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Original article

Prevalence and predictors of residual antibiotics in children's blood in community settings in Tanzania

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ARSTRACT

Objectives: Children account for a significant proportion of antibiotic consumption in low- and middleincome countries, with overuse occurring in formal and informal health sectors. This study assessed the prevalence and predictors of residual antibiotics in the blood of children in the Mbeya and Morogoro regions of Tanzania.

Methods: The cross-sectional community-based survey used two-stage cluster sampling to include children aged under 15 years. For each child, information on recent illness, healthcare-seeking behaviour, and use of antibiotics, as well as a dried blood spot sample, were collected. The samples underwent tandem mass spectrometry analysis to quantify the concentrations of 15 common antibiotics. Associations between survey variables and the presence of residual antibiotics were assessed using mixedeffects logistic regression.

Results: In total, 1742 children were surveyed, and 1699 analysed. The overall prevalence of residual antibiotics in the blood samples was 17.4% (296/1699), the highest among children under the age of 5 years. The most frequently detected antibiotics were trimethoprim (144/1699; 8.5%), sulfamethoxazole (102/1699; 6.0%), metronidazole (61/1699; 3.6%), and amoxicillin (43/1699; 2.5%). The strongest predictors of residual antibiotics in the blood were observed presence of antibiotics at home (adjusted odds ratio $[aOR] = 2.9$; 95% CI, 2.0-4.1) and reported consumption of antibiotics in the last 2 weeks (aOR = 2.5; 95% CI, 1.6-3.9). However, half (145/296) of the children who had residual antibiotics in their blood, some with multiple antibiotics, had no reported history of illness or antibiotic consumption in the last 2 weeks, and antibiotics were not found at home.

Discussion: This study demonstrated a high prevalence of antibiotic exposure among children in Tanzanian communities, albeit likely underestimated, especially for compounds with short half-lives. A significant proportion of antibiotic exposure was unexplained and may have been due to unreported selfmedication or environmental pathways. Incorporating biomonitoring into surveillance strategies can help better understand exposure patterns and design antibiotic stewardship interventions. Theopista Lotto, Clin Microbiol Infect 2024;30:1042

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Introduction

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Management of antibiotics presents a complex challenge in lowand middle-income countries. Ensuring access to this lifesaving

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drug for those who truly need it must be balanced with overconsumption [[1](#page-5-0)], which contributes to the development and spread of antimicrobial resistance (AMR). Overconsumption of antibiotics occurs in inpatient [[2](#page-5-1)] and outpatient [\[3](#page-5-2)] healthcare settings. Selfmedication is also common [\[4](#page-5-3)], with private pharmacies and informal medicine vendors being the main sources of nonprescribed antibiotics [\[5](#page-5-4)]. In Tanzania, 90% of drug shop owners report selling antibiotics based only on patients' requests, regardless of symptoms [\[6](#page-5-5)[,7\]](#page-5-6).

Young children are major consumers of antibiotics in low- and middle-income countries because of higher frequency of illnesses and healthcare-seeking [[8](#page-5-7)[,9\]](#page-6-0). Health workers at the primary care level lack sufficient clinical skills, pharmacological knowledge, and diagnostics to distinguish the majority of viral from the minority of bacterial infections [\[10](#page-6-1)]; consequently, over 60% of paediatric outpatient visits result in antibiotic prescriptions [\[11\]](#page-6-2), often unnecessarily [[3](#page-5-2)]. This represents a shift from a historical lack of access to antibiotics to a new concern of excessive antibiotic exposure [\[12\]](#page-6-3). In addition to side effects, destruction of microbiota, and compromised immunity [[13\]](#page-6-4), exposure to antibiotics in childhood is linked to long-term health consequences, such as allergies, obesity, and neurodevelopmental disorders [\[14](#page-6-5)].

Although health facility-based antibiotic exposure surveys are relatively common [\[15](#page-6-6)[,16\]](#page-6-7), community-based studies remain rare. Those that are available rely primarily on the reported history of antibiotic consumption [\[8,](#page-5-7)[17\]](#page-6-8), resulting in a lack of reliable data on the prevalence of community exposure. This study, conducted in the Mbeya and Morogoro regions of Tanzania, aimed to establish a community-level prevalence of residual antibiotics in children's blood and assess individual and household-level risk factors of antibiotic exposure.

Methods

Study setting

Tanzania has four administrative levels: region, council, ward, and village or street. The survey was conducted in five councils of two regions: Mbeya City Council (CC) and Mbeya District Council (DC) in Mbeya, and Mlimba DC, Ulanga DC, and Ifakara Town Council (TC) in Morogoro (Fig. S1 and Table S1). HIV prevalence among children is low (0.5% in both regions), similar to the national prevalence of 0.4% among the 0-14 years age group [\[18\]](#page-6-9). The study area was chosen because of a future antibiotic stewardship intervention planned to be implemented in a randomly selected sample of public primary health facilities. The councils were chosen arbitrarily and represent the average epidemiological and healthseeking conditions in Mbeya and Morogoro regions.

Study design and sample size

The cross-sectional survey employed a two-stage cluster sampling approach, with the ward as the primary and the village as the secondary cluster. From the 20 wards that contained a randomly selected public primary health facility (health centre or dispensary) for the future intervention, ten were purposively selected for the survey (Fig. S1) to achieve a balance among study councils, malaria endemicity, and access to healthcare services. The expected prevalence of residual antibiotics in the blood of children was unknown. A feasible sample of 1700 children, approximately 170 from each of the ten wards, was sufficiently powered to measure a prevalence of 3% or higher (with a power of 80%, confidence level of 95%, and intracluster correlation coefficient of 0.05).

Sampling procedure

Two villages were purposively selected from each ward based on proximity to the future intervention health facility. Within villages, half of the sub-villages were randomly selected. A total of 170 children per ward were allocated to villages proportionately to the population size from the regional profiles [\[19,](#page-6-10)[20](#page-6-11)]. The village sample was allocated to sub-village level proportionately to the number of households, and households were randomly selected using a household list (Table S2). In each household, all children aged under 15 years whose caregivers consented were included; those with chronic or severe conditions requiring regular hospital attendance were excluded. Although a true probability sample was not used, the sampled population represents an average healthcare access in the study area (Fig. S1).

Field data collection

The survey was conducted between 1 February and 14 March 2021. The questionnaire was administered in Swahili on tablets using Open Data Kit. Household-level data were collected first, followed by individual-level data for each eligible child (Tables S3 and S4). Printed visual aids depicting commonly available antibiotics were used to assess self-reported antibiotic consumption. A malaria rapid diagnostic test (mRDT) was performed on-site, and a dried blood spot (DBS) sample was collected by finger prick.

Laboratory procedures

DBS samples were dried at room temperature for 2 hours and stored at -10 °C in the field in resealable plastic bags with desiccant for a maximum of 6 days. Samples were then transferred to the main research laboratories at the National Institute for Medical Research - Mbeya Medical Research Centre and Ifakara Health Institute and stored at -80° C before being shipped to Switzerland on dry ice for analysis, per the signed Material Transfer Agreements. DBS samples were analysed for 15 antibiotics using liquid chromatography and tandem mass spectrometry using an adaptation of a previously developed assay for plasma samples [\[21](#page-6-12)]. Antibiotics were selected based on the Tanzania essential medicine list, local availability, and common use (Table S5).

Statistical analysis

Data was cleaned in Stata (version 16.1) and analysed in R software (version 4.1.2). Differences in distributions of categorical variables were assessed using a χ^2 test [\[22\]](#page-6-13). Concordance between two binary proxy measures of antibiotic exposure and the presence of antibiotics in the blood was assessed using a χ^2 test and a φ correlation coefficient. Mixed-effects logistic regression was used to identify factors associated with antibiotic presence in the blood. Ward was included as a random effect to account for the clustering of observations. All variables were considered for inclusion in the analysis, but some were excluded based on lack of relevance or limited sample size (Tables S3 and S4). Principal component analysis was used to reduce the dimensionality of the socio-economic variables (Table S6) into the socio-economic status (SES) quintile.

Ethics statement

The ethical review boards of Ifakara Health Institute (IHI/IRB/ No: 20-2020) and National Institute for Medical Research (NIMR/ HQ/R.8a/Vol. IX/3463) in Tanzania and the Ethikkommission Nordwest-und Zentralschweiz (AO_2020-00050) in Switzerland approved the study protocol. For each child, an adult (aged $18+$

years) provided written informed consent in Swahili. If they could not read or write, a witness signed in addition. Children aged $12+$ years also provided written assent.

Results

During recruitment, 1668 households were approached and 1104 (66.2%) had eligibility criteria assessed. Reasons for not assessing eligibility included inability to locate the household $(n = 309)$, no one being home $(n = 167)$, and other reasons $(n = 88)$. Of the 1104 households, 294 (26.6%) did not have children under the age of 15. Of the remaining 810 households, 735 (91%) consented. The study households contained 1879 children; however, 125 were not home and 12 declined to participate, resulting in 1742 surveyed children. Furthermore, we excluded 43 children due to mislabelled, misplaced, or poor-quality DBS samples. The final dataset included 1699 children with complete survey data and laboratory results ([Fig. 1](#page-2-0)).

Approximately 60% (1010) of the sampled children were from Morogoro and 40% (689) from Mbeya ([Table 1\)](#page-3-0). Sex distribution was equal, and the predominant age group was under 5 years (43%). Over 90% of participants lived in households where a health facility (public or private) was the usual place to seek care for illness. However, households in Morogoro reported longer travel times to their usual place of healthcare and had a lower SES [\(Table 1\)](#page-3-0). Approximately 30% of children had been sick within 14 days of the survey, and 9% reported having taken an antibiotic. Of all the surveyed children, 27% in Morogoro and none in Mbeya had a positive mRDT result. Mbeya had a higher prevalence of illness history (34.1% vs. 27.1%) and reported consumption of antibiotics (11.3% vs. 7.2%) than Morogoro ($p = 0.004$). Self-reported storage of medicines (31.3% vs. 18.2%) and observed presence of antibiotics at home $(15.5\% \text{ vs. } 8.8\%)$ were also higher in Mbeya ($p < 0.001$). A total of 296 children (of 1699) had at least one residual antibiotic detected in their blood, with an overall prevalence of 17.4% (95% CI, $15.6-19.2$), and unlike for self-reported variables, there was no significant difference between Mbeya (18.6%) and Morogoro (16.7%) regions $(p > 0.05)$ ([Table 1](#page-3-0)).

All 15 antibiotics were detected, with the most prevalent being trimethoprim (8.5%) and sulfamethoxazole (6%), representing exposure to co-trimoxazole [\(Table 2\)](#page-3-1). Lab-quantified antibiotic presence in the blood was compared with two proxy measures of exposure: observed storage of antibiotics at home and caregiverreported consumption. There were weak but statistically significant correlations between antibiotic presence in the blood and observed storage ($\varphi = 0.19$, $p < 0.001$) and reported consumption (φ = 0.17, p < 0.001) ([Table 2](#page-3-1)). Correlation values were higher for antibiotics with longer half-lives (e.g. trimethoprim, sulfamethoxazole, metronidazole, and azithromycin) as compared to those with short half-lives (e.g. amoxicillin, ciprofloxacin, and cloxacillin) ([Table 2\)](#page-3-1).

Under-five children had the highest prevalence (22%) of residual antibiotics. Ages $5-9$ and $10-14$ years ([Table 3](#page-4-0)) were associated with nearly 40% lower odds of antibiotic exposure ([Table 3\)](#page-4-0). Selfreported consumption of antibiotics in the last 14 days $(aOR = 2.47)$ and observed storage at home $(aOR = 2.86)$ increased the odds of having antibiotics in the blood ($p < 0.001$). Travel time to the usual place of healthcare (normally a health facility) of more than 1 hour was associated with 35% lower odds of antibiotic exposure as compared with travel time of less than 15 minutes $(p < 0.05$ in adjusted and unadjusted models).

Illness history and high SES (4th and 5th quintile) increased the odds of having antibiotics in the blood in the univariable models but not in the multivariable model. On the other hand, lower odds of antibiotic exposure resulting from usually seeking care in a pharmacy or drug shop (as compared with a health facility) became nearly significant ($p = 0.053$) in the multivariable model. Sex and mRDT result were not significant but were retained for potential comparability with other studies that control for these variables.

Of the 296 children with antibiotics in their blood, 171 (58%) had one antibiotic, 98 (33%) had two, and 27 (9%) had three or more. The maximum number of residual antibiotics detected in a child's blood sample was seven. Of the 27 children with three or more

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Table 1
Characteristics — n (%) of study participants (children below 15 y of age)

RDT, rapid diagnostic test; SES, socio-economic status.

^a Denotes statistically significant (p < 0.05) difference in the variable distribution between regions according to a χ^2 test.

Table 2

Prevalence of antibiotics quantified in blood samples, found stored at home during the survey, and consumed by the child in the last 14 d according to the caregiver (of the total 1699 children)

Phi correlation coefficients (φ) between presence in blood and the two survey variables (last two columns) are also presented, with statistical significance (p < 0.05) indicated

by *.
^a Presence of trimethoprim and sulfamethoxazole in blood was equated to exposure to co-trimoxazole.

b Presence of amoxicillin in blood was equated to exposure to amoxicillin or amoxicillin clavulanate.

 c^c Presence of ampicillin in blood was equated to exposure to ampicillin or ampiclox, and presence of cloxacillin to ampiclox only.

^d Narrow-spectrum antibiotic, those unmarked are broad-spectrum.

Table 3

Results of the univariable and multivariable mixed-effects logistic regression models explaining the presence of residual antibiotic in the blood samples of the study participants ($N = 1699$)

aOR, adjusted odds ratio; RDT, rapid diagnostic test; SES, socio-economic status.

The multivariable model explained 12.8% of the variability in the outcome (9.6% by the fixed effects and 3.2% by the cluster random effect).

^a OR or aOR and 95% CI for fixed effects are shown. All models also included cluster as a random effect.

b Exemption status was excluded from multivariable model due to correlation with age and medicines typically stored at home due to correlation with antibiotics found at home.

antibiotics, 24 had trimethoprim and sulfamethoxazole; cooccurrence of trimethoprim, sulfamethoxazole and metronidazole was also common (9/27). Only about half of these children had been ill (15/27) in the last 14 days and fewer sought care (12/27). Seven children, including the one with seven residual antibiotics, were not ill, did not report taking antibiotics, and did not have antibiotics stored at home (Table S7). In fact, nearly half (145/296, 49%) of all the children with residual antibiotics in their blood had no significant risk factors of exposure.

Discussion

This study presents community-level prevalence and predictors of residual antibiotics in the blood of children under 15 years of age in the Mbeya and Morogoro regions of Tanzania. The overall prevalence of antibiotics in DBS samples was 17.4%, with the most common being trimethoprim and sulfamethoxazole (co-trimoxazole), metronidazole, and amoxicillin. These trends are consistent with recent data from the Tanzania Medicines and Medical Devices Authority, reporting doxycycline, amoxicillin and co-trimoxazole as the three most frequently consumed antibiotics [\[23\]](#page-6-14). Extensive cotrimoxazole exposure is concerning because high rates of resistance have been reported in sub-Saharan Africa and Tanzania [[24](#page-6-15)[,25\]](#page-6-16). Doxycycline was rarely detected in our study, probably because it is not recommended for children aged below 8 years. Several broad-spectrum antibiotics (e.g. erythromycin, azithromycin, ciprofloxacin, and ceftriaxone) belonging to the 'Watch' group of the WHO AWaRe Classification [\[26](#page-6-17)] were detected. These drugs have a higher resistance potential and are prioritized for monitoring and stewardship programmes [[26](#page-6-17)]; as such, community providers should be discouraged from overprescribing them.

The main risk factors of antibiotic exposure were younger age, self-reported antibiotic consumption (mostly because of reported illness and healthcare-seeking behaviour), observed antibiotic storage at home, and shorter travel time to the usual place of healthcare. The high prevalence of antibiotic residuals among younger children was expected due to their higher frequency of illness and healthcare-seeking. Consistent with the exposure profile, the most commonly stored antibiotics were amoxicillin, metronidazole, and co-trimoxazole, also similar to the findings of other studies [[27,](#page-6-18)[28\]](#page-6-19).

Our findings of generally better access to healthcare facilities and higher SES (albeit only in univariable analysis) being associated with higher antibiotic exposure agree with those of a Brazilian

study [\[29\]](#page-6-20). However, contrary to the findings of a recent metaanalysis [[30](#page-6-21)], a negative mRDT test result did not increase antibiotic exposure. In fact, in our adjusted analysis, it was a positive mRDT result that was nearly significantly associated with increased odds of having antibiotics in the blood, probably because of easier general access to medicines. The practice of prescribing antibiotics to children with malaria in the study area while mRDTs are widely used warrants further investigation.

Some children had several residual antibiotics in their blood, which leads to adverse drug reactions [[31\]](#page-6-22), unfavourable health consequences later in life [[14\]](#page-6-5), and potentiation of microorganisms' resistance to common antibiotics due to increased drug selection pressure [[32](#page-6-23)]. A study in China also found up to six antibiotics in urine samples of healthy primary school children [[33](#page-6-24)]. Notably, in our study, half of the children who had antibiotics in their blood had not been ill, did not report taking antibiotics and no antibiotics were found in their homes. Further investigation of these findings is needed to determine if there is substantial under-reporting of risk factors or potential exposure from environmental sources, since several of the detected antibiotics are also used in the agricultural sector in Africa and Tanzania $[34-36]$ $[34-36]$ $[34-36]$ $[34-36]$ $[34-36]$.

In our study, the correlation between self-reported consumption of antibiotics and antibiotic presence in the blood was weak (0.19). Correlation values with self-reporting were higher for antibiotics with longer half-lives, reflecting underestimates of the prevalence of antibiotics with short half-lives that may have been eliminated by the time blood samples were collected. A study using similar methods to investigate the relationship between selfreporting and the presence of anti-malarials in DBS samples found a similarly poor correlation [[37\]](#page-6-26).

This study has several limitations. Although we measured 15 of Tanzania's commonly used antibiotics, a few others may have been missed. In the risk factor survey, a relatively long recall period of 14 days was used, which somewhat impaired our ability to fully assess the relationship between self-reported variables and measured antibiotic presence, particularly for drugs with short half-lives. Another potential limitation is that we did not assess HIV or malnutrition status during the survey. The presence of a chronic or severe condition that required regular healthcare visits (such as diagnosed HIV and severe acute malnutrition) warranted exclusion from the study. However, it is possible that a few children with these conditions were included, and their exposure to cotrimoxazole could be explained by its empirical use in treating these conditions. Finally, the survey took place during the COVID-19 pandemic, with potentially atypical distribution of symptoms and antibiotics. However, we do not expect that the paediatric population had been significantly affected. Overall, we believe that the results of this study are generalizable to similar settings.

Conclusion

Our study demonstrated a high prevalence of residual antibiotics in the paediatric population. Many children had several residual antibiotics in their blood, including broad-spectrum antibiotics in the 'Watch' group, which risk the development of AMR. A significant proportion of antibiotic exposure was unexplained and may have been due to unreported self-medication or environmental pathways. We recommend using objective measurements of antibiotic exposure in DBS samples in further studies and monitoring approaches, especially for antibiotics with longer half-lives. Conversely, developing more precise self-reporting instruments for antibiotics with short half-lives is needed. Clear labelling of antibiotics for community members to identify can help. Together, these complementary approaches can yield better estimates of overall antibiotic exposure. Lastly, we recommend considering the one health approach in questionnaires to integrate animal, environmental, and human perspectives, broadening exposure knowledge and subsequent efforts to mitigate AMR.

Author contributions

B.G. and V.D.A. conceptualized the project and acquired the funding. T.L., S.R., and A.V.K. developed the study protocol and data collection plan. T.L. and S.R. collected the data and performed data quality assurance. T.L., B.T., and L.A.D. conducted the laboratory analyses. T.L. and A.K. conducted the statistical analysis and drafted the manuscript. B.G., V.D.A, H.M., and E.K. provided critical review of the manuscript.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at [https://doi.org/10.1016/j.cmi.2024.05.004.](https://doi.org/10.1016/j.cmi.2024.05.004)

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