The time has come: sparing injectables in paediatric MDR-TB

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Proponents of critical thinking recount this fable: a daughter asks, "Mother, why do you cut the end off the holiday ham?" Her mother answers, "Because that's the way Grandma always did it." The daughter, an inquisitive sort, then asks her grandmother, "Grandma, why do you cut the end off of the holiday ham?" Her grandmother replies, "Because my pan is too small." In matters of medicine, progress demands that clinicians and investigators continuously challenge practices that are more aligned with convention than with strong scientific rationale. Nowhere is this more imperative than in cases where treatment dictated by long-standing practice carries with it a high prevalence of permanent harm. And when irreversible toxicities affect children, they cast a long and terrible shadow, because children are affected for their entire lives. We argue that injectables should no longer be the standard of care for paediatric multidrug-resistant (MDR) tuberculosis, which is resistant to isoniazid and rifampicin.

First, injectable anti-tuberculosis drugs are unacceptably toxic. Amikacin, kanamycin, and capreomycin are part of the backbone of current WHO recommended MDR tuberculosis regimens. Every medical student learns that the efficacy of aminoglycosides is concentration-dependent; what is less emphasised is that aspects of their toxicity are time-dependent.[1] Elegant studies in guinea pigs established that the cumulative area under the concentration–time curve of amikacin in perilymph strongly predicts ototoxicity.[2] Animal studies show that once aminoglycosides have penetrated the inner ear, they take up to 38 days to clear.[3] Emerging data in adults with MDR tuberculosis indicate a strong association of cumulative amikacin exposure with hearing loss.[4] Considering the recommended treatment duration of injectables for MDR tuberculosis (≥4 months),[5] this exposure is vastly higher than that experienced, for example, by neonates treated for sepsis with 2 weeks of gentamicin, where risk-benefit considerations are clearly different.

Irreversible toxicities from injectables, such as hearing loss or vestibular damage, occur in at least 25% of children treated with these drugs.[5] Impaired hearing, in turn, adversely affects neurocognitive and language development, psychosocial functioning, and school performance.[5,6] Some of this damage can be arrested—but not reversed—if the injectable is stopped at the earliest signs of toxicity, if there is careful monitoring. However, this type of monitoring is resource intensive, infrequently available in settings where MDR tuberculosis is common, and challenging in young children. Daily intramuscular injections are programmatically challenging and painful, causing prolonged distress for children and their caregivers.

Second, the evidence that injectables provide meaningful microbiological activity to MDR tuberculosis treatment regimens is, at best, mixed. Given the high risk of serious permanent toxicity, the threshold for benefit should be high. However, in clinical studies of early bactericidal activity, amikacin as monotherapy at doses of 5–15 mg/kg per day had no measurable effect on sputum bacterial load, by contrast with all other tuberculosis drugs in use.[7] Notably, there have been no randomised trials of injectable-containing versus injectable-sparing regimens.[8] A meta-analysis of adults with MDR tuberculosis showed that adults with tuberculosis resistant to aminoglycosides do not have worse outcomes than those without aminoglycoside resistance.[9] In a meta-analysis of children programmatically treated for MDR tuberculosis, 119 of 842 children were treated without an injectable. Of these, 41 (72%) of 57 with culture-confirmed MDR tuberculosis and 58 (94%) of 62 with probable MDR tuberculosis had successful treatment outcomes.[10] Indeed, paediatric tuberculosis generally has a low organism burden and better observed treatment response than adult tuberculosis; this paucibacillary nature makes childhood tuberculosis in some sense easier to treat from an efficacy perspective, and this paves the way for evaluating and implementing injectable-sparing treatment approaches. In 2016, WHO guidance, for the first time, states that paediatric MDR tuberculosis can be treated without injectables in many cases, based on the high risk of toxicity and favourable treatment outcomes.

Third, though in the past there were no good alternatives to injectables for paediatric MDR tuberculosis, drugs are now available with better activity against the disease. Linezolid and clofazamine are recommended in the current WHO guidance for paediatric MDR tuberculosis; emerging paediatric pharmacokinetic and safety data will further inform their use in children. Delamanid has potent sterilising activity in pre-clinical studies, in addition to achieving highly favourable microbiological outcomes in phase 2 studies in adults.[11–13] Delamanid also has a favourable safety profile when given to children in phase 1–2 clinical trials, with no cases of QTc prolongation greater than

480 ms.[14] In Oct 2016, WHO released interim guidance on the use of delamanid in children aged 6 years or older; data in younger children are expected in 2017. Delamanid is now being used for children with MDR and XDR tuberculosis in many settings. The recent WHO recommendations form a strong foundation on which to build an argument for the use of injectable-sparing regimens in all children with MDR tuberculosis. The high risk of toxicity from injectable agents might have been tolerable until now given the lack of other treatment options; however, with new, safer, effective medications, this risk is increasingly difficult to justify.

Lastly, the ethical rationale for injectable-sparing regimens for children cannot be ignored. It is a priority of justice to ameliorate systematic clusters of disadvantage during childhood, lest they become entrenched for entire lifetimes.[15] We must share in this general duty to reduce the substantial burdens suffered by children with MDR tuberculosis. We must strengthen advocacy and research efforts to minimise suffering and increase the probability of successful treatment completion for children with MDR tuberculosis, while decreasing treatment toxicity. By replacing injectables with more effective and less toxic drugs, we will minimise both treatment-related and disease-related burdens for these children and their families.

From these considerations, there arises a strong mandate for further research to expand and optimise the repertoire of safer, better paediatric MDR tuberculosis drugs and regimens, and increase children's access to them. Replacing the injectables with better and safer drugs in all children at a programmatic level should occur, in parallel with careful, controlled studies to generate high-quality evidence relevant to children with the range of MDR tuberculosis disease. Advocacy for injectable-sparing regimens can and should occur, even as such research is still ongoing. Even when the ethical threshold for a given general approach to disease control has been clearly met, sometimes the standards required by regulatory or governmental bodies for licensure or implementation of a drug or treatment might lag behind. In the words of Warren Buffet, "chains of habit are too light to be felt until they are too heavy to be broken". Let us challenge the global community to be proactive, wherever chains are perceived, in breaking them. Otherwise, we risk injuring children for the sake of questionable clinical gain, and become like the incurious cook who, each year, continues to discard valuable ham through unquestioned ritual, despite now having a pan that is perfectly adequate in size.

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EDW is protocol co-chair for IMPAACT 2005, a phase 1-2 trial of the safety and pharmacokinetics of delamanid in combination with optimised background regimen for MDR-TB in children with and without HIV infection. The manufacturer of delamanid, Otsuka, agreed to donate drug to be used in the study, and share PK modelling and safety PK data from their ongoing trials in children, so that the protocol team could arrive at rational dosing decisions. AJG-P and ACH report grants from Otsuka Pharmaceutical Development and Commercialization, outside of the submitted work. ACH also reports an NIH-funded phase 1–2 trial (IMPAACT P1108) to study the dosing and safety of bedaquiline in children with MDR-TB. JJF, TCB, and KED declare no competing interests. The authors received funding from NIH/DAIDS UM1 AI068632, NIH T32 GM066691-11, NIH T32 GM066691-12 (NIGMS), Pearl M Stetler Research Award for Women Physicians, IMPAACT Network, and Johns Hopkins University Center for AIDS Research (P30AI094189). We thank Kathryn Lypen for her steadfast and heroic assistance in crafting the IMPAACT 2005 protocol.

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