistan: Treatment Complexity and XDR-TB among Treatment Failures** | PLOS One | 157 | |
| 2008 Nov | **Emergence of Extensive Drug Resistance during Treatment for Multidrug-Resistant Tuberculosis** | NEJM | 117 | |

# Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance

The DOTS (directly observed treatment short-course) strategy for tuberculosis (TB) control is recommended by the World Health Organization globally. However, there are few studies of long-term TB treatment outcomes from DOTS programs in high-burden settings and particularly settings of high drug resistance. A DOTS program was implemented progressively in Karakalpakstan, Uzbekistan starting in 1998. The total case notification rate in 2003 was 462/100,000, and a drug resistance survey found multidrug-resistant (MDR) Mycobacterium tuberculosis strains among 13% of new and 40% of previously treated patients. A retrospective, observational study was conducted to assess the capacity of standardized short-course chemotherapy to effectively cure patients with TB in this setting.

Using routine data sources, 213 patients who were sputum smear-positive for TB, included in the drug resistance survey and diagnosed consecutively in 2001–2002 from four districts, were followed up to a median of 22 months from diagnosis, to determine mortality and subsequent TB rediagnosis. Valid follow-up data were obtained for 197 (92%) of these patients. Mortality was high, with an average of 15% (95% confidence interval, 11% to 19%) dying per year after diagnosis (6% of 73 pansusceptible cases and 43% of 55 MDR TB cases also died per year). While 73 (74%) of the 99 new cases were “successfully” treated, 25 (34%) of these patients were subsequently rediagnosed with recurrent TB (13 were smear-positive on rediagnosis). Recurrence ranged from ten (23%) of 43 new, pansusceptible cases to six (60%) of ten previously treated MDR TB cases. MDR *M. tuberculosis* infection and previous TB treatment predicted unsuccessful DOTS treatment, while initial drug resistance contributed substantially to both mortality and disease recurrence after successful DOTS treatment.

These results suggest that specific treatment of drug-resistant TB is needed in similar settings of high drug resistance. High disease recurrence after successful treatment, even for drug-susceptible cases, suggests that at least in this setting, end-of-treatment outcomes may not reflect the longer-term status of patients, with consequent negative impacts for patients and for TB control.

## Impact on policy and guidelines

- Used as source evidence in the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis (2011 update)*, informing recommendations on monitoring treatment in patients with multidrug-resistant TB using sputum smear microscopy and culture.

## Humanitarian focus

The prevalence of MDR-TB in Karakalpakstan highlights the long-term consequences of the collapse of the Soviet-era healthcare system and the subsequent lack of access to effective medical care. Drug resistance in this setting has become a health care emergency; and unnecessarily so as treatment for this illness does exist. MSF's work in addressing MDR-TB through innovative treatment models and improved diagnostics reflects its dedication to mitigating the systemic failures that have fuelled this problem.

## Activity summary:

From 2009 to 2015, MSF and the MoH jointly scaled up the comprehensive TB programme, treating over 2,000 patients with DR TB by 2015, using innovative diagnostics and treatment methods like GeneXpert and individualised regimens with second-line drugs, while expanding ambulatory care through outpatient DOTS corners. MSF collaborated with the MoH to introduce shorter 9-month MDR-TB regimens by 2013 and supported a local TB hospital in Nukus alongside providing psychosocial care to improve treatment adherence.

| Year/Month | Article | Journal | Citations | QR Code |
|---|---|---|---|---|
| 2009 Aug | **Sequence Analyses of Just Four Genes To Detect Extensively Drug-Resistant Mycobacterium tuberculosis Strains in Multidrug-Resistant Tuberculosis Patients Undergoing Treatment** | Antimicrobial Agents and Chemotherapy | 134 | |
| 2009 Nov | **Tuberculosis ethambutol resistance: Concordance between phenotypic and genotypic test results** | Tuberculosis | 48 | |
| 2010 Apr | **embCAB sequence variation among ethambutol-resistant Mycobacterium tuberculosis isolates without embB306 mutation** | Journal of Antimicrobial Chemotherapy | 102 | |
| 2012 Dec | **Public health advocacy for the Berlin Declaration on tuberculosis in the former Soviet Union: the view of Médecins Sans Frontières** | European Journal of Microbiology and Immunology | 19 | |
| 2013 Oct | **Multidrug-resistant tuberculosis in Uzbekistan: results of a nationwide survey, 2010 to 2011** | Eurosurveillance | 66 | |
| 2013 Nov | **Risk Factors Associated with Default from Multi- and Extensively Drug-Resistant Tuberculosis Treatment, Uzbekistan: A Retrospective Cohort Analysis** | PLOS One | 62 | |
| 2014 Dec | **Ambulatory tuberculosis treatment in post-Semashko health care systems needs supportive financing mechanisms** | IJTLD | 17 | |
| 2015 Jun | **Factors Associated with Unfavorable Treatment Outcomes in New and Previously Treated TB Patients in Uzbekistan: A Five Year Countrywide Study** | PLOS One | 84 | |

# Sequence analyses of just four genes to detect extensively drug-resistant *Mycobacterium tuberculosis* strains in multidrug-resistant tuberculosis patients undergoing treatment

The rapid detection of *Mycobacterium tuberculosis* isolates resistant to second-line drugs is crucial for the institution of appropriate treatment regimens as early as possible. Although molecular methods have successfully been used for the rapid detection of resistance to first-line drugs, there are limited data on mutations that confer resistance to second-line drugs. To address this question, we analyzed *Mycobacterium tuberculosis* strains resistant to ofloxacin (*n* = 26) and to capreomycin and/or amikacin (*n* = 48) from Uzbekistan for variations in target genes (*gyrA, gyrB, rrs,* and *tlyA*). Strains susceptible to ofloxacin (*n* = 49) and capreomycin and/or amikacin (*n* = 39) were included as controls. Mutations in *gyrA* or *gyrB* were found in 96% (25/26 strains) of the ofloxacin-resistant strains, while none of the susceptible strains displayed mutations in those two genes. The most common mutation occurred in *gyrA* at codon 94 (17/26 strains [65.4%]), followed by mutations at codons 90 and 91. Two strains showed a mutation in *gyrB*, at codons 485 and 543, respectively; both mutations have not been reported previously. The most frequent mutation in strains resistant to both amikacin and capreomycin was A1401G in *rrs* (34/40 strains [85.0%]). Three strains had mutations in *tlyA*, of which two (at codons 18 and 118) were associated with resistance to capreomycin alone. Overall, none of the 10 resistant strains (5 amikacin-resistant and capreomycin-susceptible strains) and none of the 39 susceptible control strains had mutations in the genes investigated. Our results clearly demonstrate the potential of sequence analyses of short regions of relatively few target genes for the rapid detection of resistance to second-line drugs among strains isolated from patients undergoing treatment for multidrug-resistant tuberculosis. The mechanisms that confer amikacin resistance in this setting remain unclear.

## Impact on policy and guidelines

- Cited in the Brazil Ministry of Health's national guidelines, *Manual of recommendations for laboratory diagnosis of tuberculosis and nontuberculous Mycobacteria of public health interest in Brazil*, providing protocols to ensure early detection, accurate diagnosis, monitoring of treatment outcomes, and effective surveillance.

## Humanitarian focus

- MSF has prioritised advancements in diagnostics to ensure timely and accurate detection of MDR-TB, particularly in regions like Karakalpakstan where diagnostic infrastructure is limited. By introducing rapid drug resistance testing and establishing a state-of-the-art lab together with the MoH, MSF bridges critical gaps in medical science research. These innovations enable tailored, person-centred care, improving patient outcomes and addressing the urgent need for progress in diagnostics.

## Activity summary:

From 2015 to 2017, MSF and MoH continued the comprehensive TB programme. By 2017, MSF began working on transitioning TB programme responsibilities to the MoH, enhancing local capacity through training and ensuring a sustainable supply of second-line drugs via partnerships with the Global Fund. The TB-PRACTECAL clinical trial also began in January 2017 with initial patient enrolment at sites in Uzbekistan.

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| Year/Month | Article | Journal | Citations | QR Code |
|---|---|---|---|---|
| 2015 Nov | **Multidrug-Resistant Tuberculosis in Child Successfully Treated with 9-Month Drug Regimen** | Emerging Infectious Diseases | 11 | |
| 2016 Feb | **Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study** | IJTLD | 69 | |
| 2016 Jul | **Where there is hope: a qualitative study examining patients' adherence to multi-drug resistant tuberculosis treatment in Karakalpakstan, Uzbekistan** | BMC Infectious Diseases | 47 | |
| 2016 Jul | **Health system support and health system strengthening: two key facilitators to the implementation of ambulatory tuberculosis treatment in Uzbekistan** | Health Economics Review | 18 | |
| 2016 Aug | **'They prefer hidden treatment': anti-tuberculosis drug-taking practices and drug regulation in Karakalpakstan** | IJTLD | 15 | |
| 2016 Nov | **Modelling the effect of short-course multidrug-resistant tuberculosis treatment in Karakalpakstan, Uzbekistan** | BMC Medicine | 25 | |
| 2017 May | **Recurrent tuberculosis and associated factors: A five - year countrywide study in Uzbekistan** | PLOS One | 39 | |
| 2017 Jul | **Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses** | European Respiratory Journal | 136 | |

# Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses

We assessed the effectiveness and safety of standardised, shorter multidrug-resistant tuberculosis (MDR-TB) regimens by pooling data from observational studies.

Published studies were identified from medical databases; unpublished studies were identified from expert consultation. We conducted aggregate data meta-analyses to estimate pooled proportions of treatment outcomes and individual patient data (IPD) meta-regression to identify risk factors for unsuccessful treatment in patients treated with 9- to 12-month MDR-TB regimens composed of a second-line injectable, gatifloxacin/moxifloxacin, prothionamide, clofazimine, isoniazid, pyrazinamide and ethambutol.

We included five studies in which 796 out of 1279 (62.2%) individuals with confirmed MDR-TB (98.4%) or rifampin-resistant TB (1.6%), and not previously exposed to second-line drugs, were eligible for shorter regimens. 669 out of 796 participants were successfully treated (83.0%, 95% CI 71.9–90.3%). In IPD meta-regression (three studies, n=497), failure/relapse was associated with fluoroquinolone resistance (crude OR 46, 95% CI 8–273), pyrazinamide resistance (OR 8, 95% CI 2–38) and no culture conversion by month 2 of treatment (OR 7, 95% CI 3–202). Two participants acquired extensive drug resistance. Four studies reported grade 3 or 4 adverse events in 55 out of 304 (18.1%) participants.

Shorter regimens were effective in treating MDR-TB; however, there is uncertainty surrounding the generalisability of the high rate of treatment success to less selected populations, to programmatic settings and in the absence of drug susceptibility tests to key component drugs.

## Impact on policy and guidelines

- Informed the WHO *Consolidated guidelines on drug-resistant tuberculosis treatment (2018 update)* by contributing to the evidence base and methodology for assessing shorter MDR/RR-TB regimens.
- Cited in the WHO *Best-practice statement on the off-label use of bedaquiline and delamanid*, as observational evidence supporting the safety and effectiveness of repurposed TB medicines.
- Referenced in the WHO *Technical report on the pharmacokinetics and pharmacodynamics of medicines for drug-resistant TB*, specifically in discussions on resistance testing and decisions around pyrazinamide use in shorter treatment regimens.
- Cited by the Canadian Agency for Drugs and Technologies in Health (CADTH) in the report *Interventions for the treatment or management of tuberculosis: clinical effectiveness and guidelines*, contributing to national-level evidence reviews on TB treatment strategies.

## Humanitarian focus

The study on the effectiveness and safety of standardised, shorter regimens for multidrug-resistant tuberculosis (MDR-TB) represents a significant step forward in the global fight against TB. By contributing to evidence-based solutions, MSF in collaboration with the MoH has provided invaluable insights into the feasibility of shorter regimens, which could revolutionise the way MDR-TB is treated globally. Shorter treatment durations not only reduce the burden on patients but also improve adherence, lower costs, and minimise the risk of adverse events associated with prolonged drug exposure.

## Activity summary:

From 2017 to 2020, MSF and MoH continued its tuberculosis (TB) programme, using rapid diagnostics like GeneXpert and also introducing shorter 9–11-month MDR-TB regimens, while expanding decentralised ambulatory care through outpatient DOTS corners. By 2020, MSF intensified efforts to transition the TB programme to the MoH, focusing on capacity building through training.

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| Year/Month | Article | Journal | Citations | QR Code |
|---|---|---|---|---|
| 2017 Oct | **Off-Label Use of Bedaquiline in Children and Adolescents with Multidrug-Resistant Tuberculosis** | Emerging Infectious Diseases | 68 | |
| 2018 Mar | **Outcomes of HIV-infected versus HIV-non-infected patients treated for drug-resistance tuberculosis: Multicenter cohort study** | PLOS One | 41 | |
| 2018 May | **Impact of pyrazinamide resistance on multidrug-resistant tuberculosis in Karakalpakstan, Uzbekistan** | IJTLD | 14 | |
| 2018 Jul | **Treatment and outcomes in children with multidrug-resistant tuberculosis: A systematic review and individual patient data meta-analysis** | PLOS Medicine | 124 | |
| 2020 Mar | **Standardised shorter regimens versus individualised longer regimens for rifampin- or multidrug-resistant tuberculosis** | European Respiratory Journal | 91 | |
| 2020 Sep | **Person-centred care in practice: perspectives from a short course regimen for multi-drug resistant tuberculosis in Karakalpakstan, Uzbekistan** | BMC Infectious Diseases | 28 | |
| 2020 Oct | **Cost-effectiveness of new MDR-TB regimens: study protocol for the TB-PRACTECAL economic evaluation substudy** | BMJ Open | 13 | |
| 2020 Nov | **Patient and health-care worker perspectives on the short-course regimen for treatment of drug-resistant tuberculosis in Karakalpakstan, Uzbekistan** | PLOS One | 4 | |

# Off-label use of bedaquiline in children and adolescents with multidrug-resistant tuberculosis

Children with multidrug-resistant tuberculosis (MDR TB) face significant treatment challenges. Although bedaquiline has shown promise in adults, its use in children has been restricted due to a lack of safety and efficacy data, despite the US Centers for Disease Control and Prevention stating that bedaquiline use can be considered when treatment options are limited. The aim of this report is to describe experiences treating children and adolescents with MDR TB with drug regimens that included bedaquiline.

Data were collected retrospectively on 27 patients under 18 years of age treated between 2014 and 2017 in South Africa, Tajikistan, Uzbekistan, and Belarus. Patients were included based on confirmed or presumed extensive drug resistance. Clinical data, drug regimens, adverse events, and treatment outcomes were documented.

Bedaquiline was well tolerated, with no treatment stopped due to adverse effects. QT prolongation (grade 3 or 4) occurred in 5 patients but was reversible and did not require discontinuation of bedaquiline. All 23 patients with available follow-up data were culture-negative by February 2017.

This suggests that bedaquiline can be used safely in children >12 years of age with appropriate monitoring and could be considered in younger children in select circumstances when benefits are likely to outweigh risks.

## Impact on policy and guidelines

- Cited by the U.S. Centers for Disease Control and Prevention (CDC) in the *ATS/CDC/ERS/IDSA clinical practice guideline on the treatment of drug-resistant tuberculosis*, which provides updated recommendations for treating MDR-TB, as well as isoniazid-resistant but rifampin-susceptible TB.

## Humanitarian focus

MSF's research into the off-label use of bedaquiline for children with MDR-TB exemplifies its commitment to addressing the needs of vulnerable populations. By demonstrating the safety and efficacy of this treatment in paediatric patients, MSF is paving the way for expanded access to effective care for children, a group often overlooked in TB treatment protocols. This innovation highlights MSF's dedication to ensuring no patient is left behind in the fight against TB.

## Activity summary:

From 2021 to 2022, MSF in Karakalpakstan, Uzbekistan, focused on supporting the MoH by providing technical assistance and training to sustain treatment for DR TB. MSF ensured the continuity of decentralised ambulatory care through outpatient DOTS corners as well as provision of psychosocial support for treatment adherence. By 2022, MSF's role shifted more towards monitoring and advisory support, collaborating with the MoH and partners like the Global Fund to maintain access to second-line drugs and strengthen local TB management capacity. The first interim results for the TB PRACTECAL clinical trial were publicly shared in October 2021 at the 52nd Union World Conference on Lung Health, following an early trial closure in March 2021 due to compelling results at that stage in the trial.

| Year/Month | Article | Journal | Citations | QR Code |
|---|---|---|---|---|
| 2021 Jan | **Accuracy of molecular drug susceptibility testing amongst tuberculosis patients in Karakalpakstan, Uzbekistan** | Tropical Medicine & International Health | 1 | |
| 2021 Jan | **Outcomes with a shorter multidrug-resistant tuberculosis regimen from Karakalpakstan, Uzbekistan** | ERJ Open Research | 14 | |
| 2021 Aug | **A Framework for Assessing Import Costs of Medical Supplies and Results for a Tuberculosis Program in Karakalpakstan, Uzbekistan** | Health Data Science | 3 | |
| 2021 Sep | **Capturing patient-reported and quality of life outcomes with use of shorter regimens for drug-resistant tuberculosis: mixed-methods substudy protocol, TB PRACTECAL-PRO** | BMJ Open | 8 | |
| 2021 Dec | **Optimising recruitment to a late-phase tuberculosis clinical trial: a qualitative study exploring patient and practitioner experiences in Uzbekistan** | Trials | 0 | |
| 2022 Jan | **Programme costs of longer and shorter tuberculosis drug regimens and drug import: a modelling study for Karakalpakstan, Uzbekistan** | ERJ Open Research | 15 | |
| 2022 Jun | **TB-PRACTECAL: study protocol for a randomised, controlled, open-label, phase II–III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis** | Trials | 42 | |
| 2022 Jul | **Acquired bedaquiline resistance in Karakalpakstan, Uzbekistan** | IJTLD | 12 | |

# TB-PRACTECAL: study protocol for a randomised, controlled, open-label, phase II–III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis

Globally rifampicin-resistant tuberculosis disease affects around 460,000 people each year. Currently recommended regimens are 9–24 months duration, have poor efficacy and carry significant toxicity. A shorter, less toxic and more efficacious regimen would improve outcomes for people with rifampicin-resistant tuberculosis.

TB-PRACTECAL is an open-label, randomised, controlled, phase II/III non-inferiority trial evaluating the safety and efficacy of 24-week regimens containing bedaquiline and pretomanid to treat rifampicin-resistant tuberculosis. Conducted in Uzbekistan, South Africa and Belarus, patients aged 15 and above with rifampicin-resistant pulmonary tuberculosis and requiring a new course of therapy were eligible for inclusion irrespective of HIV status. In the first stage, equivalent to a phase IIB trial, patients were randomly assigned one of four regimens, stratified by site. Investigational regimens include oral bedaquiline, pretomanid and linezolid. Additionally, two of the regimens also included moxifloxacin (arm 1) and clofazimine (arm 2) respectively. Treatment was administered under direct observation for 24 weeks in investigational arms and 36 to 96 weeks in the standard of care arm. The second stage of the study was equivalent to a phase III trial, investigating the safety and efficacy of the most promising regimen/s. The primary outcome was the percentage of unfavourable outcomes at 72 weeks post-randomisation. This was a composite of early treatment discontinuation, treatment failure, recurrence, lost-to-follow-up and death. The study is being conducted in accordance with ICH-GCP and full ethical approval was obtained from Médecins sans Frontières ethical review board, London School of Hygiene and Tropical Medicine ethical review board as well as ERBs and regulatory authorities at each site.

TB-PRACTECAL is an ambitious trial using adaptive design to accelerate regimen assessment and bring novel treatments that are effective and safe to patients quicker. The trial took a patient-centred approach, adapting to best practice guidelines throughout recruitment. The implementation faced significant challenges from the COVID-19 pandemic. The trial was terminated early for efficacy on the advice of the DSMB and will report on data collected up to the end of recruitment and, additionally, the planned final analysis at 72 weeks after the end of recruitment.

## Impact on policy and guidelines

- Results of this study prompted a review and update of the WHO *Consolidated guidelines on drug-resistant tuberculosis treatment (2022)*, contributing new evidence on shorter, all-oral regimens.

## Humanitarian focus

MSF's sponsorship of the TB-PRACTECAL trial has had a transformative impact on global TB treatment guidelines. The trial's findings led to the adoption of shorter, safer, and more effective MDR-TB regimens by organisations like the WHO. This underscores MSF's role in advancing evidence-based care and shaping the future of TB treatment, benefiting patients worldwide and reinforcing its leadership in humanitarian medical research.

## Activity summary:

From 2022 to 2024, MSF continued supporting the MoH sustaining its comprehensive TB programme which continues to treat around 2,000 patients annually. MSF also supported the expansion of MDR-TB support to the neighbouring Khorezm region in 2024.

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| Year/Month | Article | Journal | Citations | QR Code |
|---|---|---|---|---|
| 2022 Aug | **The contribution of drug import to the cost of tuberculosis treatment: A cost analysis of longer, shorter, and short drug regimens for Karakalpakstan, Uzbekistan** | PLOS Global Public Health | 6 | |
| 2022 Dec | **A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis** | New England Journal of Medicine | 282 | |
| 2023 May | **Primary bedaquiline resistance in Karakalpakstan, Uzbekistan** | IJTLD | 9 | |
| 2023 Jun | **Costs and import costs of past, present, and future TB drug regimens: a case study for Karakalpakstan, Uzbekistan** | Journal of Public Health | 4 | |
| 2024 Feb | **Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial** | The Lancet Respiratory Medicine | 53 | |
| 2024 Mar | **Safety and Tolerability of Linezolid in Novel Short-Course Regimens Containing Bedaquiline, Pretomanid, and Linezolid to Treat Rifampicin-Resistant Tuberculosis: An Individual Patient Data Meta-analysis** | Clinical Infectious Diseases | 18 | |
| 2024 Jun | **How much should we still worry about QTc prolongation in rifampicin-resistant tuberculosis? ECG findings from TB-PRACTECAL clinical trial** | Antimicrobial Agents and Chemotherapy | 3 | |
| 2024 Jul | **A 10-year review of isoniazid-resistant TB management in Uzbekistan 2009-2020** | IJTLD Open | 0 | |

# A 24-week, all-oral regimen for rifampin-resistant tuberculosis

In patients with rifampin-resistant tuberculosis, all-oral treatment regimens that are more effective, shorter, and have a more acceptable side-effect profile than current regimens are needed.

We conducted an open-label, phase 2–3, multicenter, randomized, controlled, noninferiority trial to evaluate the efficacy and safety of three 24-week, all-oral regimens for the treatment of rifampin-resistant tuberculosis. Patients in Belarus, South Africa, and Uzbekistan who were 15 years of age or older and had rifampin-resistant pulmonary tuberculosis were enrolled. In stage 2 of the trial, a 24-week regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) was compared with a 9-to-20-month standard-care regimen. The primary outcome was an unfavorable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 72 weeks after randomization. The noninferiority margin was 12 percentage points.

Recruitment was terminated early. Of 301 patients in stage 2 of the trial, 145, 128, and 90 patients were evaluable in the intention-to-treat, modified intention-to-treat, and per-protocol populations, respectively. In the modified intention-to-treat analysis, 11% of the patients in the BPaLM group and 48% of those in the standard-care group had a primary-outcome event (risk difference, –37 percentage points; 96.6% confidence interval [CI], –53 to –22). In the per-protocol analysis, 4% of the patients in the BPaLM group and 12% of those in the standard-care group had a primary-outcome event (risk difference, –9 percentage points; 96.6% CI, –22 to 4). In the as-treated population, the incidence of adverse events of grade 3 or higher or serious adverse events was lower in the BPaLM group than in the standard-care group (19% vs. 59%).

In patients with rifampin-resistant pulmonary tuberculosis, a 24-week, all-oral regimen was noninferior to the accepted standard-care treatment, and it had a better safety profile.

## Impact on policy and guidelines

- Directly led to updated WHO *Consolidated guidelines on drug-resistant tuberculosis treatment (2022)*, which now recommend the BPaLM regimen.
- Informed new national guidance across Europe, including the *Guideline on the Treatment of MDR, Pre-XDR, XDR, and Rifampicin-Resistant Tuberculosis* (Austria, Germany, Switzerland).
- Cited in the WHO *Operational handbook on tuberculosis* on critical concentrations for pretomanid and cycloserine.
- Updated clinical guidelines published by The Association of the Scientific Medical Societies in Germany – results led to replaced recommendations on "Therapy for MDR, pre-XDR, XDR Tuberculosis and Rifampicin Resistance or for Drug Intolerance to at least Rifampicin."

## Humanitarian focus

Shorter, all-oral MDR-TB regimens are a cornerstone of person-centred care. These treatments reduce the physical, social, and overall toll on patients, making it easier for them to adhere to therapy while minimizing disruptions to their daily lives and livelihoods. By prioritising regimens that align with patients' needs, MSF ensures that TB care is not only effective but also humane and accessible.

## Activity summary:

From 2024 to the present, MSF has focussed on treatment of people with forms of tuberculosis resistant to drugs commonly used in MDR-TB treatment regimens. People suffering with these forms of resistant TB require individually designed regimens which often includes painful injections and large number of pills. Despite this, treatment outcomes are poor. We have been collaborating to introduce Next Generation Sequencing to improve and fasten the diagnosis of drug resistance with the aim to improve treatment outcomes.

| Year/Month | Article | Journal | Citations | QR Code |
|---|---|---|---|---|
| 2024 Aug | **Pregnancy Outcomes in Multidrug-Resistant Tuberculosis in TB-PRACTECAL** | Clinical Infectious Diseases | 1 | |
| 2024 Sep | **Second-line drug-resistant TB and associated risk factors in Karakalpakstan, Uzbekistan** | IJTLD Open | 3 | |
| 2024 Sep | **Prevalence, treatment, and outcomes of hepatitis C in an MDR/RR-TB trial cohort** | PLOS Global Public Health | 0 | |
| 2025 Feb | **24-week, all-oral regimens for pulmonary rifampicin-resistant tuberculosis in TB-PRACTECAL trial sites: an economic evaluation** | The Lancet Global Health | 0 | |
| 2025 Feb | **Effectiveness and Safety of Bedaquiline, Pretomanid, and Linezolid (BPaL)–Based Regimens for Rifampicin-Resistant Tuberculosis in Non-Trial Settings—A Prospective Cohort Study in Belarus and Uzbekistan** | Clinical Infectious Diseases | 3 | |
| 2025 Feb | **Characteristics of children and adolescents with multidrug-resistant and rifampicin-resistant tuberculosis and their association with treatment outcomes: a systematic review and individual participant data meta-analysis** | The Lancet Child & Adolescent Health | 2 | |

# Second-line drug-resistant TB and associated risk factors in Karakalpakstan, Uzbekistan

Drug-resistant TB (DR-TB) remains a major public health threat. In 2022, Uzbekistan reported 2,117 cases of DR-TB, with 69% tested for fluoroquinolone resistance. Limited information is available on the prevalence of resistance to bedaquiline, linezolid, and fluoroquinolone, which are key components of the all-oral treatment regimen for rifampicin-resistant TB in Uzbekistan.

A retrospective study was conducted using extensive programmatic data from 2019 to 2023 in Uzbekistan. We assessed second-line drug-resistant TB (SLDR-TB) rates using phenotypic drug susceptibility testing (pDST). Demographic and clinical characteristics associated with SLDR-TB were analysed using multivariable logistic regression models based on the Allen-Cady approach.

In total, 2,405 patients with TB who had undergone pDST were included (median age 40 years, 47% female). The overall SLDR-TB resistance rate was 24% (95% CI 22–26). Prevalence of resistance to bedaquiline, linezolid, moxifloxacin, levofloxacin, and amikacin were respectively 3.1%, 0.8%, 15%, 13%, and 12%. Risk factors for SLDR-TB were resistance to rifampicin and/or isoniazid, exposure to clofazimine, retreatment status, contact with drug-susceptible TB case or DR-TB case, and diabetes.

The high prevalence of SLDR-TB is of major concern, emphasising the need for baseline pDST in RR-TB treatment. Identified risk factors can aid early detection of at-risk individuals and inform clinical practice.

## Impact on policy and guidelines

- This study expanded our understanding of the evolution of drug resistance in *Mycobacterium tuberculosis*. The high prevalence of resistance to bedaquiline, linezolid, and fluoroquinolones highlighted the need for continued research in the care for people affected by these highly resistant strains of *M. tuberculosis*. This research was cited by the expert publication "Clinical best practices for caring for people with expanded resistance to newer TB drugs", which helped guide the programmatic care of these people.

## Humanitarian focus

MSF's ongoing research into resistance to second-line TB drugs reflects its unwavering commitment to addressing the evolving challenges of MDR-TB. By investigating emerging resistance, such as acquired bedaquiline resistance, MSF ensures that patients continue to receive effective care despite new obstacles. This dedication to reducing suffering and mortality highlights MSF's humanitarian commitment and its resolve to follow through on complex health issues to the very end.

From MSF side, we would like to sincerely thank all our partners, dedicated health professionals, and – most importantly – the patients and communities we worked with in Karakalpakstan. They made this valuable research possible hence contributing to significant progress on the way to overcoming tuberculosis.

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