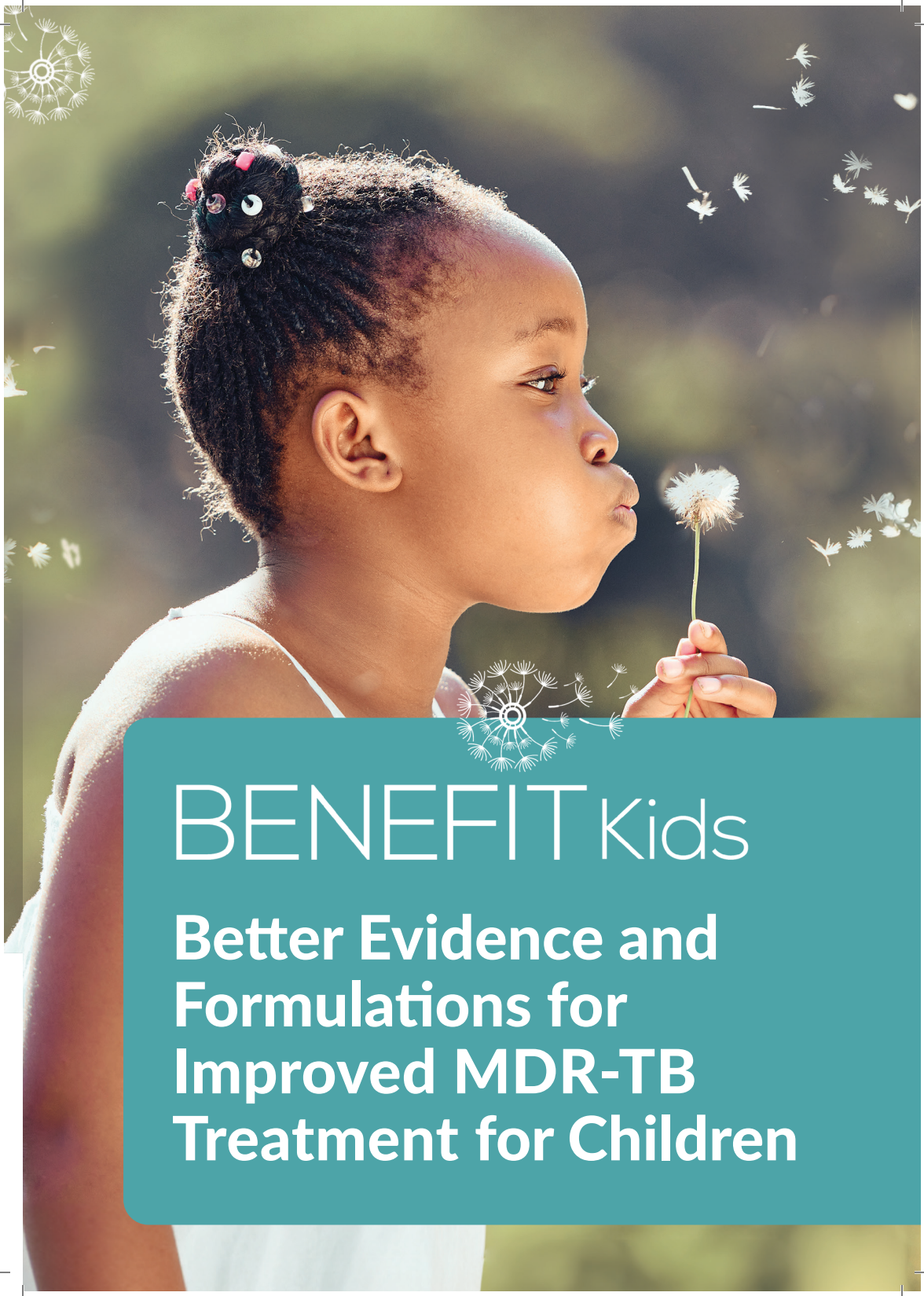


BENEFIT Kids

Better Evidence and Formulations for Improved MDR-TB Treatment for Children

Context

Children with multidrug-resistant (MDR) tuberculosis (TB) are a neglected population suffering from a largely neglected disease.

- TB remains one of the top causes of death in children in the world. In 2021 alone, more than 215,000 children died from this preventable and curable disease. More than 95% of these deaths occur in children under 5 years of age not receiving TB treatment.
- Every year, an estimated 30,000 children develop MDR-TB, a type of TB that does not respond to two of the most used anti-TB drugs: isoniazid and rifampicin. Most of these children were in close contact with an adult or adolescent with MDR-TB.
- Fewer than 15% of children with MDR-TB are diagnosed and start treatment every year. Yet if they start treatment, nearly 80% are successfully cured.

Children need access to MDR-TB treatment that is not only effective but is also safe, well tolerated, and palatable.

- There are important evidence gaps about how to optimally dose existing medicines used for MDR-TB. This puts children at increased risk of side-effects if we are dosing too high, or increased risk of poor treatment response if we are dosing too low.
- Despite improved access to child-friendly formulations in recent years, caregivers often need to cut, break, crush and mix foul-tasting tablets that are made for adults and are not designed to disperse or dissolve.
- Breaking or crushing adult medicines to give to children can lead to dosing errors or make the medicines taste very bitter. Often times, children simply refuse to take the medicine due to the foul taste.
- Even some newly available child-friendly formulations still have a bad taste.
- The treatment journey can last anywhere from nine months to two years, and may still involve long-term hospitalisation. In some cases, treatment still includes painful daily injections that can result in permanent hearing loss.
- As MDR-TB is treated with multidrug regimens in which each drug is important, the lack of access to even one medication can be a barrier to children being treated with the best, safest and most effective newer regimens.

BENEFIT Kids Model

OUR GOAL is to improve access to better MDR-TB treatment and prevention for children.

Improved evidence from existing data for better MDR-TB treatment

- Systematic review and individual patient-data meta-analysis of children and adolescents treated for rifampicin-resistant TB
- Systematic review and individual patient-data meta-analysis on the pharmacokinetics of key 2nd-line TB drugs in children

Improved evidence from new studies for better MDR-TB prevention, treatment

- PERFORM trial
- CATALYST trial
- TB-CHAMP trial
- Delamanid Crush trial
- PETITE platform (PETITE, PETITE DTG (dispersible tablet and orodispersible film), PETITE Accept)
- Clofazimine PK 2 trial

Targeted formulations development to improve availability of child-friendly formulations

- Extemporaneous formulation development to address gaps in MDR-TB medication
- Child-friendly formulations enhancement for linezolid, moxifloxacin
- ChilPref platform (ChilPref ML, ChilPref SF, ChilPref Ext): Taste test evaluations

The Solution

The BENEFIT Kids project is bringing together a unique consortium of partners to improve access to better MDR-TB treatment and prevention for children of all ages to reduce sickness and death.

The Unitaid-funded BENEFIT Kids Project is a joint effort with partners from countries affected by MDR-TB. It is led by the Desmond Tutu TB, Stellenbosch University and includes close partnerships with colleagues from De La Salle Medical and Health Sciences Institute, Johns Hopkins University, B.J. Medical College Pune, Uppsala University, University of San Francisco, Chiang Mai University, University of Wisconsin-Madison and TB Alliance.

The Project is generating the priority evidence on dosing, safety, acceptability, costs and effectiveness needed to inform WHO policy recommendations as well as production of key TB drugs for children. Unlike standalone research efforts that are too often siloed, BENEFIT Kids represents a consolidated effort to tackle evidence gaps in paediatric MDR-TB treatment and prevention, helping to identify which treatments to use and in what ways. The project is conducting seven clinical treatment and prevention trials—in South Africa, the Philippines and India—and completing two systematic reviews of evidence for MDR-TB treatment.

Photo credit: John-Michael Maas for TB Alliance

Examples of our trials and evidence reviews, and their corresponding results, include:

- An evidence-synthesis assessed data on more than 20,000 children and adolescents treated for rifampicin-resistant TB. Analysis of this large data set showed that treatment with WHO Group A drugs, including bedaquiline, linezolid and levofloxacin or moxifloxacin, was associated with improved outcomes.

  RESULT: This highlights the critical importance of treating children with the best available medications. The data also showed the benefit of treating young children with bedaquiline. This evidence contributed to the 2022 WHO guideline that recommended children of all ages with rifampicin-resistant TB receive bedaquiline.

- The **PERFORM trial** (Pharmacokinetics of IEvofloxacin FORmulations in children with MDR-TB exposure) looked at the pharmacokinetics and acceptability of novel paediatric dispersible tablets (Macleods Pharmaceuticals, Mumbai, India) compared to levofloxacin adult tablets (crushed/dissolved) in 24 children at a single site in Cape Town, South Africa.

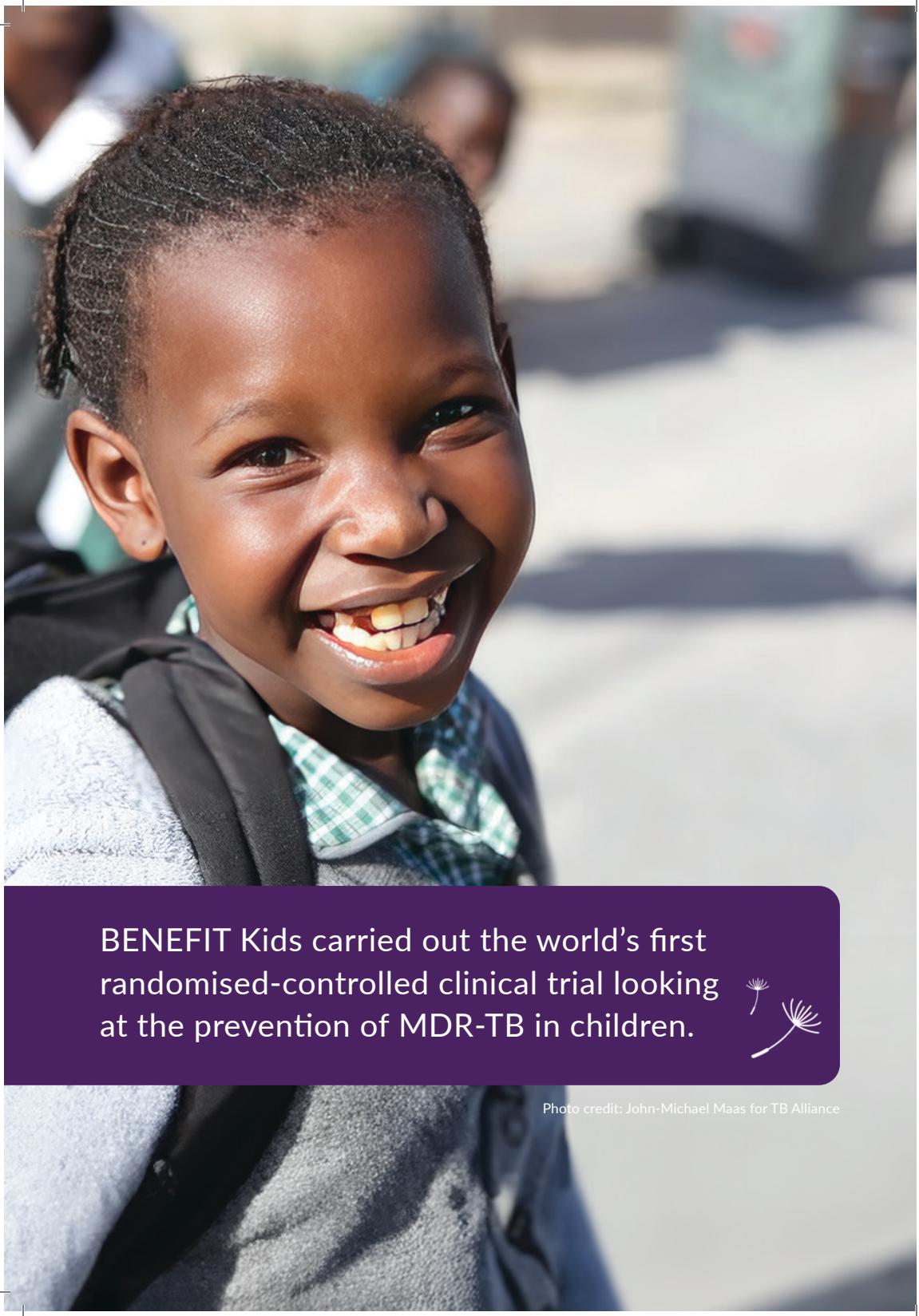
  RESULT: PERFORM showed that the dispersible tablets result in higher drug exposure than crushed adult tablets, and will inform evidence-based guidance on the most effective and safe levofloxacin dosing for children. The study also showed that caregivers preferred the dispersible tablet formulation for children, highlighting the importance of accessibility.

- The **CATALYST trial** (Clofazimine and moxifloxacin PK, safety and AccepTAbiLitY for paediatric TB treatment) is a trial of the pharmacokinetics, safety, tolerability, and acceptability of new more child-friendly formulations of clofazimine and moxifloxacin in children treated for rifampicin-resistant TB.

  RESULT: This multi-country study (South Africa, India, and the Philippines) will provide much needed evidence on how to best dose these new formulations of two key drugs—moxifloxacin and clofazimine—in children. It will also provide important data on how acceptable these treatments are to children and families, and will investigate their treatment experiences, including stigma. Nested health economics work will explore formulation costs and patient costs.

- The **Delamanid Crush trial** looked at the pharmacokinetics and acceptability of crushed or dissolved delamanid 50 mg solid tablets compared to dispersible delamanid tablets in 24 healthy adult volunteers to inform their use for children affected by MDR-TB.

  RESULT: This study showed that dissolving the adult tablets did not affect delamanid pharmacokinetics, so this formulation can be used in children safely and effectively where the dispersible tablet is not available. This important evidence has informed WHO guidance documents.



BENEFIT Kids carried out the world's first randomised-controlled clinical trial looking at the prevention of MDR-TB in children.

Photo credit: John-Michael Maas for TB Alliance

Children are at higher risk than adults of becoming sick with MDR-TB after exposure, yet we still know very little about how to best prevent MDR-TB in children.

- TB-CHAMP is a trial which investigated the efficacy and safety of levofloxacin in preventing TB in children and adolescents. Nearly one thousand healthy children who had been exposed to an adult with MDR-TB were recruited at five sites in South Africa.
- Data from this trial will provide high-quality evidence to support WHO recommendations for TB preventive treatment in children exposed to MDR-TB.

In BENEFIT Kids, Stellenbosch University and the TB Alliance also conducted a first of its kind "swish-and-spit" taste test in children of two drugs used in the treatment of MDR-TB. If children refuse to take their medicine or spit it out because of foul taste, they are not receiving the treatment they need. When medicines taste better it makes them easier for children to take, and for caregivers to administer. This facilitates good adherence and improves children's and caregivers' treatment experience.

- When developing child-friendly formulations, pharmaceutical companies tend to focus on safety, effectiveness, and dosing, but not necessarily taste.
- To address this gap, BENEFIT Kids conducted the CHILPREF ML study, a taste test of three different tasting formulations of moxifloxacin and three of linezolid, from each of two manufacturers, among 96 healthy children ages 5-17 across two sites in South Africa.
- Children were asked their opinion about which medicine they would prefer to take.
- The study provided recommendations for manufacturers about which formulations were preferred by children, and is supporting the development of these to make better tasting formulations globally available for children with MDR-TB.
    - It also demonstrated that it is feasible to carry out studies among children to improve taste.
    - In the case of moxifloxacin, most children (>50%) rejected the manufacturers' existing formulation and preferred different formulation blends, leading the manufacturer to change course and produce formulations deemed more palatable.

By working closely with the World Health Organisation, BENEFIT Kids is reducing delays between the generation of data and the adoption of new guidelines and policies.

- The project team proactively shares results with the WHO to inform policy recommendations.
- We are focused on improving children's lives as quickly as possible, as opposed to prioritising scientific recognition through journal publications.

Community Involvement

The BENEFIT Kids Project views partnerships with communities as central to our work overall, and the success of the project. An internationally representative Community Advisory Board (CAB), including several TB survivors, was established to guide study implementation, broader community engagement and dissemination to ensure that the voices of those most affected by TB and MDR-TB are heard. Throughout our various studies as part of the BENEFIT Kids Project, community representatives provided early input on study design, implementation, messaging and local social values. A key part of engaging with communities is continued advocacy for improved access to diagnosis, prevention, and acceptable treatment regimens for children with or at risk of MDR-TB. As part of the engagement process with community stakeholders, the BENEFIT Kids CAB, with other key community representative groups, launched a call in an incisive article in the International Journal of TB and Lung Disease to improve access to better treatment and formulations for children and to consider local community voices when developing formulations for children.


Photo credit: John-Michael Maas for TB Alliance

What more is needed?

Researchers/ clinicians

We want you to read the results of our research to better understand how these drugs and regimens can be used in children, and how best we can work together to deliver optimal care. We also hope that our work will demonstrate the feasibility of research with young children and inspire others—including researchers in high TB-burden countries—to address the remaining research gaps.

Policymakers in a high TB-burden country

We want you to use the latest evidence and guidelines to recommend and purchase the most child-friendly drugs and regimens for children suffering from, or exposed to, MDR-TB. We also want you to use this newly available evidence to prioritise diagnosis and case finding of children who might have been exposed to or are sick with MDR-TB.


Photo credit: John-Michael Maas for TB Alliance

Public health/ TB advocates

We want you to demand that kids have equitable access to the best possible treatment and prevention regimens for MDR-TB. Children often do not have the ability to make their voices heard and need your support.

Global health organisations/ funders active in the TB space

We need your support to ensure that the evidence we develop translates into new investments, policies, and programs quickly, and at scale. We also need to continue investing in the research needed for children to access new treatment and prevention innovations quickly and equitably.

Our research work is only one piece of the puzzle, and we must all work together so that children can benefit from the best and latest innovations in MDR-TB prevention, treatment and care.

Learn more about
BENEFIT Kids

Funded by

Unitaid
SAVE LIVES FASTER

Project leads

Stellenbosch University
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Desmond Tutu TB Centre
Every breath counts

Our partners

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