Retooling Existing Tuberculosis Drugs for Children

To the Editor—The article by Dooley and colleagues [1], on behalf of the efficacy subgroup of Research Excellence to Stop TB Resistance (RESIST-TB), is timely and much needed. New tuberculosis drugs are indeed likely to be several years away from widespread use, necessitating our continued reliance on existing drugs. Because combinations of 3 or more new drugs are even further away, the first new agents licensed will need to be protected by multidrug regimens of existing medications. Regimens of existing drugs require optimization of dose, treatment duration, and treatment combinations. This paper serves as a call to action to address these research priorities.

Despite the much-needed perspective provided, we note with concern the absence of any discussion regarding the existing, albeit limited, evidence base for pediatric use of existing tuberculosis drugs and the retooling of dosages and regimens necessary to optimize treatment in children. Furthermore, no research priorities are identified for the
investigation of existing pediatric drugs. Children with tuberculosis differ from adults in many respects: the spectrum of disease manifested, the way medications are administered, the manner in which drugs are absorbed, and also the adverse effects experienced. Young children tend to metabolize drugs more rapidly than adults [2], resulting in lower serum concentrations following like-for-like dosing. Specific forms of tuberculosis, such as tuberculous meningitis, are more common in children; specific drug properties, for example, cerebrospinal fluid penetration should therefore be considered.

The discussion regarding retooling of existing tuberculosis drugs should stimulate consideration of the appropriate timing to include children in drug trials of both novel and existing agents. Given the paucibacillary nature of most forms of pediatric tuberculosis, at least equal efficacy can be expected for the treatment of drug-resistant disease in children compared to adults. However, the high frequency of adverse drug effects, for example, thyroid toxicity in developing children [3], make the urgent evaluation of shorter and less toxic combination regimens mandatory.

Knowledge of the pharmacokinetics of existing and novel drugs in children, drug-drug interactions, and the development of child-friendly formulations are also priorities. The effect of human immunodeficiency virus (HIV) coinfection and the interaction between tuberculosis drugs and antiretroviral therapy is a further important pediatric consideration, given the high prevalence of pediatric HIV infection in settings where drug-resistant tuberculosis is increasing [4].

There is an increasing awareness of the importance of including children in clinical research on new and existing drugs [5]. Regulatory authorities have now made pediatric evaluation of novel drugs a prerequisite for regulatory approval in Europe and the United States [6–7]. However, major gaps remain in our knowledge of existing tuberculosis drugs and drug regimens in children and for the retooling of these drugs with new drug candidates. As researchers, international policymakers, implementers, and civil society we should be advocating for the needs of children, the most vulnerable members of our society.

Note

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References