VOLUME 26 NO 4 PP 397–409 APRIL 2021

Determinants and patterns of antibiotic consumption for children under five in Nepal: analysis and modelling of Demographic Health Survey data from 2006 to 2016

Charlotte Zheng[1,2], Abilasha Karkey[1,3], Tianyi Wang[1,4], Gerald Makuka[1,5], H. Rogier van Doorn[1,6] and Sonia Lewycka[1,6]

1 *Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam*
2 *Chelsea and Westminster NHS Foundation Trust, West Middlesex University Hospital site, London, UK*
3 *Patan Hospital and the Patan Academy of Health Sciences, Kathmandu, Nepal*
4 *Princeton University, Princeton, USA*
5 *Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania*
6 *Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK*

Abstract

OBJECTIVES Our aims were to examine AMR-specific and AMR-sensitive factors associated with antibiotic consumption in Nepal between 2006 and 2016, to explore health care-seeking patterns and the source of antibiotics.

METHODS Cross-sectional data from children under five in households in Nepal were extracted from the 2006, 2011 and 2016 Demographic Health Surveys (DHS). Bivariable and multivariable analyses were carried out to assess the association of disease prevalence and antibiotic use with age, sex, ecological location, urban/rural location, wealth index, household size, maternal smoking, use of clean fuel, sanitation, nutritional status, access to health care and vaccinations.

RESULTS Prevalence of fever, acute respiratory infection (ARI) and diarrhoea decreased between 2006 and 2016, whilst the proportion of children under five receiving antibiotics increased. Measles vaccination, basic vaccinations, nutritional status, sanitation and access to health care were associated with antibiotic use. Those in the highest wealth index use less antibiotics and antibiotic consumption in rural areas surpassed urban regions over time. Health seeking from the private sector has overtaken government facilities since 2006 with antibiotics mainly originating from pharmacies and private hospitals. Adherence to WHO-recommended antibiotics has fallen over time.

CONCLUSIONS With rising wealth, there has been a decline in disease prevalence but an increase in antibiotic use and more access to unregulated sources. Understanding factors associated with antibiotic use will help to inform interventions to reduce inappropriate antibiotic use whilst ensuring access to those who need them.

keywords antibiotics, ARI (acute respiratory infection), DHS (Demographic health survey), diarrhoea, fever, under-five

Sustainable Development Goals (SDGs): 3.2, 3.c, 6, 8.4

Introduction

Antimicrobial resistance (AMR) is a global health threat driven by increased and inappropriate use of antibiotics. Antibiotic consumption in low- and middle-income countries (LMICs) is increasing rapidly, converging to rates seen in high-income settings [1]. Despite this, knowledge on antibiotic use and resistance in these settings is insufficient; particularly regarding community antibiotic use in common childhood infections. Infections such as pneumonia and diarrhoea remain major global burdens of disease in under-fives (U5) [2] and are a significant driver of antibiotic consumption. Both ‘AMR-specific’ actions whose primary purpose is to target AMR (such as antimicrobial stewardship) and ‘AMR-sensitive’ measures that contribute indirectly to AMR containment (such as public health interventions to reduce disease prevalence), are necessary in tackling drug resistance [3].

Nepal is a landlocked country in South Asia with a population of around 30 million. It is one of the poorest countries in the world with 21.6% of the population living below the poverty line in 2018 [4]. However, the economy is developing rapidly; Kathmandu is the fastest-growing metropolitan area in South Asia [5] and the number of those living below the poverty line has declined substantially since 2003 [6]. The majority of health care is community-based with primary healthcare centres and community health volunteers serving as the first port of call [7]. Recent years have seen a substantial increase in the number of private hospitals and clinics in urban areas, likely reflecting the demands of an increasingly wealthy population.

The Global Antibiotic Resistance Partnership situation analysis for Nepal reports that antibiotics are the most frequently prescribed medication, used both prophylactically and therapeutically and can be purchased routinely in the community from pharmacies, drug stores and informal drug sellers [8]. There are no antibiotic stewardship guidelines, and there is little education of AMR amongst health professionals [8]. Total U5 mortality in Nepal was estimated at 32 per 1000 live births in 2018 (globally it was 39 per 1000 live births) with pneumonia, neonatal asphyxia and diarrhoeal diseases amongst the leading causes [8, 9].

The Demographic Health Survey (DHS) provides data on the prevalence and management of childhood acute respiratory infection (ARI), diarrhoea and fever and the social, demographic and economic characteristics of the households surveyed. The data have not previously been used to examine AMR-sensitive and AMR-specific determinants of childhood antibiotic consumption use in Nepal, knowledge of which is sparse. This paper provides insights into these areas that could inform health policy and methods in rationalising antibiotic use to reduce resistance.

Aims and objectives

Our aims were to examine the AMR-specific factors associated with antibiotic use in ARI, fever and diarrhoea and whether AMR-sensitive factors related to disease prevalence would have an indirect but measurable effect on antibiotic use. We also wanted to explore the source of antibiotics as a proxy for prescriptions and investigate whether antibiotics were used appropriately. By analysing data captured between 2006 and 2016, we sought to explore how behaviours have changed over time.

Methods

Data sets

Cross-sectional data on living children under five in households in Nepal were extracted from the 2006, 2011 and 2016 DHS surveys through datasets and survey reports. The DHS survey collects data using a stratified 2-stage cluster sampling method. The time frame for data collection was from February to August in 2006, February to June in 2011 and June to January in 2016.

Definitions

ARI was defined as fast breathing and/or difficulty breathing due to a problem in the chest with or without cough in the 2 weeks preceding the survey. This is concordant with the definition given by the WHO Integrated Management of Childhood Illnesses (IMCI) for pneumonia. Fever (parameters not specified in the survey) and diarrhoea (frequent loose or liquid stools) were defined as occurrence of the symptoms in the last 2 weeks. Dysentery was ascertained as the presence of diarrhoea with bloody stools. Occurrence of these symptoms was based on maternal/care-giver recall. Care seeking was defined by whether the mother sought advice or treatment for the illness from any healthcare facility. Antibiotic treatment was assessed by asking the mother if the child had taken any drugs during the illness and if so, whether this consisted of antibiotic pills, syrups or injections. Rates of antibiotic use were calculated with the total under-five population as the denominator to reflect antibiotic consumption at the population level. A full list of definitions can be found in Table S1.

Analysis

A descriptive analysis was carried out on the survey reports and datasets to identify changes from 2006 to 2016 with regard to demographics, disease prevalence and antibiotic use. A bivariable analysis was performed to evaluate both direct (AMR-specific) risk factors (age, sex, wealth, location, maternal education, household size) and indirect (AMR-sensitive) risk factors (maternal smoking, use of clean fuel, sanitation, water source, nutritional status, access to health care and vaccinations) for antibiotic use. Variables were chosen based on existing literature and expert opinion [10, 11]. Bivariable models were included to provide a comprehensive overview of all the risk factors being explored, including those that were not significant. The consistently significant factors in the bivariable analysis (age, wealth and location) were then included in the multivariable analysis using logistic regression. Factors not associated with the outcome in bivariable models were omitted from adjusted models to avoid data sparsity.

Each survey year's data set was modelled separately and results then compared across time periods. Sample weights provided by the DHS data were applied to account for over and undersampling of particular regions, and adjustments were made for clustering of data using Taylor-linearised variance estimation. Health care-seeking behaviours, the source of antibiotics and appropriate use in accordance with the WHO IMCI guidelines were also examined. Data management and analysis were carried out using Stata version SE 12. All data were publicly available and anonymised with ethical approval covered under the original data collection.

Results

Background characteristics

5457, 5054 and 4861 children (unweighted data) were included in the 2006, 2011 and 2016 surveys, respectively. The background characteristics of the population studied are summarised in Table 1. There were 14 sampling strata for 2016 and 13 for 2006 and 2011 [12–14]. Girls and boys were equally represented and numbers within each age group were evenly spread across the surveys. The majority of the population sampled lived in the *terai* (flat lands) region, representative of the general population. The proportion of mothers achieving secondary and higher level education increased from 2006 to 2016. There was a higher representation of urban populations in 2016 which reflects increasing urbanisation and updated urban–rural classifications by the National Population and Housing Census [14].

Overall, the reported percentage prevalence of disease decreased from 5.9% to 2.4% and from 11.9% to 7.6% between 2006 and 2016 for ARI and diarrhoea respectively, whilst the reported prevalence of fever increased over this time (Figure 1a). Despite this, the reported antibiotic use increased for all three conditions from 2006 to 2016 (Figure 1b).

AMR-specific factors and antibiotic use

The peak prevalence of illness for all three conditions was in those aged 6–23 months. Antibiotic use was generally greater in this than in other age groups although it did not achieve statistical significance in the majority of cases. The prevalence of ARI was highest in the hill areas in all three surveys. Diarrhoea prevalence was lowest in

Table 1 Background characteristics of U5s alive at the time of the survey. Numbers represent weighted numbers in each category to enable comparison between years

	2006	2011	2016
U5 population	5252	5140	4887
Male	2681 (51.0%)	2649 (51.5%)	2563 (52.4%)
Female	2571 (49.0%)	2490 (48.4%)	2324 (47.6%)
Age (months)			
<6	484 (9.2%)	531 (10.3%)	423 (8.7%)
6–11	494 (9.4%)	491 (9.1%)	476 (9.7%)
12–23	984 (18.7%)	1000 (19.4%)	1029 (21.1%)
24–35	1147 (21.8%)	1013 (19.7%)	928 (19.0%)
36–47	1049 (20.0%)	1106 (21.5%)	970 (19.8%)
48–59	1094 (20.8%)	999 (19.4%)	1060 21.7%)
Urban	652 (12.4%)	483 (9.4%)	2649 (54.2%)
Rural	4600 (87.6%)	4656 (90.1%)	2238 (45.8%)
Mountain	443 (8.4%)	400 (7.8%)	342 (7.0%)
Hill	2171 (41.3%	2033 (39.6%)	1857 (38.0%)
Terai (flat lands)	2638 (50.2%)	2707 (52.7%)	2688 (55.0%)
Wealth index			
Poorest	1328 (25.3%)	1322 (25.7%)	1041 (21.3%)
Second	1117 (21.3%)	1212 (23.6%)	1028 (21.0%)
Middle	1053 (20.0%)	1071 (20.8%)	1087 (22.2%)
Fourth	950 (18.1%)	899 (17.5%)	999 (20.4%)
Richest	804 (15.3%)	726 (14.1%)	732 (15.0%)
Mother's education			
No education	3129 (59.6%)	2410 (46.9%)	1663 (34.0%)
Primary	957 (18.2%)	1032 (20.1%)	981 (20.1%)
Secondary	1038 (19.8%)	1411 (27.5%)	1564 (32.0%)
Higher	128 (2.4%)	287 (5.6%)	679 (13.9%)

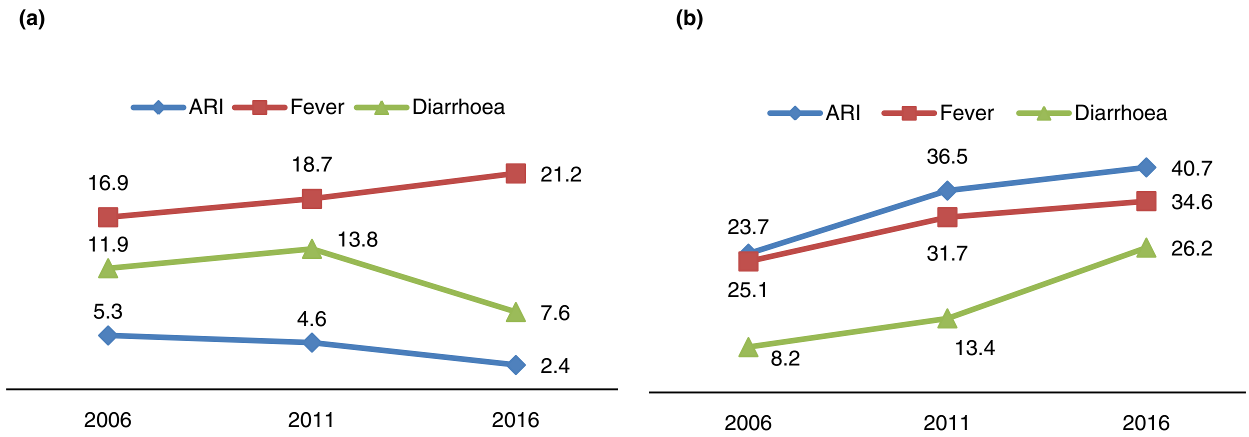

Figure 1 Overall disease prevalence and antibiotic use from 2006 to 2016. (a) Overall percentage prevalence of disease from 2006–2016. (b) Overall percentage of antibiotic use in the disease population 2006–2016. [Colour figure can be viewed at wileyonlinelibrary.com]

the *terai* region for 2006, but highest in 2011 and 2016 (Table 2, Tables S2 and S4). On the other hand, there was no difference observed between disease prevalence and urban/rural locations. In contrast to urban areas, antibiotic use in rural areas increased during each time interval with 2016 data demonstrating rural antibiotic consumption for ARI and fever surpassing those in urban regions (Figure 2a). Changes in wealth did not really affect ARI prevalence in 2006 but by 2016, increasing wealth was associated with decreasing rates of disease with the largest reductions seen in the highest wealth quintiles, particularly for 2011 and 2016 (Figure 2b). Whilst there was a trend for increasing antibiotic use with increasing wealth for 2006, the 2016 data suggested a reduction in antibiotic use for the wealthiest quintile, though numbers in this group were small (Figure 2c). Antibiotic consumption for diarrhoea was highest in the middle and fourth wealthiest quintiles for diarrhoea in 2016, whilst rates were highest in the wealthiest quintile in 2006 and 2011. Higher levels of maternal education were associated with increased prevalence of fever in 2006 and 2011. No association was found for maternal education and prevalence of ARI or diarrhoea (Table 2 and Tables S2 and S4). Higher levels of maternal education were generally associated with increased antibiotic use, particularly for fever, where the effect was present in all three time periods (Table 3 and Tables S3 and S5).

AMR-sensitive factors and antibiotic use

Wasting, which is a proxy for acute malnutrition, was associated with increased rates of fever in 2006 and 2016 (Table 2 and Table S2) as well as greater rates of antibiotic consumption (Table 4). Difficulty accessing health care was consistently associated with higher rates of fever from 2006 to 2016 as well as increased prevalence of diarrhoea in 2016. Whilst associated with reduced antibiotic consumption in 2006, problems with healthcare access led to increased antibiotic use in 2016 (Table 4). Although there was no association found between measles vaccination and disease prevalence (Table 2 and Tables S2 and S4), U5s with diarrhoea receiving the measles vaccine in 2016 had lower rates of antibiotic consumption (Table 4). There was no association between disease prevalence and clean fuel, maternal smoking, water source or improved toilet sanitation in the adjusted model (Table 2 and Tables S2 and S4). However, improved toilet sanitation was associated with reduced antibiotic use for diarrhoea in 2011 alone (Table 4).

Health-seeking behaviours

There was a decrease in the proportion of people seeking care from the public sector from 2006–2016 for all conditions, whilst the proportion visiting the private sector has steadily increased. The pharmacy remained a predominant healthcare provider. Unregulated facilities, including traditional healers and shop-keepers, make up a minority of the healthcare facilities initially visited (Figure 3a). Accordingly, the source of antibiotics reflected these changes in health care-seeking behaviour, with the majority of those receiving antibiotics visiting a private sector facility first as opposed to the public sector in previous years. Of note, the majority of antibiotics for diarrhoea appears to be consistently coming from pharmacies since 2006 (Figure 3b).

Table 2 Determinants of disease prevalence as demonstrated by the odds ratio of having the illness given the presence of the variable in a bivariable and adjusted analysis (2016 data)

Variable	Illness	% with illness (*n*)	Association of variable with disease prevalence Odds ratio (95% CI)	Adjusted model† Odds ratio (95% CI)
AMR-specific (direct) variables				
Age	ARI	1.3 (5)		
<6 months		4.5 (21)	**3.59** (1.40–9.26)	
6–11 months		4.0 (41)	**3.16** (1.28–7.79)	
12–23 months		2.2 (20)	1.71 (0.67–4.41)	
24–35 months		1.3 (13)	1.01 (0.38–2.71)	
36–47 months		1.6 (17)	1.28 (0.49–3.32)	
48–59 months				
<6 months	Fever	16.2 (69)	**2.10** (1.45–3.05)	
6–11 months		29.0 (138)	**1.70** (1.19–2.43)	
12–23 months		24.8 (255)	1.43 (1.00–2.04)	
24–35 months		21.7 (202)	1.16 (0.82–1.62)	
36–47 months		18.3 (178)	1.15 (0.78–1.71)	
48–59 months		18.3 (193)		
<6 months	Diarrhoea	6.0 (25)	**2.49** (1.45–4.29)	
6–11 months		13.7 (65)	**1.93** (1.19–3.15)	
12–23 months		10.9 (112)	1.09 (0.68–1.74)	
24–35 months		6.5 (60)	1.06 (0.63–1.80)	
36–47 months		6.3 (61)	0.74 (0.45–1.21)	
48–59 months		4.5 (48)		
Urban	ARI	2.1 (55)		
Rural		2.8 (63)	1.36 (0.90–2.07)	
Urban	Fever	22.7 (600)		
Rural		19.4 (434)	0.82 (0.66–1.02)	
Urban	Diarrhoea	7.8 (207)		
Rural		7.4 (165)	0.94 (0.66–1.34)	
Mountain	ARI	2.9 (10)		
Hill		3.4 (62)	1.17 (0.64–2.12)	
Terai		1.7 (46)	0.58 (0.32–1.06)	
Mountain	Fever	16.4 (56)		
Hill		21.6 (402)	1.40 (0.97–2.02)	
Terai		21.4 (576)	1.38 (0.97–1.98)	
Mountain	Diarrhoea	5.2 (18)		
Hill		6.4 (120)	1.26 (0.73–2.16)	
Terai		8.7 (234)	**1.74** (1.15–6.65)	
Wealth index				
Poorest	ARI	3.3 (34)		
Second		3.1 (32)	0.94 (0.57–1.56)	
Middle		2.4 (26)	0.73 (0.38–1.38)	
Fourth		2.1 (20)	0.61 (0.34–1.10)	
Richest		0.6 (4)	**0.17** (0.06–0.47)	
Poorest	Fever	17.9 (186)		
Second		21.4 (220)	1.25 (0.99–1.59)	
Middle		23.0 (251)	**1.38** (1.06–1.79)	
Fourth		21.3 (213)	1.25 (0.95–1.64)	
Richest		22.5 (164)	1.33 (0.97–1.83)	
Poorest	Diarrhoea	5.9 (61)		
Second		8.0 (82)	1.40 (0.95–2.05)	
Middle		8.4 (91)	1.46 (0.96–2.24)	
Fourth		8.3 (83)	**1.46** (1.02–2.09)	
Richest		7.3 (54)	1.26 (0.70–2.28)	

Table 2 (*Continued*)

Variable	Illness	% with illness (*n*)	Association of variable with disease prevalence Odds ratio (95% CI)	Adjusted model† Odds ratio (95% CI)
Maternal education				
No education	ARI	2.1 (35)		
Primary education		2.8 (28)	1.34 (0.77–2.33)	
Secondary/higher		2.5 (55)	1.16 (0.72–1.87)	
No education	Fever	19.7 (327)		
Primary education		21.5 (211)	1.12 (0.87–1.44)	
Secondary/higher		22.1 (496)	1.16 (0.93–1.44)	
No education	Diarrhoea	8.5 (142)		
Primary education		8.4 (82)	0.98 (0.73–1.32)	
Secondary/higher		6.6 (148)	0.76 (0.55–1.05)	
Household members				
1–3	ARI	2.8 (18)		
4–6		2.5 (61)	0.92 (0.48–1.75)	
7–10		2.2 (32)	0.79 (0.39–1.58)	
>10		1.9 (7)	0.68 (0.25–1.85)	
1–3	Fever	21.3 (135)		
4–6		22.3 (536)	1.06 (0.80–1.40)	
7–10		20.3 (299)	0.94 (0.69–1.27)	
>10		17.2 (64)	0.77 (0.45–1.30)	
1–3	Diarrhoea	6.8 (43)		
4–6		7.3 (175)	1.08 (0.69–1.69)	
7–10		8.6 (127)	1.29 (0.77–2.17)	
>10		7.1 (26)	1.05 (0.49–2.25)	
AMR-sensitive (indirect) variables				
Received measles vaccine	ARI	3.4 (68)	1.49 (0.88–2.51)	1.67 (0.84–3.31)
	Fever	23.2 (463)	0.99 (0.79–1.22)	0.79 (0.59–1.05)
	Diarrhoea	8.5 (169)	0.78 (0.55–1.11)	0.64 (0.34–1.18)
All basic vaccinations	ARI	3.4 (57)	1.25 (0.77–2.03)	1.21 (0.65–2.26)
	Fever	23.0 (394)	0.96 (0.78–1.19)	0.84 (0.65–1.09)
	Diarrhoea	8.3 (141)	0.77 (0.52–1.15)	0.69 (0.41–1.17)
Clean fuel	ARI	1.4 (16)	**0.48** (0.28–0.84)	0.98 (0.53–1.81)
Maternal smoking	ARI	4.3 (8)	1.86 (0.73–4.74)	1.61 (0.60–4.30)
Improved toilet sanitation	Diarrhoea	6.7 (231)	0.68 (0.46–1.00)	0.66 (0.42–1.03)
Improved water source	Diarrhoea	7.3 (315)	0.99 (0.55–1.75)	0.91 (0.50–1.63)
Wasting	ARI	2.9 (6)	1.16 (0.53–2.54)	0.95 (0.43–2.11)
	Fever	28.5 (61)	**1.56** (1.08–2.24)	**1.54** (1.07–2.23)
	Diarrhoea	9.9 (21)	1.40 (0.77–2.55)	1.13 (0.61–2.07)
Difficult access to health care	ARI	2.9 (86)	**1.81** (1.16–2.82)	1.44 (0.91–2.28)
	Fever	22.8 (670)	**1.29** (1.06–1.57)	**1.44** (1.17–1.76)
	Diarrhoea	9.1 (266)	**1.75** (1.33–2.32)	**1.95** (1.45–2.62)

Wealth index – wealth quintile of household as determined by ownership of selected assets.
All basic vaccinations – includes BCG, 3x DPT, 3X Polio, Measles.
Clean fuel – gas, kerosene, electric. Unclean fuel – wood, charcoal, animal dung, straw, agricultural crop.
Improved toilet sanitation – sewer system, septic tank, VIP, covered pit, composting toilet. Unimproved toilet sanitation – no facility/bush/field, open pit, pit latrine without slab, flush to unknown place.
Improved water source – piped, public tap, tube well or borehole, protected well, protected spring or bottled water.
Wasting – weight for height less than 2 SD of median.
Difficult access to health care – distance to health facility is a problem for getting medical advice and treatment.
Bold values are statistically significant at $p < 0.05$.
†Variables in adjusted analysis – age, wealth index, urban/rural location.

Inappropriate use of antibiotics

According to the IMCI guidelines, children with cough only should not be treated with antibiotics. From 2006 to 2011, the percentage of U5s with cough only receiving antibiotics increased from 7% (n = 15) to 12% (n = 39). The figure for 2016 could not be calculated as this question was not asked. Those receiving an IMCI-recommended antibiotic, specifically oral co-trimoxazole (before 2014), amoxicillin (after 2014) or IV/IM procaine penicillin, decreased from 99.9% (n = 68) in 2006 to 81.6% (n = 71) in 2011, and then to 50% (n = 24) in 2016. The IMCI guidelines stipulate that children with dysentery (diarrhoea and bloody stools) should receive antibiotic therapy. In 2006 and 2011, only 11.5% (n = 12) and 23.1% (n = 23) of children with dysentery received antibiotics respectively, whilst 75% of children who received antibiotics for diarrhoea did not meet the required indication. Again, this question was omitted in the 2016 questionnaire and could not be evaluated.

Discussion

From our analysis, the prevalence of ARI and diarrhoea in U5s in Nepal declined from 2006 onwards. This was particularly pronounced in ARI amongst the highest wealth quintiles with the difference between rich and poor widening over time (Figure 2b), which has been the global trend over the last few decades [15]. It is often the case that the wealthiest groups are the first to access new services and treatments. Conversely, overall antibiotic use in Nepal has been rising, reflecting increasing consumption in the low- and middle-income groups. The marked

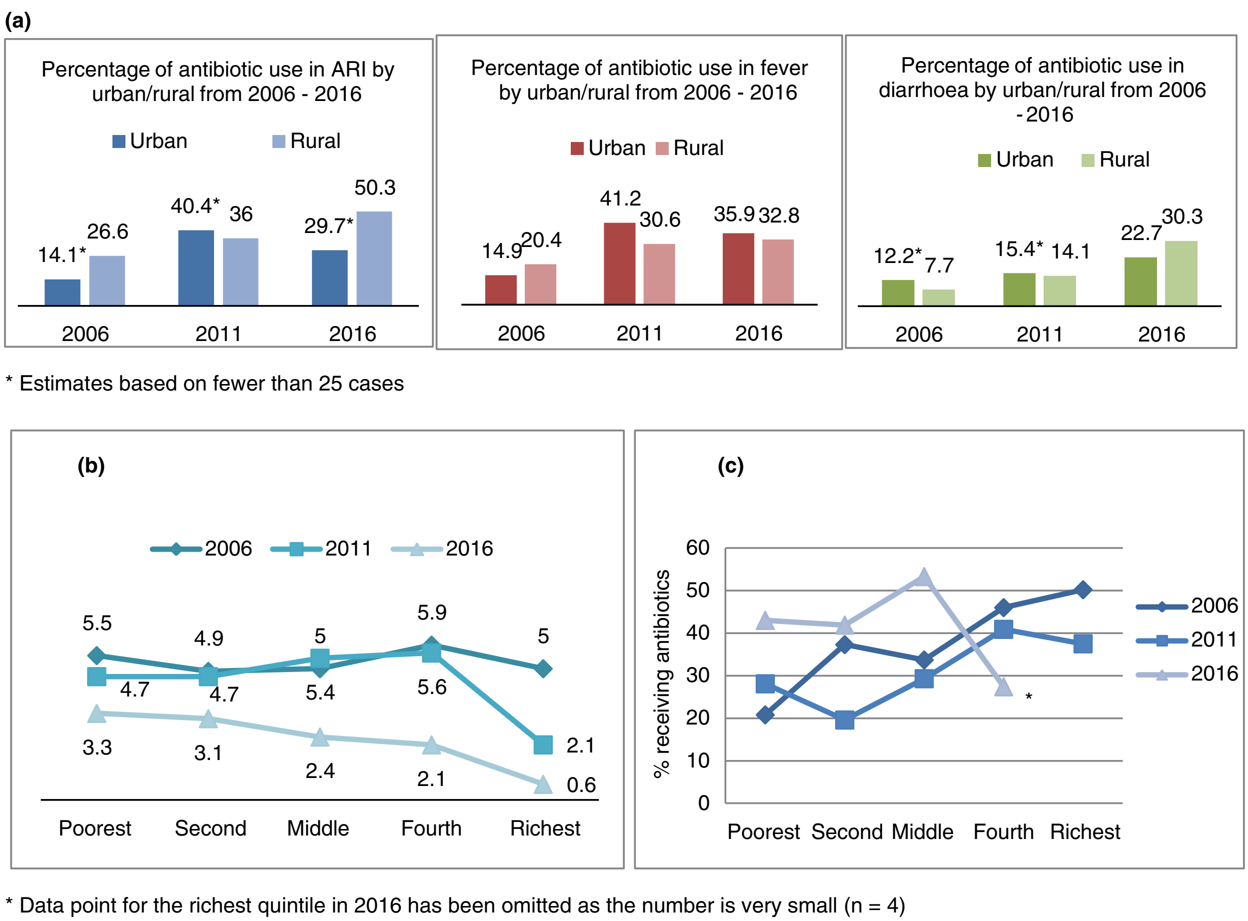

Figure 2 Determinants of disease prevalence and antibiotic consumption from 2006 to 2016. (a) Urban and rural rates of antibiotic consumption for ARI, fever and diarrhoea from 2006–2016. (b) Percentage prevalence of ARI by wealth quintile. (c) Percentage of children with ARI receiving antibiotics by wealth quintile 2006–2016. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 3 Determinants of antibiotic use for ARI, fever and diarrhoea demonstrated by the odds ratio of antibiotic use given the presence of the variable in a bivariable and adjusted analysis (2016 data)

Variable	Illness	% antibiotic use (n)‡	Association of variable with antibiotic use for each illness Odds ratio (95% CI)	Adjusted model† Odds ratio (95% CI)
AMR-specific (direct) variables				
Age	ARI			
<6 months		0.8 (3)		
6–11 months		2.3 (11)	2.93 (0.71–2.09)	
12–23 months		1.6 (17)	2.08 (0.55–7.90)	
24–35 months		0.7 (6)	0.89 (0.20–3.90)	
36–47 months		0.5 (5)	0.68 (0.15–3.12)	
48–59 months		0.5 (6)	0.69 (0.16–2.97)	
<6 months	Fever	4.7 (20)		
6–11 months		11.3 (54)	**2.60** (1.36–4.99)	
12–23 months		8.7 (90)	**1.95** (1.05–3.62)	
24–35 months		7.5 (70)	1.66 (0.90–3.05)	
36–47 months		6.3 (61)	1.37 (0.75–2.50)	
48–59 months		6.0 (64)	1.31 (0.67–2.53)	
<6 months	Diarrhoea	2.0(9)		
6–11 months		4.4 (21)	2.21 (0.86–5.67)	
12–23 months		3.4 (35)	1.69 (0.75–3.80)	
24–35 months		1.5 (15)	0.75 (0.30–1.87)	
36–47 months		0.7 (7)	**0.34** (0.14–0.81)	
48–59 months		0.9 (10)	0.46 (0.15–1.45)	
Urban	ARI	0.6 (16)		
Rural		1.4 (32)	**2.31** (1.10–4.85)	
Urban	Fever	8.1 (215)		
Rural		6.4 (142)	0.77 (0.52–1.13)	
Urban	Diarrhoea	1.7 (47)		
Rural		2.2 (50)	1.27 (0.75–2.16)	
Mountain	ARI	0.6 (2)		
Hill		1.5 (29)	2.76 (0.64–11.92)	
Terai		0.7 (17)	1.15 (0.25–5.18)	
Mountain	Fever	4.3 (15)		
Hill		7.0 (130)	1.67 (0.69–4.01)	
Terai		7.9 (213)	1.92 (0.82–4.47)	
Mountain	Diarrhoea	1.1 (4)		
Hill		1.0 (19)	0.87 (0.32–2.37)	
Terai		2.7 (74)	2.39 (0.95–6.02)	
Wealth index				
Poorest	ARI	1.4 (15)		
Second		1.3 (13)	0.92 (0.43–1.95)	
Middle		1.3 (14)	0.91 (0.35–2.34)	
Fourth		0.6 (6)	0.39 (0.14–1.12)	
Richest	Fever	0 (0)	N/A	
Poorest		4.9 (51)		
Second		8.7 (89)	**1.85** (1.25–2.75)	
Middle		7.4 (81)	1.56 (0.98–2.49)	
Fourth		9.0 (90)	**1.92** (1.25–2.94)	
Richest		6.4 (47)	1.33 (0.82–2.18)	
Poorest	Diarrhoea	0.8 (9)		
Second		1.9 (20)	2.29 (0.98–5.40)	
Middle		2.6 (29)	**3.16** (1.59–6.28)	
Fourth		2.6 (27)	**3.24** (1.55–6.77)	
Richest		1.6 (12)	1.97 (0.81–4.75)	

Table 3 (*Continued*)

Variable	Illness	% antibiotic use (n)‡	Association of variable with antibiotic use for each illness Odds ratio (95% CI)	Adjusted model† Odds ratio (95% CI)
Maternal education				
No education	ARI	0.8 (12)		
Primary education		1.1 (11)	1.44 (0.51–4.08)	
Secondary/higher		1.1 (25)	1.50 (0.66–3.38)	
No education	Fever	6.1 (102)		
Primary education		6.2 (60)	1.01 (0.70–1.46)	
Secondary/higher		8.7 (195)	**1.46** (1.02–2.09)	
No education	Diarrhoea	2.2 (38)		
Primary education		2.2 (22)	1.01 (0.57–1.76)	
Secondary/higher		1.6 (37)	0.75 (0.42–1.32)	
Household members				
1–3	ARI	1.8 (11)		
4–6		0.9 (21)	0.49 (0.19–1.26)	
7–10		0.9 (14)	0.52 (0.20–1.39)	
>10		0.7 (2)	0.38 (0.07–1.95)	
1–3	Fever	9.5 (60)		
4–6		7.6 (183)	0.79 (0.52–1.19)	
7–10		6.6 (98)	0.68 (0.44–1.04)	
>10		4.6 (17)	**0.47** (0.22–0.98)	
1–3	Diarrhoea	1.4 (9)		
4–6		1.7 (41)	1.18 (0.52–2.69)	
7–10		2.3 (35)	1.61 (0.65–3.97)	
>10		3.2 (12)	2.30 (0.72–7.36)	
AMR-sensitive (indirect) variables				
Received measles vaccine	ARI	1.3 (27)	1.16 (0.51–2.62)	1.98 (0.81–4.86)
	Fever	7.8 (156)	0.88 (0.63–1.21)	0.62 (0.35–1.12)
	Diarrhoea	2.2 (44)	**0.55** (0.33–0.91)	**0.41** (0.18–0.95)
All basic vaccinations	ARI	1.4 (24)	1.25 (0.55–2.86)	1.88 (0.79–4.47)
	Fever	7.8 (133)	0.89 (0.66–1.19)	0.75 (0.53–1.06)
	Diarrhoea	2.0 (34)	**0.51** (0.32–0.82)	**0.43** (0.25–0.76)
Clean fuel	ARI	0.3 (3)	**0.22** (0.07–0.71)	0.71 (0.22–2.26)
Maternal smoking	ARI	1.8 (3)	1.95 (0.31–12.50)	1.73 (0.24–12.70)
Improved toilet sanitation	Diarrhoea	1.6 (56)	0.57 (0.31–1.07)	0.59 (0.72–5.99)
Improved water source	Diarrhoea	1.8 (82)	0.96 (0.30–3.09)	1.92 (0.40–9.16)
Wasting	ARI	0.4 (1)	0.36 (0.05–2.76)	0.26 (0.03–2.06)
	Fever	10.7 (23)	1.64 (0.98–2.74)	1.52 (0.93–2.51)
	Diarrhoea	4.2 (9)	**2.76** (1.04–7.29)	2.29 (0.87–6.03)
Difficult access to health care	ARI	(33)	1.46 (0.71–3.00)	1.00 (0.48–2.08)
	Fever	8.1 (239)	1.14 (0.79–1.65)	**1.52** (1.10–2.09)
	Diarrhoea	2.3 (70)	1.73 (0.98–3.04)	**1.93** (1.09–3.43)

Wealth index – wealth quintile of household as determined by ownership of selected assets.
All basic vaccinations – includes BCG, 3x DPT, 3X Polio, Measles.
Clean fuel – gas, kerosene, electric. Unclean fuel – wood, charcoal, animal dung, straw, agricultural crop.
Improved toilet sanitation – sewer system, septic tank, VIP, covered pit, composting toilet. Unimproved toilet sanitation – no facility/bush/field, open pit, pit latrine without slab, flush to unknown place.
Improved water source – piped, public tap, tube well or borehole, protected well, protected spring or bottled water.
Wasting – weight for height less than 2 SD of median.
Difficult access to health care – distance to health facility is a problem for getting medical advice and treatment.
†Variables in adjusted analysis – age, wealth index, urban/rural location.
‡Antibiotic use is expressed as a percentage of the total population, that is those with and without illness.
Bold values are statistically significant at $p < 0.05$.

redistribution of urban and rural populations in 2016 may be partially explained by the authorisation of labour emigration by the Home and Labour Ministry in 2011. Those returning from working abroad have been able to afford to move from rural villages to urban areas with improved access to health care. Falling rates of antibiotic use in the wealthier quintiles over time (Figure 2c) probably reflect concomitant reduction in disease prevalence. Even within Nepal, patterns of antibiotic consumption reflect global trends as described by Klein et al [1]. This is not necessarily undesirable given poorer populations are often in most need of health care but it highlights the need for education and regulation amongst these groups to prevent inappropriate use.

Overall, wasting and difficult access to health care were associated with increased disease prevalence. Improved toilet sanitation, measles vaccination, all basic vaccinations and access to health care were associated with reduced antibiotic use whilst wasting was associated with increased antibiotic consumption in the adjusted models (Table 4). These findings emphasise the importance of optimising existing public health strategies, which could have significant impacts on antibiotic use and AMR. Improved toilet sanitation reduced antibiotic use, but this was not seen with improved water sources, suggesting that the former could be more important in reducing enteric infections by preventing contamination of water sources in the first place. The association between measles vaccination and reduced antibiotic use in diarrhoea may be explained by similar findings elsewhere. Measles vaccination has been associated with non-specific effects, including reduced prevalence in diarrhoea in India, Pakistan, Nigeria and the Democratic Republic of Congo [16]. It has also been associated with increased child survival unrelated to measles prevention and reduction in hospital admissions for other infections [17, 18]. Nutritional status was consistently associated with reduced illness and antibiotic use in our analysis. The 2017 Global Burden of Disease study identified wasting as the strongest risk factor for mortality associated with pneumonia [19]. Public health policy should therefore make childhood nutrition a priority.

Individuals are increasingly seeking health care and thus receiving antibiotics from private facilities, which is reflected by the greater number of private hospitals (364) vs. government hospitals (103) available [7]. Similarly, analysis of DHS and Service Provision Assessment surveys on eight LMICs by Fink et al. found a greater number of U5 attendances and mean antibiotics prescribed at private health facilities than public ones [20]. Care seeking at pharmacies has remained frequent from 2006 to 2016, particularly for diarrhoea. Pharmacies often provide quicker perceived solutions to more minor ailments compared to the opportunity cost of spending time being assessed in the hospital. They are likely to be a significant contributor to inappropriate antibiotic use. A study by Wachter et al. demonstrated that antibiotics were supplied inappropriately by 97% of surveyed pharmacists in Kathmandu for childhood diarrhoea [21]. Simulated client studies carried out in pharmacies in India and Thailand reported inappropriate antibiotic use for diarrhoea of 40% and 52.2%, respectively [22, 23].

Falling adherence to IMCI-recommended antibiotics for ARI and dysentery has also been observed in other LMICs. A prospective study by Ragowski et al examining antibiotic use in children up to 2 years old in eight LMICs in

Table 4 Summary of significant AMR-sensitive determinants of antibiotic use from 2006 to 2016

Variable	Illness	Year	Adjusted model† Odds ratio (95% CI)
Measles vaccine	Diarrhoea	2016	OR **0.41** (0.18–0.95)
All basic vaccinations	Diarrhoea	2016	OR **0.43** (0.25–0.76)
Improved toilet sanitation	Diarrhoea	2011	OR **0.48** (0.24–0.95)
Difficult access to health care	ARI	2006	OR **0.36** (0.20–0.65)
	Fever	2016	OR **1.52** (1.10–2.09)
	Diarrhoea	2016	OR **1.93** (1.09–3.43)
Wasting	ARI	2006	OR **2.72** (1.26–5.86)
	Fever	2006	OR **1.97** (1.28–3.02)

Antibiotic use is expressed as a percentage of the total population, that is those with and without illness
Improved toilet sanitation – sewer system, septic tank, VIP, covered pit, composting toilet. Unimproved toilet sanitation – no facility/bush/field, open pit, pit latrine without slab, flush to unknown place.
Wasting – weight for height less than 2 SD of median.
Difficult access to health care – distance to health facility is a problem for getting medical advice and treatment.
†Variables in adjusted analysis – age, wealth index, urban/rural location.

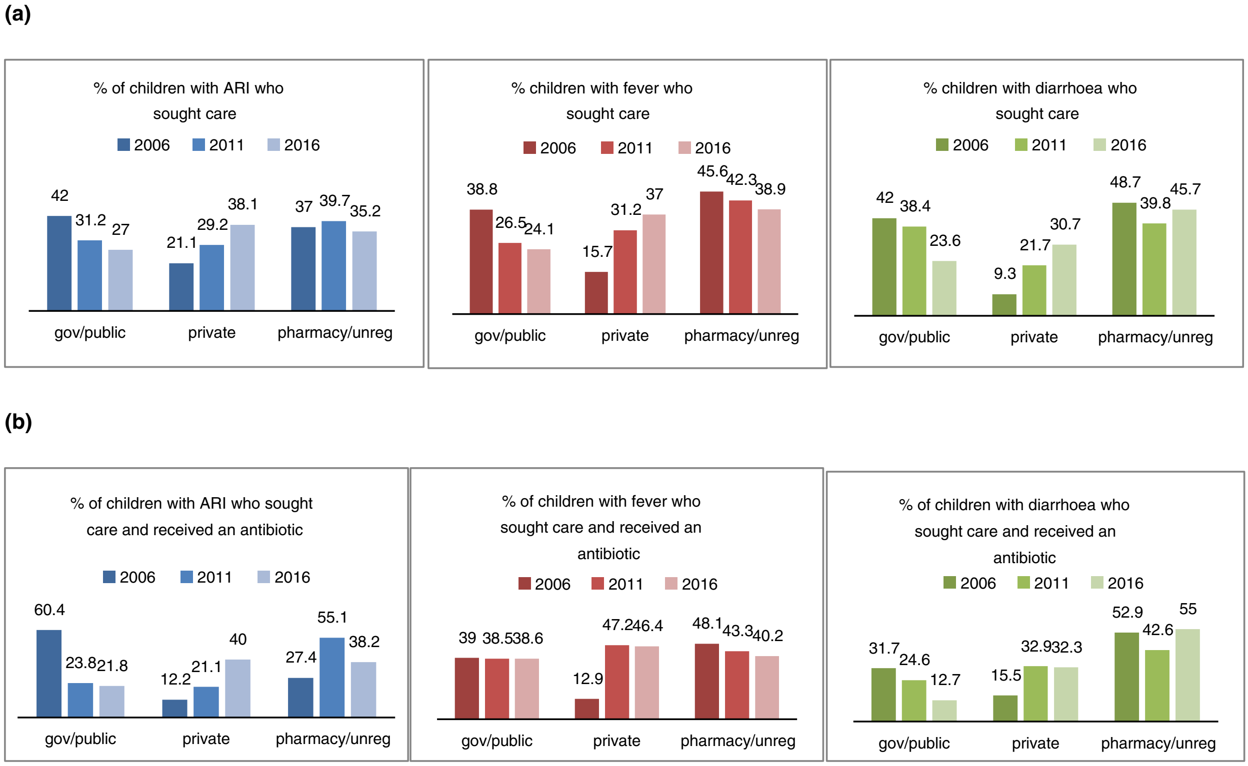

Figure 3 (a) Percentage of children with ARI, fever and diarrhoea seeking care from a government/public, private or pharmacy/unregulated health facility from 2006 to 2016. (b) Proportion of children with ARI, fever and diarrhoea who sought care and received an antibiotic from a government/public, private or pharmacy/unregulated health facility from 2006 to 2016. Government/public: government hospital, primary health care centre, health post/sub health post, primary healthcare outreach post, female community health volunteer, NGOs. Private: private hospital, private clinic, private doctor. Pharmacy/unregulated: pharmacy, shop, traditional practitioner/healer. [Colour figure can be viewed at wileyonlinelibrary.com]

South Asia, Africa and South America noted substantial variation from IMCI-recommended antibiotics for ARI and, in particular, bloody diarrhoea [24]. Deviation from guidelines may be due to reduced drug availability, poor knowledge of local resistance rates, financial incentives for certain antibiotics and lack of legal consequences for incorrect antibiotic prescribing [25, 26]. The government needs to tackle unregulated antibiotic use in the private sectors but this will be challenging given prescribing laws are often ignored and difficult to implement [21]. Strategies could be targeted at educating and raising awareness about AMR amongst these healthcare professionals.

Limitations

Due to the method of data collection in the DHS, there is a risk of recall bias. Non-response and selection bias was minimised by weighted data. Our analysis provides insight into the associations of AMR-specific and AMR-sensitive variables with antibiotic use but does not attempt to establish a causal relationship between exposure and outcome. As the total population was used as a denominator, the trends for antibiotic use are likely to reflect those for disease prevalence. However, it is interesting to note the analysis did not demonstrate this. Exact information on antibiotic prescriptions was not available, so we used antibiotic source as a proxy for this. However, it is important to note that over-prescription of antibiotics in healthcare settings is common and does not necessarily mean that antibiotics were required. We therefore also included measures of self-reported disease severity to identify children who were likely to have self-limiting infections. Small sample sub-group sizes made it difficult to examine certain associations, in particular the impact of maternal smoking and breastfeeding on illness and antibiotic use. This may have also affected data precision for examining the associations of ARI with wealth and ecological zone. 2016 data were collected later in the year compared to 2006 and 2011 perhaps reflecting the disruption from the April 2015 earthquake. This (seasonal) bias along with the effect of the earthquake may have influenced trends in disease prevalence and make the 2016 data less comparable. Lastly, the data only provided a limited perspective on the 'appropriate' use of antibiotics, as neither clinical information nor microbiology results were available.

Conclusion

The results of our study highlight the importance of the following specific primary strategies that were proposed in the Situation Analysis conducted with the Global Antibiotic Resistance Partnership to improve antibiotic use: reduce the need for antibiotics by improving public health (in particular sanitation, nutrition, vaccination and access to health care), rationalise antibiotic use in the community and educate health professionals, policymakers and the public on sustainable antibiotic use [8]. Tackling antimicrobial resistance requires both AMR-specific and AMR-sensitive measures whilst ensuring access to antibiotics for those who need them the most.

References

1. Klein EY, Van Boeckel TP, Martinez EM *et al.* Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci USA* 2018: **115**(15): E3463–E3470.
2. The World Health Organisation (WHO). WHO factsheet. Children: reducing mortality; 2018.
3. World Bank. 2017. *Drug-Resistant Infections: A Threat to Our Economic Future*. World Bank: Washington, DC. © World Bank. (Available from https://openknowledge.worldbank.org/handle/10986/26707) License: CC BY 3.0 IGO.
4. Government of Nepal. *Ministry of Finance. Economic Survey 2017/18*. Singha Durbar: Kathmandu.
5. Muzzini E, Aparicio G. *Urban Growth and Spatial Transition in Nepal*. World Bank: Washington, DC, 2013.
6. The World Bank. Poverty and Equity Data Portal - Nepal. URL (Available from http://povertydata.worldbank.org/poverty/country/NPL).
7. Ministry of Health Nepal. New E.R.A Nepal; Nepal Health Sector Support Program (NHSSP); and ICF. *Nepal Health Facility Survey 2015*. Ministry of Health, Nepal: Kathmandu, Nepal, 2017.
8. Basnyat B. Situation analysis and recommendations: antibiotic use and resistance in Nepal: The Global antibiotic resistance partnership - Nepal national working group; 2015.
9. UN Inter-agency Group for Child Mortality Estimation (UNICEF, WHO, World Bank, UN DESA Population Division) at childmortality.org.
10. Troeger CE, Khalil IA, Blacker BF *et al.* Quantifying risks and interventions that have affected the burden of diarrhoea among children younger than 5 years: an analysis of the Global Burden of Disease Study 2017. *Lancet Infect Dis* 2020: **20**(1): 37–59.
11. Troeger CE, Khalil IA, Blacker BF *et al.* Quantifying risks and interventions that have affected the burden of lower respiratory infections among children younger than 5 years: an analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis* 2020: **20**(1): 60–79.
12. Ministry of Health and Population Nepal. New E. R. A. Nepal. Macro. International. Nepal Demographic And Health Survey 2006.
13. Ministry of Health and Population Nepal. New E. R. A. Nepal. I. C. F. International. Nepal Demographic and Health Survey 2011.
14. Ministry of Health Nepal. New E. R. A. Nepal. Icf. Nepal Demographic and Health Survey 2016.
15. Victora CG, Joseph G, Silva ICM *et al.* The inverse equity hypothesis: analyses of Institutional deliveries in 286 National Surveys. *Am J Public Health* 2018: **108**(4): 464–471.
16. Bawankule R, Singh A, Kumar K, Shetye S. Does measles vaccination reduce the risk of acute respiratory infection (ARI) and diarrhea in children: a multi-country study? *PLoS ONE* 2017: **12**(1): e0169713.
17. Welaga P, Hodgson A, Debpuur C *et al.* Measles vaccination supports millennium development goal 4: increasing coverage and increasing child survival in Northern Ghana, 1996–2012. *Front Public Health* 2018: **6**: 28.
18. Sorup S, Benn CS, Poulsen A, Krause TG, Aaby P, Ravn H. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. *JAMA* 2014: **311**(8): 826–835.
19. Institute for Health Metrics and Evaluation (IHME). *Findings from the Global Burden of Disease Study 2017*. IHME: Seattle, WA, 2018.
20. Fink G, D'Acremont V, Leslie HH, Cohen J. 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* 2020: **20**(2): 179–187.
21. Wachter DA, Joshi MP, Rimal B. Antibiotic dispensing by drug retailers in Kathmandu, Nepal. *Trop Med Int Health* 1999: **4**(11): 782–788.
22. Diwan V, Sabde YD, Bystrom E, De Costa A. Treatment of pediatric diarrhea: a simulated client study at private pharmacies of Ujjain, Madhya Pradesh, India. *J Infect Dev Ctries* 2015: **9**(5): 505–511.
23. Saengcharoen W, Lerkiatbundit S. Practice and attitudes regarding the management of childhood diarrhoea among pharmacies in Thailand. *Int J Pharm Pract* 2010: **18**(6): 323–331.
24. Rogawski ET, Platts-Mills JA, Seidman JC *et al.* Use of antibiotics in children younger than two years in eight countries: a prospective cohort study. *Bull World Health Organ* 2017: **95**(1): 49–61.

25. Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. *Antimicrob Resist Infect Control* 2017: **6**: 47.
26. Tangcharoensathien V, Chanvatik S, Sommanustweechai A. Complex determinants of inappropriate use of antibiotics. *Bull World Health Organ* 2018: **96**(2): 141–144.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Definitions of the variables analysed.

Table S2. Determinants of disease prevalence as demonstrated by the odds ratio of having the illness given the presence of the variable in a bivariable and adjusted analysis (2006 data).

Table S3. Determinants of antibiotic use for ARI, fever and diarrhoea demonstrated by the odds ratio of antibiotic use given the presence of the variable in a bivariable and adjusted analysis (2006 data).

Table S4. Determinants of disease prevalence as demonstrated by the odds ratio of having the illness given the presence of the variable in a bivariable and adjusted analysis (2011 data).

Table S5. Determinants of antibiotic use for ARI, fever and diarrhoea demonstrated by the odds ratio of antibiotic use given the presence of the variable in a bivariable and adjusted analysis (2011 data).

Corresponding Author Charlotte Zheng, Chelsea and Westminster NHS Foundation Trust, West Middlesex University Hospital site, Twickenham Road, London, TW7 6AF, UK. E-mail: charlotte.zheng247@gmail.com