TITLE PAGE

Title: Cumulative Antibiotic Exposure in the First Five Years of Life: Estimates for 45 Low- and Middle-income Countries from Demographic and Health Survey Data

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Key words: pediatrics; antibiotics; low- and middle-income countries; care-seeking; national estimates

Running title: Antibiotic exposure in children in LMICS

Main points: In 45 low- and middle-income countries, we estimated children received an average of 18.5 antibiotic treatments in their first 5 years of life. A median of 9% of antibiotic treatments were attributable to informal care, and 17% to self-medication.

ABSTRACT

Background: Estimates of the total cumulative exposure to antibiotics of children in low-resource settings, and the source of these treatments, are limited.

Methods: We estimated the average number of antibiotic treatments children received in the first five years of life in 45 low- and middle-income countries (LMICs) using Demographic and Health Survey (DHS) data. The two-week point prevalence of fever, diarrhea or cough and antibiotic treatment for these illnesses were estimated for ages 0-59 months and aggregated to estimate cumulative illness and antibiotic treatment for each country. We estimated treatment rates and contribution to total antibiotic use attributable to medical care, informal care, and self-medication.

Results: Forty-five countries contributed 438,140 child-observations. The proportion of illness episodes treated with antibiotics ranged from 10% (95% CI: 9-12) (Niger) to 72% (95% CI: 69-75) (Jordan). A mean of 42·7% (95% CI: 42.1-43.3) of febrile and 32.9% of non-febrile illness (95% CI: 32.4-33.5) episodes received antibiotics. In their first five years, we estimate children received 18.5 antibiotics treatments on average (IQR: 11.6-24.6) in LMICs. Cumulative antibiotic exposure ranged from 3.7 treatments in Niger (95% CI: 2.8-4.6) to 38·6 treatments in DR Congo (95% CI: 34.7-42.4). A median of 9.0% of antibiotic treatment was attributable to informal care (IQR: 5.9-21.2), and 16.9% to self-medication (IQR: 9.5-26.2).

Conclusions: Childhood antibiotic exposure is high in some LMICs, with considerable variability. While access to antibiotics for children is still not universal, important opportunities for reducing excess use also exist, particularly with respect to the informal care sector and self-medication.

MAIN TEXT

INTRODUCTION

Child mortality risk has declined in many low-resource settings, but infectious illnesses remain common in young children and contribute substantially to global morbidity [1-4]. Appropriate case-management, including antibiotics for suspected bacterial infections prevents mortality and severe morbidity. However, antibiotic treatment in early life increases risk of resistant infections and is associated with microbiome disturbances, allergic and inflammatory conditions, obesity and metabolic disorders [5-8]. Widespread antibiotic use has contributed to rising antimicrobial resistance and reduction in the effectiveness of available antimicrobials [9-12].

The majority of illnesses in young children are mild or self-limiting and do not require or benefit from antibiotics [13, 14]. Availability and access to antibiotics has increased and it is possible to obtain antibiotics without medical prescriptions in many settings. Improved antibiotic access prevents unnecessary deaths, but also contributes to inappropriate and overuse.

Data on total antibiotic use in early childhood in LMICs are sparse. Pharmaceutical sales data and prescription databases from primarily high- and middle-income countries indicate substantial but highly variable pediatric antibiotic consumption [15-18]. However, purchasing data does not directly indicate individual use, and are available for few LMICs, and national prescription databases are rarely available. The majority of LMIC estimates of antibiotic exposure in children are not from nationally representative samples, limiting the ability to extrapolate or make cross-country comparisons. Previous estimates primarily cover short periods or single illness episodes, and do not reflect total exposure in childhood or national estimates [19, 20]. Recent estimates of

cumulative antibiotic use in children indicate frequent use in health-facilities, but include few countries and are limited to treatments from medical prescriptions [13].

The objective of this analysis was to estimate the total number of antibiotic treatments children receive in the first five years of life in LMICs using data from the Demographic and Health Survey (DHS) program. We aimed to describe antibiotic treatment patterns by age and morbidity, country, region, and income-level, and to characterize antibiotic use practices as they relate to care-seeking in medical and informal care settings and to self-medication.

METHODS

Datasets and observations

The Demographic and Health Surveys (DHS) are nationally representative cross-sectional standardized household surveys among samples of 5,000-30,000 households per country, conducted in over 80 LMICs approximately every five years (https://dhsprogram.com/). The survey includes questions to caregivers about illness in the previous two weeks for all children under age five in the household. Caregivers report if and where care or treatment was sought, and medications received for illness. Child recode survey data files were downloaded from the DHS website March 13, 2020.

Sample Population

Surveys (country and year)

We considered all available surveys from the last ten years (2008 – 2018). Despite standardization, surveys across countries and years vary in the variables collected and in which

questions are prompted for different respondents. To be included, we required the survey systematically captured caregiver report of diarrhea; fever; and cough for all children under five; and oral antibiotic treatment for all children with recent diarrhea; fever or cough. We evaluated the coverage of relevant questions in the surveys empirically, using criteria of a minimum of 95% non-missing responses to survey items for history of diarrhea; fever and cough and at least 90% for antibiotic treatment among children with each morbidity. To avoid missing treatments, surveys that only asked about antibiotic treatment for cough among cases that also reported difficulty breathing with or without a problem with the chest (to align with pneumonia case-definitions) were excluded. Surveys that did not differentiate oral antibiotics from other treatments were also excluded. We included only the most recent eligible survey per country.

Observations

Observations for surviving children age zero to 59 months were included. Observations missing recent diarrhea, fever or cough responses were excluded.

Figure 1 describes the sample inclusion and exclusion.

Definitions

Caregiver reports of diarrhea, fever or cough in the previous two weeks were considered recent illness. These were further classified as any illness, non-febrile and febrile illness as described in Table 1.

Caregiver reports of antibiotic pill, tablet, syrup, or injection were considered antibiotic treatment. Treatment was considered to be for the illness episode, irrespective of the symptom combination. We allowed one treatment per recall period, which could represent an unspecified number of exposure-days or doses, which are not captured in the survey. Reports of antibiotics without illness or illness "unknown", and "other" or "unknown" treatments were classified as not receiving antibiotics.

The location where care was sought was classified as medical care, informal care or no care or treatment, as described in Table 1. Observations missing all care-seeking responses were excluded from care-seeking analyses.

Child age and sociodemographic characteristics were based on standard DHS recode classifications (https://dhsprogram.com/publications/publication-dhsg4-dhs-questionnaires-and-manuals.cfm). Country income level and geographic region were defined by World Bank 2017 classifications (https://www.worldbank.org).

Statistical analyses

Recent illness and antibiotics – Descriptive analysis

We estimated the mean point-prevalence of illness in the previous two weeks by age in months separately for each country, and the probability of antibiotic treatment among children with "any" illness; febrile and non-febrile illness. For each group, we calculated the proportions for whom no care, informal care and medical care were sought. Estimates and 95% confidence intervals are binomial proportions.

Prediction

To predict two-week illness and treatment probabilities by age in months by country, we used generalized linear regression. The models used illness or antibiotic treatment as the outcome (respectively), and a fourth-order polynomial term for age in months as the primary predictor for smoothing. The treatment probabilities given each morbidity in each age period and overall were similarly estimated. All predictions were censored to the [0,1] range.

Cumulative incidence of illness and antibiotics

We estimated the cumulative incidence of illness and antibiotic treatment in the first five years of life and the uncertainty around these estimates in a two-step process, using a method similar to that of Fink et al [13]. Briefly, first, we used linear regression to estimate the predicted probabilities of illness and antibiotic treatment in each two-week age period in simple models with age smoothing as described above, and multiplied estimates and standard errors by 30/14 to derive month-of-life estimates, and summed estimates for a cumulative five-year estimate. We aggregated the period-specific standard errors, and determined 95% confidence intervals assuming a normal distribution and complete independence in the variance. Estimates were calculated separately for each country and pooled across represented countries, geographic regions and income groups.

The r^2 value from a linear regression of country-level predicted cumulative treatment frequency regressed on country-level cumulative illness frequency was used to evaluate the variation in antibiotic use explained by illness burden.

Antibiotics source

We estimated the proportion of total antibiotic treatments attributable to medical care, informal care and self-medication, using the method described above. Linear regression models parameterized as previously described were used to predict the likelihood of both care-seeking and antibiotic receipt, in each age period, in three separate unconditional models per country that included all child-observations. Cumulative 59-month total treatment estimates were calculated for care-seeking in each sector using methods similar to those above. The proportion of total antibiotic treatments attributable to each care-seeking sector in the country were estimated by dividing total cumulative treatments by treatments from that care-seeking sector.

All analyses were adjusted for complex survey design and individual sampling and selection weights, with variance adjusted for stratum, using Stata's *svyset* command for country-specific estimates and the *subgroup* option for conditional analyses. Income-specific, region-specific and pooled estimates across countries weighted results of each country equally, using de-normalized survey and sampling weights. All analyses were conducted using Stata version 15. Source code are available by request.

Ethical Clearance

Data were publicly available and do not include personal identifying information. The analysis does not qualify as human subjects research.

Our approach adheres with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) (http://gather-statement.org/).

RESULTS

Population

Two hundred ninety-nine child health surveys were available from 82 countries, from which 45 countries had at least one that met inclusion criteria, contributing a total of 438,140 child-observations (Figure 1). The most common reasons for survey exclusion were not systematically including questions about cough, diarrhea and fever for all children; not asking about antibiotic use for all those with each of the primary morbidities; and not differentiating antibiotics from other medications. Many recent surveys were excluded because antibiotic treatment for cough was only asked if difficulty breathing was also reported. Table S1 reports represented countries and sample sizes.

Table 2 summarizes the study population. Forty-nine percent of the sample was female, 64.9% resided rurally, and 31.5% of caregivers had not attended any education.

Illness

In the two weeks preceding the survey, on average, 38.7% (95% CI: 38.4, 39.0) of children had experienced illness (Table 2). The average point prevalence of illness with and without fever was 21.6% (95% CI: 21.3, 21.8) and 17.1% (95% CI: 16.9, 17.4), respectively. Recent illness was reported less commonly in early infancy and peaked around 18 months (Figure S1).

Care-seeking for illness

Among children with recent illness, medical care or treatment was sought in 48.8% (95% CI: 48.3, 49.2) of cases, 13.3% (95% CI: 13.0, 13.7) of cases sought informal care, and 37.9% (95% CI: 37.4, 38.4) of cases sought no advice or treatment (Table 3).

Antibiotics for illness

On average, 38.4% (95% CI: 37.9, 38.8) of children with illness received antibiotics: 42.7% (95% CI: 42.1, 43.3) of febrile and 32.9% (95% CI: 32.4, 33.5) of non-febrile cases. Treatment likelihood differed by symptom. Antibiotic treatment was less common in ill young infants than older children (Figure S2). At all ages, antibiotic treatment was more common with fever than non-febrile illness.

Within countries, the proportion of ill children treated with antibiotics ranged from 10% (95% CI: 9, 2%) in Niger to 72% (95% CI: 69, 75%) in Jordan (Figure 2). Similar treatment probabilities were observed across countries for febrile (from 10% Niger to 84% Jordan) and non-febrile illness (11% Senegal to 60% Jordon) (Figures S3a-c). Figure 3 shows the average number of antibiotic treatments received per month of life by country. The number of treatments in early infancy was relatively low, with the highest treatment probabilities between 12 and 18 months. More variation existed across countries than age groups.

Antibiotics according to care-seeking

Among illness cases that received medical or informal care, on average, 53.7% (95% CI: 53.1, 54.3) and 43.6% (95% CI: 42.4, 44.8) received antibiotics, respectively (Table 3). With medical

care, antibiotics were slightly more common among febrile than non-febrile cases (55.6%, 95% CI: 54.8, 56.3 febrile; 50.4%, 95% CI: 49.4, 51.4 non-febrile). With informal care, 44.1% (95% CI: 42.6, 45.7) of febrile and 42.9 % (95% CI: 41.3, 44.5) of non-febrile cases received antibiotics. 17.3% (95% CI: 16.7, 17.8) of those with recent illness for whom no advice or treatment was sought received antibiotics: 18.9% (95% CI: 18.1, 19.8) of febrile, and 15.9% (95% CI: 15.2, 16.7) of non-febrile cases.

Cumulative illness and antibiotic exposure

Across the 45 countries, we estimate children experienced an average of 50.6 illness episodes (IQR: 36.8, 59.6) in their first five years. This ranged from 13.8 episodes (95% CI: 10.5, 17.2) in Kyrgyz Republic to 83.2 episodes (95% CI: 79.0, 87.3) in Uganda (Figure S4) in the first five years.

Within the first five years of life, the median cumulative incidence of antibiotic exposure was 18.5 treatments (IQR: 11·6, 24·6). The average number of antibiotic treatments in the first five years ranged from 3.7 (95% CI: 2.8, 4.6) in Niger to 38.6 treatments (95% CI: 34.7, 42.4) in the Republic of Congo (Figure 4, S5, S6).

Correlation between illness and antibiotic use

In all regions and income groups, there was a positive correlation between illness frequency and antibiotic treatment frequency, but the extent of correlation varied (Figure 5). Illness frequency explained 64% of the variability in the average number of antibiotic treatments in the first five years across countries ($R^2 = 0.64$).

Antibiotic sources

Across the 45 countries, a median of 68.7% (IQR: 59.6-78.2) of antibiotic treatments were attributable to medical care, 9.0% to informal care (IQR: 6.1-19.0), and 16.9% to episodes for which no care was sought (IQR: 9.5-26.2). The proportion of total antibiotic use that resulted from informal care ranged from 0.0% (Armenia) to 43.9% (Cameroon). Self-medication was responsible for between 3.7% (Indonesia) and 44.0% (Kyrgyz Republic) of antibiotic treatments (Table S2, Figure S6a).

DISCUSSION

We present estimates for cumulative antibiotic treatment for young children in a large number of LMICs, based on nationally representative samples incorporating all treatment sources, including illness treated at home. We estimate that children in LMICs receive an average of 18.5 antibiotic treatments in their first five years, 9% of which are obtained from informal sources and 17% from self-medication, on average.

Our results substantiate a growing literature indicating high antibiotic exposure in young children, including in many LMICs. Previous estimates generated using various methods are broadly in line with our estimates: 24·5 antibiotic treatments in the first five years in a modeling study from cross-sectional data; 16 treatments in the first five years from pharmaceutical sales data; and 10 treatments in the first two years in a multi-country cohort study [13, 15, 19]. Some of our estimates for illness and antibiotic exposure seem extreme. In Uganda, for example, estimates equate with an illness approximately every 3 weeks during the first five years. Data

from cohort studies, which may be less vulnerable to recall errors, are rare in LMICs, thus an accepted gold-standard comparison is unavailable, but our estimates are generally within the range observed in longitudinal studies [19]. Estimates are not comparable to evaluations in high-income settings, where estimates are lower on average, but also highly variable [18], and are generated using different methodologies and data sources.

Our results highlight several challenges in balancing access and excess antibiotic use in LMICs. More than half of ill children who accessed medical care received antibiotics. This exceeds the WHO target of a maximum of 30% antibiotic prescriptions in ambulatory consultations [21]. Antibiotics use was surprisingly high for non-febrile illness episodes treated at healthcare facilities, despite less than 5% of diarrhea cases on average, and at most 20-40% of respiratory illness expected to meet antibiotic treatment criteria [19, 21, 23, 24]. Therefore, a substantial proportion of treatment is likely unwarranted and inappropriate. Excessive antibiotic treatment in medical settings in LMICs may be the result of insufficient training and limited access to diagnostics among health workers, and antibiotic treatment as a safety net when medical re-evaluation is unlikely due to barriers in accessing care. It is not possible from the available data to identify episodes for which antibiotics were indicated and not prescribed.

More than 40% of ill children that received informal care and almost 20% of ill children who did not access any care were self-medicated. Economic incentives for informal drug sellers, lack of regulation, misinformation and demand from caregivers all likely contribute to unnecessary treatment. Although the overall proportion treated with antibiotics was somewhat lower in informal than medical care, in informal care non-febrile and febrile illnesses were equally likely

to receive antibiotics, indicating health workers in medical settings are likely better able to differentiate when antibiotics are indicated. Treatment practices at informal settings, drug sellers and self-medication from left-overs or stockpiles are critical issues for addressing antimicrobial resistance [25-28]. Access without consultation with a skilled provider alleviates barriers in hard-to-reach and vulnerable populations, but also limits the impact of antibiotic stewardship initiatives focused exclusively on formal medical systems. Effective stewardship approaches must include drug shops and address caregiver beliefs and practices.

We observed a more than ten-fold difference in the average rate of childhood antibiotic exposure across LMICs. Variation was partially explained by illness epidemiology and care-seeking, but some countries with relatively similar illness risks differed considerably in antibiotic exposure estimates. This is indicative of different treatment practices, including possible overuse in some settings, but also of gaps and challenges to access, resulting in potential under-use in others. There are also likely substantial within-country differences not investigated here.

This analysis has limitations. Caregiver reports could result in misclassification due to recall errors and inability to accurately differentiate antibiotics from other medicines [29, 30]. However, caregiver reports have been previously validated [19, 22, 29, 31, 32]. Errors are unlikely to result in systematic over- or under-reporting of illness or antibiotic treatment, and thus could bias estimates in either direction. Estimates are based on aggregated period-specific estimates from multiple children and do not represent the actual experiences of any child, but should provide a valid population-level estimate. We considered illness and treatment were independent over periods, yet for a specific child, recent illness and treatment could be

associated with a negative or positive propensity for subsequent events. In aggregate, these propensities likely average out. Estimates do not include treatments for illness other than cough, diarrhea and fever; treatment for other illnesses, prophylaxis or mass drug administration are not included, resulting in potential underestimates of antibiotic exposures. Antibiotic use and illness rates have likely changed over the inclusion period, thus direct comparison across countries should be conducted with caution. However, we used the most recent surveys available, and the magnitude of change is small [15]. The countries with available data are not necessarily a representative sample of all LMIC countries or regions. Few South and South East Asian countries were included, and results may be less generalizable to this region. However, we observed substantial variability across countries even within the same regions, thus substantial variability is also likely in this region.

Conclusion

The high and in some cases likely unjustified use of antibiotics for young children in LMICs is concerning in light of rising resistance [8, 9, 12]. Yet access to life-saving antibiotics still appears limited in some settings. It is unlikely that a single strategy will be suitable to address this imbalance [30]. Context-specific policies and tools to support appropriate empiric treatment and guideline adherence, limit inappropriate use, and stewardship programs that address health systems and informal drug sources are needed. Countries should consider care-seeking and community treatment practices to identify opportunities and ideal intervention points to support optimal antibiotic use.

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Conflicts of interest

Gillian Levine: No conflicts

Julia Bielicki: No conflicts

Günther Fink: No conflicts

REFERENCES

1. *Levels and Trends in Child Mortality: Report 2019, Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation (UN IGME)*. 2019, UNICEF: New York, NY.
2. McAllister, D.A., et al., *Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis.* The Lancet Global Health, 2018. **7(1): e47 - e57**.
3. Reiner, R.C., Jr., et al., *Variation in Childhood Diarrheal Morbidity and Mortality in Africa, 2000-2015.* N Engl J Med, 2018. **379**(12): p. 1128-1138.
4. Collaborators, G.D.a.I.I.a.P., *Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet, 2018. **392**(10159): p. 1789-1858.
5. Donovan, B.M., et al., *Dose, Timing, and Type of Infant Antibiotic Use and the Risk of Childhood Asthma.* Clin Infect Dis, 2019.
6. Kumbhare, S.V., et al., *Factors influencing the gut microbiome in children: from infancy to childhood.* J Biosci, 2019. **44**(2).
7. Meropol, S.B. and A. Edwards, *Development of the infant intestinal microbiome: A bird's eye view of a complex process.* Birth Defects Res C Embryo Today, 2015. **105**(4): p. 228-39.
8. Medernach, R.L. and L.K. Logan, *The Growing Threat of Antibiotic Resistance in Children.* Infect Dis Clin North Am, 2018. **32**(1): p. 1-17.
9. Chatterjee, A., et al., *Quantifying drivers of antibiotic resistance in humans: a systematic review.* Lancet Infect Dis, 2018. **18**(12): p. e368-e378.
10. Michael, C.A., D. Dominey-Howes, and M. Labbate, *The antimicrobial resistance crisis: causes, consequences, and management.* Front Public Health, 2014. **2**: p. 145.
11. Ginsburg, A.S., et al., *Antibiotic non-susceptibility among Streptococcus pneumoniae and Haemophilus influenzae isolates identified in African cohorts: a meta-analysis of three decades of published studies.* Int J Antimicrob Agents, 2013. **42**(6): p. 482-91.
12. Shrestha, P., et al., *Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use.* Antimicrob Resist Infect Control, 2018. **7**: p. 98.
13. Fink, G., et al., *Antibiotic exposure among children younger than 5 years in low-income and middle-income countries: a cross-sectional study of nationally representative facility-based and household-based surveys.* Lancet Infect Dis, 2019.
14. *World Health Organization Report on Surveillance of Antibiotic Consumption: 2016-2018 Early Implementation*. 2018, World Health Organization: Geneva, Switzerland.
15. Jackson, C., et al., *Estimating global trends in total and childhood antibiotic consumption, 2011-2015.* BMJ Glob Health, 2019. **4**(1): p. e001241.
16. Hsia, Y., et al., *Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an*

analysis of sales data from 70 middle-income and high-income countries. Lancet Infect Dis, 2019. **19**(1): p. 67-75.
17. Li, G., et al., *Global sales of oral antibiotics formulated for children.* Bull World Health Organ, 2020. **98**(7): p. 458-466.
18. Youngster, I., et al., *Antibiotic Use in Children - A Cross-National Analysis of 6 Countries.* J Pediatr, 2017. **182**: p. 239-244.e1.
19. Rogawski, E.T., et al., *Use of antibiotics in children younger than two years in eight countries: a prospective cohort study.* Bulletin of the World Health Organization, 2017. **95**(1): p. 49-61.
20. Allwell-Brown, G., et al., *Trends in reported antibiotic use among children under 5 years of age with fever, diarrhoea, or cough with fast or difficult breathing across low-income and middle-income countries in 2005-17: a systematic analysis of 132 national surveys from 73 countries.* Lancet Glob Health, 2020. **8**(6): p. e799-e807.
21. *Using indicators to measure country pharmaceutical situations: Fact Book on WHO Level I and Level II monitoring indicators*, ed. W.H. Organization. 2006, Geneva, Switzerland: World Health Organization.
22. Campbell, H., et al., *Measuring coverage in MNCH: challenges in monitoring the proportion of young children with pneumonia who receive antibiotic treatment.* PLoS Med, 2013. **10**(5): p. e1001421.
23. Fink, G., D'Acremont, V., Leslie, H. H., Cohen, J., *Antibiotic use among children under age five in low and middle income countries: Evidence from nationally representative facility and household surveys.* Lancet Infectious Diseases, 2019.
24. *Integrated Management of Childhood Illness*. 2014, Geneva, Switzerland: World Health Organization.
25. Sun, C., et al., *Influence of leftover antibiotics on self-medication with antibiotics for children: a cross-sectional study from three Chinese provinces.* BMJ Open, 2019. **9**(12): p. e033679.
26. Le, T.H., et al., *Drug use and self-medication among children with respiratory illness or diarrhea in a rural district in Vietnam: a qualitative study.* J Multidiscip Healthc, 2011. **4**: p. 329-36.
27. Nsimba, S.E., *Assessing the performance, practices and roles of drug sellers/dispensers and mothers'/guardians' behaviour for common childhood conditions in Kibaha district, Tanzania.* Trop Doct, 2007. **37**(4): p. 197-201.
28. Lee, A.C., et al., *Treatment of Infections in Young Infants in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis of Frontline Health Worker Diagnosis and Antibiotic Access.* PLoS Med, 2014. **11**(10): p. e1001741.
29. Ayede, A.I., et al., *A prospective validation study in South-West Nigeria on caregiver report of childhood pneumonia and antibiotic treatment using Demographic and Health Survey (DHS) and Multiple Indicator Cluster Survey (MICS) questions.* J Glob Health, 2018. **8**(2): p. 020806.
30. Do, N.T.T., et al., *Community-based antibiotic access and use in six low-income and middle-income countries: a mixed-method approach.* Lancet Glob Health, 2021. **9**(5): p. e610-e619.

31. Hazir, T., et al., *Measuring coverage in MNCH: a prospective validation study in Pakistan and Bangladesh on measuring correct treatment of childhood pneumonia.* PLoS Med, 2013. **10**(5): p. e1001422.
32. Baqui, A.H., et al., *Methodological issues in diarrhoeal diseases epidemiology: definition of diarrhoeal episodes.* Int J Epidemiol, 1991. **20**(4): p. 1057-63.

Table 1. Definition of illness, care-seeking location and source of antibiotic treatment in the analysis

Recent illness[a]	
Any illness	At least one of diarrhea, fever or cough
Non-febrile illness	Diarrhea or cough without fever
Febrile illness	Fever alone or with diarrhea or cough
Care-seeking for recent illness and treatment source	
Medical care	Public or private hospital, health center, health post, clinic, or trained health worker[b]
Informal care	Private pharmacy, drug seller, chemist, traditional healer, refugee camp, or non-governmental organization
No care or treatment	Report no care or treatment outside of the household, “other” and “don’t know” to if or where care was sought[b]
Self-medication	Report not seeking care or treatment outside the household, but reported antibiotic treatment for the illness, treatments from shops or markets

[a] Illness within the two weeks preceding the survey
[b] The standard recode classifications of “medical care” or “no care or treatment” were applied if there was a valid DHS recode classification but the specific treatment location was missing

Table 2. Sample summary characteristics and recent illness in children 0-59 months from 45 included LMIC surveys

Characteristics	Frequency (n/N) [a]	Mean proportion across countries (95% CI) [b]
Household		
Rural residence	295,169/438,140	64.9 (64.4, 65.4)
Mother's highest level of education attended		
None	164,678/422,805	31.5 (31.1, 31.9)
Primary	121,833/422,805	29.3 (29.0, 29.6)
Secondary	111,260/422,805	31.5 (31.1, 31.8)
Higher	25,034/422,805	7.8 (7.6, 8.0)
Child		
Female	215,607/438,140	49.3 (49.0, 49.5)
Age (months)		
0 - 11	92,407/438,140	21.4 (21.3, 21.6)
12 - 23	88,215/438,140	20.4 (20.3, 20.6)
24 - 35	86,919/438,140	19.8 (19.6, 20,0)
36 - 47	87,610/438,140	19.7 (19.5, 19.8)
48 – 59	82,989/438,140	18.6 (18.5, 18.8)
Delivered in health facility [c]	265,953/434,976	67.8 (67.4, 68.3)
Child illness in previous two weeks [d]		
Any illness (diarrhea, fever or cough)	170,109/438,140	38.7 (38.4, 39.0)
Febrile illness	96,868/438,140	21.6 (21.3, 21.8)
Non-febrile illness	73,241/438,140	17.1 (16.9, 17.4)
Illness symptoms		
Diarrhea only (no cough or fever)	28,920/438,140	6.3 (6.2, 6.4)
Fever only (no cough or diarrhea)	26,490/438,140	5.8 (5.7, 5.9)
Cough only (no fever or diarrhea)	35,080/438,140	8.6 (8.5, 8.8)
Fever and cough (no diarrhea)	36,757/438,140	8.4 (8.3, 8.6)
Diarrhea and fever (no cough)	13,069/438,140	2.8 (2.7, 2.9)
Diarrhea and cough (no fever)	13,069/438,140	2.3 (2.2, 2.3)
Diarrhea, fever and cough	20,552/438,140	4.5 (4.4, 4.7)

a Numerator is raw frequency, denominator is number of observations with non-missing values. Raw frequencies will not align with mean proportions across countries due to sampling weights and selection probabilities, and de-normalization of weights for aggregated estimates across countries.
b Summaries account for country-specific individual and stratum sampling weights in each survey year and country, with weights de-normalized so that each country contributes equally to the total pooled estimate. Estimates can be interpreted as the mean of country-specific estimates accounting for sampling and selection probability weights, with equal weight for each country.
c Among those with complete response; 'other' considered missing. N=434,976
d Relates to two-week point prevalence of all children in the sample unless otherwise specified. Relates to the presence of the illness/symptom with or without presence of other illnesses/symptoms unless otherwise specified.
Sub-total categories may not total 100% due to rounding.

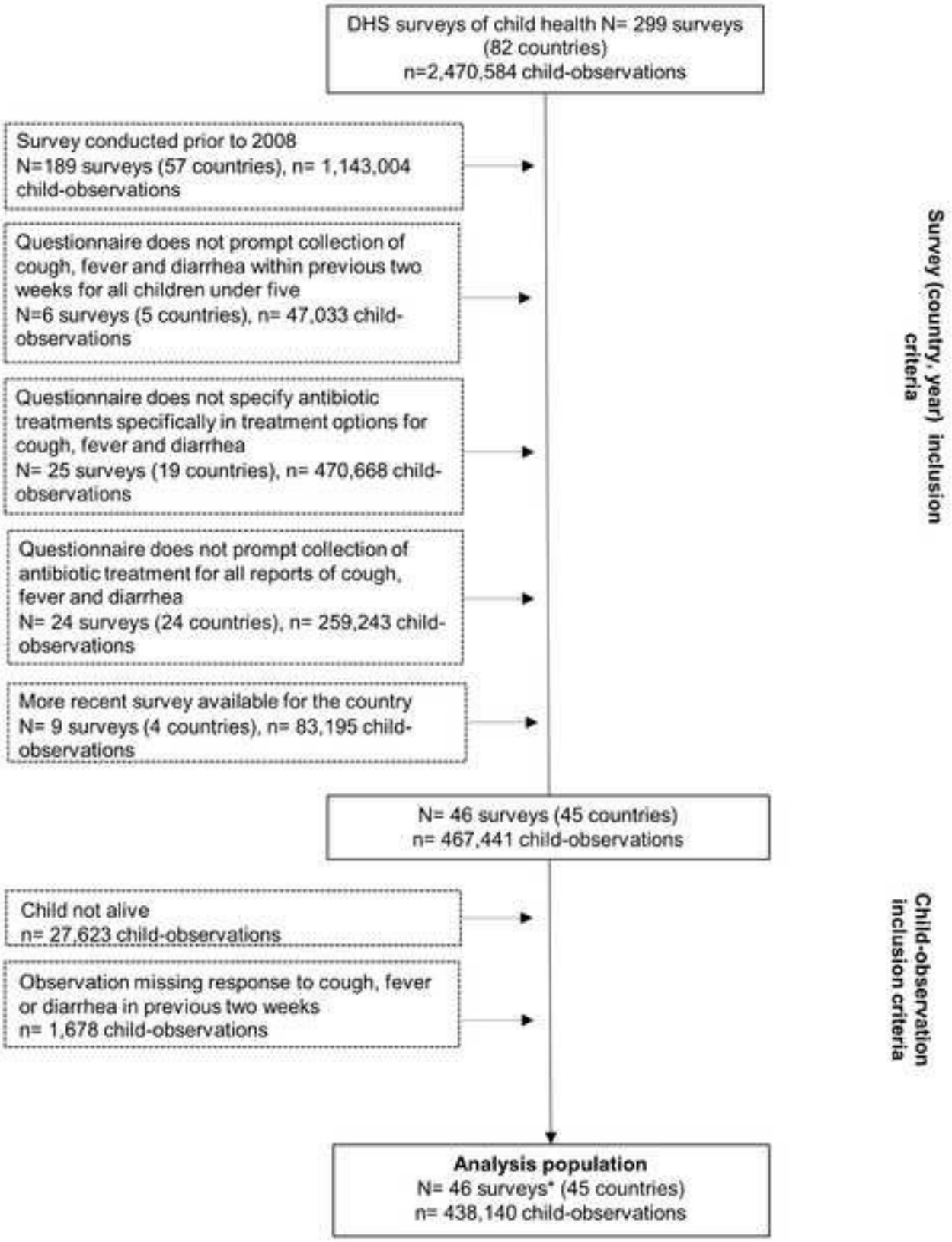
Table 3. Care-seeking and antibiotic treatment among children 0-59 months with recent illness [a] in 45 LMICs

	Care-seeking			Antibiotic treatment			
Illness	No advice or treatment [c,d] (%)	Informal care [d,e] (%)	Medical care [e,f] (%)	Among those who sought no advice or treatment [c,d] (%)	Among those who sought informal care [d,e] (%)	Among those who sought medical advice or treatment [d,f] (%)	Total treated with antibiotics [d] (%)
Any illness[a]	37.9 (37.4, 38.4)	13.3 (13.0, 13.7)	48.8 (48.3, 49.2)	17.3 (16.7, 17.8)	43.6 (42.4, 44.8)	53.7 (53.1, 54.3)	38.4 (37.9, 38.8)
Febrile illness [b]	30.5 (29.9, 31.1)	13.6 (13.2, 14.0)	55.9 (55.3, 56.5)	18.9 (18.1, 19.8)	44.1 (42.6, 45.7)	55.6 (54.8, 56.3)	42.7 (42.1, 43.3)
Non-febrile illness	47.3 (46.7 47.9)	13.0 (12.6, 13.4)	39.7 (39.1, 40.3)	15.9 (15.2, 16.7)	42.9 (41.3, 44.5)	50.4 (49.4, 51.4)	32.9 (32.4, 33.5)
Diarrhea only	47.2 (46.2, 48.1)	12.1 (11.6, 12.7)	40.7 (39.8, 41.7)	10.3 (9.4, 11.2)	25.8 (23.8, 27.9)	35.0 (33.6, 36.4)	22.2 (21.4, 23.0)
Fever only	39.2 (38.2, 40.2)	13.1 (12.4, 13.8)	47.8 (46.8, 48.7)	12.6 (11.5, 13.8)	32.0 (29.3, 34.9)	40.1 (38.8, 41.5)	27.9 (27.0, 28.8)
Cough only	50.9 (50.0, 51.7)	13.2 (12.7, 13.9)	35.9 (35.0, 36.8)	18.1 (17.1, 19.2)	51.8 (49.4, 54.2)	59.2 (57.5, 60.8)	36.9 (36.1, 37.8)
Fever and cough (no diarrhea)	30.2 (29.4, 31.0)	13.5 (12.9, 14.1)	56.3 (55.4, 57.2)	22.4 (21.2, 23.8)	50.1 (47.9, 52.4)	58.6 (57.4, 59.8)	46.4 (45.5, 47.3)
Diarrhea and fever (no cough)	26.7 (25.5, 27.9)	14.0 (13.1, 14.9)	59.4 (58.0, 60.7)	20.2 (18.2, 22.5)	38.9 (35.8, 42.1)	56.1 (54.2, 58.0)	44.1 (42.7, 45.5)
Diarrhea and cough (no fever)	34.2 (32.6, 35.7)	14.6 (13.6, 15.6)	51.3 (49.7, 52.8)	25.3 (22.8, 28.0)	51.7 (48.0, 55.4)	61.1 (58.9, 63.3)	47.5 (46.0, 49.1)
Diarrhea, fever and cough	22.3 (21.4, 23.4)	14.2 (13.4, 14.9)	63.5 (62.3, 64.6)	23.1 (21.2, 25.2)	50.9 (48.1, 53.7)	65.3 (64.0, 66.6)	53.8 (52.7, 55.0)

Pooled estimates with each survey/country contributing equal weight and samples within countries weighted based on probability of sampling and selection

a Includes diarrhea, fever or cough in previous two weeks
b Includes presentation with only that symptom or with multiple symptoms
c No advice or treatment defined as report of not seeking any medical or non-medical care or advice outside the home for recent illness
d Among those with the illness specified in the first column. Treatment and care seeking includes all care and treatment for the reporting period, regardless of indication/morbidity the care-seeking or treatment was associated with. (eg. antibiotic treatment reported for diarrhea in a child who also has fever, but reported no antibiotic for fever, would be considered receiving an antibiotic for illness with fever)
e Informal care is care or treatment sought for illness from a non-medical provider and outside of a health facility (drug seller, traditional healer or practitioner, private pharmacy, NGO, refugee camp)
f Medical care is care or treatment sought for illness from a medical provider or at a health facility (care from public or private hospital, health center, health post, clinic, community health worker)

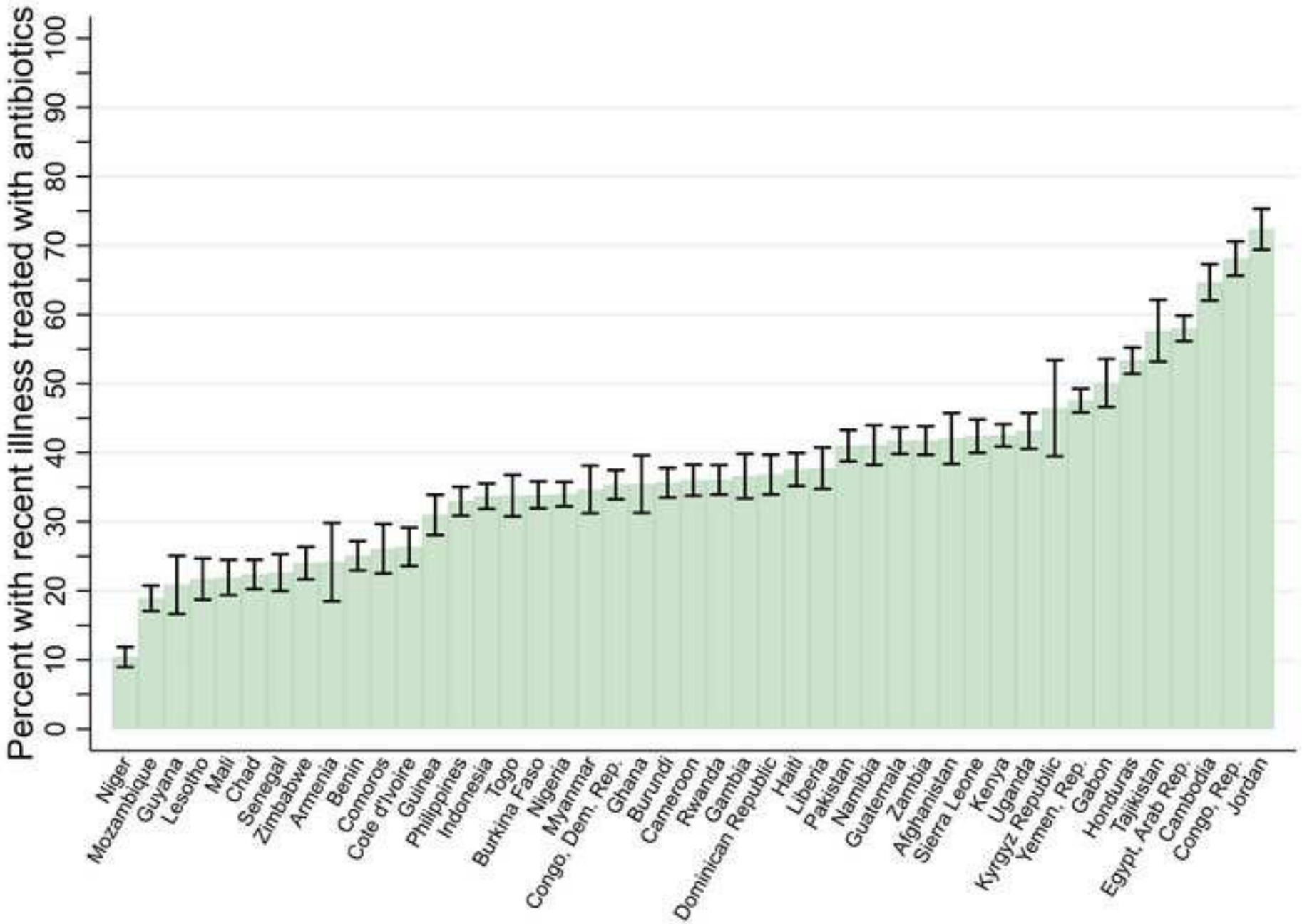
Figure 1. Selection of study population into analysis of childhood illness and antibiotic treatment estimates in LMICs



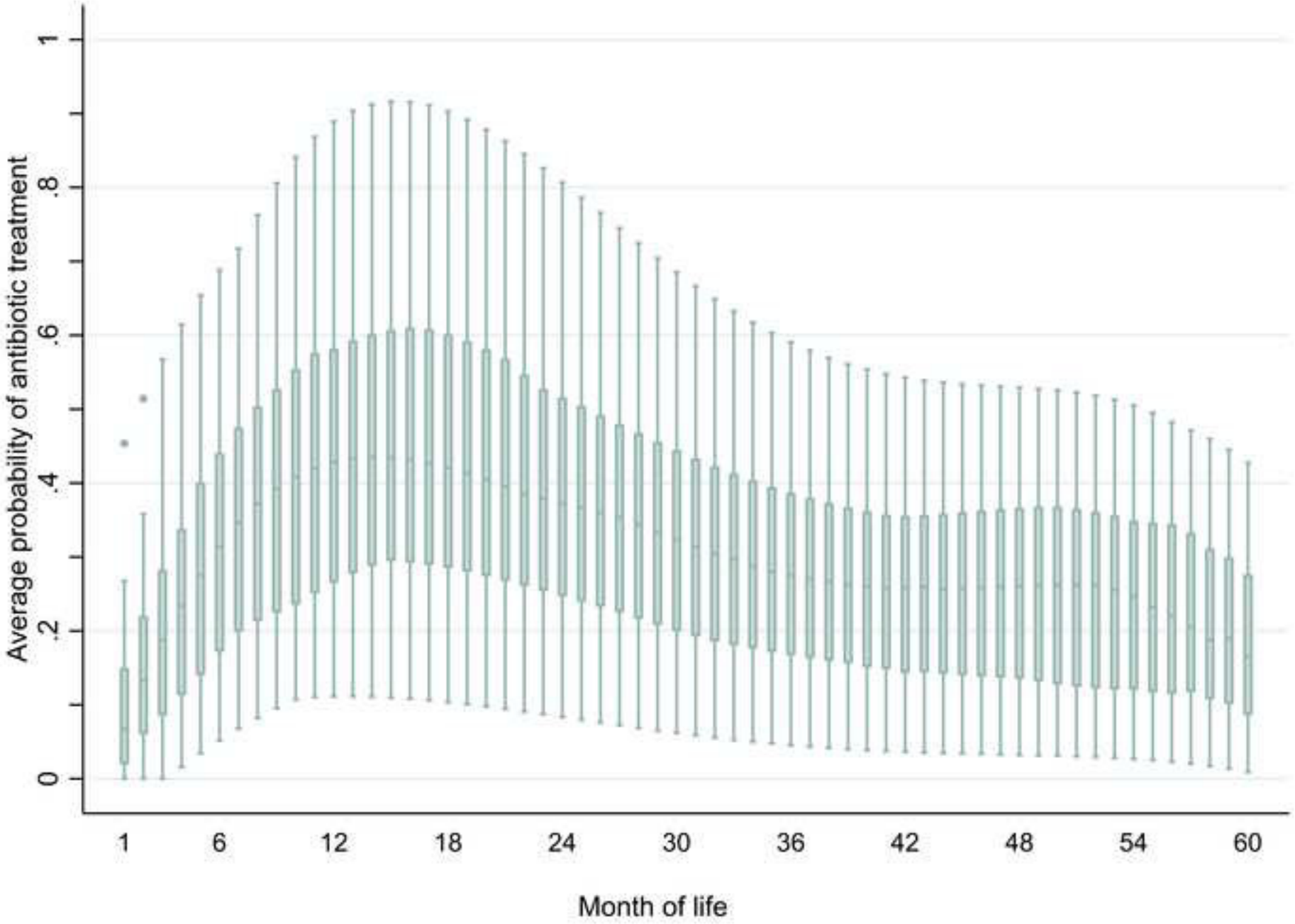
*Dominican Republic conducted two surveys in the same year; samples from both are included.

Figure (.tif and .eps files only)

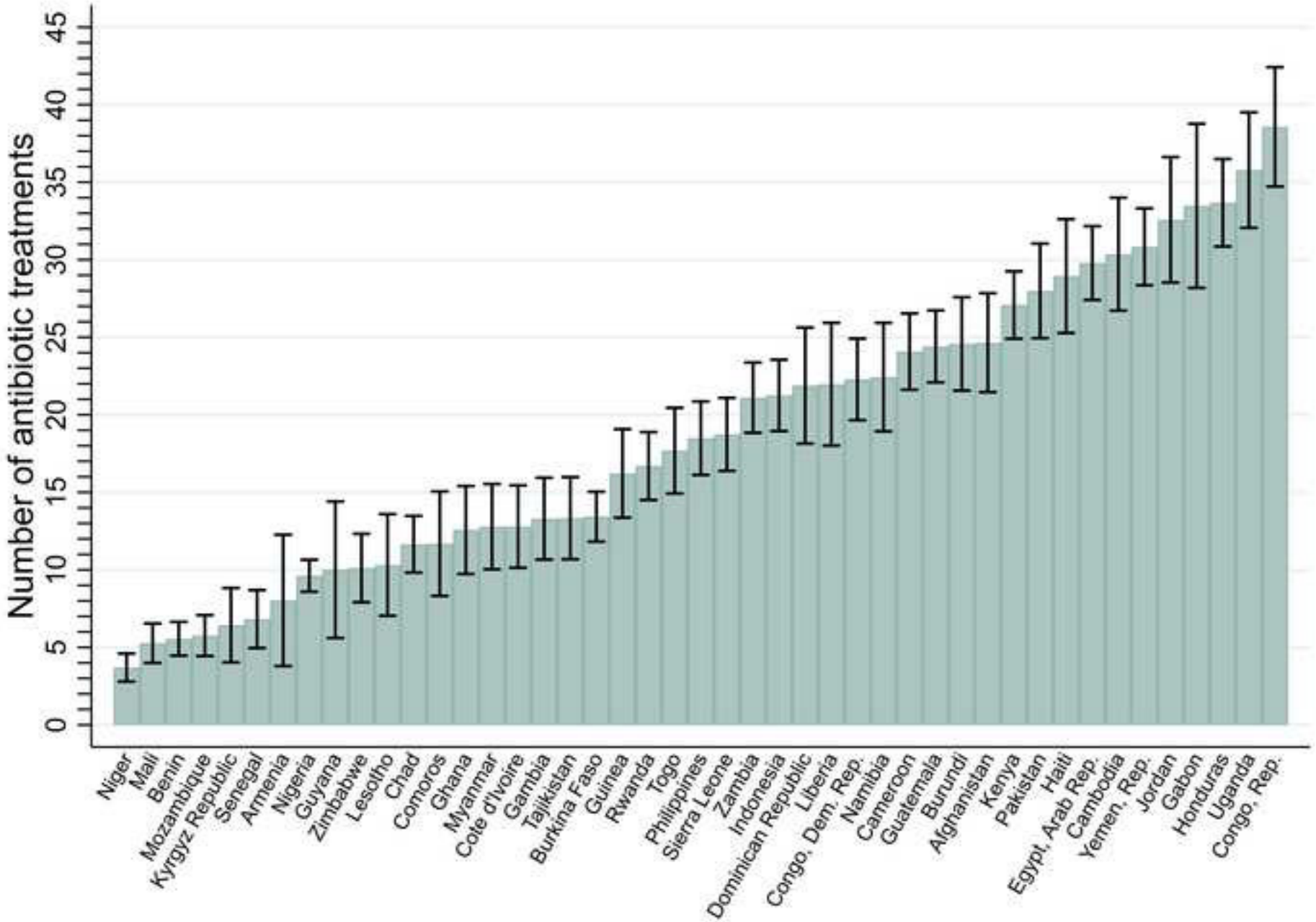
Click here to access/download;Figure (.tif and .eps files only);F2 Percent treated with abx when ill by country1.tif



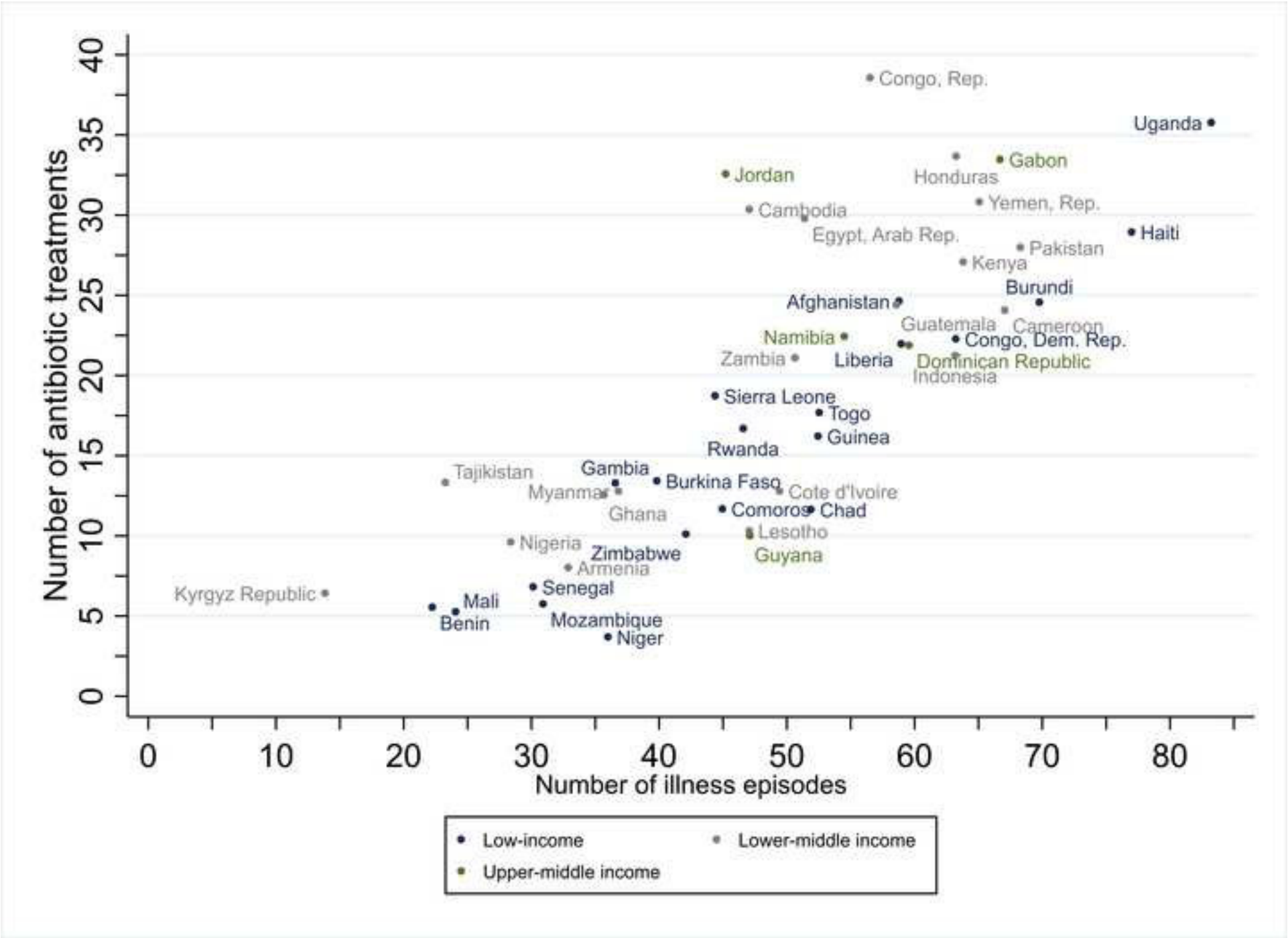
F2 Percent treated with abx when ill by country.tif



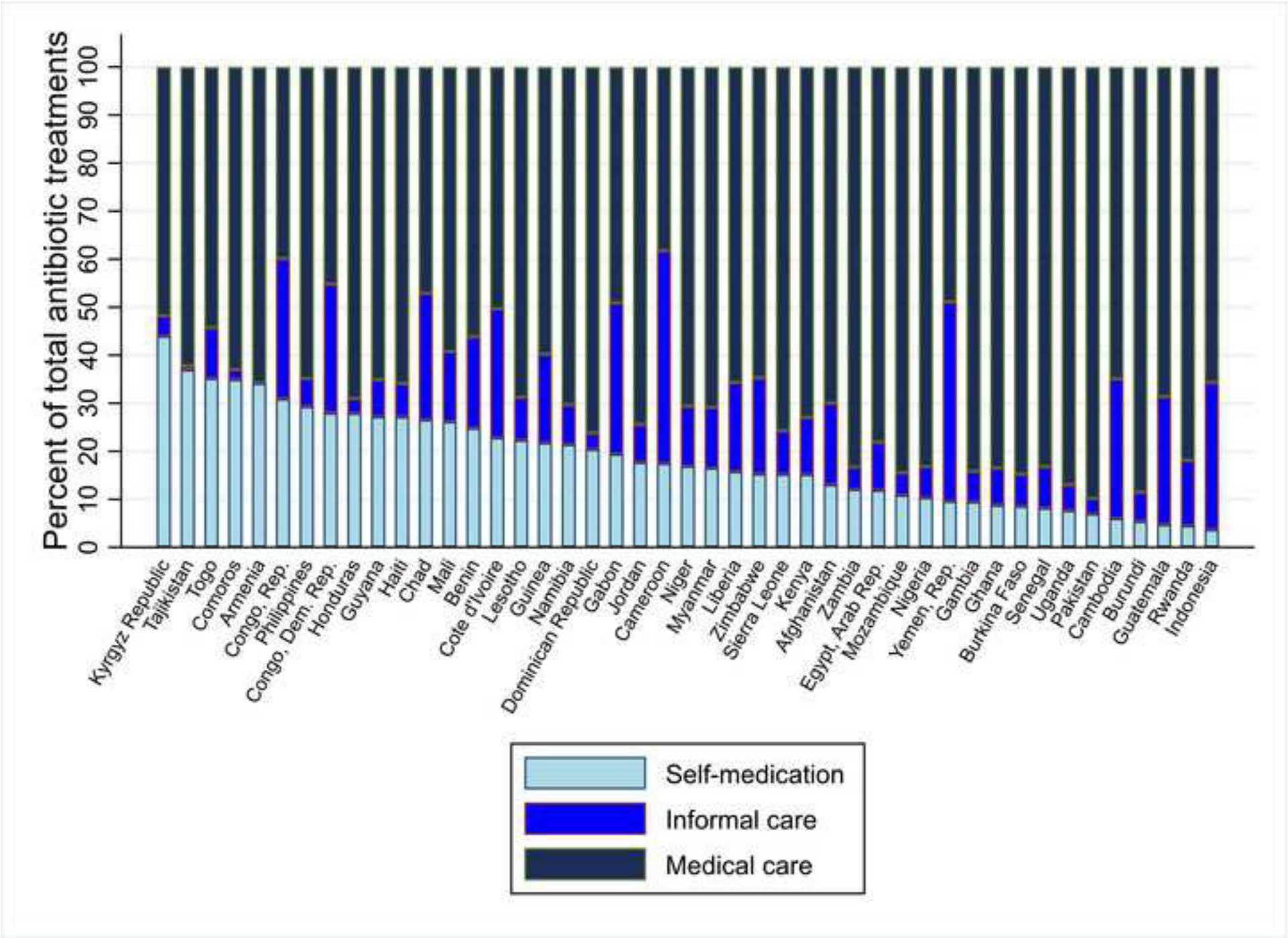
F3 Avg antibiotics treatment per month.tif



F4 Total treatments per country bar graph.tif



F5 Scatter country illness and abx.tif



F6 Proport. source of abx treatments by country cc.tif

SUPPLEMENTARY MATERIAL

Table S1. Summary of countries, DHS survey year and number of observations in study sample

Country name	Survey year	N
Afghanistan	2015	30,858
Armenia	2010	1,448
Benin	2011	12,651
Burkina Faso	2010	13,692
Burundi	2010	7,222
Cambodia	2014	6,970
Cameroon	2011	10,692
Chad	2014	16,780
Comoros	2012	2,982
Congo, Dem. Rep.	2013	17,180
Congo, Rep.	2011	8,834
Cote d'Ivoire	2011	7,034
Dominican Republic	2013	4,476
Egypt, Arab Rep.	2014	15,459
Gabon	2012	5,660
Gambia	2013	7,738
Ghana	2014	5,592
Guatemala	2014	12,066
Guinea	2012	6,392
Guyana	2009	2,060
Haiti	2012	6,736
Honduras	2011	10,585
Indonesia	2012	17,311
Jordan	2012	10,128
Kenya	2014	20,053
Kyrgyz Republic	2012	4,226
Lesotho	2014	2,915
Liberia	2013	7,040
Mali	2012	9,582
Mozambique	2011	10,291
Myanmar	2015	4,594
Namibia	2013	4,802
Niger	2012	11,545
Nigeria	2013	28,331
Pakistan	2012	10,898
Philippines	2013	7,003
Rwanda	2014	7,542
Senegal	2016	6,417
Sierra Leone	2013	10,537
Tajikistan	2012	4,821
Togo	2013	6,521
Uganda	2011	7,344
Yemen, Rep.	2013	15,291
Zambia	2013	12,640
Zimbabwe	2010	5,201
Total		438,140

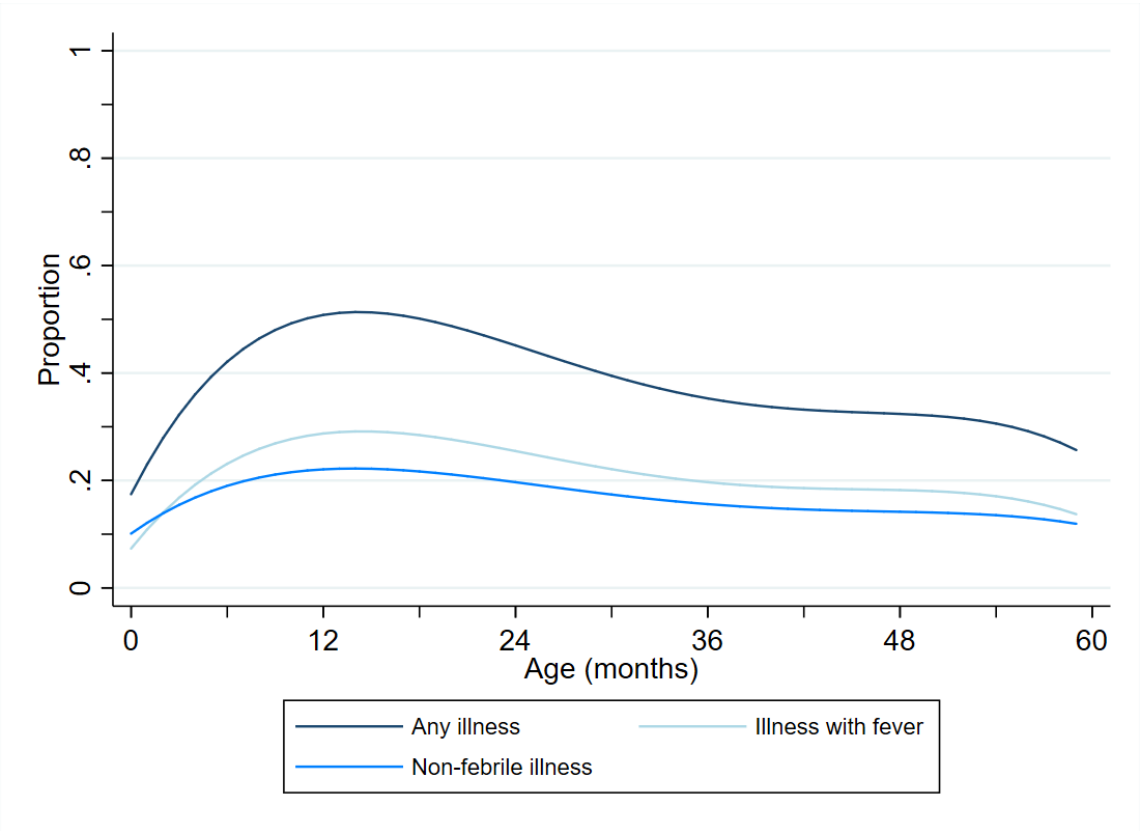
Table S2. Sources of oral antibiotic treatments for illness in the first 5 years of life in 45 LMICs

Country	% Antibiotic use attributable to sector		
	Medical care or treatment	Informal care	No care or treatment
Afghanistan	70.1	16.6	13.3
Armenia	65.9	0.0	34.1
Benin	56.2	19.0	24.8
Burkina Faso	84.8	6.6	8.6
Burundi	88.5	6.1	5.4
Cambodia	65.0	29.0	5.9
Cameroon	38.7	43.9	17.4
Chad	48.1	25.8	26.1
Comoros	63.0	2.0	34.9
Congo, Dem. Rep.	45.3	26.8	28.0
Congo, Rep.	39.9	29.2	30.9
Cote d'Ivoire	50.2	26.3	23.5
Dominican Republic	75.9	3.3	20.7
Egypt, Arab Rep.	78.2	10.0	11.9
Gabon	49.2	31.4	19.4
Gambia	84.3	6.3	9.5
Ghana	83.5	7.7	8.8
Guatemala	68.7	26.6	4.7
Guinea	59.6	18.4	22.1
Guyana	65.2	7.7	27.2
Haiti	65.9	6.9	27.2
Honduras	69.1	3.0	27.9
Indonesia	65.7	30.6	3.7
Jordan	74.4	7.9	17.7
Kenya	73.0	11.8	15.2
Kyrgyz Republic	51.8	4.2	44.0
Lesotho	68.8	8.9	22.3
Liberia	65.7	18.5	15.8
Mali	59.3	14.5	26.2
Mozambique	84.5	4.6	10.9
Myanmar	71.4	12.4	16.2
Namibia	70.4	7.9	21.7
Niger	70.6	12.5	16.9
Nigeria	83.3	6.4	10.3
Pakistan	89.9	3.2	7.0
Philippines	64.9	5.8	29.3
Rwanda	81.9	13.6	4.6
Senegal	83.3	8.6	8.2
Sierra Leone	75.8	9.0	15.2

Tajikistan	62.0	0.8	37.2
Togo	53.9	10.5	35.6
Uganda	87.0	5.3	7.7
Yemen, Rep.	49.4	41.2	9.4
Zambia	83.5	4.5	12.0
Zimbabwe	64.8	20.0	15.3

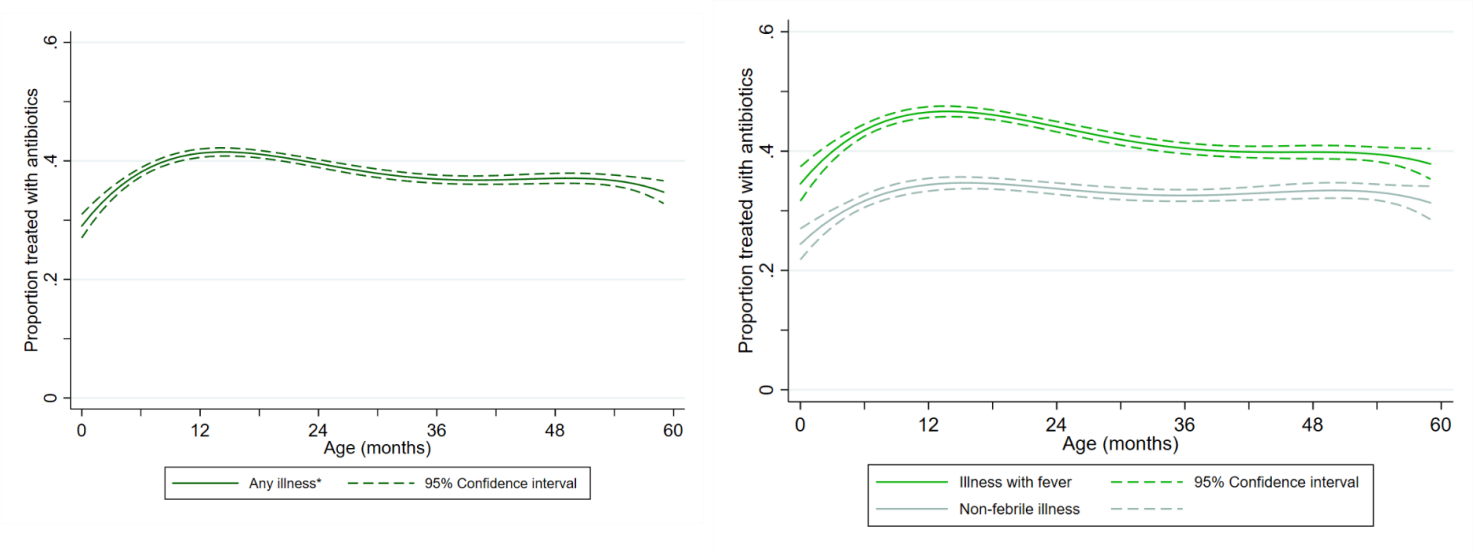
Illness includes diarrhea, fever or cough
Observations with a reported illness for which the care-seeking history for that specific illness were missing are excluded

Figure S1. Age-specific probability of illness in the previous two weeks in children 0-59 months of life in 45 low-and-middle-income countries



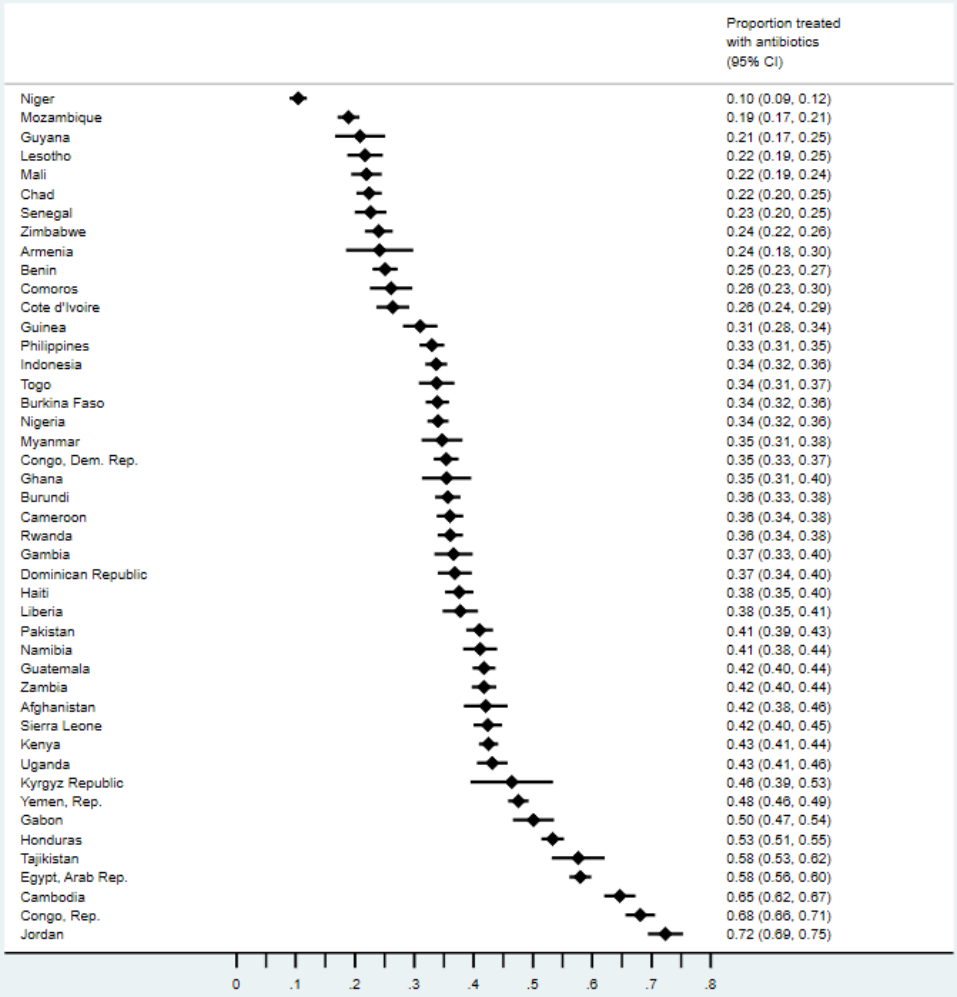
Estimates from linear regression with age smoothing from pooled sample from 45 countries, with equal weights across countries Any illness relates to fever, cough, and/or diarrhea. Illness with fever includes fever alone or with diarrhea and/or cough. Non-febrile illness relates to diarrhea and/or cough without report of fever.

Figure S2. Age-specific probability of antibiotic treatment among children with recent illness in 45 low-and middle-income countries



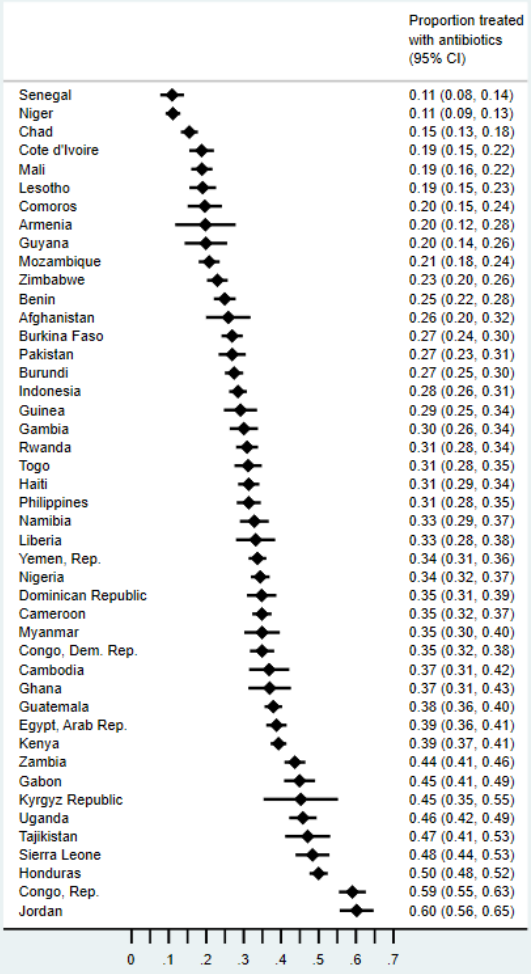
Estimates from linear regression with age smoothing from pooled samples from 45 countries with equal weights across countries. Any illness relates to fever, cough, and/or diarrhea. Illness with fever includes fever alone or with diarrhea and/or cough. Non-febrile illness relates to diarrhea and/or cough without report of fever.

Figure S3a. Estimated probability of antibiotic treatment with illness in children under 5 years of age for 45 low- and middle-income countries



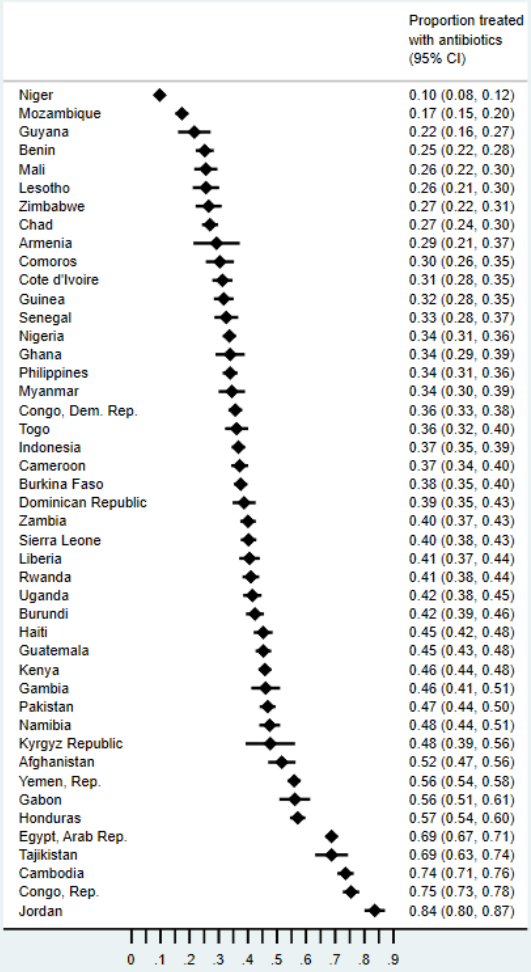
Illness includes fever, diarrhea, or cough.

Figure S3b. Estimated probability of antibiotic treatment with non-febrile illness in children under 5 years of age for 45 low- and middle-income countries



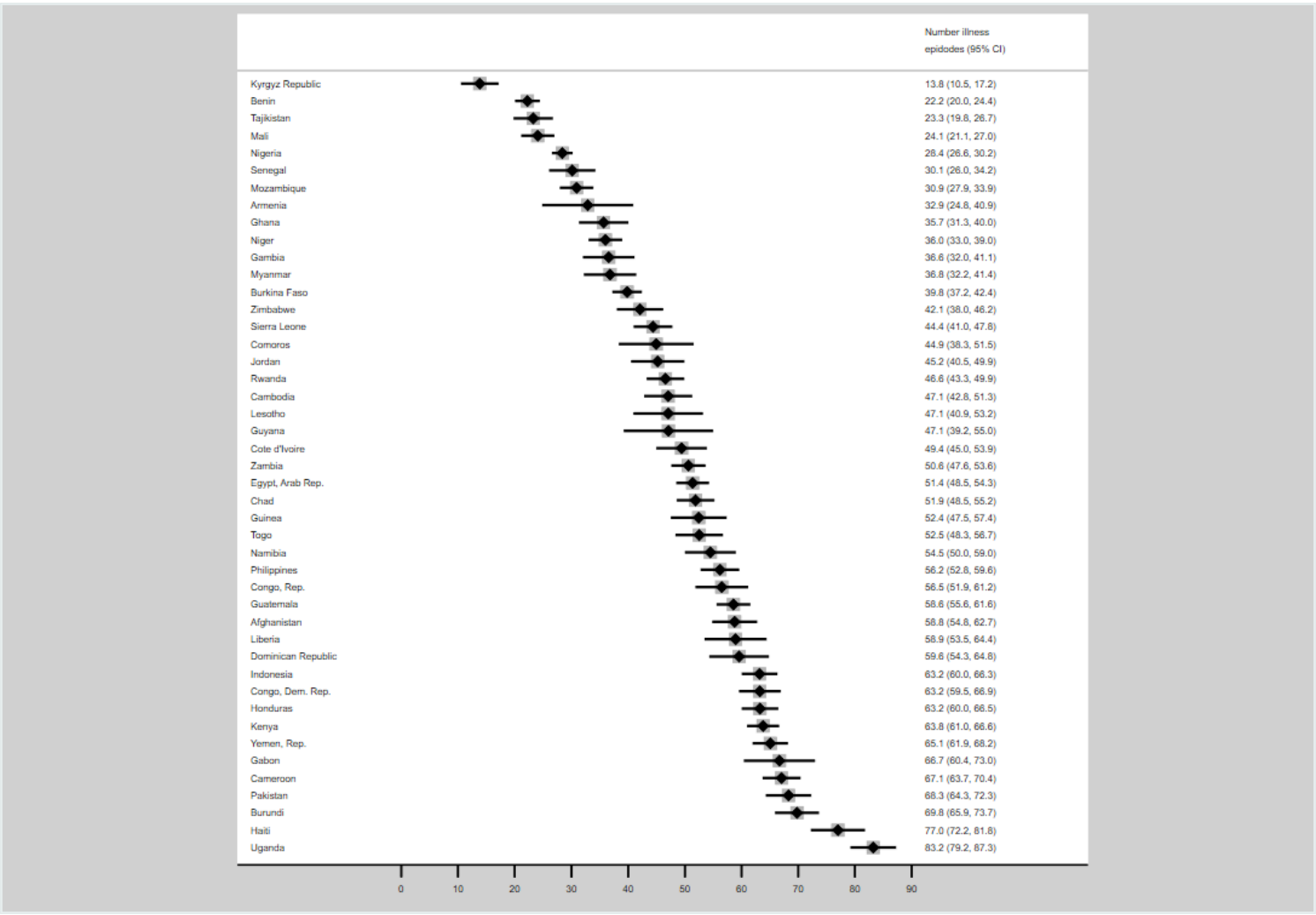
Non-febrile illness relates to diarrhea or cough without report of fever.

Figure S3c. Estimated probability of antibiotic treatment for illness with fever in children under 5 years of age in 45 low- and middle-income countries



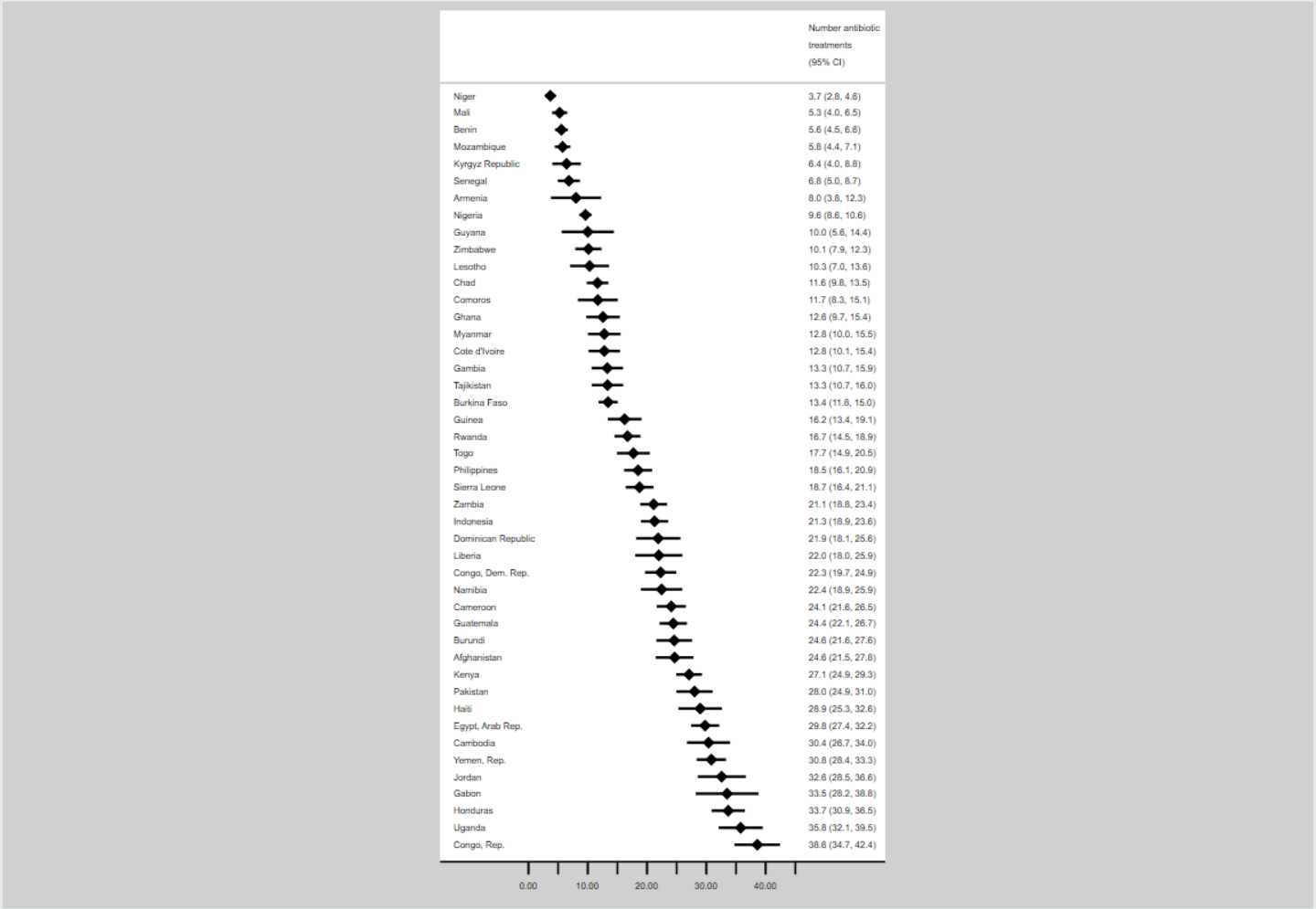
Febrile illness includes fever alone or with diarrhea or cough.

Figure S4. Estimated total illness episodes in the first 5 years of life in 45 low- and middle-income countries



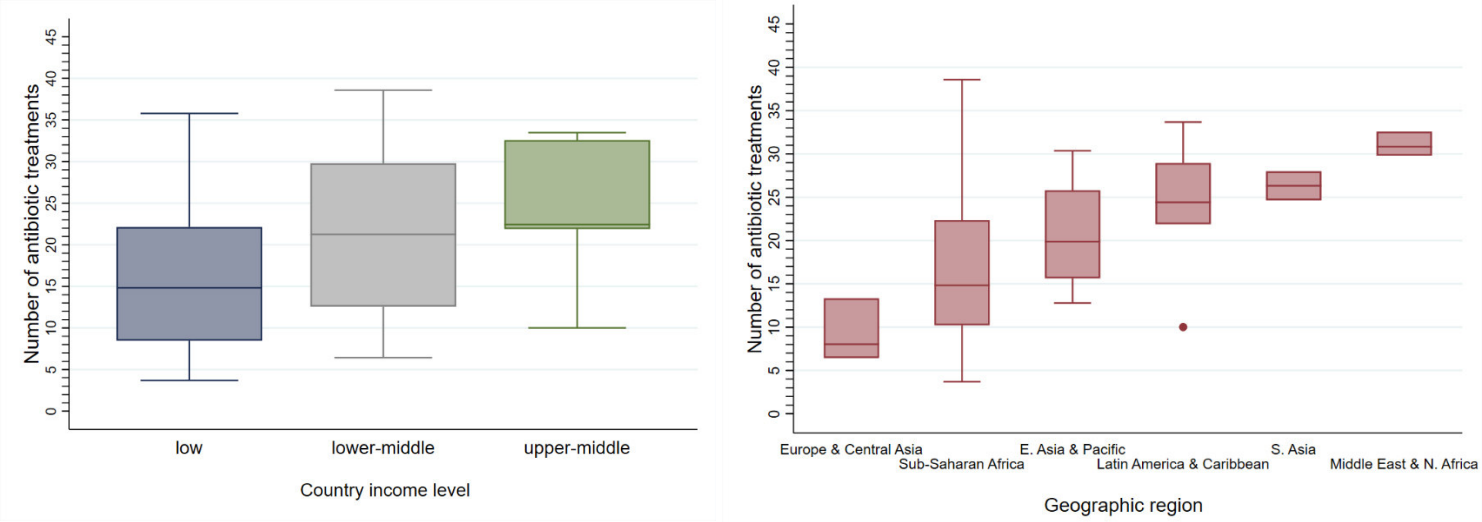
Estimates from cumulative additive models of age-specific exposure probabilities from linear probability regression models with age-smoothing, accounting for survey sampling and selection probability in each country. Illness includes diarrhea, fever, or cough.

Figure S5. Country-specific estimates of total antibiotic exposures in the first 5 years of life in 45 low- and middle-income countries



Estimates from cumulative additive models of age-specific exposure probabilities from linear probability regression models with age-smoothing, accounting for survey sampling and selection probability in each country. Includes antibiotic treatments for fever, cough, and/or diarrhea.

Figure S6a-b. Estimated total antibiotic exposures in the first 5 years of life in 45 LMICs, by country income group and geographic region



Boxes are median, 25th and 75th percentile of country-specific estimates within each country income group or geographic region. Outliers noted with dots.