International Journal of Infectious Diseases 108 (2021) 473–482

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Determinants of trends in reported antibiotic use among sick children under five years of age across low-income and middle-income countries in 2005–17: A systematic analysis of user characteristics based on 132 national surveys from 73 countries

Gbemisola Allwell-Brown[a,*], Laith Hussain-Alkhateeb[b], Maquins Odhiambo Sewe[c], Freddy Eric Kitutu[a,d], Susanne Strömdahl[e], Andreas Mårtensson[a], Emily White Johansson[a]

[a] Department of Women's and Children's Health, International Maternal and Child Health (IMCH), Uppsala University, SE-751 85 Uppsala, Sweden
[b] Global Health, School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, SE-405 30 Gothenburg, Sweden
[c] Department of Public Health and Clinical Medicine, Sustainable Health Section, Umeå University, SE-901 87, Umeå, Sweden
[d] Sustainable Pharmaceutical Systems (SPS) Unit, Department of Pharmacy, School of Health Sciences, Makerere University, PO Box 7072, Kampala, Uganda
[e] Section of Infectious Diseases, Department of Medical Sciences, Uppsala University, SE-751 85 Uppsala, Sweden

A R T I C L E I N F O

Article history:
Received 2 February 2021
Received in revised form 26 April 2021
Accepted 21 May 2021

Keywords:
Antibiotic use
Antibiotic consumption
Determinants
Children
Low- and middle-income countries
Global trends

A B S T R A C T

Objectives: This study aimed to analyze any reported antibiotic use for children aged <5 years with fever, diarrhea or cough with fast or difficult breathing (outcome) from low-income and middle-income countries (LMICs) during 2005–2017 by user characteristics: rural/urban residence, maternal education, household wealth, and healthcare source visited.
Methods: Based on 132 demographic and health surveys and multiple indicator cluster surveys from 73 LMICs, the outcome by user characteristics for all country-years was estimated using a hierarchical Bayesian linear regression model.
Results: Across LMICs during 2005–2017, the greatest relative increases in the outcome occurred in rural areas, poorest quintiles and least educated populations, particularly in low-income countries and South-East Asia. In low-income countries, rural areas had a 72% relative increase from 17.8% (Uncertainty Interval (UI): 5.2%–44.9%) in 2005 to 30.6% (11.7%–62.1%) in 2017, compared to a 29% relative increase in urban areas from 27.1% (8.7%–58.2%) in 2005 to 34.9% (13.3%–67.3%) in 2017. Despite these increases, the outcome was consistently highest in urban areas, wealthiest quintiles, and populations with the highest maternal education.
Conclusion: These estimates suggest that the increasing reported antibiotic use for sick children aged <5 years in LMICs during 2005–2017 was driven by gains among groups often underserved by formal health services.

Introduction

Antimicrobial resistance is a growing global challenge, with the greatest health and economic consequences for low-income and middle-income countries (LMICs), where infectious disease burden is high and health systems remain weak (Pokharel et al., 2019). Antibiotic use, especially excessive use, is a known driver of antibiotic resistance (Michael et al., 2014; Holmes et al., 2016); however, since lack of access to antibiotics is associated with substantial mortality in LMICs there is also a need to ensure antibiotic access to those most in need (Laxminarayan et al., 2016; Sulis and Gandra, 2021).

Global assessments of antibiotic consumption since 2000 have reported increasing total antibiotic consumption, with most of the increase attributed to LMICs (Van Boeckel et al., 2014; Klein et al., 2018). At the same time, these studies have also highlighted an

* Corresponding author at: Department of Women's and Children's Health, International Maternal and Child Health (IMCH), Uppsala University, SE-751 85 Uppsala, Sweden.
E-mail address: gbemisola.allwell-brown@kbh.uu.se (G. Allwell-Brown).

https://doi.org/10.1016/j.ijid.2021.05.058
1201-9712/

access-excess divide in antibiotic consumption between countries based on regional and economic differences, such that antibiotic consumption per person in most high-income countries exceeds that in LMICs, despite the greater infectious disease burden in LMICs (Van Boeckel et al., 2014; Klein et al., 2018; Jackson et al., 2019; Klein et al., 2020). However, this access-excess divide in antibiotic consumption is more complicated than simply between rich and poor countries (So et al., 2013). Within countries, and especially in LMICs where wide social disparities commonly exist, variations in socioeconomic status or access to health services may further delineate their own access-excess divide (Heyman et al., 2014).

There is limited evidence about this access-excess divide within LMICs, since global assessments to date have primarily relied on pharmaceutical sales data that do not provide sub-national estimates or report user characteristics (Van Boeckel et al., 2014; Klein et al., 2018; Jackson et al., 2019; Klein et al., 2020). A previous study examined trends in reported antibiotic use among sick children aged <5 years in 2005–2017 across LMICs by geographic region and country income grouping, but without further investigation by user characteristics (Allwell-Brown et al., 2020). Understanding the determinants of the earlier documented upward trends in antibiotic consumption in LMICs (Van Boeckel et al., 2014; Klein et al., 2018; Jackson et al., 2019; Allwell-Brown et al., 2020; Klein et al., 2020) by user characteristics could help to elucidate patterns of inequities in antibiotic use over time, particularly among populations with poor access to medicines and formal health services.

This study aimed to examine trends and differentials in reported antibiotic usage among sick children aged <5 years across LMICs during 2005–2017 by the following user characteristics: rural/urban residence, maternal education, household wealth, and healthcare source visited.

Methods

Data sources

USAID-supported Demographic and Health Surveys (DHS) and UNICEF-supported Multiple Indicator Cluster Surveys (MICS) are cross-sectional, population-based cluster sample surveys based on nationally representative samples that have been comparably conducted every 3 to 5 years in LMICs for the past few decades (USAID, 2018; UNICEF, 2019). Both survey programs use similar methods and questionnaires to collect standardized information on a wide range of key demographic and health issues. Survey methods are described elsewhere, including procedures for obtaining ethical approval and participant consent (USAID, 2018; UNICEF, 2019). For this study, DHS and MICS conducted since 2000 were systematically screened for inclusion, which was guided by the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA, 2015). DHS and MICS were included if the final dataset was publicly available by 15 August 2018, the survey was conducted in a country classified as low-income, lower-middle income, or upper-middle income during the study period (World Bank), and the questionnaire collected information to measure the primary outcome as described below. Surveys were excluded if the questionnaire was not publicly available, the treatment question did not contain an antibiotic response category for one or more symptoms, or the skip pattern was not consistent with the defined primary outcome.

Primary outcome

The primary outcome was defined as the proportion of children aged <5 years with reported symptoms of fever, diarrhea, or cough with fast or difficult breathing in the 2 weeks preceding the survey interview and who reportedly received antibiotics. This outcome is referred to in this paper as reported antibiotic use for sick children aged <5 years. DHS and MICS interviews were conducted with women aged 15–49 years in each sampled household to collect information on each of their children aged <5 years at the time of the interview. Caregivers reported whether a child had illness symptoms in the 2 weeks preceding the survey, including: fever, diarrhea, and cough with fast or difficult breathing. For each symptom separately, the caregiver reported where the sick child was taken for care and the medicines given for treatment, including antibiotics. Caregivers were asked to report the names of the medications given or to show their packets, and medically trained personnel on survey teams classified the medications as appropriate. A positive outcome was defined as any antibiotic (pill/syrup, injection or specific antibiotic type) that was reportedly given to a child aged <5 years with reported fever, diarrhea or cough with fast or difficult breathing symptoms in the 2 weeks preceding the survey. Information on antibiotic type, dosage or completion of the treatment course was not typically recorded.

User characteristics

User characteristics for reported antibiotic use among sick children aged <5 years were examined by urban and rural residence, maternal education, household wealth, and healthcare source visited. Selection of these user characteristics was based on empirical evidence of their relationship with access to medicines and treatment outcomes in LMICs (Sultana et al., 2019; Van Malderen et al., 2019; Yaya et al., 2019). Rural or urban residence was determined by population size and/or infrastructure classifications, and defined in the surveys as specified by each country's national statistical office (USAID, 2018). Maternal education level was grouped into three categories: no formal education or some primary school attendance; primary school completion or some secondary school attendance; and secondary school completion or higher education. Household wealth index is a composite measure of the relative economic position of households within a country based on asset ownership and housing characteristics (Filmer and Pritchett, 2001). The asset wealth index is derived using principal component analysis to divide the population into wealth quintiles based on asset ownership (Rutstein and Johnson, 2004). Each asset is assigned a weight and the resulting asset scores are standardized to a normal distribution that rank orders the population on a continuous scale of relative economic status (Rutstein and Johnson, 2004). The current study used the survey-specific wealth indices as a measure of relative economic status of households within their own society at the time of the survey interview. The healthcare source visited was based on maternal reports of where advice or treatment for the sick child was sought from, and responses were grouped into three categories: 1) public medical sector (government hospitals, government health centers, government health posts, mobile clinics, community health workers, or other country-specific public sector); 2) private medical source (private hospitals or clinics, pharmacies, private doctors, or other country-specific medical private sector); 3) private informal source (shops, traditional practitioners, or other informal sources) or no care sought. This variable was coded such that if a sick child was taken to multiple sources, the public medical source took priority, followed by private medical and informal source.

Statistical analysis

This study employed a hierarchical Bayesian linear modelling approach to model trends in reported antibiotic use among children aged <5 years, accounting for uncertainty around estimates, as previously performed in other global trend analyses

(Moller et al., 2017; Chawanpaiboon et al., 2019). Computed antibiotic use prevalence for available country-years were logit transformed to ensure that predicted and fitted estimates always fell between 0 and 1 before regression models were run.

Supplementary Table 1 shows survey inputs into the statistical model by country and year. To generate estimates for country-years with no survey data, country-level socioeconomic, disease incidence, and health system covariates were used together with the estimated regional intercepts. These included: (1) Human Development Index (HDI) value (UNDP, 2018); (2) national population of children aged <5 years (UN-DESA, 2017); (3) national incidence rates of malaria, respiratory, and diarrheal infections for ages 0-4 years (Roth et al., 2018); and (4) national public and private health spending per capita (in international dollars), along with the regional estimates (WHO, 2018).

The posterior distributions of the model coefficients were simulated using the Markov Chain Monte Carlo method. This was used to generate predictions for all country-years from the estimated model parameters. A burn-in period of 30,000 samples and three chains each with a sample size of 10,000 were used. Non-informative priori was employed in this analysis. Country-level values for the proportion of reported antibiotic use for sick children aged <5 years were weighted to regional or country income groupings using national population estimates for children under 5 years. To reflect uncertainty around estimates for countries without data, random intercepts and slopes for these countries were simulated from the posterior means and covariance of country intercepts and slopes for countries with data. Uncertainty intervals were generated using weighted 10th and 90th percentiles of the posterior samples based on 30,000 posterior draws. Each country was classified according to its WHO regional grouping and World Bank income classification in each year during the study period, which was allowed to shift over time during the regression modelling process. For analyses by user characteristics, the same statistical approach described above was applied to the subset of observations in each grouping. For specific analyses in Africa and South-East Asia, the sample was limited to these two regions. Stata 15·1 (Stata Corp., College Station, TX) and R version 4·01 were used for this analysis (R Core Team, 2020).

Role of the funding source

The funders had no role in the study design, data collection, analysis, interpretation, manuscript preparation, or decision to publish. All authors had full access to all the data in the study, and accept responsibility to submit for publication.

Results

This study identified 365 surveys conducted between 01 January 2000 and 31 December 2017. Of these surveys, 314 had

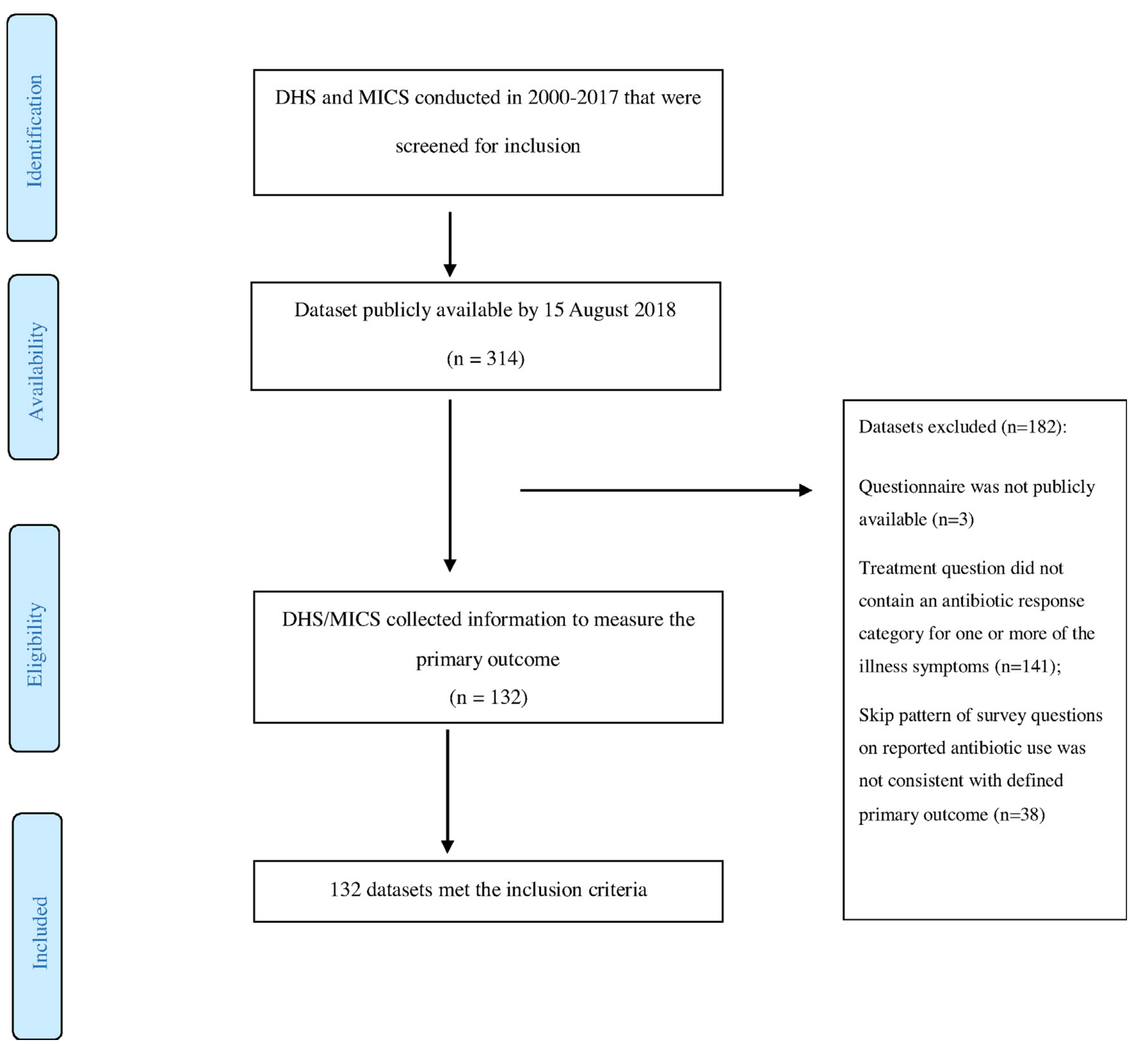

Table 1
User characteristics of sick children aged <5 years included in the study, from low-income and middle-income countries (LMICs), low-income countries, African LMICs, and South-East Asian LMICs.

	N (%) LMICs	N (%) Low-income countries	N (%) African LMICs	N (%) South-East Asian LMICs
Total	**443, 272 (100%)**	**177,849 (100%)**	**218,133 (100%)**	**92,054 (100%)**
Place of residence				
Rural	304,210 (68.6%)	137,297 (77.2%)	162,119 (74.3%)	65,728 (71.4%)
Urban	139,062 (31.4%)	40,552 (22.8%)	56,014 (25.7%)	26,326 (28.6%)
Healthcare source visited				
Public sector	160,439 (36.2%)	70,175 (39.5%)	87,169 (40.0%)	23,065 (25.1%)
Private medical	108,120 (24.4%)	28,026 (15.8%)	31,509 (14.4%)	43,260 (47.0%)
Informal source or did not seek care	168,886 (38.1%)	76,934 (43.3%)	94,857 (43.5%)	25,514 (27.7%)
Not reported	5,827 (1.3%)	2,714 (1.5%)	4,598 (2.1%)	215 (0.2%)
Maternal education				
None or some primary	130,638 (29.5%)	73,764 (41.5%)	80,099 (36.7%)	24,594 (26.7%)
Primary complete or some secondary	148,418 (33.5%)	66,089 (37.2%)	89,619 (41.1%)	18,771 (20.4%)
Secondary complete or higher	156,836 (35.4%)	30,638 (17.2%)	48,398 (22.2%)	48,671 (52.9%)
Not reported	7,380 (1.7%)	7,358 (4.1%)	17 (0.01%)	18 (0.02%)
Household wealth				
Poorest	116,605 (26.3%)	43,554 (24.5%)	56,821 (26.1%)	22,310 (24.2%)
Poorer	101,563 (22.9%)	38,902 (21.9%)	49,357 (22.6%)	20,523 (22.3%)
Middle	88,862 (20.1%)	36,041 (20.3%)	43,415 (19.9%)	18,822 (20.5%)
Richer	76,064 (17.2%)	32,891 (18.5%)	38,194 (17.5%)	16,854 (18.3%)
Richest	59,083 (13.3%)	26,461 (14.9%)	30,346 (13.9%)	13,545 (14.7%)
Not reported	1,095 (0.3%)	..	..	..

datasets publicly available by 15 August 2018 and were eligible for screening. Three surveys were excluded because the questionnaires were not publicly available, 141 surveys were excluded because the treatment question did not contain an antibiotic response category for one or more symptoms, and 38 surveys were excluded because the skip pattern was not consistent with the defined primary outcome (Figure 1). Therefore, 132 surveys from 73 countries conducted during 2005-2017 met inclusion criteria (Figure 1). Of the 73 LMICs, 37 were African and 11 were South-East Asian countries, which together accounted for 83 of the 132 survey data points (Supplementary Table 2). Thirty-eight of the 73 LMICs had at least two survey data points (Supplementary Table 2).

A total of 1,507,521 children aged <5 years were surveyed across LMICs during 2005–2017. Of these observations, 443,272 were reported to have had either fever, diarrhea, or cough with fast or difficult breathing in the 2 weeks preceding the survey. Among these 443,272 observations, 304,210 (68.6%) lived in rural areas, 116,605 (26.3%) came from the poorest household wealth quintile, 156,836 (35.4%) had mothers with secondary or higher education, and 160,439 (36.2%) were taken to a public medical source for healthcare (Table 1). Observed trends in reported antibiotic use for sick children aged <5 years during 2005-2017 are presented: i) across LMICs, ii) in low-income countries (LICs), and iii) in the African and South East Asian regions.

Trends across low-income and middle-income countries

Across LMICs, modelled estimates indicated that the greatest relative increases in reported antibiotic use for sick children aged <5 years during 2005–2017 occurred in rural areas, poorest wealth quintiles, and populations with the lowest maternal education levels, and that these trends were most prominent in LICs and the South-East Asian region (Table 2). Specifically, across LMICs, there was a 33% relative increase in the outcome in rural areas from 30.0% (UI: 9.0%–63.7%) in 2005 to 39.9% (UI: 14.4%–76.2%) in 2017, compared to a 21% relative increase in urban areas (Table 2). Among the poorest wealth quintile, there was a 30% relative increase from 27.1% (UI: 9.0%–53.6%) in 2005 to 35.2% (UI: 14.3%–64.6%) in 2017, compared to a 17% gain for the richest wealth quintile. Despite these increases, reported antibiotic use for sick children aged <5 years remained highest in every year during the study period among those living in urban areas, richest households, with mothers having the highest education levels, and if taken to private medical sources for care (Figure 2).

Trends in low-income countries

Modelled estimates indicated that during 2005–2017, relative increases in the outcome were greater among the rural, poorest, and least educated populations in LICs than for LMICs on average (Table 2, Figure 3). Across LICs, rural areas experienced a 72% relative increase in reported antibiotic use among sick children aged <5 years from 17.8% (UI: 5.2%–44.9%) in 2005 to 30.6% (UI: 11.7%–62.1%) in 2017, compared to a 29% gain in urban areas across LICs (Table 2). In the poorest wealth quintile, there was a 67% relative increase from 16.6% (UI: 4.6%–40.6%) in 2005 to 27.6% (UI: 11.6%–55.8%) in 2017 compared to a 24% rise in the richest wealth quintile. Among sick children aged <5 years having mothers with the lowest education, there was a 72% relative increase from 16.6% (UI: 3.9%–44.8%) in 2005 to 28.5% (UI: 11.8%–56.7%) in 2017 compared to a 40% rise for those having mothers with the highest education levels. There were limited differences in the relative increases in reported antibiotic use for sick children aged <5 years by healthcare source visited in LICs during 2005–2017 (Table 2).

Trends in Africa and South-East Asia

Within countries in the WHO African and South-East Asian regions that constitute most LICs in this study, modelled estimates indicated that the relative gains in the outcome among rural children, the poorest, and those having mothers with the lowest education levels were greater in South-East Asian than African countries (Figure 4, Table 2). In South-East Asia in 2005-2017, rural areas experienced an 81% relative increase in reported antibiotic use among sick children aged <5 years from 25.9% (UI: 7.1%–73.0%) in 2005 to 46.8% (UI: 15.8%–93.0%) in 2017 compared to a 7% rise in South-East Asian urban areas. In comparison, rural African areas experienced a 28% relative increase from 24.0% (UI: 5.7%–56.9%) in 2005 to 30.8% (UI: 12.0%–61.0%) in 2017 compared to 19% rise in urban African areas. Similarly, for the poorest wealth quintile in

Table 2
Reported antibiotic use among sick children aged <5 years across low-income and middle-income countries in 2005 and 2017, by country income group and WHO region.

		Percentage of reported antibiotic use among sick children aged <5 years, mean (Uncertainty Interval (UI) 10th and 90th percentile)											
		LMIC		Low-income		Lower middle-income		Upper middle-income		African LMIC		SE Asian LMIC	
		2005	2017	2005	2017	2005	2017	2005	2017	2005	2017	2005	2017
Place of residence	Rural	30·0 (9·0–63·7)	39·9 (14·4–76·2)	17·8 (5·2–44·9)	30·6 (11·7–62·1)	26·1 (8·8–54·6)	30·5 (11·7–63·1)	45·9 (22·9–76·8)	57·3 (29·8–87·9)	24·0 (5·7–56·9)	30·8 (12·0–61·0)	25·9 (7·1–73·0)	46·8 (15·8–93·0)
	Urban	36·2 (13·0–68·7)	43·9 (17·4–77·9)	27·1 (8·7–58·2)	34·9 (13·3–67·3)	30·5 (11·0–59·1)	34·8 (14·4–66·0)	49·9 (25·9–79·2)	60·1 (32·5–89·1)	32·2 (9·0–65·8)	38·2 (15·7–70·1)	35·1 (12·9–77·4)	37·4 (8·8–85·4)
Household wealth	Lowest	27·1 (9·0–53·6)	35·2 (14·3–64·6)	16·6 (4·6–40·6)	27·6 (11·6–55·8)	23·4 (9·4–43·9)	26·0 (12·2–48·7)	41·8 (24·7–63·1)	52·1 (32·8–74·5)	19·4 (3·0–76·4)	29·0 (9·2–63·8)	20·8 (3·7–76·8)	46·2 (11·9–93·5)
	Second	29·9 (10·2–57·8)	38·8 (16·1–68·8)	18·5 (5·3–43·1)	31·9 (14·0–61·4)	25·0 (10·5–45·8)	27·7 (12·5–51·8)	46·6 (28·4–67·1)	57·0 (37·6–77·4)	21·5 (3·0–80·2)	33·1 (11·3–68·4)	24·1 (5·2–77·5)	49·2 (14·5–93·3)
	Middle	33·3 (12·3–60·2)	40·5 (17·5–69·2)	21·9 (7·7–47·1)	32·2 (14·9–59·9)	29·1 (12·1–50·9)	31·4 (14·9–55·2)	48·2 (29·4–68·9)	57·1 (37·6–77·7)	26·4 (4·4–84·6)	34·8 (12·2–70·5)	28·2 (6·6–80·1)	51·7 (15·5–93·6)
	Fourth	34·6 (13·1–61·5)	44·2 (20·4–71·4)	25·4 (9·3–52·9)	37·4 (17·5–65·2)	28·7 (11·5–51·5)	35·5 (17·5–59·5)	48·9 (29·7–69·6)	58·5 (38·8–78·9)	29·2 (4·9–86·6)	39·7 (14·4–75·2)	28·7 (6·2–82·5)	56·7 (19·0–94·6)
	Highest	39·2 (17·0–65·0)	46·0 (22·5–72·4)	31·7 (11·3–61·2)	39·4 (19·8–68·1)	33·0 (15·3–55·2)	36·8 (19·1–59·8)	51·9 (33·5–71·3)	60·5 (41–79·9)	35·2 (5·5–89·9)	44·4 (16·9–79·6)	36·1 (11·0–82·3)	41·8 (8·8–89·5)
Maternal education	None/some primary	33·3 (8·9–70·4)	38·7 (12·5–77·7)	16·6 (3·9–44·8)	28·5 (11·8–56·7)	31·4 (10·6–63·9)	23·2 (8·7–52·7)	51·9 (24·9–79·7)	64·6 (37·6–87·9)	24·6 (5·7–56·6)	27·8 (11·1–58·2)	23·7 (5·7–76·7)	40·5 (12·4–89·6)
	Primary complete/ some secondary	34·3 (10·3–67·4)	39·8 (15·6–73·3)	22·3 (6·2–52·8)	33·2 (14·7–62·2)	30·6 (9·9–61·1)	28·2 (11·1–56·3)	48·8 (25·1–75·8)	57·6 (32·2–83·5)	28·3 (7·1–60·0)	31·7 (14·5–58·4)	28·4 (8·9–76·8)	45·1 (17·3–89·8)
	Secondary complete or higher	37·8 (12·4–69·6)	45·4 (19·3–76·7)	29·2 (8·4–63·5)	40·8 (18·7–71·4)	31·4 (10·9–60·2)	34·4 (14·5–63·2)	51·4 (27·4–76·9)	59·8 (35·0–84·5)	37·8 (11·3–70·7)	39·5 (18·6–67·7)	32·8 (9·8–81·4)	49·4 (19·8–91·9)
Healthcare source visited	Public	46·0 (24·3–68·1)	54·3 (29·7–77·4)	40·9 (20·9–64·6)	51·6 (27·6–79·4)	39·0 (20·8–59·0)	44·5 (25·1–65·5)	56·9 (38·8–73·5)	65·5 (46·7–81·0)	46·0 (25·0–68·3)	48·9 (27·5–72·8)	36·2 (16·5–68·7)	54·6 (26·4–92·0)
	Private medical	50·5 (25·7–74·7)	58·2 (30·6–82·0)	44·3 (22·6–68·4)	56·0 (30·5–82·8)	39·4 (20·6–59·7)	43·3 (24·2–65·3)	65·9 (47·6–80·9)	73·0 (55·7–85·7)	48·7 (25·6–72·2)	51·8 (27·7–78·1)	35·9 (14·9–74·5)	56·8 (24·3–92·7)
	Informal source or no care sought	19·5 (7·6–39·0)	21·8 (8·6–45·4)	13·2 (4·8–29·6)	17·1 (6·9–38·4)	16·2 (7·6–30·0)	15·8 (7·3–30·6)	29·6 (17·5–46·2)	34·0 (19·5–53·4)	16·3 (6·3–34·8)	17·2 (6·7–39·6)	12·9 (4·6–39·6)	19·9 (8·4–49·2)

South-East Asia there was a 122% relative increase in the outcome from 20.8% (UI: 3.7%–76.8%) in 2005 to 46.2% (UI: 11.9%–93.5%) in 2017 compared to a 16% rise for the richest wealth quintile in this region. The poorest children in the African region had a 49% relative increase from 19.4% (UI: 3.0%–76.4%) in 2015 to 29.0% (UI: 9.2%–63.8%) in 2017, while the richest wealth quintile in this region experienced a 26% rise.

In South-East Asia, there was a 71% relative increase in reported antibiotic use among sick children aged <5 years with the least educated mothers, rising from 23.7% (UI: 5.7%–76·7%) in 2005 to 40.5% (UI: 12.4%–89·6%) in 2017 compared to a 51% gain among those with the most highly educated mothers. In Africa, the relative increase in the outcome was 13% among sick children aged <5 years with mothers having the lowest education levels from 24.6% (UI: 5.7%–56.6%) in 2005 to 27.8% (UI: 11.1%–58.2%) in 2017, compared to 4.5% for those having mothers with the highest education levels. For both Africa and South-East Asian countries, the outcome was similar among those taken to public facilities and private medical sources during the study period. In Africa, the relative increase in both groups during the study period was 6.3% (Table 2, Figure 4), while in South-East Asia the greatest relative increase (58%) was seen in private medical sources, rising from 35.9% (UI: 14.9%–74.5%) in 2005 to 56.8% (UI: 24.3%–92.7%) in 2017.

Discussion

Across LMICs during 2005-2017, this study found that the greatest relative increases in reported antibiotic use for sick children in LMICs were observed in rural areas, poorest households, and among those having mothers with the lowest education. This trend during the study period was most prominent in LICs and in the South-East Asian region. However, despite these increases, reported antibiotic use for sick children aged <5 years remained highest in each year during the study period among those living in urban areas, wealthiest households, having mothers with the highest education levels, and if taken to private medical sources for care. It is believed that this is the first study to investigate trends in reported antibiotic use among sick children aged <5 years across LMICs by user characteristics, in order to understand the determinants of the earlier documented upward trends in antibiotic consumption and reported use in LMICs since 2000 (Van Boeckel et al., 2014; Klein et al., 2018; Jackson et al., 2019; Allwell-Brown et al., 2020; Klein et al., 2020).

There are several reasons that could potentially explain these findings, particularly the increased reported antibiotic use among rural, poor, and least educated population groups during the study period. First, this period was marked by economic growth in some

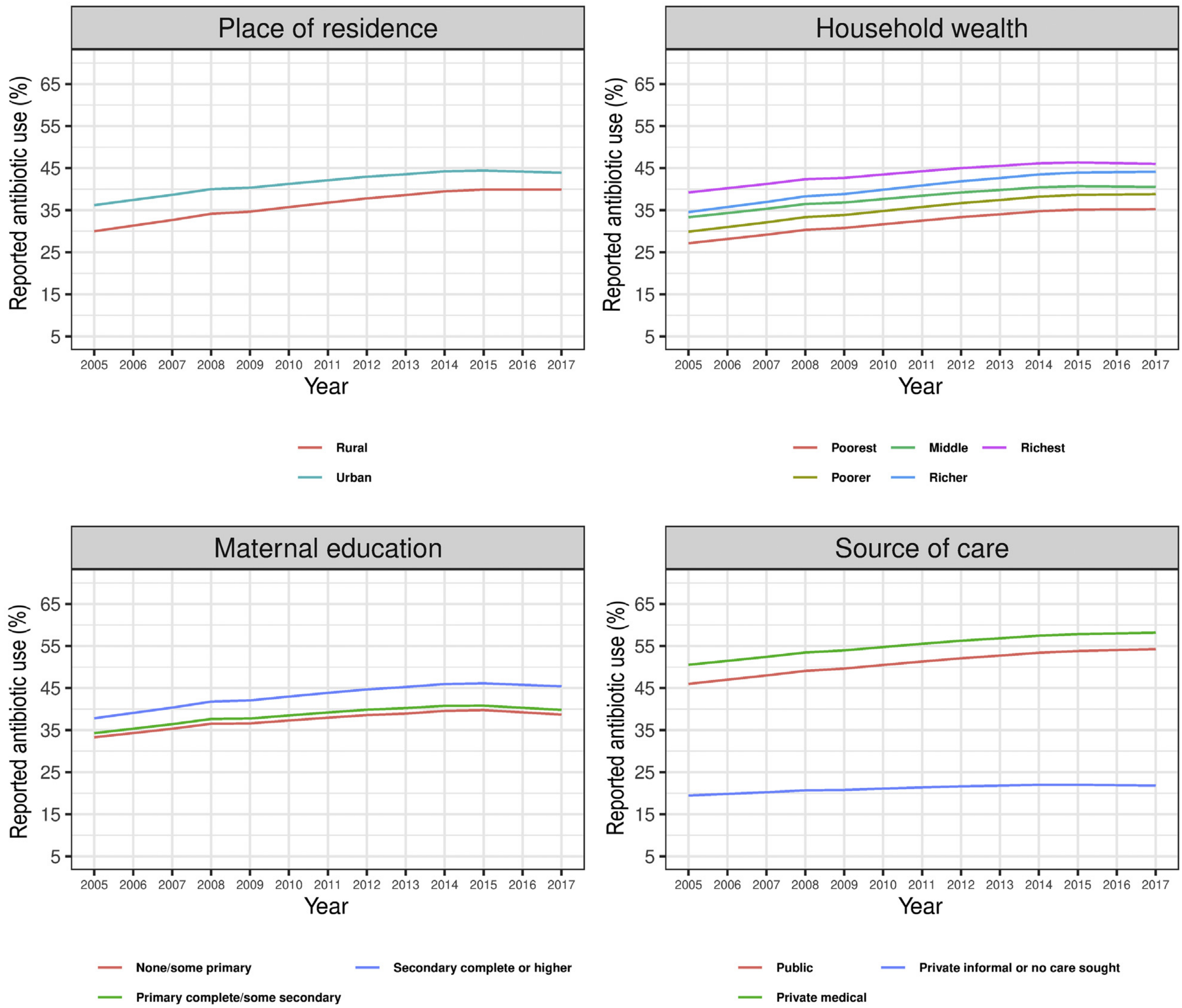

Figure 2. Trends in reported antibiotic use among sick children aged <5 years across low-income and middle-income countries in 2005-2017 by user characteristics. Note: Lines represent mean values for reported antibiotic use in specified user groups. 10^{th}-90^{th} percentile uncertainty intervals for percentage of reported antibiotic use for sick children in 2005 and 2017 are presented in Table 2, and values for all years are presented in Supplementary Table 3.

LMICs (Van Boeckel et al., 2014; Klein et al., 2018) that could have led to greater availability of medicines, and expansion of health services including the private sector. More so, declining poverty rates (World Bank, 2020) could imply increasing financial access to health services and essential medicines in LMIC populations. Second, many countries implemented programs to extend the reach of health services to underserved populations during this period (WHO, 2019; Wehrmeister et al., 2020): for example, the integrated community case management (iCCM) program aimed at extending the coverage of essential fever-care services to remote rural areas, including antibiotics for suspected pediatric pneumonia cases (Diaz et al., 2014). Third, and importantly, there has also been increasing availability of antibiotics in these settings (McGettigan et al., 2017; Malik and Figueras, 2019), especially in South-East Asia where the most substantial increases in reported antibiotic use were seen among sick children aged <5 years in the various user groups. While this indicates improving antibiotic access even among marginalized groups, the increasing antibiotic availability in South-East Asia could also raise concern, given the ubiquity and high levels of consumption of broad-spectrum antibiotics in the region (Nguyen et al., 2020; Do et al., 2021). The current estimates for South-East Asia are largely driven by trends in India, which is one of the world's leading countries in antibiotic production and sales (McGettigan et al., 2017). Several studies have documented large increases in antibiotic consumption in India since 2000 (Van Boeckel et al., 2014; Farooqui et al., 2018; Klein et al., 2018; Klein et al., 2020), although one study showed that despite these increases, antibiotic consumption rates in India remained lower than average consumption in European countries (Farooqui et al., 2018).

The current results are in line with findings from other analyses of trends in related child health indicators in LMICs during the same period, which also point to increasing antibiotic use in the same population groups (WHO, 2015; Liu et al., 2016; McAllister et al., 2019). For instance, one report showed faster increases in care-seeking for pneumonia symptoms in children aged <5 years in rural areas compared to urban areas during 2005–2013 (WHO, 2015), which could suggest increased antibiotic treatment for pneumonia symptoms in these settings. Another study found that countries in South-East Asia saw faster declines in mortality in children <5 years that was attributable to pneumonia during 2000–2015, compared to African countries (Liu et al., 2016). This difference in progress rate between the regions has partly been attributed to improved care-seeking and quality of hospital care for

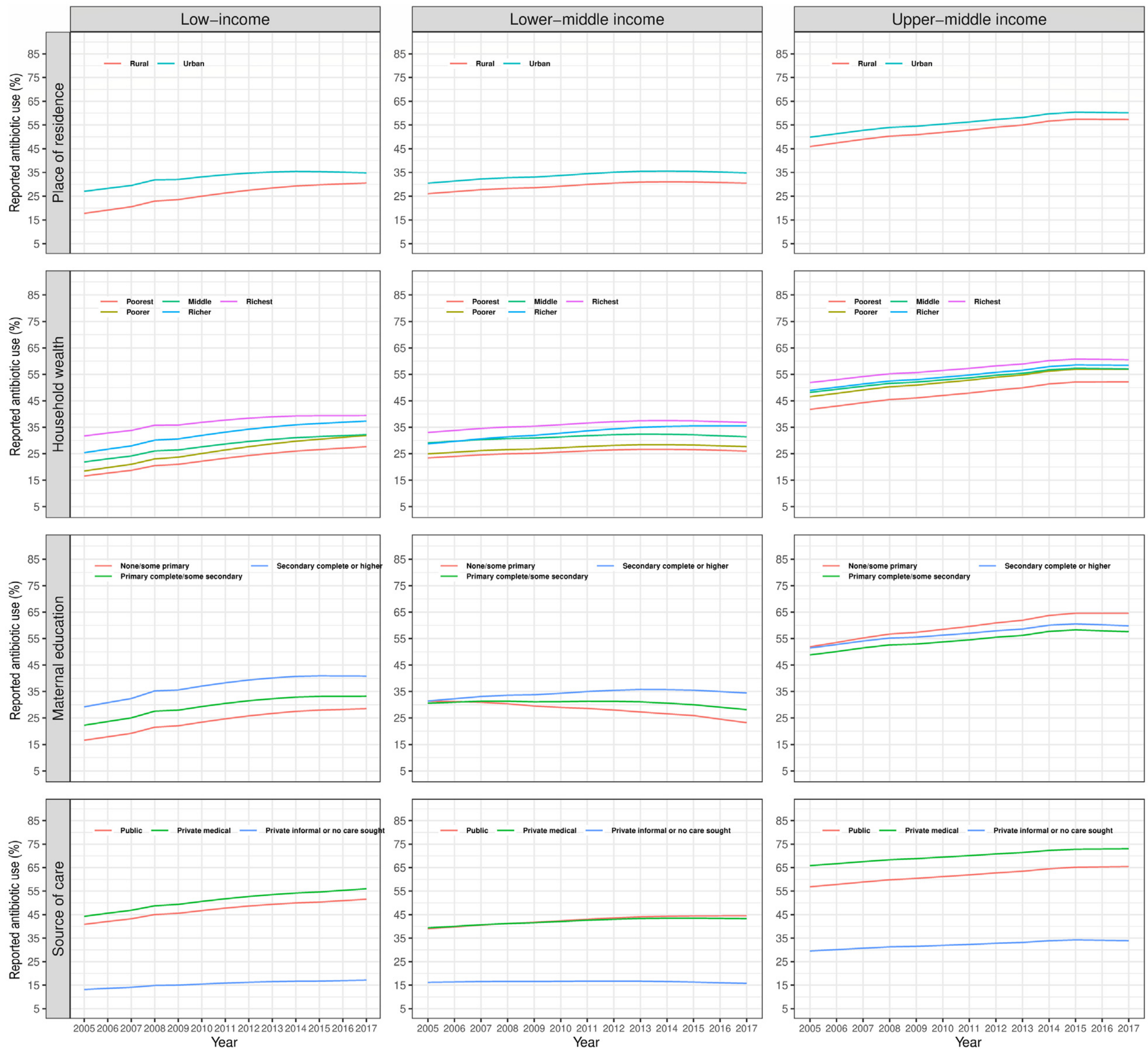

Figure 3. Trends in reported antibiotic use among sick children aged <5 years in low-income countries, lower-middle income countries, and upper-middle-income countries in 2005-2017 by user characteristics.

Note: Lines represent mean values for reported antibiotic use in specified user groups. 10th-90th percentile uncertainty intervals for percentage of reported antibiotic use for sick children in 2005 and 2017 are presented in Table 2, and values for all years are presented in Supplementary Table 4.

pneumonia symptoms [including antibiotic treatment] in South-East Asia (McAllister et al., 2019).

Although the current results indicate improved access to antibiotics in LMICs during the study period, field studies from African and South-East Asian settings suggest that this may be accompanied by inappropriate use, particularly among the rural, poor, and the least educated (Barker et al., 2017b; Barker et al., 2017a; Afari-Asiedu et al., 2018; Mboya et al., 2018; Afari-Asiedu et al., 2020; Nahar et al., 2020). Poorer populations may not typically purchase a full course of prescribed antibiotics (Barker et al., 2017b; Barker et al., 2017a; Mboya et al., 2018; Afari-Asiedu et al., 2020; Nahar et al., 2020) and are often reluctant to seek care from formal healthcare providers due to cost and distance barriers, or long waiting times (Barker et al., 2017a; Afari-Asiedu et al., 2018). Furthermore, the burden of sub-standard or falsified medicines disproportionately affects low socioeconomic status and rural populations, leading to higher treatment costs and even greater inequities (Evans et al., 2019). This implies that efforts to increase access to antibiotics in groups underserved by formal health services must go hand-in-hand with health systems strengthening initiatives to assure their quality and support their appropriate use. In addition, promoting immunization (Lewnard et al., 2020) and investing in infrastructure to improve sanitation and hygiene in these settings could lead to a reduction in infectious disease burden and need for antibiotics in LMICs (Klein et al., 2018).

This study was subject to some important limitations. First, it was unable to determine the appropriateness of the reported antibiotic use, as the surveys did not provide information on the etiologies of the reported illness symptoms, the type and dosage of antibiotics, and completion of the treatment course. Second, there could have been poor recall among respondents and therefore misclassification of medications used by sick children, which could have influenced the results in either direction. However, interview teams included trained medical personnel who helped to appropriately classify medications reported by respondents, which may have reduced such biases (USAID, 2018; UNICEF, 2019). In

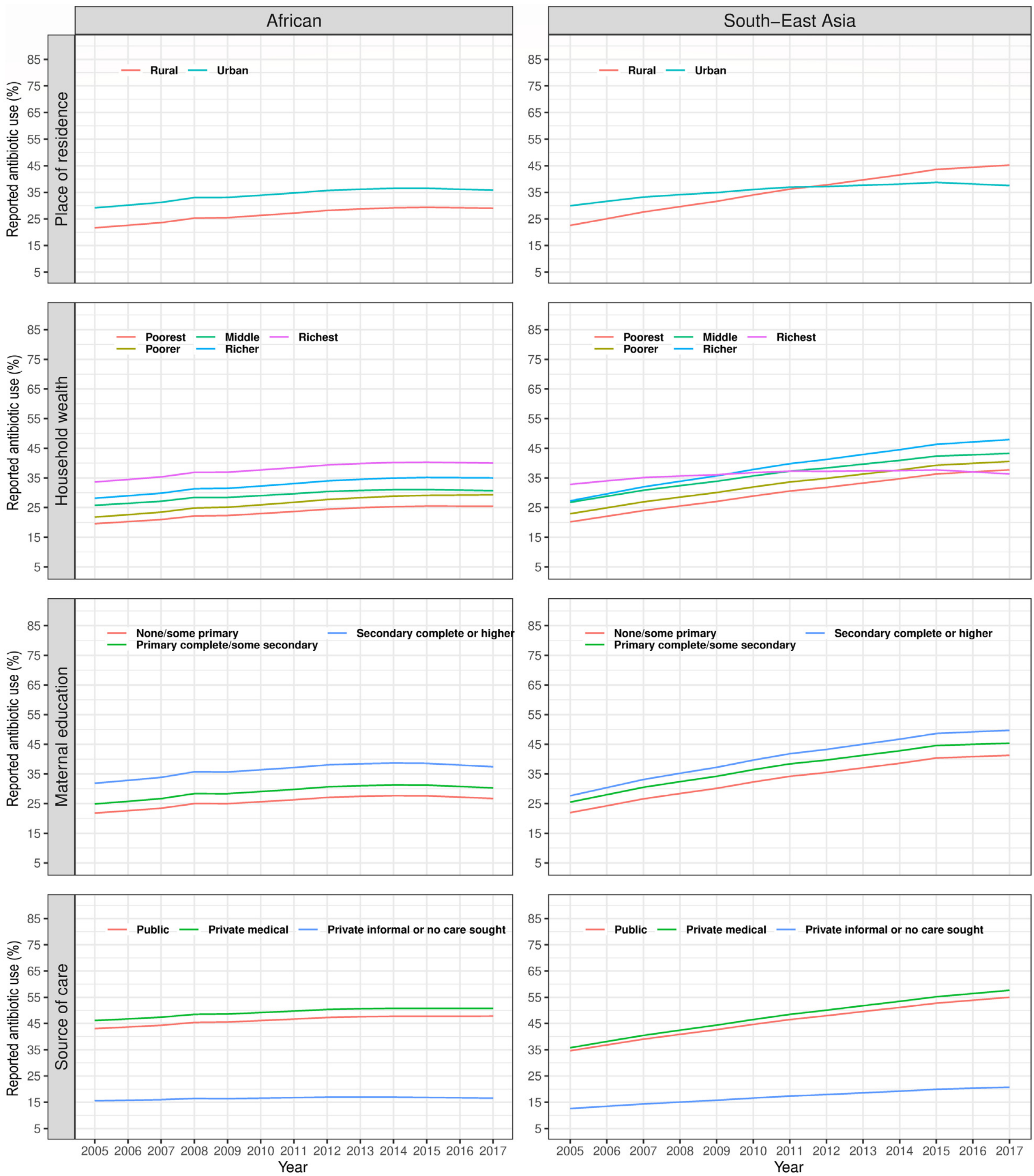

Figure 4. Trends in reported antibiotic use among sick children aged <5 years in World Health Organization regions Africa and South-East Asia in 2005-2017 by user characteristics.
Note: Lines represent mean values for reported antibiotic use in specified user groups. 10th-90th percentile uncertainty intervals for percentage of reported antibiotic use for sick children in 2005 and 2017 are presented in Table 2, and values for all years are presented in Supplementary Tables 5 and 6.

addition, it is not expected that recall behavior would have changed over time and impacted interpretation of trend results. Third, in the analyses of trends in reported antibiotic use by household wealth index, survey-specific wealth indices were used as a measure of relative economic status of children within their society at the time of the interview, rather than an absolute measure accounting for different poverty levels across all countries and years. Finally, and importantly, data were not available for all country-years in the study period; hence, modelling of the outcome was required to fill data gaps, leading to wide uncertainty intervals, so the results should be interpreted with caution. Countries with data contributed to the estimation of regional intercepts, which were used together with covariate coefficients such as the Human Development Index to estimate rates for countries without data. Hence, it was possible for countries with no data to mirror patterns of the regional estimates based on countries with data if the covariate patterns were similar. This data paucity problem is pervasive in such global trend analyses (Moller et al., 2017; Chawanpaiboon et al., 2019) and a similar statistical approach was employed to account for uncertainty around estimates due to missing data.

Conclusion

Based on 132 national surveys from 73 countries, this study examined trends in reported antibiotic use among sick children aged <5 years across LMICs during 2005–2017 by user characteristics. It found that during 2005–2017, the greatest relative increases in reported antibiotic use among sick children aged <5 years occurred in rural areas, poorest households, and among those with the least educated mothers who also had the lowest starting levels. This trend was most prominent in LICs and South-East Asia. Yet, despite these gains, reported antibiotic use for sick children aged <5 years remained highest in urban areas, wealthiest households, and most educated populations across LMICs during 2005–2017.

These results suggest that the increasing reported antibiotic use for sick children aged <5 years across LMICs during 2005–2017 was mainly driven by gains among population groups often under-served by formal health services. Observational studies in primary care and community settings are needed to understand the appropriateness of antibiotic use among population groups that are increasingly gaining access to antibiotics.

Author contributions

GA-B, LH-A, and EWJ designed and conceptualized the study. GA-B, LH-A, and EWJ compiled and prepared the data. LH-A and MOS analyzed the data. GA-B, LH-A, MOS, FEK, SS, AM, and EWJ contributed to interpretation of findings. GA-B and EWJ wrote the first draft of the paper. GA-B, LH-A, MOS, FEK, SS, AM, and EWJ reviewed, revised, and contributed writing to the paper. All authors read and approved the final manuscript.

Data sharing

The data that support the findings of this study are publicly available from The DHS Program at https://dhsprogram.com.

Declarations of interest

All authors declare no competing interests.

Funding

Uppsala Antibiotic Center and Uppsala University.

Ethical approval

This study used open-access datasets. Procedures for ethical approval are available at https://dhsprogram.com.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.05.058.

References

Afari-Asiedu S, Kinsman J, Boamah-Kaali E, Abdulai MA, Gyapong M, Sankoh O, et al. To sell or not to sell; the differences between regulatory and community demands regarding access to antibiotics in rural Ghana. J Pharm Policy Pract 2018;11(1):30.

Afari-Asiedu S, Oppong FB, Tostmann A, Ali Abdulai M, Boamah-Kaali E, Gyaase S, et al. Determinants of inappropriate antibiotics use in rural Central Ghana using a mixed methods approach. Front Public Health 2020;8:.

Allwell-Brown G, Hussain-Alkhateeb L, Kitutu FE, Strömdahl S, Mårtensson A, Johansson EW. 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):e799–807.

Barker AK, Brown K, Ahsan M, Sengupta S, Safdar N. Social determinants of antibiotic misuse: a qualitative study of community members in Haryana. India. BMC Public Health 2017a;17(1).

Barker AK, Brown K, Ahsan M, Sengupta S, Safdar N. What drives inappropriate antibiotic dispensing? A mixed-methods study of pharmacy employee perspectives in Haryana. India. BMJ Open 2017b;7(3).

Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health 2019;7(1):e37–46.

Diaz T, Aboubaker S, Young M. Current scientific evidence for integrated community case management (iCCM) in Africa: findings from the iCCM Evidence Symposium. J Glob Health 2014;4(2)020101.

Do NTT, Vu HTL, Nguyen CTK, Punpuing S, Khan WA, Gyapong M, 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):e610–709.

Evans DR, Higgins CR, Laing SK, Awor P, Ozawa S. Poor-quality antimalarials further health inequities in Uganda. Health Policy Planning 2019;34(Supplement_3): iii36–47.

Farooqui HH, Selvaraj S, Mehta A, Heymann DL. Community level antibiotic utilization in India and its comparison vis-à-vis European countries: evidence from pharmaceutical sales data. PLoS One 2018;13(10).

Filmer D, Pritchett LH. Estimating wealth effects without expenditure data—or tears: an application to educational enrollments in states of India. Demography 2001;38(1):115–32.

Heyman G, Cars O, Bejarano M-T, Peterson S. Access, excess, and ethics—towards a sustainable distribution model for antibiotics. Ups J Med Sci 2014;119(2):134–41.

Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet 2016;387(10014):176–87.

Jackson C, Hsia Y, Bielicki JA, Ellis S, Stephens P, Wong ICK, et al. Estimating global trends in total and childhood antibiotic consumption, 2011-2015. BMJ Glob Health 2019;4(1)e001241.

Klein EY, Milkowska-Shibata M, Tseng KK, Sharland M, Gandra S, Pulcini C, et al. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: an analysis of pharmaceutical sales data. Lancet Infect Dis 2020;21 (1):107–15, doi:http://dx.doi.org/10.1016/S1473-3099(20)30332-7.

Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A 2018;115(15):E3463–e70.

Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J-A, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. Lancet 2016;387 (10014):168–75.

Lewnard JA, Lo NC, Arinaminpathy N, Frost I, Laxminarayan R. Childhood vaccines and antibiotic use in low- and middle-income countries. Nature 2020;581 (7806):94–9.

Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet 2016;388 (10063):3027–35.

Malik F, Figueras A. Analysis of the antimicrobial market in Pakistan: is it really necessary such a vast offering of “watch” antimicrobials?. Antibiotics (Basel) 2019;8(4):189.

Mboya EA, Sanga LA, Ngocho JS. Irrational use of antibiotics in the Moshi Municipality Northern Tanzania: a cross sectional study. Pan Afr Med J 2018;31:165.

McAllister DA, Liu L, Shi T, Chu Y, Reed C, Burrows J, 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. Lancet Glob Health 2019;7(1):e47–57.

McGettigan P, Roderick P, Kadam A, Pollock AM. Access, watch, and reserve antibiotics in India: challenges for WHO stewardship. Lancet Glob Health 2017;5(11):e1075–6.

Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health 2014;2:145.

Moller A-B, Petzold M, Chou D, Say L. Early antenatal care visit: a systematic analysis of regional and global levels and trends of coverage from 1990 to 2013. Lancet Glob Health 2017;5(10):e977–83.

Nahar P, Unicomb L, Lucas PJ, Uddin MR, Islam MA, Nizame FA, et al. What contributes to inappropriate antibiotic dispensing among qualified and unqualified healthcare providers in Bangladesh? A qualitative study. BMC Health Serv Res 2020;20(1):656.

Nguyen NV, Do NTT, Nguyen CTK, Tran TK, Ho PD, Nguyen HH, et al. Community-level consumption of antibiotics according to the AWaRe (Access, Watch, Reserve) classification in rural Vietnam. JAC-Antimicrobial Resistance 2020;2(3).

Pokharel S, Raut S, Adhikari B. Tackling antimicrobial resistance in low-income and middle-income countries. BMJ Glob Health 2019;4(6)e002104.
PRISMA. Transparent Reporting of Systematic Reviews and Meta-analyses. 2015 Available from: http://www.prisma-statement.org/. [Accessed 27 January 2019].
R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1736–88.
Rutstein SO, Johnson K. The DHS wealth index. DHS Comparative Reports No 6. Calverton. Maryland, USA: ORC Macro; 2004.
So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ. Part 5: the access and excess dilemma. “Antibiotic resistance—the need for global solutions”. Lancet Infect Dis 2013;13(12):1057–98.
Sulis G, Gandra S. Access to antibiotics: not a problem in some LMICs. Lancet Glob Health 2021;9(5):e561–2.
Sultana M, Sarker AR, Sheikh N, Akram R, Ali N, Mahumud RA, et al. Prevalence, determinants and health care-seeking behavior of childhood acute respiratory tract infections in Bangladesh. PLoS One 2019;14(1).
UN-DESA. World population prospects: the 2017 revision. New York: United Nations Population Division; 2017.
UNDP. Human development indices and indicators: 2018 statistical update. New York: UNDP; 2018.
UNICEF. Multiple Indicator Cluster Surveys. 2019 Available from: https://mics.unicef.org/. [Accessed 25 June 2018].
USAID. The DHS Program. 2018 Available from: https://dhsprogram.com/. [Accessed 25 June 2018].
Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 2014;14(8):742–50.
Van Malderen C, Amouzou A, Barros AJD, Masquelier B, Van Oyen H, Speybroeck N. Socioeconomic factors contributing to under-five mortality in sub-Saharan Africa: a decomposition analysis. BMC Public Health 2019;19(1):760.
Wehrmeister FC, Fayé CM, da Silva ICM, Amouzou A, Ferreira LZ, Jiwani SS, et al. Wealth-related inequalities in the coverage of reproductive, maternal, newborn and child health interventions in 36 countries in the African region. Bull World Health Organ 2020;98(6):394–405.
WHO. State of inequality: reproductive, maternal, newborn and child health. Geneva: World Health Organization; 2015.
WHO. Global health expenditure database. Geneva: World Health Organization; 2018.
WHO. Review of 40 years of primary health care implementation at country level. Geneva: World Health Organization; 2019.
World Bank. World Bank bountry and lending groups; Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. [Accessed 1 April 2020].
World Bank. Poverty and shared prosperity 2020: reversals of fortune. Overview booklet. Washington, DC: World Bank; 2020.
Yaya S, Uthman OA, Okonofua F, Bishwajit G. Decomposing the rural-urban gap in the factors of under-five mortality in sub-Saharan Africa? Evidence from 35 countries. BMC Public Health 2019;19(1):616.