HHS Public Access

Author manuscript

Int J Tuberc Lung Dis. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Int J Tuberc Lung Dis. 2021 January 01; 25(1): 36–42. doi:10.5588/ijtld.20.0301.

Effect of Malnutrition on the Pharmacokinetics of Anti-tuberculosis Drugs in Ghanaian Children

Nana Ayegua Hagan Seneadza[1,2], **Sampson Antwi**[3,4], **Hongmei Yang**[5], **Anthony Enimil**[3,4], **Albert Dompreh**[3], **Lubbe Wiesner**[6], **Charles A Peloquin**[7], **Margaret Lartey**[8,9], **Michael Lauzardo**[10], **Awewura Kwara**[10]

[1]Department of Epidemiology, University of Florida

[2]Department of Community Health, University of Ghana Medical School

[3]Directorate of Child Health, Komfo Anokye Teaching Hospital, Kumasi, Ghana

[4]Department of Child Health, School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

[5]Department of Biostatistics and Computational Biology, University of Rochester School of Medicine and Dentistry, Rochester, NY, United States

[6]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

[7]Deaprtment of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL

[8]Department of Medicine and Therapeutics, University of Ghana Medical School, Accra, Ghana

[9]Fevers Unit, Korle Bu Teaching Hospital, Accra, Ghana

[10]Division of Infectious Diseases and Global Medicine, College of Medicine, University of Florida, Gainesville, FL

Summary

Background: Antituberculosis (anti-TB) drugs dosing based on only weight may contribute to suboptimal drug concentrations and poor treatment outcomes in malnourished children. We examined the effect of malnutritional state on pharmacokinetics (PK) of the first-line anti-TB drugs in children.

Methods: Drug concentrations were measured in Ghanaian children during intensive-phase of tuberculosis (TB) treatment. Weight-for-age (WFA), height-for-age (HFA), weight-for-height

Corresponding author and request for reprints: Dr. Awewura Kwara, University of Florida College of Medicine, 2055 Mowry Road, P.O. Box 103600, Gainesville, FL 32610, USA. Telephone: +1 325 273-9501, Fax: +1 352 273-9275., awewura.kwara@medicine.ufl.edu.

Author declaration of individual contribution

NAHS, AK: Conception and study design. SA, AE, AD: Acquisition of data

LW, CAP: Sample assays and PK analysis. NAHS, HY, CAP, ML, ML, AK: Analysis and interpretation of data. All authors were involved in drafting the paper and revising it critically for important intellectual content. All authors reviewed and approved the final version.

Conflict of interest: All authors have declared no conflict of interest.

(WFH) and body mass index-for-age (BFA) were calculated and children with z-scores <−2SD (standard deviations) were considered as having malnutrition. Differences in anti-TB drugs PK by nutritional status were compared.

Results: Of 100 participants, 24/48 (50.0%) of those younger than 5 years had wasting, 58/86 (67.4%) were underweight, 56/99 (56.6%) had stunting and 22/51(43.1%) of children 5 years/ older had low BFA. Children with stunting were more likely than controls to have lower mean RIF and PZA C_{max} and $AUC_{0\text{-}8h}$, as well as a higher frequency of mean C_{max} below the normal range. Wasting and underweight were associated with lower mean EMB C_{max} and $AUC_{0\text{-}8h}$.

Conclusions: The current World Health Organization recommended dosages were associated with lower plasma exposure of RIF, PZA and EMB in children with stunting, wasting and underweight. Anti-TB drugs dosing models for children may need to include height.

Keywords

First-line; treatment; dosing regimen; Paediatric TB

Malnutrition remains a major public health problem globally affecting 22%-30% of children under 5 years in 2018[1], with the greatest burden in sub-Saharan Africa[2]. The causes of malnutrition are multidimensional, often resulting in suboptimal growth, poor drug treatment outcome for several diseases and death in severe cases[3,4]. Tuberculosis (TB), an infectious disease often associated with malnutrition[5,6], may cause decreased appetite, malabsorption of nutrients and changes in one's metabolism resulting in an impaired nutritional status[7]. The combination of malnutrition and TB in a child poses serious challenges to effective management.

Anti-tuberculosis (anti-TB) therapy has significantly reduced the morbidity and mortality associated with TB[3]. However, the response to anti-TB drug therapy is affected by several factors including malnutrition, especially in children. Malnutrition may affect TB treatment response through processes such as malabsorption and alterations in protein binding of drugs, changes in the pharmacokinetics (PK) of anti-tuberculosis drugs[8,9]. Though there is lack of consensus on the effect of malnutrition on drug PK, there is evidence to suggest variations in drug PK may result from differences in body composition, surface area and the stage of maturation of liver enzymes [10,11]. Some studies have reported reduced concentrations of the first-line anti-TB drugs in malnourished children[10], while others found no effect or increased drug concentrations[12,13]. In this study, we examined the effect of malnutrition on the PK of first-line anti-TB drugs in Ghanaian children with TB, who were treated according to current World Health Organization (WHO) guidelines. We hypothesized that malnutrition will be associated with lower plasma exposure and a higher frequency of subtherapeutic concentrations of the first-line anti-TB drugs given that the current dosing guidelines is based only on weight.

METHODS

Data from 113 children clinically diagnosed with TB between October 2012 and August 2015 in Kumasi, Ghana were retrieved for this current study[14,15]. Thirteen (13) children in the cohort who received the previous WHO recommended lower drug dosages were

excluded from this analysis. All participants were prescribed a regimen consisting of isoniazid (7 to 15 mg/kg), rifampin (10 – 20 mg/kg), pyrazinamide (30 – 40 mg/kg) and ethambutol (15 – 25 mg/kg) daily for 2 months then isoniazid and rifampin daily for 4 months[16]. The medications were dosed according to WHO revised guidelines for children using available dispersible fixed-dose combination (FDC) pediatric tablets in the weight bands 5 – 7 kg, 8 – 14 kg, 15 – 20 kg, 21 – 30 kg, 31 – 39 kg and 40 – 54 kg. Pharmacokinetic sampling was performed after at least 4 weeks of anti-TB treatment as previously described[14]. Blood samples were collected at times 0 (pre-dose), 1, 2, 4 and 8-hours after directly observed dosing in the hospital. The samples collected in EDTA-coated tubes were processed and plasma stored at – 80°C until shipment on dry ice to University of Cape Town, Cape Town, South Africa for drug concentrations assays.

Drug concentrations were determined using validated liquid chromatography tandem with mass spectrometry (LC/MS/MS) methods as we previously described[14]. The observed C_{max} and time to C_{max} (T_{max}) were determined by inspection of the serum concentration-time graphs for each drug and AUC from time 0 to 8 hours ($AUC_{0–8h}$) was calculated using noncompartmental analysis (Phoenix Software; Pharsight Corporation, Mountain View, CA). Reference target ranges of C_{max} for INH, RIF, PZA and EMB were 3–6 μg/mL, 8–24 μg/mL, 20–50 μg/mL and 2 to 6 μg/mL, respectively [17].

The Institutional Review Board of Kwame Nkrumah University of Science and Technology, Ghana and Lifespan Hospitals, Providence, Rhode Island (PI institution at time of the study) and University of Florida approved the study. All parents and guardians of the children provided signed informed consent. The parent study was registered with ClinicalTrials.gov, number NCT01687504.

Statistical analysis

Children were characterized using weight-for-age, height-for-age, weight-for-height and BMI-for-age. Children were underweight if their WFA < –2 standard deviations (SD), stunted if their HFA was < –2 SD, wasted if their WFH was < –2 SD of the WHO Child Growth Standards and malnourished (or thinness) when BMI-for-age (BFA) < −2SD below the medians [18–21]. Z-scores for WFA, HFA, WFH and BFA were calculated using Z-score calculators based on WHO reference standards to determine the nutritional status of the children. WFH classification was used for only children < 5 years[10,22], whilst BFA was used for older children ≥ 5 years[22,23]. The WHO reference for WFA scores are available for up to 10 years in children and therefore 14 participants older than 10 years had no WFA z-scores and were excluded from the analysis on WFA.

Demographic and nutritional status characteristics of the participants were described based on the following age categories: less than 2, 2-5, 5-10, 10-14years. Proportions were calculated to describe categorical characteristics of participants whilst medians with ranges were used for continuous variables. The proportion of participants with drug concentration below the reference range by nutritional status was compared using chi-square test. The geometric means (with 95% confidence intervals, CI) of the pharmacokinetic parameters (C_{max} and AUC_{0-8h}) of the anti-TB drugs taken by participants in the different nutritional

status categories were compared for differences using the t-test on log-transformed data for independent groups.

Multivariate logistic regression models using stepwise variable selection with low mean C_{max} of INH, RIF, PZA and EMB as outcome was done. A significance level of 0.15 is required to allow a variable into the model and stay in the model. For the first-line anti-TB drugs, both C_{max} divided by minimum inhibitory concentration C_{max}/MIC and AUC divided by MIC (AUC/MIC) are associated with mycobacterial killing[24]. We focused on C_{max} < the lower reference value (low C_{max}) for this analysis because it is frequently used for therapeutic drug monitoring as it is more convenient to obtain than AUC. We included age, HIV status and weight as they were found to be associated with the C_{max} and $AUC_{(0-8h)}$ of the drugs[14]. Underdosing was included as a covariate in the multivariate logistic regression because 64.0% of the participants had underdosing of at least one of the anti-TB drugs. All analyses were done using the statistical software SAS 9.4 (SAS Institute, Cary NC).

RESULTS

Of the 100 participants, the median age was 5 years (range: 0.4-14 years) with 52.0% being 5 years or older and 58.0% being male. The site of TB was predominantly pulmonary (75.0%) and 50.0% were HIV positive. Based on the WHO standards, 50.0% of the participants aged less than 5 years were wasted (WFH <- 2SD), 67.4% were underweight (WFA <- 2SD), 56.6% were stunted (HFA <- 2SD) and 43.1% of those 5 years and older had low BFA. The profile of the children by age categories is summarized in Table 1.

Apart from PZA which had a lower median dosage of 27.3 mg/kg (outside of the recommended 30 to 40 mg/kg range), all the other drugs had median dosage ranges within WHO-recommended ranges. The proportions of INH, RIF, PZA and EMB underdosing were 1%, 1%, 64% and 16% respectively with 64.0% having underdosing of at least one of the anti-TB drugs.

Among children with wasting, underweight and stunting, the proportions that had C_{max} of INH < 3 μg/ml were 16.7%, 10.3% and 10.7% respectively compared to their counterparts with normal nutritional status where the proportions were 8.3%, 3.6% and 7.0% respectively. None of those with low BFA had low C_{max} of INH. The geometric mean C_{max} and AUC_{0-8h} of INH were not statistically significantly different between those who had stunting, wasting, underweight and low BFA and the children who had normal nutritional status profiles (Table 2).

Children with stunting were more likely to have C_{max} of RIF < 8 μg/ml compared to those who had normal nutritional status (76.8% versus 41.9%), respectively. Stunting was associated with a significantly lower geometric mean C_{max} and AUC_{0-8h} compared to those who had normal HFA and, respectively (Table 3).

Among children with wasting, underweight and stunting, the proportions that had C_{max} of PZA < 20 μg/ml were 33.3%, 19.0% and 25.9% compared to their counterparts with normal nutritional status where the proportions were 21.7%, 20.0% and 7.1%, respectively (Table 4). There was a significantly lower mean C_{max} of PZA among those who had stunting but

higher among those who had low BFA compared to their counterparts who had normal HFA and BFA, respectively. Those who were stunted had a significantly lower AUC_{0-8h} compared to those who had normal HFA, whilst those with low BFA had a significantly higher mean AUC_{0-8h} compared to those who had normal BFA as shown in Table 4.

Children with wasting were also more likely to have mean C_{max} of EMB < 2 μg/ml compared to those who had normal nutritional status (87.0% versus 56.5%), respectively. The children who were wasted and underweight had a statistically significantly lower mean EMB C_{max} respectively, compared to their normal nutritional status counterparts. The mean $AUC_{(0-8h)}$ of EMB for children who were wasted and underweight were also significantly lower, respectively compared to those who had normal HFA and WFA respectively (Table 5).

In the multiple logistic regression analyses, stunting was a significant predictor of mean RIF C_{max} < 8 μg/ml, PZA C_{max} < 20 μg/ml and EMB C_{max} < 2 μg/ml, with adjusted odds ratios of 6.75 (95% CI;1.76-25.83), 5.79 (95% CI; 1.13-29.62) and 20.70 (95% CI; 2.50-171.67) respectively. In addition, TB/HIV coinfection and underdosing were risk factors for low mean EMB C_{max} with adjusted odds ratios of 11.28 (95% CI; 1.64-77.86) and 8.42 (95% CI; 1.20-59.15) respectively (Table 6). Secondary analysis using C_{max} cut-off of <35μg/ml as used by other researchers[25] showed a higher proportion of children with low C_{max} of PZA in all the nutritional status categories (44.9% to 69.9%).

DISCUSSION

This study examined the effect of malnutrition on the PK of first-line anti-TB drugs in Ghanaian children with TB and found that nutritional status was significantly associated with RIF, PZA and EMB but not INH concentrations. Malnutrition, especially stunting was associated low mean C_{max} of RIF, PZA and EMB in our study population. Children with stunting compared to those who had normal nutritional status were more likely to have low mean C_{max} of RIF and PZA. In addition, underdosing and HIV infection were risk factors low mean EMB C_{max}.

Underweight and stunting were present in over 50% of our study participants. In Ghana, reported rates of underweight, wasting and stunting were 10.4%, 5.3%, and 18.4% respectively among children under 5 years without TB [26]. Our study found higher proportions of malnutrition than the rates cited above but lower than reported among children with TB (77%) in Tanzania[27]. As with our study, other researchers also found malnutrition to be common, with stunting being the most common type[26,28] among Ghanaian children even without TB. The higher rates of malnutrition could also be because TB results in nutrient malabsorption and changes in the body's metabolism leading to forms of undernutrition such as wasting[10,11,31].

The prevalence of low C_{max} of first-line anti-TB drugs among malnourished children in our study is similar to the findings by Justine M. et al.[27] where the C_{max} of RIF and EMB were significantly lower compared to those who had normal nutritional status even with WHO revised doses of anti-TB drugs. In our study, higher proportions of children who had poorer

nutritional status had lower C_{max} than targeted compared to those who had normal nutritional status. This further emphasizes the point made by other researchers[31] for a critical review of dosages of anti-TB drugs in children based on other factors including nutritional status.

Nutritional status did not statistically significantly influence INH PK in our study. This finding is similar to the results of the studies by other researchers [10,12,13,19]. In contrast, Ramachandran[32] found low peak concentrations of INH among children with stunting, underweight, and low BFA compared to their normal counterparts. In Tanzania, malnutrition in children was found to be a significant risk factor for low plasma levels of INH[27].

In the current study stunting was a significant predictor of low RIF concentrations after adjusting for sex, HIV coinfection status, WFA, WFH and BFA. Our findings are consistent with those of Ramachandran and colleagues who found significantly lower peak concentrations of RIF among children who were malnourished compared to those who were not [32]. However, Mukherjee et al.[13] found no difference in the C_{max} of RIF of children who were severely malnourished compared to those who were not.

The relationship between nutritional status and PZA PK was contrary to the general trend seen with the other drugs in this study. Whilst the C_{max} and $AUC_{0\text{-}8h}$ of PZA were significantly lower for those who had stunting, they were significantly higher for those with low BFA compared to those who had normal nutritional status parameters. Dayal et al.[10] and Oshikoya et al.[22] found low BFA to be associated with significantly lower mean C_{max} and $AUC_{0\text{-}8h}$ of PZA. These differences could be due to differences in the study populations used for the assessment of BFA. In our study, we considered BFA for children 5 years and older whilst Dayal[10] assessed BFA for all the participants aged 1-15 years.

For EMB, underweight and wasting were associated with lower mean EMB C_{max} and $AUC_{0\text{-}8h}$ in our study. In addition, the logistic regression analysis identified stunting, underdosing and coinfection with HIV EMB to be associated with low C_{max} of EMB. Whether a higher dose of EMB is needed in children, especially those with malnutrition is unknown as the relationship between TB treatment outcome and EMB concentrations is not established.

Dosing recommendations for children with malnutrition based only on weight may lead to suboptimal drug concentration and treatment outcomes. Body surface area (BSA) that incorporates both weight and height might be a better indicator of body size in children, especially those who are malnourished. Future population pharmacokinetic modeling and simulations to determine the optimal dose of the anti-TB drugs in children should consider using BSA rather than weight alone for dosing decisions.

The strengths of this study include the comparatively large sample used as well as the simultaneous comparison of the PK of the four first line anti-TB drugs used in the intensive-phase of therapy in contrast to other studies that used relatively smaller samples[10,19,23] and/or compared 2 or 3 of the drugs[10]. A notable limitation of our study is the use of anthropometry as a proxy for assessing body fat/mass. This method is unable to distinguish between body fat and lean mass[33].

In summary, children with stunting had lower plasma RIF and PZA exposure, underscoring the need to incorporate height in procedures to derive the dosing of these drugs for children. In addition, after adjusting for weight and HIV status, stunting was associated with RIF, PZA and EMB mean C_{max} below the lower limit of widely accepted normal range. Radtke and colleagues have proposed a simple change in dosing procedures to include age and nutritional status to improve TB treatment outcomes in children, especially malnourished children who are at high risk of death[31]. Our finding suggests future models to derive optimal doses of first-line anti-TB drugs in children, especially RIF should consider using BSA rather than weight alone in the simulations.

Acknowledgements

We thank the study participants and the supportive staff of the TB and HIV clinics at KATH who helped with patient enrolment. We also thank Antoinette Ortsin, Dennis Bosomtwe, and Theresa Opoku for participant enrolment and data collection as well as Maxwell Owusu and Eugene Adu Ahwireng for their assistance in specimen handling and processing. Dr. Nana A Hagan Seneadza was supported by University of Florida-University of Ghana Training Program in Tuberculosis and HIV Research in Ghana funded by Fogarty International Center at the National Institutes of Health [grant number TW010055]. This parent project that provided the data for these analyses was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health [grant number HD071779].

The University of Cape Town Clinical PK Laboratory is supported in part via the Adult Clinical Trial Group (ACTG), by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health under award numbers UM1 AI068634, UM1 AI068636, and UM1 AI106701; as well as the Infant Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), funding provided by National Institute of Allergy and Infectious Diseases (U01 AI068632), The Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Institute of Mental Health grant AI068632.

References

1. Development Initiatives. 2018 Global Nutrition Report: Shining a light to spur action on nutrition. Bristol, UK: Development Initiatives. https://globalnutritionreport.org/reports/global-nutrition-report-2018/executive-summary/. Published 2018. Accessed April 24, 2020.
2. Food and Agriculture Organization of the United Nations (FAO), International Fund for Agricultural Development, United Nations Children's Fund, World Food Programme WHO. FOOD SECURITY AND NUTRITION IN THE WORLD THE STATE OF BUILDING CLIMATE RESILIENCE FOR FOOD SECURITY AND NUTRITION.; 2018. www.fao.org/publications. Accessed March 8, 2020.
3. Drobac PC, Shin SS, Huamani P, et al. Risk factors for in-hospital mortality among children with tuberculosis: The 25-year experience in Peru. Pediatrics. 2012;130(2):e373–9. doi:10.1542/peds.2011-3048 [PubMed: 22826566]
4. Hicks RM, Padayatchi N, Shah NS, et al. Malnutrition associated with unfavorable outcome and death among South African MDR-TB and HIV co-infected children. Int J Tuberc Lung Dis. 2014;18(9):1074–1079. doi:10.5588/ijtld.14.0231 [PubMed: 25189555]
5. Sinha P, Davis J, Saag L, et al. Undernutrition and Tuberculosis: Public Health Implications. J Infect Dis. 2019;219(9):1356–1363. doi:10.1093/infdis/jiy675 [PubMed: 30476125]
6. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: Evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis. 2004;8(3):286–298. [PubMed: 15139466]
7. Gupta KB, Gupta R, Atreja A, Verma M, Vishvkarma S. Tuberculosis and nutrition. Lung India. 2009;26(1):9–16. doi:10.4103/0970-2113.45198 [PubMed: 20165588]
8. Mukherjee A, Velpandian T, Singla M, Kanhiya K, Kabra SK, Lodha R. Pharmacokinetics of isoniazid, rifampicin, pyrazinamide and ethambutol in Indian children. BMC Infect Dis. 2015;15(1):126. doi:10.1186/s12879-015-0862-7 [PubMed: 25887748]

9. Oshikoya KA, Senbanjo IO. Pathophysiological changes that affect drug disposition in protein-energy malnourished children. Nutr Metab. 2009;6:50. doi:10.1186/1743-7075-6-50
10. Dayal R, Singh Y, Agarwal D, et al. Pharmacokinetic study of isoniazid and pyrazinamide in children: impact of age and nutritional status. Arch Dis Child. 2018;103(12):1150–1154. doi:10.1136/archdischild-2017-313910 [PubMed: 29514812]
11. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children. Wood AJJ, ed. N Engl J Med. 2003;349(12):1157–1167. doi:10.1056/NEJMra035092 [PubMed: 13679531]
12. Thee S, Seddon JA, Donald PR, et al. Pharmacokinetics of isoniazid, rifampin,and pyrazinamide in children younger than two years of age with tuberculosis: Evidence for implementation of revised World Health Organization recommendations. Antimicrob Agents Chemother. 2011;55(12):5560–5567. doi:10.1128/AAC.05429-11 [PubMed: 21968358]
13. Mukherjee A, Velpandian T, Singla M, Kanhiya K, Kabra SK, Lodha R. Pharmacokinetics of isoniazid, rifampicin, pyrazinamide and ethambutol in Indian children. BMC Infect Dis. 2015. doi:10.1186/s12879-015-0862-7
14. Kwara A, Enimil A, Gillani FS, et al. Pharmacokinetics of First-Line Antituberculosis Drugs Using WHO Revised Dosage in Children With Tuberculosis With and Without HIV Coinfection. J Pediatric Infect Dis Soc. 2016;5(4):356. doi:10.1093/JPIDS/PIV035 [PubMed: 26407268]
15. Antwi S, Yang H, Enimil A, et al. Pharmacokinetics of the first-line antituberculosis drugs in Ghanaian children with tuberculosis with or without HIV coinfection. Antimicrob Agents Chemother. 2017;61(2). doi:10.1128/AAC.01701-16
16. World Health Organization. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. World Health Organization; 2014. http://www.ncbi.nlm.nih.gov/pubmed/24999516. Accessed April 5, 2020.
17. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs. 2002;62(15):2169–2183. doi:10.2165/00003495-200262150-00001 [PubMed: 12381217]
18. De Onis M, Onyango AW, Borghi E, Garza C, Yang H. Comparison of the World Health Organization (WHO) Child Growth Standards and the National Center for Health Statistics/WHO international growth reference: Implications for child health programmes. Public Health Nutr. 2006;9(7):942–947. doi:10.1017/PHN20062005 [PubMed: 17010261]
19. Simon Schaaf H, Cilliers K, Willemse M, Labadarios D, Kidd M, Donald PR. Nutritional status and its response to treatment of children, with and without HIV infection, hospitalized for the management of tuberculosis. Paediatr Int Child Health. 2012;32(2):74–81. doi:10.1179/2046905512Y.0000000008 [PubMed: 22595213]
20. World Health Organization. WHO | Growth reference data for 5-19 years. WHO. 2013.
21. World Health Organization. WHO | BMI-for-age (5-19 years). WHO. 2019.
22. Oshikoya KA, Senbanjo IO. Caution when treating tuberculosis in malnourished children. Arch Dis Child. 2018;103(12):1101–1103. doi:10.1136/archdischild-2018-314972 [PubMed: 30131349]
23. Verhagen LM, López D, Hermans PWM, et al. Pharmacokinetics of anti-tuberculosis drugs in Venezuelan children younger than 16 years of age: supportive evidence for the implementation of revised WHO dosing recommendations. Trop Med Int Health. 2012;17(12):1449–1456. doi:10.1111/tmi.12003 [PubMed: 23094704]
24. Egelund EF, Alsultan A, Peloquin CA. Optimizing the Clinical Pharmacology of Tuberculosis Medications. Clin Pharmacol Ther. 2015;98(4):387–393. doi:10.1002/cpt.180 [PubMed: 26138226]
25. Tappero JW, Bradford WZ, Agerton TB, et al. Serum Concentrations of Antimycobacterial Drugs in Patients with Pulmonary Tuberculosis in Botswana. Clin Infect Dis. 2005;41(4):461–469. doi:10.1086/431984 [PubMed: 16028152]
26. Boah M, Azupogo F, Amporfro DA, Abada LA. The epidemiology of undernutrition and its determinants in children under five years in Ghana. Zereyesus Y, ed. PLoS One. 2019;14(7):e0219665. doi:10.1371/journal.pone.0219665 [PubMed: 31365528]

27. Justine M, Yeconia A, Nicodemu I, et al. Pharmacokinetics of First-Line Drugs Among Children With Tuberculosis in Rural Tanzania. J Pediatric Infect Dis Soc. November 2018. doi:10.1093/jpids/piy106

28. Glover-Amengor M, Agbemafle I, Hagan LL, et al. Nutritional status of children 0–59 months in selected intervention communities in northern Ghana from the africa RISING project in 2012. Arch Public Heal. 2016;74(1):12. doi:10.1186/s13690-016-0124-1

29. Gupta K, Gupta R, Atreja A, Verma M, Vishvkarma S. Tuberculosis and nutrition. Lung India. 2009;26(1):9–16. doi:10.4103/0970-2113.45198 [PubMed: 20165588]

30. Macallan DC, McNurlan MA, Kurpad A V., et al. Whole body protein metabolism in human pulmonary tuberculosis and undernutrition: Evidence for anabolic block in tuberculosis. Clin Sci. 1998;94(3):321–331. doi:10.1042/cs0940321

31. Radtke KK, Dooley KE, Dodd PJ, et al. Alternative dosing guidelines to improve outcomes in childhood tuberculosis: a mathematical modelling study. Lancet Child Adolesc Heal. 2019;3(9):636–645. doi:10.1016/S2352-4642(19)30196-8

32. Ramachandran G, Hemanth Kumar AK, Bhavani PK, et al. Age, nutritional status and INH acetylator status affect pharmacokinetics of anti-tuberculosis drugs in children. Int J Tuberc Lung Dis. 2013;17(6):800–806. doi:10.5588/ijtld.12.0628 [PubMed: 23676165]

33. Chung S Body mass index and body composition scaling to height in children and adolescent. Ann Pediatr Endocrinol Metab. 2015;20(3):125. doi:10.6065/apem.2015.20.3.125 [PubMed: 26512347]

Table 1.

Profile of Ghanaian children receiving first line anti-TB drugs by age categories (N=100)

Characteristic	Age < 2 (N= 23) n (%)	2 <= Age < 5 (N=25) n (%)	5 <= Age < 10 (N=35) n (%)	10 <= Age <= 14 (N= 17) n (%)	Total N (%)
Sex					
Male	17 (73.9)	12 (48.0)	20 (57.1)	9 (52.9)	58 (58.0)
Female	6 (26.1)	13 (52.0)	15 (42.9)	8 (47.1)	42 (42.0)
Site of TB					
Extrapulmonary	4 (17.4)	6 (24.0)	10 (28.6)	5 (29.4)	25 (25.0)
Pulmonary	19 (82.6)	19 (76.0)	25 (71.4)	12 (70.6)	75 (75.0)
HIV status					
Positive	11 (47.8)	10 (40.0)	20 (40.0)	9 (52.9)	50 (50.0)
Negative	12 (52.2)	15 (60.0)	15 42.9)	8 (47.1)	50 (50.0)
Weight (kg), median (range)	6.3 (3.2-14.0)	11.1 (7.5-17.4)	17.5 (10.6-26.9)	24.0 (16.1-35.5)	
Height (cm), median range	72.0 (51.0-91.0)	86.0 (76.0-114.0)	109.0 (91.0-198.0)	131.0 (110.0-154.0)	
BMI (kg/m^2), median range	12.6 (11.3-20.1)	14.1 (9.1-18.3)	13.6 (4.9-16.6)	13.5 (9.4-16.3)	
WFH * (n=48)					
Normal	5 (21.7)	19 (76.0)	-	-	24 (50.0)
Wasting	18 (78.3)	6 (24.0)	-	-	24 (50.0)
WFA (n=86)					
Normal	2 (8.7)	10 (40.0)	15 (42.9)	1 (33.3)	28 (32.6)
Underweight	21 (91.3)	15 (60.0)	20 (57.1)	2 (66.7)	58 (67.4)
HFA (n=99)					
Normal	9 (39.1)	10 (40.0)	16 (47.1)	8 (47.1)	43 (43.4)
Stunted	14 (60.9)	15 (60.0)	18 (52.9)	9 (52.9)	56 (56.6)
BFA ** (n=51)					
Normal	-	-	23(67.7)	6 (35.3)	29 (56.9)
Low (malnourished)	-	-	11 (32.4)	11 (64.7)	22 (43.1)

BFA, body mass index -for-age; WFA, weight-for-age; HFA, height-for-age; WFH, weight-for-height,

* WFH was determined for only children < 5years,

** BFA was determined for only children ≥ 5years.

Table 2.

Relationship between nutritional status and isoniazid pharmacokinetic parameters among Ghanaian children with tuberculosis

	Cmax < 3 µg/ml n (%)	p-value	C_{max}, µg/ml Geometric Mean (95% CI)	p-value	AUC_{0-8} µg.h/ml Geometric Mean (95% CI)	p-value
Nutritional Status						
ZWFH *						
Wasting (n=24)	4 (16.7)	0.42	4.90 (4.01-6.00)	0.55	16.25 (12.89-20.49)	0.48
Normal (n=24)	3 (8.3)		5.45 (4.01-7.40)		18.84 (13.06-27.19)	
ZWFA						
Underweight (n=58)	6 (10.3)	0.42	5.28 (4.58-6.09)	0.20	17.47 (14.74-20.70)	0.17
Normal (n=28)	1 (3.6)		6.16 (5.08-7.47)		21.32 (17.17-26.48)	
ZHFA						
Stunting (n=56)	6 (10.7)	0.73	5.16 (4.42-6.03)	0.14	16.97 (14.07-20.47)	0.05
Normal (n=43)	3 (7.0)		6.04 (5.28-6.91)		21.44 (18.52-24.81)	
ZBFA **						
Malnourished (n=22)	0 (0.0)	0.25	6.21 (5.24-7.37)	0.44	22.10 (17.84-27.38)	0.24
Normal (n=29)	3 (10.3)		5.65 (4.76-6.71)		18.68 (15.34-22.74)	

* ZWFH was determined for children < 5years,

** ZBFA was determined for children ≥ 5years

Table 3.

Relationship between nutritional status and rifampin pharmacokinetic parameters among Ghanaian children with tuberculosis

	Cmax < 8 µg/ml n (%)	p-value	C_{max}, µg/ml Geometric Mean (95% CI)	p-value	AUC_{0-8} µg.h/ml Geometric Mean (95% CI)	p-value
Nutritional status						
ZWFH *						
Wasting (n=24)	14 (58.3)	0.12	5.62 (4.47-7.06)	0.47	23.66 (18.64-30.04)	0.33
Normal (n=24)	19 (79.2)		4.92 (3.68-6.60)		19.41 (13.82-27.26)	
ZWFA						
Underweight (n=58)	38 (65.5)	0.17	5.73 (4.83-6.78)	0.37	23.50 (19.68-28.05)	0.31
Normal (n=28)	14 (50.0)		6.51 (5.21-8.14)		27.42 (21.60-34.80)	
ZHFA						
Stunting (n=56)	43 (76.8)	<0.01 ***	5.33 (4.43-6.42)	<0.01 ***	21.84 (17.95-26.57)	<0.01 ***
Normal (n=43)	18 (41.9)		7.23 (6.43-8.13)		31.17 (27.61-35.18)	
ZBFA **						
Malnourished (n=22)	12 (54.6)	0.96	6.68 (4.86-9.17)	0.64	29.13 (21.95-38.66)	0.74
Normal (n=29)	16 (55.2)		7.22 (6.24-8.35)		30.69 (26.15-36.02)	

* ZWFH was determined for children < 5years,

** ZBFA was determined for children ≥ 5years

*** statistically significant p-value.

Table 4.

Relationship between nutritional status and pyrazinamide pharmacokinetic parameters among Ghanaian children with tuberculosis

	C_{max} < 20 µg/ml n (%)	**p-value**	**C_{max}, µg/ml Geometric Mean (95% CI)**	**p-value**	**AUC_{0-8} µg.h/ml Geometric Mean (95% CI)**	**p-value**
Nutritional Status						
ZWFH *						
Wasting (n=24)	8 (33.3)	0.37	22.23 (18.45-26.79)	0.71	117.7 (99.70-139.0)	0.70
Normal (n=23)	5 (21.7)		23.33 (19.38-28.10)		123.3 (102.5-148.2)	
ZWFA						
Underweight (n=58)	11 (19.0)	0.91	23.91 (21.43-26.69)	0.90	124.0 (118.6-137.6)	0.89
Normal (n=25)	5 (20.0)		23.48 (18.08-30.50)		126.3 (97.34-164.0)	
ZHFA						
Stunting (n=54)	14 (25.9)	0.02 ***	22.84 (19.54-26.69)	0.02 ***	117.2 (101.0-136.1)	<0.01 ***
Normal (n=42)	3 (7.1)		28.11 (25.59-30.88)		153.9 (139.7-169.5)	
ZBFA **						
Malnourished (n=22)	0 (0)	0.12	32.76 (28.64-37.47)	0.02 ***	172.1 (150.2-197.1)	0.02 ***
Normal (n=27)	4 (14.8)		23.64 (18.63-30.01)		125.1 (97.93-159.7)	

* ZWFH was determined for children < 5years,

** ZBFA was determined for children ≥ 5years

*** statistically significant p-value.

Table 5.

Relationship between nutritional status and ethambutol pharmacokinetic parameters among Ghanaian children with tuberculosis

	Cmax < 2 µg/ml n (%)	p-value	C_{max}, µg/ml Geometric Mean (95% CI)	p-value	AUC_{0-8} µg.h/ml Geometric Mean (95% CI)	p-value
Nutritional Status						
ZWFH *						
Wasting (n=23)	20 (87.0)	0.02 ***	0.84 (0.60-1.17)	<0.01 ***	3.46 (2.62-4.57)	<0.01 ***
Normal (n=23)	13 (56.5)		1.63 (1.27-2.09)		5.74 (4.48-7.36)	
ZWFA						
Underweight (n=56)	40 (71.4)	0.08	1.24 (1.02-1.50)	0.02 ***	4.68 (3.97-5.51)	0.02 ***
Normal (n=27)	14 (51.8)		1.87 (1.43-2.45)		6.53 (5.11-8.34)	
ZHFA						
Stunting (n=53)	35 (66.0)	0.31	1.39 (1.14-1.69)	0.16	5.09 (4.27-6.06)	0.08
Normal (n=43)	24 (55.8)		1.71 (1.37-2.13)		6.36 (5.27-7.69)	
ZBFA **						
Malnourished (n=22)	10 (45.5)	0.41	2.15 (1.62-2.86)	0.29	7.83 (6.14-9.98)	0.17
Normal (n=28)	16 (57.1)		1.79 (1.44-2.23)		6.34 (5.19-7.75)	

* ZWFH was determined for children < 5years,

** ZBFA was determined for children ≥ 5years

*** statistically significant p-value.

Table 6.

Predictors of peak concentration (C_{max}) of firstline Anti-Tuberculosis drugs among Ghanaian children with tuberculosis using stepwise logistic regression models

Drug	Factors	Adjusted odds ratio	95% CI
Rifampin C_{max} < 8 μg/ml			
	stunting vs normal	6.75	1.76-25.83
Pyrazinamide C_{max} < 20 μg/ml			
	stunting vs normal	5.79	1.13-29.62
Ethambutol C_{max} < 2 μg/ml			
	TB/HIV vs TB	11.28	1.64-77.86
	stunting vs normal	20.70	2.50-171.67
	Underdosing	8.42	1.20-59.15

Covariates included in the multivariate logistic regression models were gender, age, HIV status, stunting, wasting, underweight, low BFA and underdosing.