no symptoms. Travellers, particularly pregnant women or their partners, should be counselled about possible risks and should be aware that we often do not have real-time regional epidemiological data on Zika virus transmission, and travel guidance should consider the limitations of available epidemiological data. Thailand, and presumably many countries in southeast Asia, have experienced variable transmission across many regions. The findings from Salje and colleagues regarding the distribution of symptomatic persons in Thailand heighten concerns there might be lower levels of population immunity than expected and therefore an ongoing risk to pregnant women travelling to or living in endemic settings.[7]

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# The STREAM trial: missed opportunities and lessons for future clinical trials

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Final results of the STREAM trial were presented at the 2018, 49th Union World Conference on Lung Health, held in The Hague, The Netherlands. STREAM is a randomised controlled trial comparing the 18–24 month WHO-recommended multidrug-resistant tuberculosis (MDR-TB) treatment regimen with a 9–12 month regimen similar to that first described in Bangladesh.[1] Under programmatic conditions, the longer regimen results in treatment success for approximately 50% of patients,[2] whereas the shorter 9–12 month regimen improved treatment success to 80% or higher in selected countries.[3,4] Because these countries had relatively low HIV prevalence and relatively high percentages of treatment success with the longer regimens, questions around generalisability were raised.[4] STREAM was a multi-million dollar undertaking that took almost 10 years from the time of study design until the release of final results. Given the time and costs involved it is essential to reflect on lessons learned, and what the trial results tell us to inform how we accumulate future evidence to guide MDR-TB treatment.

STREAM found that both the longer and shorter regimens performed well, with 80% and 79% favourable outcomes, respectively. In routine programmatic settings, loss to follow-up with the longer regimen is a major contributor to poor patient outcomes.[2] By contrast, previous studies of the shorter regimen documented reduced loss to follow-up, contributing to overall improved treatment success.[3,4] However, because of the patient support provided in STREAM, as in most randomised controlled trials, the potential real-world effect of the shorter regimen on loss to follow-up could not be fully assessed. We must consider whether randomised controlled trials are the best way of evaluating the effect of a regimen on adherence and loss to follow-up. STREAM shows that improved patient support and encouragement during treatment improves

treatment outcomes, irrespective of regimen composition and duration.

During the decade between STREAM's conception and final results, improved treatment outcomes with the shortened regimen in programmatic settings led to WHO recommending this regimen for MDR-TB treatment.[5] Additionally, two new anti-tuberculosis drugs, bedaquiline and delamanid, also became available and because bedaquiline significantly improved MDR-TB patient outcomes, WHO prioritised its inclusion in all oral regimens in 2018.[6,7] Randomised controlled trials have long been considered the gold standard in study design and probably contribute important data on regimen combinations, but given the extended time needed to plan and execute such trials, results might be programmatically irrelevant when finally available. Programmatic and large-scale operational research data[3,7] have also contributed to a WHO recommendation for further operational studies of modified shorter regimens (including new drugs).[6] Furthermore, newer and more innovative study designs need to be considered. Multi-arm, multi-stage trials allow for evaluation of more than one arm and flexibility to respond to new data,[8] and Bayesian adaptive randomisation allows for reduced sample size and study time.[9]

STREAM's results also leave key questions unanswered, including the effectiveness of shortened treatment among HIV-positive patients, a group that was supposed to be a focus of the study. Overall, among HIV-positive patients, treatment success was lower and more serious adverse events and deaths occurred in the shorter than the longer treatment arm. Unfortunately, the study was insufficiently powered to definitively indicate which regimen reduces mortality and is better tolerated among this group. It is also disappointing that children were not included, because all the individual drugs in both arms are used routinely in children of all ages. Other outstanding questions include whether higher percentages of bacteriological failure documented in the shorter regimen signify a less bactericidal regimen, and whether the increased number of drug changes and loss to follow-up in the long regimen arm (contributing to poor treatment outcomes) simply reflect longer treatment duration.

Treatment adherence is a key issue in MDR-TB treatment. In-depth interviews with patients, to ascertain adherence challenges, would have contributed to a better understanding of patient perspectives, fostering more patient-centred MDR-TB treatment. Additionally, permanent hearing loss—a frequent and debilitating adverse event in MDR-TB treatment—was not formally assessed. Only one of the four countries used audiology equipment to monitor hearing loss, with the remainder relying on whisper testing or self-report, thus missing a substantial proportion of mild or moderate hearing loss. Audiometry equipment is inexpensive, can be delivered using tablet technology,[10] would have addressed the primary safety aims, while building effective MDR-TB treatment capacity in these low-income countries.

Although we have much to learn from the rigorous research of the STREAM trial, substantial work is needed to translate clinical trials into real-world conditions and extract the maximum cost-benefit. As *Mycobacterium tuberculosis* adapts and changes to its environment, we too need to adapt to the changing tuberculosis research environment to ensure attainment of the End TB strategy targets.

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# No accountability, no results—the difficult task of advocating for tuberculosis solutions

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2017–18 saw two unprecedented events in the history of tuberculosis: the WHO Ministerial Conference, which was held in Moscow in November, 2017,[1] and the High-Level Meeting on tuberculosis at the UN General Assembly (UNGA) held in September, 2018.[2] The political declaration issued by UNGA pledged to achieve the targets envisaged by the End TB strategy[3] through intermediate quantified milestones, focusing on vulnerable and marginalised populations, mobilising needed resources for research and implementation, and establishing a multisectoral accountability framework with regular reporting to UNGA. However, subsequent reflections have cast doubt over the effectiveness of the declaration, claiming that the outcomes did not include concrete political and financial commitments, especially by high-burden countries.[4–6]

Is this surprising? Advocacy for this disease of voiceless people in extreme poverty has always been a challenge. It does not have a critical mass of champions capable of articulating compelling and hopeful messages worldwide. Communication has been focused on the negative aspects of the efforts to control the disease, in sharp contrast with that of HIV activists who have promoted positive messages, emphasising the progress made and the hopes for the future. As a result, the general perception about tuberculosis control efforts is often one of hopeless failure, despite the millions of lives saved since 1990, the over 5 million people cured every year, and the slow but steady decline in incidence and mortality. In addition, tuberculosis activism has often not been directed at those who can make meaningful changes. Acknowledging and publicising the major progress achieved could make tuberculosis investment a much more attractive proposition to politicians and decision makers focused on short-term goals.

Nonetheless, beyond advocacy and communication, there are deeply rooted challenges. As noted almost a decade ago,[7] key UN agencies and their leaders have historically failed to prioritise tuberculosis as a major global health threat. Greater political commitment at WHO's highest level could have helped because when WHO is not bold, often ministers of health are not either. There have not been special initiatives by agencies, such as UNICEF, UNAIDS, or UNDP. With a couple of notable exceptions (eg, The United States Agency for International Development, US National Institutes of Health, and perhaps the Bill & Melinda Gates Foundation), important governmental and philanthropic funders are not committed to the fight against tuberculosis. There has not been a US presidential initiative on tuberculosis along the lines of what was done for HIV and malaria, nor have the European Commission and the G20 nations supported innovative solutions. The largest financing mechanisms, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and Unitaid, are still investing less than 20% of their funds in tuberculosis despite its promising progress. The World Bank has not paid tuberculosis special attention either, although three decades ago it promoted tuberculosis care as one of the most cost-effective health interventions.[8] The private sector and pharmaceutical industry have little interest in tuberculosis. Discovery and marketing of new tools will almost certainly clash with their interests given tuberculosis geopolitics. In fact, the desired profits by a drug developer can hardly be achieved from sales in low-income and middle-income countries, which have more than 90% of the global tuberculosis burden. The fact that tuberculosis advocacy has been unable to promote positive, hopeful messages building on achievements is also reflected in the general sentiments about the UNGA