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ABSTRACT

Objectives There are no reliable data on antibiotic use in Kosovo hospitals. The aim of this survey was to monitor volumes and patterns of antibiotic use in hospitalised patients in order to identify targets for quality improvement.

Methods Data on antimicrobial use were collected from seven hospitals in Kosovo during 2013 using the standardised point prevalence survey (PPS) methodology as developed by the ESAC (European Surveillance of Antimicrobial Consumption) and ARPEC (Antibiotic Resistance and Prescribing in European Children). The survey included all inpatients receiving an antimicrobial agent on the day of the PPS.

Results Overall, 1667 patients were included in the study: adults 1345 (81%) and children 322 (19%). Of the hospital inpatients, 579/1345 (43%) adults and 188/322 (58%) children received at least one antibiotic during a hospital stay. The top three antibacterial subgroups (ATC level 3) were β-lactam antibiotics, cephalosporins and aminoglycosides. In all hospital centres, the most commonly prescribed antibiotic was ceftriaxone (39% for adult and 36% for children). Antibiotics were administered mainly parenterally in 74% of adults and 94% of children. Empirical prescribing was higher in adults 498/579 (86%) and children 181/188 (96%), compared with targeted treatment based on susceptibility testing—81 (14%) and 8 (4%), respectively.

Conclusions Antibiotic use in Kosovo's hospitals is very high. Gathered data will be an important tool to identify targets for quality improvement and will support preparation of guidelines and protocols for the prudent use of antibiotics.

What this paper adds?

What is already known on this subject?

- Point prevalence surveys have been used to provide information about the antimicrobial use.
- Few reports about higher consumption of antimicrobials in Kosovo have been published.
- Monitoring volumes and patterns of antibiotic use in hospital settings lacking.

What this study adds?

- Antibiotics in Kosovo hospitals are widely and irrationally prescribed.
- Empirical prescribing occurs more often than compared to targeted treatment.

INTRODUCTION

Antimicrobial resistance is one of the major challenges of public health worldwide with its impact on increasing morbidity, mortality and costs.[1 2] Inappropriate use of antimicrobial agents is the most important cause of emerging resistant microorganisms, their spread, and persistence in the community and hospitals.[3 4] There is a consensus that coordinated action and measures are needed in order to combat this phenomenon.[5]

High antibiotic consumption is attributed to non-restrictive prescription by doctors, high levels of medication prescription errors, over-the-counter sales, lack of consistent policy on antibiotic usage in different states and patient exposure to increasingly more virulent and resistant microorganisms.[6–8]

To establish a platform for rational and effective antibiotic prescription, it is necessary to establish monitoring of antimicrobial prescription.[9–11]

Point prevalence surveys have been used for over 20 years to provide information about antimicrobial use and to assess the effect of interventions, such as antibiotic policies. They are a simple and feasible way to collect data on antimicrobial use in hospitals and create an opportunity to stimulate local networking.[12]

Healthcare in Kosovo has undergone important reforms in the past decade while facing immense difficulties and obstacles, which are reflected also in the pharmaceutical section.[13] A functional representative system for surveillance of antimicrobial consumption and antimicrobial resistance has not been in place.

A recent study of antibiotic consumption, conducted by WHO in eastern Europe, showed that Kosovo had an overall consumption level of 26.3 DID (defined daily doses/1000 inhabitants/day) and is the European leader with the highest proportional total parenteral use of ceftriaxone.[14]

In view of this, we based our study on the research project 'Capacity building to implement state of the art surveillance systems for antibiotic consumption and resistance in Kosovo', which aims to increase research capacity in the public health sector in Kosovo in order to determine the prevalence of antibiotic-resistant bacteria and to improve the quality of antibiotic prescribing in Kosovo. (This project was financed by the European Union and implemented by the National Institute of Public Health of Kosovo in collaboration with the University of Antwerp, during 2012–2014.) Surveillance

of antimicrobial use in hospitals was the first component of this project and was conducted by a point prevalence survey (PPS). After this survey, we aimed to monitor the volumes and patterns of antibiotic use in hospital settings and identify targets for quality improvement in antimicrobial prescribing for children and adults.

MATERIAL AND METHODS

Initially, all protocols, forms and guidelines for surveillance of antibiotic consumption were prepared by the University of Antwerp team and translated into the native Albanian language.[15] The next step was training on PPS methodology for our team employed in data collection and analysis (physicians, microbiologists, hospital pharmacists, pharmacologists, nurses, etc), who implemented the standardised PPS.

Two different protocols were employed, one for data collection targeting hospitalised children aged <18 and neonates (ARPEC (Antibiotic Resistance and Prescribing in European Children) PPS), another protocol targeted hospitalised adults aged ≥18 (ESAC (European Surveillance of Antimicrobial Consumption) PPS).

A PPS was carried out during 2013 in six regional hospitals in Ferizaj, Gjakova, Gjilan, Mitrovica, Prizren, Peja and in the only tertiary healthcare centre with 2100 beds—University Clinical Centre of Kosovo (UCCK).

The surveys included all inpatients (adults, children and neonates admitted to medical, surgical and intensive care units) at 8:00 receiving antibiotic treatment. Detailed data were collected for each patient receiving at least one antimicrobial prescription on the day of the survey, including age, gender, weight (children only), antimicrobial agent (type, unit dose, times/day, route of administration and susceptibility testing), the ventilation modality (children), reason for treatment, type of treatment (empirical or targeted), underlying diagnosis (children only) and indication for treatment (healthcare-associated infection, community-acquired infection, medical or surgical prophylaxis). For surgical prophylaxis, duration was encoded as a single dose, 1 day or more than 1 day prophylactic prescribing. Since surgical departments were not audited on Monday, the audit of prophylaxis was conducted for the previous 24 hours.

Another objective of data collection was to determine if the reason for treatment was recorded in the notes. Data were collected from a patient's medical records, including the treatment cards, laboratory results and other official medical documents. Daily hospitalisations and outpatients, defined as ambulatory care patients and emergency admissions on the day of the survey, were excluded from the survey. Denominator data included all eligible inpatients on the day of the survey.

The WHO Anatomical Therapeutic Chemical (ATC) classification system of drugs was used to identify the antibiotic drugs with international non-proprietary names.[16] All antibacterial drugs for systemic use (ATC J01) and the antibiotics used in the treatment of tuberculosis (ATC J04) were included, whereas antimicrobials for topical use were not. Antimicrobial use was presented as the number of treated patients and the number of antimicrobial prescriptions expressed as a proportion. Bed occupancy rate was also calculated. Data entry was centralised at one centre, the National Institute of Public Health of Kosovo. To ensure privacy, all data collected were completely anonymous. Paediatric and neonatal antimicrobial use data were entered online using the ARPEC web-based tool for data entry, verification, validation and reporting. Adult PPS data were entered using an Excel spreadsheet in accordance with the ESAC PPS templates for data collection. The data were then validated and frequency distribution and χ^2 test (when indicated) were analysed. In this study, we analysed data using Graph Prism 6.0 software. The results are presented using descriptive statistics as means and percentages. Quantitative analysis was undertaken using a methodology based on defined daily dose/1000 inhabitants/day and ATC classification, according to WHO.[16]

RESULTS

The seven participating hospitals had a total of 4399 beds (mean, 628 beds; range 93–2100 beds). One hospital was a tertiary care hospital with 2100 beds (48% of the total beds in the seven hospitals) and six were secondary care hospitals with 2299 beds (52% of the total).

Overall, 1667 patients were included in the study: 1345 adults (81%) and 322 children (19%). The majority of patients came from UCCK—757 (45%). The mean hospital bed occupancy rate was 59% for adults and 47% for children. The highest bed occupancy in the adult group was noted in UCCK (70%), while the lowest was noted in Mitrovica and Gjilan hospitals (40% and 42%, respectively) (tables 1 and 2).

Of all recorded adult admissions, the special adult medical ward had 68% of patients, followed by the adult surgery department with 25% and the intensive care unit (ICU) with 7% of total inpatients (online supplementary table s1). The reasons for the treatment are shown in online supplementary table s3.

The mean bed occupancy of medical centres for children was lower (47%) and ranged from 24% in Prizren to 80% in Ferizaj hospital (table 2). Of all recorded child admissions, the general paediatric medicine ward accounted for 38%, followed by special paediatric medical ward with 26% of patients, and the neonatal ICU and general neonatal medical ward with 23% (online supplementary table s2). The reasons for the treatment are shown in online supplementary table s4.

A total of 579 (43%) adult hospital inpatients received at least one antibiotic during a hospital stay, including 40% men and 60% women, while for children hospital inpatients, 188 (59%)

Table 1 General data: adult patients

Hospital	Patients (n)	Treated patients n (%)	Statistical significance	Prescriptions n (%)	Bed occupancy (%)	Treated male/female patients n (%)	
UCCK	606	222 (36.6)		323 (37.9)	69.5	77/145	34.7/65.3
Prizren	220	117 (53.2)		182 (21.4)	59.4	47/70	40.2/59.8
Peja	190	100 (52.6)		176 (20.6)	58.4	46/54	46.0/54.0
Gjilan	120	41 (34.2)	χ2 test=15.14, p=0.019	52 (6.1)	41.6	19/22	46.3/53.7
Gjakova	138	63 (45.7)		77 (9.0)	57.2	25/38	39.7/60.3
Ferizaj	20	14 (70.0)		18 (2.1)	48.7	7/7	50.0/50.0
Mitrovica	51	22 (43.1)		24 (2.8)	39.8	9/13	40.9/59.1
Total	1345	579 (43.0)		852		230/349	39.7/60.3

Table 2 General data: child patients

Hospital	Patients (n)	Treated patients n (%)	Statistical significance	Prescription n (%)	Bed occupancy (%)	Treated male/female patients n (%)	
UCCK	151	92 (60.9)		149 (56.4)	54.3	47/45	51.1/48.9
Prizren	33	26 (78.8)		29 (11.0)	24.2	16/10	61.5/38.5
Peja	84	36 (42.9)		49 (18.6)	54.5	18/18	50.0/50.0
Gjilan	21	12 (57.1)	$\chi 2$ test=11.49, p=0.042	14 (5.3)	39.6	7/5	58.3/41.7
Gjakova	25	14 (56.0)		15 (5.7)	44.6	6/8	42.9/57.1
Ferizaj	8	8 (100.0)		8 (3.0)	80.0	7/1	87.5/12.5
Total	322	188 (58.4)		264		101/87	53.7/46.3

The Mitrovica Hospital is a newly established medical centre and working capacities did not achieve the satisfactory level of healthcare for children.

received at least one antibiotic, including 54% male and 46% female subjects.

The adult patients were in the following age categories: 394 (68%) were aged 18–64 years; 92 (16%) were aged 65–74 years and 93 (16%) were aged >75 years.

In the child cohort, 51 (27%) were neonates, 26 (14%) were aged 1–11 months, 64 (34%) were aged 1–4 years, 23 (12%) were 5–9 years old and 24 (13%) were 10–17 years old. The reasons and indications for antibacterial treatments in adults and children are shown in online supplementary tables s3 and s4.

The most common indications for treatment among adult patients were respiratory tract infection at 214 (24%), followed by prophylaxis in gynaecology and obstetrics 150 (17%). In 86 (10%) cases, antibacterial agents were prescribed to patients with the no signs of systemic or local infections.

Among children, the most common indications for treatment were bacterial lower respiratory tract infections in 54 (20%), followed by perioperative prophylaxis and sepsis in 41 (16%), and 29 (11%), respectively. In total, 12% of children were receiving non-invasive ventilation on the day of the survey.

Most adults and children received parenteral antibiotics 429 (74%) and 177 (94%) (online supplementary tables s1 and s2).

Empirical prescribing was higher in both adults and children 498 (86%) and 181 (96%), compared with targeted treatment based on susceptibility testing 81 (14%) and 8 (4%), respectively; ($p<0.001$). Also, a statistically significant difference was found between the prescribing of antibiotics in patients without or with an indication and also for prophylaxis in adults 86 (10%), 173 (20%) and 612 (70%) and in children 12 (6%), 139 (73%) and 38 (20%), respectively; ($p<0.001$).

Hence, no difference was found between the types of antibiotic prescribed between the mentioned groups.

The rates of antimicrobial prescription among adults ranged from 34% in Gjilan hospital to 70% in Ferizaj. This rate among children ranged from 43% in Peja hospital to 100% in Ferizaj (tables 1 and 2). Statistical differences (χ^2 test and p values) between the total numbers of patients prescribed antibiotics and patients treated with antibiotics in hospitals or ward type in adults and children are shown in (tables 1 and 2) (online supplementary tables s1 and s2). Other β-lactam antibacterial agents, cephalosporins (ATC class J01D) were most often prescribed among adults (50%), followed by drugs for the treatment of tuberculosis (J04A, 18%), aminoglycoside antibacterials (J01G, 14%) and β-lactam antibacterial agents, penicillins (J01C, 7%) (figure 1).

Among children, 24 different kind antibiotics were recorded, of which most often ceftriaxone (36%) followed by equal usage of three antimicrobials, vancomycin, imipenem, and ampicillin, each counted for 9% of the prescription s(figure 2).

In children, β-lactam antibacterials, cephalosporins (J01D) were most often prescribed (52%), followed by β-lactam antibacterials, penicillin's (J01C, 18%), aminoglycoside antibacterials (J01G) and other antibacterials (J01X) (both 12%) (figure 3).

During the survey, 36 different types of antimicrobials were prescribed among adults, of which most often ceftriaxone (39% out of all prescribed antibiotics) followed by gentamicin (12%), cefazolin (8%), metronidazole (6%) and ampicillin (4%) (figure 4).

DISCUSSION

This is the first country-wide PPS performed in all acute care settings in Kosovo using ESAC and ARPEC methodology. These protocols have been shown to be a useful and feasible method for collection and comparison of basic surveillance data on antimicrobial use among Kosovo hospitals and other countries.

UCCK was the largest hospital included in this study and admitted almost half of the enrolled patients (45%). The bed occupancy rate in UCCK was 70% and higher than in other regional hospital centres. Overall prescription rates were higher in children (59%) than in adults (43%). For adult patients a great variation among regional hospitals and UCCK is seen, ranging from 34% in Gjilan to 70% in Ferizaj, where the lowest number of inpatients—only 20—was found. Overall, antibiotic prevalence rates in Kosovo are much higher than those in Europe. The European Centre for Disease Prevention and Control reported that 35% of patients received at least one antimicrobial (country range 21–55%).[17] Antimicrobial prevalence rates among children are also much higher (59%) in comparison with the results of the Antibiotic Resistance and Prescribing in European Children Point Prevalence Survey conducted in European

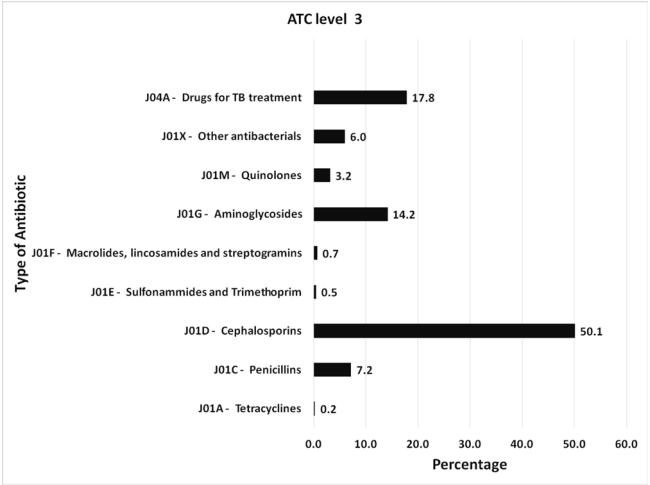

Figure 1 Antibiotic group prescription in adult patients.

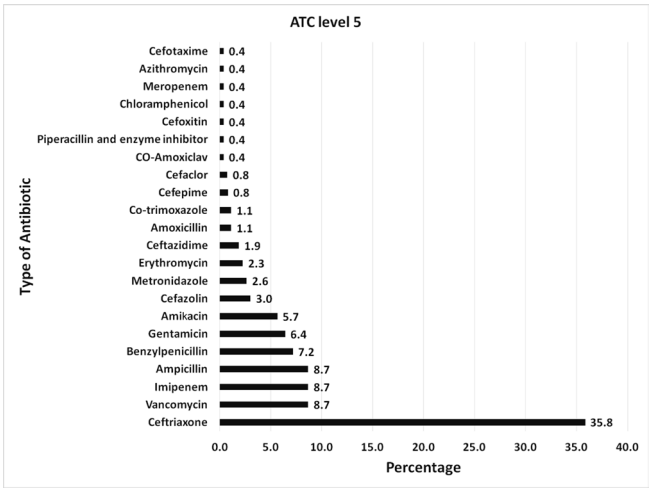

Figure 2 Antibiotic group prescription in child patients.

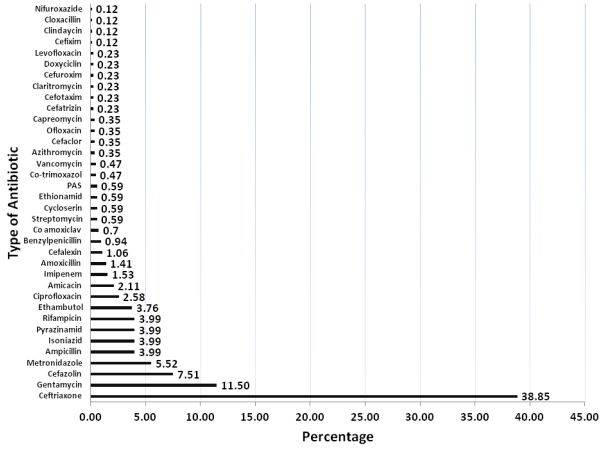

Figure 4 Type of antibiotic prescription in adult patients.

(35%; 95% CI 33% to 37%) and non-European hospitals (44%; 95% CI 41% to 46%).[18 19]

Of the patients who received antibiotics, most were treated in the department of general medicine (33%), while the prescription rate of antibiotics at a neonatal ICU and general neonatal medical ward, and a paediatric ICU was lower (33% and 2%, respectively). Our findings do not match those of some other surveys, where the highest prescription rate was registered in hospitalised patients within paediatric and neonatal ICUs.[20]

As in many other studies, the most common indications for treatment were respiratory tract infections, which is consistent with ESAC findings.[18 21]

Parenteral administration of antimicrobials is 74% in adult patients, which is comparable with European findings (71%; country range 48–91%), and 94% in children, which is higher than in Europe (82% in 2008 and 67% in 2012).[22]

The rate of targeted treatment was low for adult patients (14%) and very low for children (4%). Antibiotic prescription supported by microbiological susceptibility testing is considered to be an important factor in improving the success of treatment and shortening a patient's length of stay.[23 24] Based on our findings, treatment based on susceptibility testing was not found at Mitrovica Hospital; in UCCK it remains at 8%, The highest rate

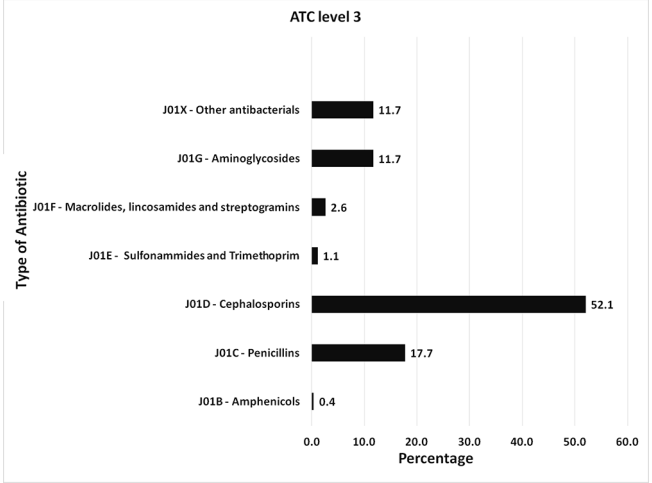

Figure 3 Type of antibiotic prescription in children patients.

registered was in Peja hospital (24%) because it is the only centre with clinical microbiology services within the hospital. All other clinical microbiology laboratories are placed within the Institutes of Public Health, which are separate from the hospitals. Since microbiological testing is not available in most patients, and does not become available for 24–72 hours, the initial treatment for infection is often empirical and guided by the clinical presentation.

A common approach is to use broad-spectrum antimicrobial agents or combinations. When microbiology results are available they tend to reduce costs and antibiotic toxicity and prevent antimicrobial resistance.[25] The small number of susceptibility tests found in our findings indicates that antibiotic therapy is widely used empirically or guided by the clinical presentation, which is an important finding. The lack of protocols in health facilities and insufficient collaboration between clinicians and microbiologists are additional contributors to this finding.

Prescription of cephalosporin antibiotics was higher than for other antibiotics among adults and children (50% and 52%, respectively), which does not conform to the antibiotic prescribing standards that recommend the penicillin group over other antibiotic groups. The use of mainly broad-spectrum, third-generation cephalosporins, including ceftriaxone, for empirical treatment of infection, reflects the substantial difference in prescription patterns from those seen in other European countries.[17]

Excessive use of ceftriaxone is an indicator of a non-rational antibiotic prescription, which needs to be urgently addressed, owing to its influence in triggering bacterial resistance, particularly for extended-spectrum β-lactamase.[26 27]

In the EU, the most frequently used classes of antimicrobials for systemic use are penicillins (31%), followed by other β-lactam antibacterials (28%). European prescribing patterns are characterised by the common use of a combination of penicillins, mainly β-lactam/β-lactam inhibitor (11% of all antimicrobial agents), in 79% of 17 European Hospitals (2000–2005).[28]

It is quite worrying to observe the very low usage of ampicillin, amoxicillin and other first-line antibiotics, which the literature confirms are more cost-effective, have fewer side effects and induce less bacterial resistance.[29]

Results show high prescription rates of aminoglycosides, which are the second most prescribed antibiotic group in adults (14%), and the third among children (12%). It is recommended that prescription of this group of antibiotics should be as

restrictive as possible and their use strictly monitored.[30] Very few narrow-spectrum antibiotics (benzylpenicillin, erythromycin, azithromycin, clarithromycin and vancomycin) are prescribed in Kosovo, which is not consistent with WHO rational prescribing recommendations.[31]

Reasons for not following a rational prescription of antibiotics include a lack of: protocols, susceptibility testing (this is reflected in the higher rate of empirical prescriptions, which we found in our study), prescription monitoring of antibiotics, decision-making by hospital pharmacists or clinical pharmacists (which has been recently introduced) and also no implementation of a stewardship programme in the health system of Kosovo.

Antibiotic misuse and resistance are a challenge for the healthcare system in Kosovo, based on reports from investigations from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) (Supplementary Table S5). The main problems in Kosovo remain over-the-counter sales of antibiotics (although prohibited by law), aggressive promotion by the pharmaceutical industry, a low level of awareness and education of the population and self-medication.

To deal with this public health concern, the Ministry of Health of Kosovo completed and approved the Strategy and Action Plan to Combat Antimicrobial Resistance in Kosovo 2011–2015. This strategy was established in collaboration with European Centre for Disease Prevention and Control and WHO and is based on the intersectoral mechanism of Kosovo, responsible for implementation of the action plan. The cornerstones of the strategy are surveillance of antimicrobial consumption and resistance, prudent use of antimicrobials in clinical practice and the veterinary sector, and infection control in healthcare settings. Surveillance of antibiotic use was examined for three sources: wholesale data, consumption in hospitals (presented in this study) and in primary care level.

The project enabled the respective structures of Kosovo to be part of international antimicrobial surveillance and this is continuing.

The role of hospital pharmacists in our study was in the use of the antimicrobials and the optimisation of treatment by coordinating with the responsible physicians. Their role is promising but is still desirable because decision-making and prescribing power belong to the physicians as observed in other related studies.[32]

This study had some limitations. We did not collect the data on clinical outcomes and duration of antimicrobial treatment. The data collection was manual and discrepancies were identified in patient data records, which required additional discussion with on-site healthcare staff. This was the first experience of data collection and participants might have had insufficient training.

In conclusion, antibiotic prescription for children and adults in Kosovo hospitals deviates from rational antibiotic prescription standards in European countries. The data from this study are an important tool to identify targets such as guideline compliance, routes of administration, hospital-acquired infections, consulting a physician, hospital pharmacists and medical microbiologists about increasing the level of susceptibility testing and decision in antimicrobial therapy and including in the notes the reason for prescribing the antimicrobials.[15] All these are necessary for quality improvement in Kosovo and will support the preparation of guidelines and protocols for prudent use of antibiotics. More should be done to ensure greater multidisciplinary cooperation for prudent use of antibiotics. One outcome after data dissemination has been the setting up of a working group by the Ministry of Health with a mandate to propose restrictions on the use of antibiotics in all levels of healthcare.

Contributors Substantial contributions to conception and design: HG, AV, SK, LR, AJ, DR, AD; acquisition of data: SK, AJ, DR, VK, ZD, AR, NB, SH, JB, BN; drafting the article or revising it critically for intellectual content: HG, AV, SK, AD, AJ and final approval of the version to be published: HG, AV, SK, LR, AD, AJ.

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