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Paediatric study of bedaquiline remains an "open issue"

To the Editor:

In their editorial, "Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence", Pontali *et al.* [1] detail and analyse the existing evidence for bedaquiline for multidrug-resistant tuberculosis (MDR-TB). The authors also discuss "open issues" or areas where additional research is required to inform use, including in children. Pontali *et al.* [1] mention the planned phase II paediatric study of bedaquiline (www.clinicaltrials.gov identifier number NCT 02354014). This study to evaluate the pharmacokinetics and safety of bedaquiline in children is crucial to guiding treatment in people under 18 years of age, who have previously been excluded from trials of bedaquiline.

An estimated 32 000 children develop MDR-TB each year [2] but evidence-based dosing guidelines, formulations and data on interactions with antiretrovirals to appropriately treat them are lacking [3]. The planned phase II paediatric study of bedaquiline would help address this gap. This study has been in development for over 5 years. In that time, an estimated 160 000 new cases of paediatric MDR-TB have appeared.

In a consensus statement published in *The Lancet*, a group of experts convened by the US National Institutes of Health recommended that paediatric investigation of new tuberculosis drugs and regimens begin as soon as efficacy and safety have been established in adults (phase IIb studies) [4]. Planning for and starting paediatric investigations earlier can help close gaps in access that currently exist between adults, adolescents and children. Favourable phase IIb data were available for bedaquiline in 2011 and the US Food and Drug Administration conditionally approved bedaquiline for use in adults in December 2012 [5]. Given the time it will take to enrol and complete the study, and file for regulatory approval for the paediatric formulation, there will be, at best, a 5-year gap between adult and paediatric formulation availability.

Several factors appear to have contributed to this delay. Janssen Pharmaceuticals (Titusville, NJ, USA), the sponsor of bedaquiline, worked for 3 years with the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network of the US National Institute of Allergy and Infectious Diseases to complete a protocol to study bedaquiline in HIV-positive and -negative children. In June 2014, Janssen ended this collaboration in favour of creating their own independent study in HIV-negative children only [6]. This decision necessitated the creation of a new protocol and introduced new challenges, as most trial site infrastructure and expertise for paediatric MDR-TB studies are concentrated in the IMPAACT network [7]. Janssen received an infusion of $1.5 million in public funds from UNITAID's STEP-TB project to support the development of a paediatric formulation of bedaquiline and, as recently as December 2015, Janssen reported that its paediatric study would open in January 2016; however, at the time of writing it had yet to start [7, 8].

In contrast, delamanid, the other newly approved drug for MDR-TB, has gone through pharmacokinetic and safety investigations in HIV-negative children as young as 6 years old, and is currently under study in children 3–5 years old. Though delamanid has not been widely registered for adults or children, children have received delamanid under compassionate use and had favourable outcomes [9].

Bedaquiline is much more widely available than delamanid for adults under programmatic conditions but nearly totally restricted from children due to lack of data [10]. Children with MDR-TB urgently need better treatment options. Expedited enrollment in Janssen's paediatric study of bedaquiline and the availability of the paediatric formulation for the IMPAACT network for its planned study of bedaquiline, including in HIV-positive children, would greatly advance treatment for paediatric MDR-TB. Children affected by MDR-TB, and those who care for them, have already waited too long.

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Paediatric study of bedaquiline is open but several years behind schedule, delaying access for children with MDR-TB http://ow.ly/4mP8wm

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New anti-tuberculosis drugs for special populations: a difficult-to-address issue

From the authors:

We read with interest correspondence from L. McKenna and L. Ruiz Mingote commenting on the editorial by Pontali *et al.* [1] "Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence". Their core message is the lack of availability of the new anti-tuberculosis (TB) drugs (*i.e.* bedaquiline and delamanid) for childhood TB. In particular, they advocate for rapid initiation of clinical trials in children after the proof of concept and dose-finding (IIa and IIb, respectively) studies carried out in adults.

Childhood TB, and specifically multidrug-resistant TB (MDR-TB) in this age group, has recently gained international relevance both in terms of numbers and difficult management [2–4]. The complicated bacteriological diagnosis in children is well known, so that often the paediatrician needs to rely on the