Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The association between enteropathogens and antimycobacterial drug pharmacokinetics in children

Published Online
April 7, 2022
https://doi.org/10.1016/
S2666-5247(21)00353-0

See Articles page e408

There were an estimated 1·09 million incident tuberculosis cases resulting in 226 000 deaths in children globally in 2020.[1] The COVID-19 pandemic is reversing recent progress, meaning tuberculosis remains a major public health problem in children.[1,2] First-line tuberculosis treatment relies on rifampicin, isoniazid, pyrazinamide, and ethambutol.[3] In response to evidence of low exposures to first-line tuberculosis drugs in children, WHO recommended paediatric doses of rifampicin, isoniazid, and pyrazinamide were increased in 2010;[3] however, even with the recommended higher doses, studies continue to demonstrate low exposures to these drugs in children, especially for the crucial drug rifampicin.[4,5] Children with most forms of tuberculosis who receive timely treatment respond well, despite low drug exposures. However, these good outcomes overall might mask subgroups with worse outcomes, such as children who are young, have severe illness, are malnourished, or are living with HIV. Additionally, as shorter drug regimens continue to be explored, it will be increasingly important to ensure optimal drug exposures to maintain regimen activity. Therefore, it is an important priority to improve first-line tuberculosis drug dosing in children, and better characterise the factors associated with low exposures.

In *The Lancet Microbe*, Daniel van Aartsen and colleagues[6] evaluated enteropathogen burden among a cohort of Tanzanian children routinely treated for tuberculosis, and they explored the effect of this burden on the pharmacokinetics of first-line tuberculosis drugs rifampicin, isoniazid, pyrazinamide, and ethambutol. 44 children younger than 15 years treated for confirmed or probable tuberculosis with the recommended doses of first-line tuberculosis drugs were included in the analyses. The authors collected baseline clinical data, including self-reported symptoms of enteropathy (ie, diarrhoea and abdominal pain), quantified the burden of enteropathogens in stool, and did pharmacokinetic sampling of the first-line tuberculosis drugs to quantify peak (C_{max}) and total area under the concentration curve over 24 h (AUC_{0-24}).

Among the 44 children, a high proportion were malnourished (n=37 [84%]), symptoms of enteropathy were common (n=32 [72·7%]), and enteropathogens were frequently identified on stool analysis (mean of 2·1 [SD 1·3] enteropathogens per participant). Overall, tuberculosis drug exposures were frequently below target.

The associations identified by the study on the effect of the type of infection (ie, bacterial and viral) and individual pathogens, such as enteropathogenic *Escherichia coli,* on the C_{max} and AUC_{0-24} of some first-line tuberculosis drugs are interesting, but they should be interpreted cautiously pending confirmation in other studies. Multiple significant associations between enteropathogens and antimycobacterial C_{max} and AUC_{0-24} were identified in the adjusted analyses, including a significant reduction in rifampicin AUC_{0-24} in participants with higher enteropathogen burden and gastrointestinal symptoms.

This study's findings are intriguing, but the authors appropriately identified several limitations, including the small sample size and the difference in time between characterisation of stool enteropathogens and the measurement of serum to assess antimycobacterial pharmacokinetics. Another important limitation is the large number of analyses done to assess the relationship between the C_{max} and AUC_{0-24} of the four antimycobacterial drugs, and several factors—enteropathogen burden, gastrointestinal symptoms, type of infection (bacterial, viral, or parasitic), and individual infectious agents—without adjustment for multiple comparisons. The high proportion of malnutrition in this population is also worth noting, and whether the findings presented would be generalisable to other populations should be considered given the impacts of malnutrition on gut function.

Despite these limitations, several important conclusions can be drawn from this study. First, the study provides additional evidence that first-line tuberculosis drugs administered to children at the current recommended doses frequently result in exposures that are below targets; rifampicin is the drug that is most affected. Second, malnutrition was very common in this cohort. The overlap of malnutrition and tuberculosis in children, and its negative effects on antimycobacterial pharmacokinetics and treatment

outcomes is increasingly being recognised and is an important area for future investigation.[7] Third, as the authors discuss, the reported association of enteropathogen burden with reduced concentrations of antimycobacterial drugs in children reporting gastrointestinal symptoms has potentially important implications. Diarrhoeal disease is a major cause of morbidity in children younger than 5 years and of mortality globally; and there is a substantial overlap of settings with high burdens of diarrhoeal disease and tuberculosis.[8] Careful assessments for diarrhoea and its management among children on tuberculosis treatment might not only reduce the effects of the diarrhoea, but might improve tuberculosis drug exposures and patient response to tuberculosis treatment.

Additionally, the effect of enteropathy in children might partly explain the high variability in antimycobacterial pharmacokinetics frequently seen between occasions, between individuals, and between studies. Although not evaluated in this study, emerging research is exploring the potential of the gut microbiome to affect the pharmacokinetics of many drugs.[9,10] This has yet to be explored robustly in children with tuberculosis but highlights the need for research to better understand the interactions of gut microbes and antimycobacterial pharmacokinetics.

Future studies are needed to confirm the main findings of enteropathogen burden with antimycobacterial concentrations reported here. Additional research exploring the effect of the gut microbiome on antimycobacterial pharmacokinetics is also of interest. Finally, it is an urgent priority to identify the first-line tuberculosis drug doses in children that will meet exposure targets and offer all children the best opportunity to have their tuberculosis effectively treated and cured.

I declare no competing interests.

Anthony J Garcia-Prats
garciaprats@wisc.edu

University of Wisconsin, School of Medicine and Public Health, Department of Pediatrics, Madison, WI 53705, USA; Stellenbosch University, Faculty of Medicine and Health Sciences, Department of Paediatrics and Child Health, Desmond Tutu Tuberculosis Centre, Tygerberg, South Africa

1 WHO. Global tuberculosis report 2021. 2021. https://www.who.int/publications/i/item/9789240037021 (accessed Dec 9, 2021).
2 Hogan AB, Jewell BL, Sherrard-Smith E, et al. Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: a modelling study. *Lancet Glob Health* 2020; **8:** e1132–41.
3 WHO. Rapid advice: treatment of tuberculosis in children. 2010. https://apps.who.int/iris/handle/10665/44444 (accessed Dec 9, 2021).
4 Denti P, Wasmann RE, van Rie A, et al. Optimizing dosing and fixed-dose combinations of rifampicin, isoniazid, and pyrazinamide in pediatric patients with tuberculosis: a prospective population pharmacokinetic study. *Clin Infect Dis* 2021; published online Oct 19. https://doi.org/10.1093/cid/ciab908.
5 Chabala C, Turkova A, Hesseling AC, et al. Pharmacokinetics of first-line drugs in children with tuberculosis using WHO-recommended weight band doses and formulations. *Clin Infect Dis* 2021; published online Aug 22. https://doi.org/10.1093/cid/ciab725.
6 Van Aartsen D, Museveni J, Mduma E, et al. Enteropathogen spectrum and effect on antimycobacterial pharmacokinetics among children with tuberculosis in rural Tanzania: a prospective cohort study. *Lancet Microbe* 2022; published online April 7. https://doi.org/10.1016/S2666-5247(21)00308-6.
7 Radtke KK, Dooley KE, Dodd PJ, et al. Alternative dosing guidelines to improve outcomes in childhood tuberculosis: a mathematical modelling study. *Lancet Child Adolesc Health* 2019; **3:** 636–45.
8 Reiner RC Jr, Wiens KE, Deshpande A, et al. Mapping geographical inequalities in childhood diarrhoeal morbidity and mortality in low-income and middle-income countries, 2000–17: analysis for the Global Burden of Disease Study 2017. *Lancet* 2020; **395:** 1779–801.
9 Tsunoda SM, Gonzales C, Jarmusch AK, Momper JD, Ma JD. Contribution of the gut microbiome to drug disposition, pharmacokinetic and pharmacodynamic variability. *Clin Pharmacokinet* 2021; **60:** 971–84.
10 Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. *Transl Res* 2017; **179:** 204–22.