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Original article

Antibiotic use prior to seeking medical care in patients with persistent fever: a cross-sectional study in four low- and middle-income countries

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ABSTRACT

Objectives: Community-level antibiotic use contributes to antimicrobial resistance, but is rarely monitored as part of efforts to optimize antibiotic use in low- and middle-income countries (LMICs). We investigated antibiotic use in the 4 weeks before study inclusion for persistent fever.

Methods: The NIDIAG-Fever (Neglected Infectious diseases DIAGnosis-Fever) study investigated aetiologies of infections in patients ≥5 years old with fever ≥1 week in six healthcare facilities in Cambodia, the Democratic Republic of the Congo (DRC), Nepal, and Sudan. In the present nested cross-sectional study, we describe prevalence and choice of antibiotics before and at study inclusion, applying the Access/Watch/Reserve (AWaRe) classification of the WHO List of Essential Medicines. Factors associated with prior antibiotic use were analysed.

Results: Of 1939 participants, 428 (22.1%) reported the prior use of one or more antibiotics, ranging from 6.3% (24/382, Cambodia) to 35.5% (207/583, Nepal). Of 545 reported antibiotics, the most frequent were Watch group antibiotics (351/545, 64.4%), ranging from 23.6% (DRC) to 82.1% (Nepal). Parenteral administration ranged from 5.9% to 69.6% between study sites. Antibiotic use was most frequent among young patients (5–17 years of age; risk ratio 1.42, 95%CI 1.19–1.71) and men (RR 1.29; 95%CI 1.09–1.53). No association was found with specific symptoms. Of 555 antibiotics started before study inclusion, 275 (49.5%) were discontinued at study inclusion.

Conclusions: Watch antibiotics were frequently used, and discontinued upon study inclusion. The antibiotic use frequency and choice varied importantly between LMICs. Data on local antibiotic use are essential to guide efforts to optimize antibiotic use in LMICs, should not be restricted to hospitals, and need to take local healthcare utilization into account. **Brecht Ingelbeen, Clin Microbiol Infect 2021;27:1293**

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Introduction

Antibiotic use is associated with the development and spread of bacterial resistance to antibiotics (AMR). Monitoring antibiotic use is one of five objectives of the World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance [1]. Low- and middle-income countries (LMICs) are hit hardest by AMR infections in terms of incidence of infections prone to AMR, and in terms of the AMR prevalence among underlying pathogens [2–5]. The most critical AMR pathogens are typically community-acquired [6–8], and up to 80% of healthcare is sought outside official healthcare facilities at private pharmacies or clinics, or informal drug sellers [9–11]. Although such antibiotic use without established diagnosis increases the risk of acquiring an AMR infection, current efforts to rationalize antibiotic use in LMICs focus exclusively on secondary or tertiary care hospitals [12]. In many high-income and some middle-income countries, nationwide human antibiotic use has been estimated from wholesaler sales data, thus considering the 'official' medicine supply chain [13,14]. In LMICs, official antibiotic use is currently not systematically monitored, let alone use of antibiotics from private or informal healthcare providers at community level.

To facilitate monitoring of antibiotic use, since 2017 the WHO categorized the antibiotics on the Essential Medicines List into three groups using the Access/Watch/Reserve (AWaRe) classification: 'Access' corresponds to antibiotics for empirical treatment of the most common or severe clinical syndromes, widely accessible at all healthcare levels; 'Watch' includes the highest priority antibiotics, most at risk of becoming ineffective due to increasing AMR, to be actively monitored; and 'Reserve' are last-resort antibiotics restricted to specific healthcare levels [15,16].

The Neglected Infectious Diseases DIAGnosis-Fever (NIDIAG-Fever) study investigated the aetiologies of infections in patients with persistent fever admitted to hospitals in four LMICs (ClinicalTrials.gov NCT01766830; http://www.nidiag.eu). We estimated and compared patients' antibiotic use prior to study inclusion, identified factors associated with community- or primary-care-level use of antibiotics, and analysed how that related to empirical antibiotic treatment in hospitals.

Methods

Patient population

All participants to the NIDIAG-Fever study were included for this nested cross-sectional study of antibiotic use. Inclusion criteria were: fever ≥1 week, age ≥5 years (≥18 years in Cambodia), no existing laboratory confirmed diagnosis at the time of consultation/admission to the hospital. Patients in need of immediate intensive care were excluded. Both hospitalized and ambulatory patients could be included in the study and were evaluated for a pre-established set of priority infections [17].

Study setting

Patients were recruited in six study sites in four countries (Table 1) between January 2013 and October 2014 (For NIDIAG-Fever data collection procedures, see Supplementary Material Text S1.).

Data analysis

We considered as *antibiotic use prior to study inclusion* any antibacterial for systemic use (Anatomical Therapeutic Chemical (ATC) classification subgroup J01) started between 28 days and 1 day before enrolment. We also included reported antibiotics with a missing starting date. Any antibacterial used on day 0 or day 1 after study inclusion was considered *antibiotic use at study inclusion*. We excluded antibiotics for systemic use that could also be used for the treatment of tuberculosis (TB) (e.g. streptomycin) in patients with active TB. For metronidazole, we considered only oral and parenteral administration as antibiotic use, according to the WHO Essential Medicines List [16]. Antibiotic names that could not be recalled were completed by asking relatives, showing pictures of packages of circulating antibiotics, or through home visits to retrieve the medicine packages or prescriptions (DRC and Nepal), or they were recorded as 'not specified' antibiotics (Sudan). In the DRC and Sudan, antibiotics for which the name or brand could not be recalled were still recorded, but as 'not specified'. This was not done in Cambodia and Nepal, where medicines of which the name or brand could not be recalled were not recorded.

We described the frequency and choice of antibiotic use prior to study inclusion by antibiotic class, by AWaRe group, and by route of administration, comparing between countries and age groups. We used a rank-sum test to compare the time (days) from initiating antibiotic use to study inclusion. We calculated three metrics to monitor antibiotic use, proposed by Hsia et al.: the percentage of amoxicillin, the percentage of Access antibiotics, and the ratio of Access to Watch antibiotics used (access-to-watch index) [18]. The association between characteristics, clinical symptoms and signs and (Watch group) antibiotic use prior to study inclusion was

Table 1
Study site and country characteristics

Country	Cambodia	DRC	Nepal	Sudan
Study site	Sihanouk Hospital Center of HOPE, Phnom Penh	1) Hôpital Général de Mosango, Kwilu Province 2) Centre de Santé de Kasay, Kwilu Province	1) Dhankuta District Hospital, Dhankuta District 2) B P Koirala Institute of Health Sciences (BPKIHS), Dharan, Sunsari District	Tabarak Allah Hospital, Gedaref Province
Type of health facility	Urban, NGO-supported referral hospital for HIV and TB care for adults	1) Rural district hospital 2) Rural health centre	1) Rural district hospital 2) Urban referral hospital	Rural NGO-supported district hospital
GDP per capita, 2014 (in constant 2010 USD)	972.7	397.3	711.3	1825.5
Human Development Index, 2014	0.558	0.425	0.555	0.488
Life expectancy, 2014	68.0	60.1	70.0	67.6
Median age of the population, 2015	23.9	16.8	23.2	18.9

Sources: World Bank national accounts data, OECD National Accounts data files, Gapminder foundation. http://gapm.io/ilex. DRC, the Democratic Republic of the Congo.

analysed in univariable and multivariable analysis, using negative binomial regression. We adjusted for two potential confounders: age group (5–17 years, 18–64 years, ≥65 years) and country. Finally, we compared the distribution of antibiotics by AWaRe group prior to and at study inclusion.

Ethical considerations

The NIDIAG-Fever study protocol was approved by the ITM Institutional Review Board, the University of Antwerp Ethical Committee (EC), Belgium, the National EC for Health Research, Cambodia, the Nepal Health Research Council, the EC of the University of Khartoum, Sudan, the National Research Ethics Review Committee, Sudan, and the University of Kinshasa School of Public Health EC, DRC. Study participants provided written informed consent, stating that the clinical data could be used for studies beyond the primary NIDIAG study objectives.

Results

Participant characteristics

Of 1939 study participants, 382 (19.7%) were from Cambodia, 300 (15.5%) from the DRC, 583 (30.1%) from Nepal and 674 (34.8%) from Sudan. Children or adolescents (aged 5–17 years) were included in the DRC (137, 45.7%), Nepal (107, 18.4%) and Sudan (135, 20.0%) (Table 2). Along with age, the frequency of chronic conditions differed between the study sites. Underlying non-communicable diseases (NCDs) (17.3%) and HIV co-infection (7.1%) were frequently reported at the Cambodian site. Active TB was reported by patients in Cambodia (1.8%) and at BP Koirala Institute of Health Sciences in Nepal (BPKIHS, 0.7%).

Antibiotic use prior to consultation or admission for persistent fever

Overall, 428 patients (22.1%) reported the use of one or more antibiotics prior to study inclusion: 24 (6.3%) in Cambodia, 29 (9.7%) in the DRC, 207 (35.5%) in Nepal, and 168 (24.9%) in Sudan; 151 (35.3%) of these patients used more than one antibiotic prior to study inclusion. Use of multiple antibiotics was especially frequent in Nepal (96 patients, 46.8%) and Cambodia (ten, 41.7%), followed by the DRC (nine, 31.0%) and Sudan (36, 21.4%).

Of patients reporting antibiotic use prior to study inclusion at the study site, 362 (84.6%) patients were able to specify which antibiotic they used. Specifics on antibiotic names were obtained from all patients reporting antibiotic use in Cambodia and Nepal, from 27 patients (93.1%) in the DRC and 104 (61.9%) in Sudan. Of 545 reported antibiotics, cephems (185, 33.9%), fluoroquinolones (92, 16.9%), macrolides (77, 14.1%), and β-lactamase-labile penicillins (70, 12.8%) were most frequently used. Use of cephems was highest in Nepal (154, 44.5%) and consistent among patients from both study sites (45.2% at BPKIHS and 33.3% at Dhankuta Hospital). In other countries, cephem use was lower: 10.5% in the DRC, 14.8% in Sudan, and 23.1% in Cambodia. Use of fluoroquinolones ranged between 7.9% of antibiotics used in the DRC and 20.5% in Cambodia. Use of macrolides ranged between 4.1% in Sudan and 18.8% in Nepal. While β-lactamase-labile penicillins were the most frequently used antibiotic class in Sudan (40.2%), they were rarely used in Cambodia (2.6%) and Nepal (4.0%). However, amoxicillin was used in combination with a β-lactamase inhibitor (β-lactam combination) in 17.9% of patients in Cambodia and 4.6% in Nepal. Metronidazole (nitroheterocyclics class; active on anaerobic bacteria and protozoa) was the most frequently used antibiotic in the DRC (34.2%) but was hardly used in Nepal (1.7%) or Cambodia (2.6%). Carbapenems (imipenem) were used by one patient in Nepal (0.3%). Glycopeptides (vancomycin) were used by three patients, all in Nepal (0.9%).

Oral (335, 60.4%) and parenteral administration (220, 39.6%) was reported. The proportion of parenteral administration varied widely between sites, and also within countries; in the DRC it ranged from 5.9% to 69.6%, in Nepal from 9.5% to 51.6%, in Sudan it was 27.6% and in Cambodia 35.9% (Fig. 1).

Distribution of AWaRe antibiotics

When classifying the antibiotics by AWaRe group, 188 (34.5%) were Access antibiotics. Most frequently reported were Watch antibiotics (351, 64.4%). Use of Watch antibiotics was highest in

Table 2
Reported characteristics of NIDIAG-Fever (Neglected Infectious diseases DIAGnosis-Fever) study participants, by study site

Country		Cambodia		DRC				Nepal				Sudan	
Site		Sihanouk hospital (*n* = 382)		Mosango hospital (*n* = 213)		Kasay health centre (*n* = 87)		BPKIHS (N = 430)		Dhankuta hospital (*n* = 153)		Tabarak allah hospital (*n* = 674)	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age group	5–17 years	0[a]	0.0	85	39.9	52	59.8	87	20.2	20	13.1	135	20.0
	18–64 years	319	83.5	124	58.2	33	37.9	307	71.4	113	73.9	493	73.1
	65+ years	63	16.5	4	1.9	2	2.3	36	8.4	20	13.1	46	6.8
Sex	Female	195	51.0	115	54.0	49	56.3	176	40.9	78	51.0	386	57.3
	Male	187	49.0	98	46.0	38	43.7	254	59.1	75	49.0	288	42.7
Co-morbidity	NCD	66	17.3	14	6.6	6	6.9	27	6.3	0	0.0	33	4.9
	HIV+	27	7.1	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0
	Tuberculosis[b]	7	1.8	0	0.0	0	0.0	3	0.7	0	0.0	0	0.0
Clinical symptom or sign	Anorexia/cachexia	306	80.1	81	38	41	47.1	224	52.1	31	20.3	464	68.8
	Respiratory	243	63.6	53	24.9	19	21.8	131	30.5	58	37.9	315	46.7
	Digestive (other)	141	36.9	63	29.6	28	32.2	97	22.6	9	5.9	332	49.3
	Headache	150	39.3	53	24.9	27	31	102	23.7	28	18.3	268	39.8
	Urinary	40	10.5	3	1.4	2	2.3	30	7	2	1.3	185	27.4
	Skin problem (incl. rash)	66	17.3	12	5.6	4	4.6	36	8.4	0	0	113	16.8
	Tonsillitis/pharyngitis	29	7.6	10	4.7	4	4.6	29	6.7	21	13.7	128	19
	Diarrhoea	33	8.6	9	4.2	4	4.6	17	4	0	0	73	10.8
	Jaundice	23	6	8	3.8	2	2.3	10	2.3	0	0	4	0.6

Co-morbidities were self-reported medical history. NCD, non-communicable disease; DRC, the Democratic Republic of the Congo.
[a] Children 5–17 years old were not included in the study in Cambodia.
[b] Active tuberculosis.

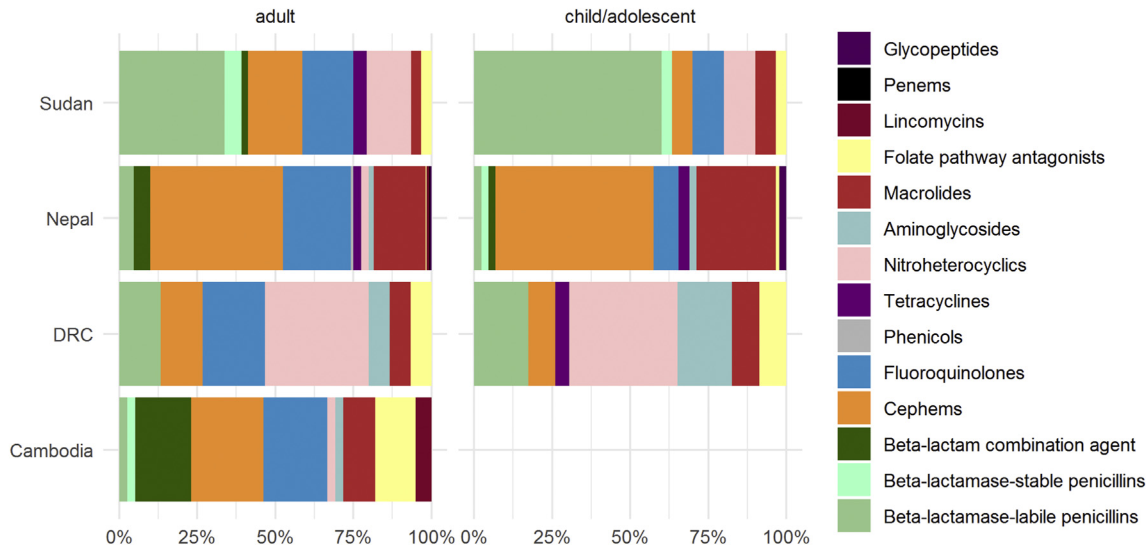

Fig. 1. Distribution of antibiotic classes used 28 days prior to study inclusion, by country and by age group (5–17 years, ≥18 years). Non-specified antibiotics ($n = 87$) are excluded.

Nepal (284, 82.1%), with ceftriaxone (97), cefixime (45) and ofloxacin (38) as main contributors, followed by Cambodia (20, 51.2%), Sudan (38, 31.1%) and DRC (9, 23.6%). Ceftriaxone (cephem), azithromycin (macrolide), ciprofloxacin, ofloxacin (fluoroquinolones) and cefixime (cephem) were all used more frequently than any Access antibiotic. One (0.2%) Reserve antibiotic was used: cefepime (fourth-generation cephem) in Cambodia. Five (0.9%) did not belong to the WHO essential medicines list and were therefore not classified (two oral cefuroxime, one parenteral lincomycin, one oral lincomycin, and one oral tetracycline) (Fig. 2).

Among adults, amoxicillin percentages were 2.6% (Cambodia), 13.3% (DRC), 3.9% (Nepal) and 10.9% (Sudan), Access percentages were 41.0% (Cambodia), 66.7% (DRC), 18.5% (Nepal) and 65.2% (Sudan), and access-to-watch indices were 0.8 (Cambodia), 2.0 (DRC), 0.2 (Nepal) and 1.9 (Sudan). Among adolescents, amoxicillin percentages were 8.6% (DRC), 2.2% (Nepal) and 2.7% (Sudan), Access percentages were 82.6% (DRC), 13.8% (Nepal) and 76.7% (Sudan), and access-to-watch indices were 4.8 (DRC), 0.2 (Nepal) and 3.3 (Sudan).

Time between initiating antibiotic use and consultation/admission with persistent fever

Patients started antibiotics a median 6 days prior to study inclusion (interquartile range (IQR) 3–11; range 1–28). This median time span between starting an antibiotic and study inclusion was 7 days (IQR 3–13) among adults and shorter, 5 days (IQR 2–8), among children and adolescents ($p < 0.01$). In Cambodia this median time span was 7 days (IQR 3–13), in the DRC 3 days (IQR 1–7), in Nepal 4 days (IQR 2–7), and in Sudan 9 days (IQR 6–16) (Fig. 3a). Access antibiotics were started a median 6 days (IQR 3–11) prior to study inclusion; Watch antibiotics 3 days (IQR 1–7) (Fig. 3b).

Factors associated with prior antibiotic use

Antibiotic use prior to study inclusion was more frequent in children and adolescents than in adults (adjusted risk ratio (aRR) 1.44, 95%CI 1.15–1.77), but threefold less in those over 65 years of age (aRR 0.37, 95%CI 0.20–0.61). Men reported prior antibiotic use more frequently than women (aRR 1.25, 95%CI 1.03–1.52). We found no clinical signs or symptoms to be strongly associated with antibiotic use prior to study inclusion. Patients with tonsillitis or pharyngitis reported prior antibiotic use most frequently (27.1%), but the association was not significant when controlling for age groups and study country (Table 3).

Among patients having used antibiotics prior to study inclusion, the use of Watch antibiotics was lower among children (48.3%) than among adults (61.2%, RR 0.79, 95%CI 0.64–0.97), and slightly higher among male (63.0%) than among female patients (51.3%, RR 1.23, 95%CI 1.04–1.45). We found no clinical sign or symptom to be associated with the use of Watch antibiotics (see Supplementary Material Table S3).

Changes in antibiotic use at study inclusion

Of 555 antibiotic courses used prior to study inclusion, 275 (49.5%) were discontinued and not replaced with an antibiotic at study inclusion, ranging from 29.3% (Sudan) to 68.0% (Nepal). Watch antibiotics were more frequently (60.1%) discontinued and not replaced than Access antibiotics (47.9%). Moreover, 16.0% of prior Watch antibiotics were replaced by Access antibiotics at study inclusion (see Supplementary Material Fig. S4). If an antibiotic was used at study inclusion, 121 (43.2%) were Access and 158 (56.4%) were Watch antibiotics. No Reserve antibiotics were initiated or continued at study inclusion (Fig. 4).

Discussion

We found that two thirds of antibiotics used by patients with persistent fever at community or primary healthcare level in four LMICs were Watch antibiotics—most threatened to become ineffective due to AMR—ranging from 23.6% in the DRC to 82.1% in Nepal; 40% of the antibiotics were administered intravenously. The use of first-choice antibiotics for primary care, such as amoxicillin, was below 15% in all study countries and across age groups. That we observed no differences between clinical presentations could indicate that such antibiotic use is based on availability rather than on the presenting syndrome. One in two antibiotic courses started prior to study inclusion, and even 60.1% of Watch antibiotics were discontinued following a consultation by a qualified healthcare worker, despite study clinicians frequently having to rely on just presumptive diagnoses in the absence or limited performance of diagnostic tests. The prevalence of antibiotic use prior to study inclusion, including self-medication through informal healthcare

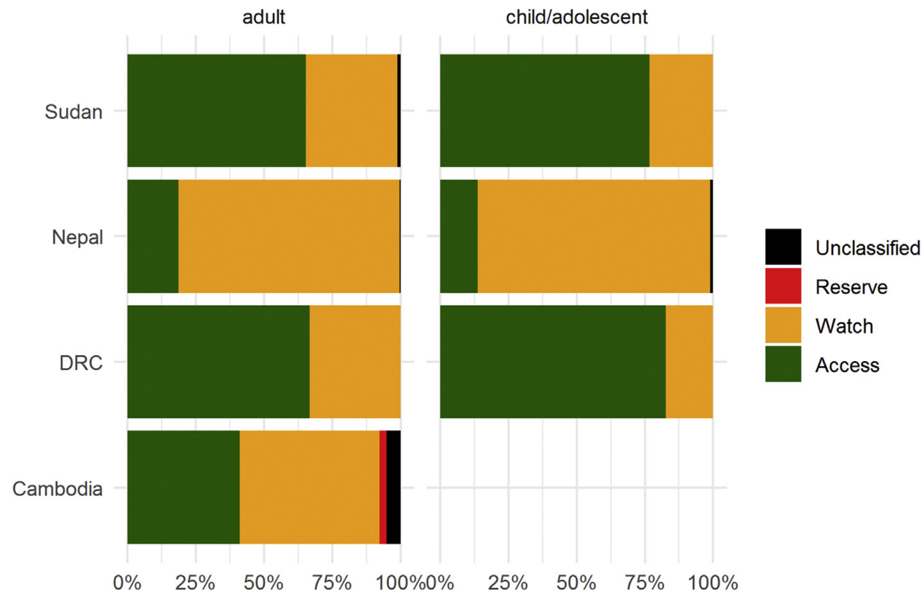

Fig. 2. AWaRe (Access, Watch, Reserve) group distribution of antibiotics used 28 days prior to study inclusion, by country and by age group (5–17 years, ≥18 years). Non-specified antibiotics ($n = 87$) are excluded.

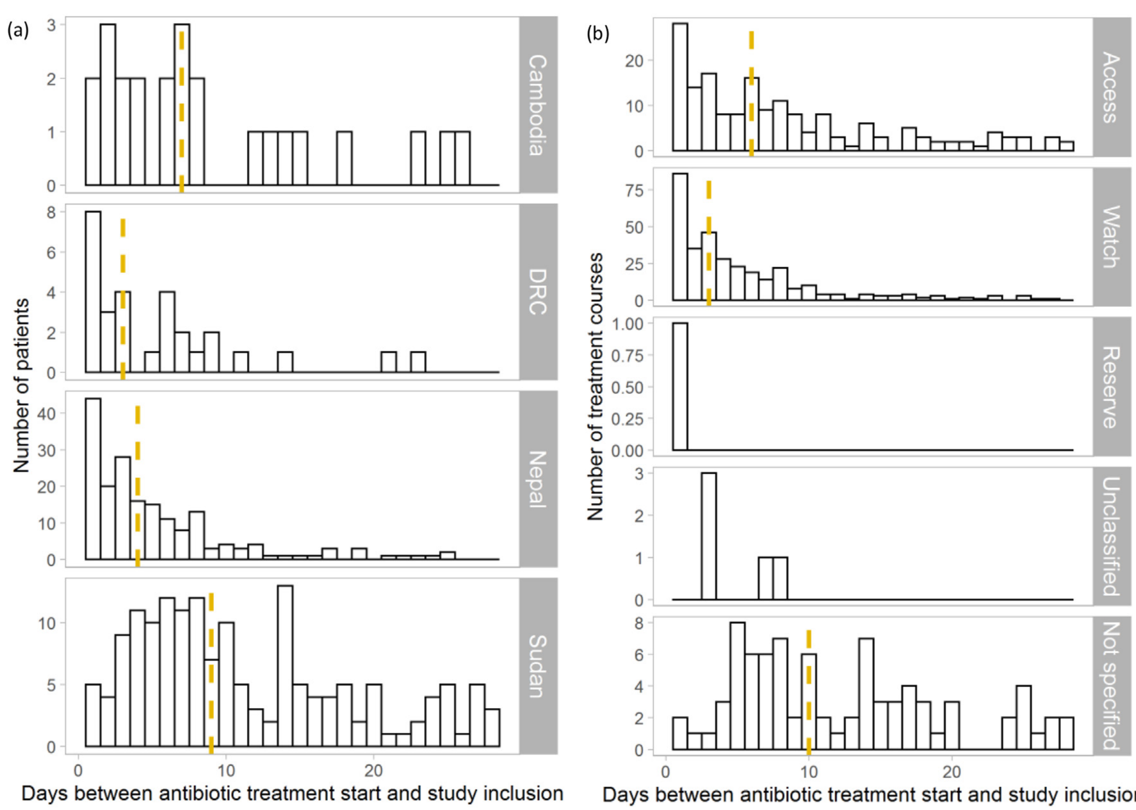

Fig. 3. Histogram of the time (in days) between the start of antibiotic treatment and study inclusion of patients, by country (a), and of treatment courses, by AWaRe group (b). Dashed yellow lines are medians.

which is frequent in LMICs [14,18,19], and the proportion of Watch/Reserve group antibiotics were highest in Nepal and Cambodia.

Most studies reporting prior antibiotic use in LMICs are limited to patients with bloodstream infections, and generally they found that reported antibiotic use was higher than that in our study [20–23]. Patients with (potentially septic) shock, likely to report prior antibiotic use, were not included in the present study. Moreover, most bloodstream infections are reported in children, who also report more frequent prior antibiotic use [23,24]. Furthermore, our study found more frequent prior antibiotic use in children than in adults. In adults, the use of Watch antibiotics was surprisingly frequent, and even accounted for more than half of

Table 3
Characteristics, clinical symptoms and signs associated with antibiotic use 28 days prior to study inclusion. The clinical symptoms and signs were those reported at study inclusion, in addition to fever

		Prior ABU (n)	No prior ABU (n)	Prior ABU (%)	Crude RR	95%CI lower	95%CI upper	Adjusted RR[a]	95%CI lower	95%CI upper
Age group	5–17 years	116	263	30.6	1.42	1.19	1.71	1.44	1.15	1.79
	18–64 years	299	1090	21.5	1	ref	ref	1	ref	ref
	≥65 years	13	158	7.6	0.35	0.21	0.6	0.37	0.20	0.61
Sex	Female	193	806	19.3	1	ref	ref	1	ref	ref
	Male	235	705	25.0	1.29	1.09	1.53	1.25	1.03	1.52
Underlying NCD		28	126	18.2	0.81	0.57	1.15	1.23	0.82	1.79
Clinical symptoms and signs	Anorexia/cachexia	270	877	23.5	1.15	0.97	1.37	1.34	1.09	1.65
	Skin problem (incl. rash)	47	184	20.3	0.90	0.69	1.18	0.99	0.72	1.34
	Jaundice	9	38	19.1	0.86	0.47	1.55	1.28	0.61	2.34
	Tonsillitis/pharyngitis	60	161	27.1	1.25	0.99	1.58	1.14	0.86	1.50
	Respiratory	166	653	20.3	0.85	0.72	1.01	0.95	0.78	1.16
	Diarrhoea	35	101	25.7	1.17	0.87	1.57	1.29	0.89	1.80
	Digestive (other)	159	511	23.7	1.10	0.93	1.31	1.24	1.01	1.53
	Urinary	67	195	25.6	1.17	0.94	1.47	1.13	0.85	1.48
	Headache	125	503	19.9	0.85	0.70	1.02	0.92	0.74	1.14
	Other	358	1212	22.8	1.14	0.90	1.45	1.47	1.12	1.94

ABU, antibiotic use; RR, risk ratio; 95%CI, 95% confidence interval; NCD, non-communicable disease.
[a] Adjusted for age group and study country.

antibiotic treatment courses in adults in Cambodia (51.3%) and Nepal (81.1%), explained especially by the frequent use of ceftriaxone (cephem), which also resulted in frequent parenteral administration. Another study in Nepal reported that 38% of patients in private pharmacies in Nepal received antibiotics, of which over half were cephems [25]. In many settings in South-East Asia and Sub-Saharan Africa—where multidrug-resistant Gram-negative bloodstream infections are frequent but clinical microbiology capacity is absent—cephems and macrolides can be the only effective and accessible treatment options left, proving the need to carefully monitor their use [21,22].

To our knowledge, the AWaRe metrics have not previously been used for low-income or African countries, and for adult antibiotic use data, and were calculated using national level sales data. The amoxicillin and Access percentages we calculated were far lower than those observed in a paediatric antibiotic consumption study in 70 high- and middle-income countries (median 30.7% and 76.3%) [18], which also found the lowest Access-to-Watch index in Asian countries.

The antibiotic use prevalence and distribution between antibiotic groups that we have reported need to be interpreted with caution and should not be used as a standalone estimate of antibiotic use in these countries, for the following reasons. Only patients with persistent fever (eventually) seeking formal healthcare were included. Self-reporting of antibiotic use may result in an underestimation of the prevalence of actual prior antibiotic exposure [24]. The extent to which antibiotics were recorded and verified also varied slightly among study sites, potentially resulting in an underestimation (Cambodia, Nepal) or overestimation (Sudan, DRC) of the frequency of antibiotic use. Additionally, including antibiotics for which the start date was missing might result in an overestimation of antibiotic use within the month prior to consultation, although this is likely limited since very few patients with accurate start dates reported antibiotic use from more than a month. Another limitation is that the recorded clinical signs may have been different at the time when a patient started a course of antibiotics, therefore underestimating the association between signs or symptoms and antibiotic use. Finally, study sites and populations were also different in terms of pathways of care, referral behaviour, age, co-morbidities, exposure, AMR of underlying infections [3,6,22], healthcare workers' training, role of the pharmaceutical industry on prescribing behaviour [26], and availability of diagnostics, limiting both their comparability and the external validity of our findings.

The differences in antibiotic use can indeed be partially explained by differences in fever patients' demographics, in the aetiology of febrile illness, and in the (referral) role of the study healthcare facilities, but the following determinants are likely to play a significant role: patients' and providers' illness perceptions, healthcare-seeking behaviour, self-medication, and availability and affordability of (Watch group) antibiotics at community level. Differences in accessing antibiotics at community level are also reflected in the large difference in the time between initiating antibiotic use and study inclusion at the hospital reported here, varying between a median of 3 days in the DRC and 9 days in Sudan. Across study sites, several critically important Watch antibiotics were widely used in the community, even though antibiotic use is frequently deemed non-essential or ineffective (and therefore discontinued) when qualified healthcare workers consult these patients. These findings emphasize the need to monitor and optimize community- or primary-healthcare-level antibiotic use in LMICs. The present study can serve as an excellent 'baseline' for monitoring community- and primary-care antibiotic use, as recommended in the 2015 WHO Global action plan on AMR.

Author contributions

BI and KK contributed equally to this study. BI wrote the original draft and edited further revisions of the manuscript and conceptualized the data analyses. KK conceptualized the methodology, collected, curated and validated the data, and revised the manuscript. KV conceptualized the research idea and methodology, curated and validated the data, undertook data analyses, revised the manuscript, and supervised the research work. BB curated and validated the data, and revised the manuscript. DM and PT collected, curated and validated the data, and revised the manuscript. SS collected and curated the data, and revised the manuscript. LVD revised the manuscript. EB and MB developed the NIDIAG study and revised the manuscript. MvdS revised the manuscript and analyses. FC was principal investigator of the NIDIAG study, developed the study, and revised the manuscript. JJ conceptualized the research idea and methodology, validated the data, revised the manuscript, and supervised the research work.

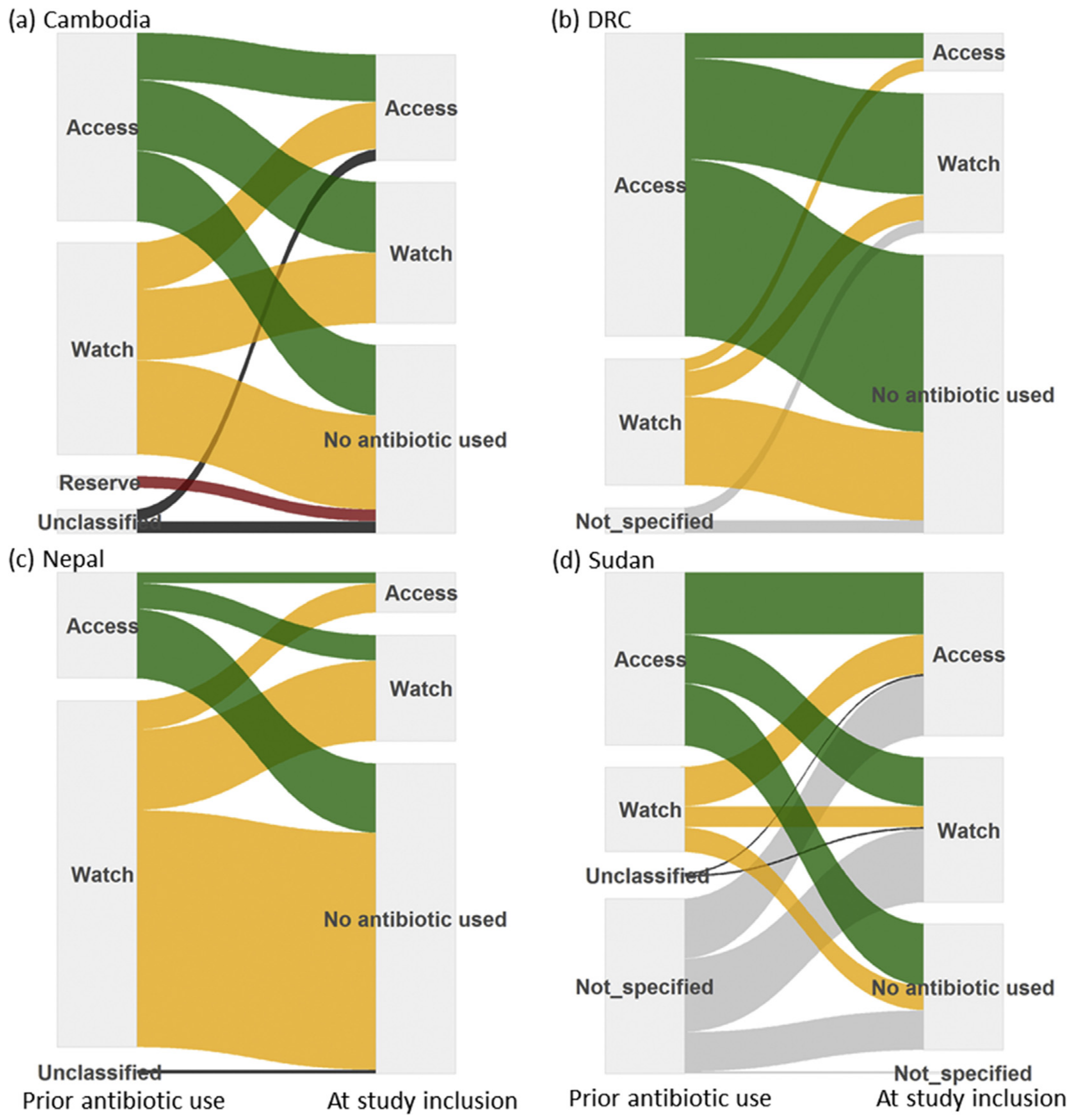

Fig. 4. Sankey diagram of the distribution of antibiotics by AWaRe (Access, Watch, Reserve) group, used 28 days prior to and at study inclusion. (a) Cambodia, (b) DRC, (c) Nepal, (d) Sudan.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.11.003.

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