IJID Regions 1 (2021) 65–71

Contents lists available at ScienceDirect

IJID Regions

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

Trends in antimicrobial consumption in Bhutan

Thupten Tshering [a,*], Sonam Wangda [b], Kirsty Buising [c]

[a] Department of Pharmacy, Jigme Dorji Wangchuk National Referral Hospital, Thimphu, Bhutan
[b] Department of Medical Services, Ministry of Health, Thimphu, Bhutan
[c] National Centre for Antimicrobial Stewardship, Royal Melbourne Hospital, Melbourne, Australia

ARTICLE INFO

Keywords:
Antimicrobial consumption
Antimicrobial resistance
Defined daily dose
trends
surveillance
broad-sepectrum antibiotic

ABSTRACT

Introduction: Antimicrobial use has been recognized as one of the main drivers of antimicrobial resistanceand it is, therefore, crucial to monitor the consumption and use of antimicrobials. This study was conducted to determine the consumption of antimicrobials in terms of defined daily doses (DDDs) per 1000 inhabitants per day (DIDs) at both national and dzongkhag levels in Bhutan, and to investigate trends from 2017 to 2019.

Methods: A retrospective analysis of antimicrobial consumption in healthcare facilities in Bhutan from 2017 to 2019 was undertaken using the national records of annual distribution of medicines. World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System/DDD methodology was used for data collection and analysis.

Results: In 2019, the consumption of antimicrobials (ATC subgroup J01) for systemic use in healthcare facilities in Bhutan was 16.29 DIDs, compared with 14.39 DIDs in 2018 and 13.27 DIDs in 2017. The most commonly used subgroup of antimicrobials was the penicillin group of beta-lactams (J01C).

Conclusion: Antimicrobial consumption in Bhutan was found to be lower than the European Union and European Economic Area average, and lower compared with most Eastern European countries and some countries in the Western Pacific region. However, overall consumption in Bhutan increased steadily over the 3-year study period. This should be monitored carefully, and appropriate interventions to optimize antimicrobial use should be put in place in the near future.

Introduction

Antimicrobial resistance (AMR) is an emerging global threat to human health (Prestinaci et al., 2015; Roca et al., 2015). While existing antimicrobial agents are increasingly being rendered ineffective due to emergence of resistant pathogens, few new antibiotics are available, especially in low- and middle-income countries (World Health Organization, 2017). Extended-spectrum beta-lactamase (ESBL)-producing Gram-negative organisms, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci have all been reported in these settings, and the recent report of pan-drug-resistant *Acinetobacter baumanii* adds to concerns regarding the looming catastrophe (Manchanda et al., 2010; World Health Organization, 2014a). Antibiotic use is one of the main drivers of AMR (Goossens et al., 2005; Manchanda et al., 2010). Although the emergence of AMR is a natural phenomenon, the use of antimicrobials hastens the process by providing selection pressure. Reduction in inappropriate use of antimicrobials is therefore crucial to slow down the emergence and spread of resistance. However, the US Centers for Disease Control and Prevention estimates that at least 30% of antibiotic prescriptions are inappropriate (US Centers for Disease Control and Prevention, 2016).

Surveillance of antimicrobial consumption and use can provide useful information on patterns of antimicrobial use, and can be of help in identifying inappropriate use. Generation of evidence on AMR and antimicrobial use through surveillance is one of the objectives of the Global Action Plan on AMR (World Health Organization, 2015). The World Health Organization (WHO) has initiated a global programme for surveillance of antimicrobial consumption to provide countries with a common methodology for reporting (World Health Organization, 2014b). The methodology utilizes the WHO Anatomical Therapeutic Chemical (ATC) Classification System and defined daily doses (DDDs) (WHO Collaborating Centre for Drug Statistics Methodology, 2019). WHO also promotes use of the AWaRe classification, which groups antibiotics into Access, Watch and Reserve categories to guide monitoring of antimicrobial consumption and use (World Health Organization, 2019). Although, to the authors' knowledge, noreports have been published on AMR patterns in Bhutan, anecdotal evidence points to the emergence and spread of multi-drug-resistant Gram-negative or-

* Corresponding author. Address: Department of Pharmacy, JDWNR Hospital, Menkhang Lam, Thimphu, Bhutan.
E-mail address: thuptent@jdwnrh.gov.bt (T. Tshering).

https://doi.org/10.1016/j.ijregi.2021.09.009
Received 28 July 2021; Received in revised form 9 September 2021; Accepted 26 September 2021

ganisms including *Escherichia coli, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and carbapenem-resistant *A. baumanii*. High resistance of *Helicobacter pylori* to metronidazole has been reported (Vilaichone et al., 2013). This could have a causal relationship with the perceived increase in antimicrobial consumption, including critical antimicrobials.

In Bhutan, all antimicrobials for systemic use in humans require a prescription. Medications are primarily dispensed from pharmacies in government healthcare facilities as part of primary and secondary healthcare service delivery. There are no private primary care clinics or hospitals. Medications are also dispensed from private pharmacies and in the military service setting, but consumption from sources other than government healthcare facilities still remians negligible. Private importation of medications from neighbouring countries (mainly India) is uncommon.

This study was conducted to determine the national consumption of antimicrobials for systemic use in terms of DDDs per 1000 inhabitants per day (DIDs). This was assessed nationally and at dzongkhag (administrative district) level from 2017 to 2019. The proportions of antimicrobials consumed were assessed by both pharmacological and AWaRe categories.

Methods

Data source

Information on quantities of antimicrobial consumption was obtained from the annual medicine distribution record maintained with the the Healthcare Diagnostics Division, Department of Medical Services, Ministry of Health from 2017 to 2019. The distribution record contains the annual quantities of medicines [from the National Essential Medicines List (NEML)] distributed to the healthcare facilities in each dzongkhag. Information on the consumption of broad-spectrum antibiotics reserved for serious/life-threatening infections was obtained from the Named-patient Medicines Unit of the major referral hospital in Bhutan (Jigme Dorji Wangchuk National Referral Hospital). Named-patient medicines refer to non-formulary medicines which physicians are required to request for supply to individual patients, and should not be confused with the system for pre-approval access in other countries. Carbapenems and colistins are only made available on a named-patient basis, and this serves as a control measure similar to that of antimicrobial pre-authorization.

The analysis included antibacterials for systemic use (ATC subgroup J01). Antivirals, antifungals, antituberculosis drugs, antileprosy drugs and antimalarial drugs were excluded. Topical antibiotics were also excluded. Consumption from private pharmacies and military hospitals was excluded from the dataset.

Measures of antibiotic consumption

Antimicrobial consumption data were standardized according to the WHO ATC classification with DDD used as the measurement unit (WHO Collaborating Centre for Drug Statistics Methodology, 2019). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Antimicrobial consumption for each year was expressed as DID for national consumption and consumption by each dzongkhag. This involved assigning DDDs to the formulations of antimicrobials on the NEML and those available on a named-patient basis, in accordance with the WHO ATC/DDD index (2020 version) (WHO Collaborating Centre for Drug Statistics Methodology, 2020). The total DDD for each item consumed was calculated by multiplying the quantity of the item with the corresponding strength in grams, and then dividing by the DDD. Data analysis was undertaken using Excel (Microsoft Corp., Redmond, WA, USA).

Table 1
Total consumption of antimicrobials (World Health Organization Anatomical Therapeutic Chemical Classification System subgroup J01) in defined daily doses (DDDs) and DDDs per 1000 inhabitants per day (DIDs).

Year	Total DDDs	Population	DIDs
2017	3,531,524	729,162[a]	13.27
2018	3,866,872	736,252[b]	14.39
2019	4,407,263	741,324 [b]	16.29

[a] Population and Housing Census of Bhutan, 2017.
[b] Population projected from 2017 census, based on the percentage change in population from the Population and Housing Census of Bhutan, 2005.

Population

The population of Bhutan and its dzongkhags was based on the Population and Housing Census of Bhutan, 2017 (National Statistics Bureau of Bhutan, 2018). Changes in the population in subsequent years were derived from the percentage change in population from the Population and Housing Census of Bhutan (Office of the Census Commissioner, 2005).

Result

Overall consumption

In 2019, the overall consumption of antimicrobials (ATC subgroup J01) for systemic use in healthcare facilities in Bhutan was 16.29 DIDs. The DIDs in 2018 and 2017 were 14.39 and 13.27, respectively. Table 1 shows antimicrobial consumption in the healthcare facilities in Bhutan from 2017 to 2019.

Antimicrobial consumption in DIDs showed wide variation between dzongkhags. In 2019, DIDs ranged from 2.94 for Haa to 23.9 for Mongar. In 2018, DIDs ranged from 2.98 for Haa to 23.24 for Zhemgang. In 2017, DIDs ranged from 5.30 for Bumthang to 22.36 for Trashigang (Figure 1). Figure 2 shows a map of Bhutan depicting variations in antimicrobial consumption in the dzongkhags.

Consumption by antimicrobial subgroup

In 2019, the penicillin group of beta-lactams (J01C) was the most commonly consumed subgroup of antimicrobials, accounting for 55% of total DIDs, followed by tetracyclines (J01A, 19%), sulfonamides and trimethoprim (J01E, 11%), and quinolones (J01M, 6%). Macrolides (J01F) and aminoglycosides (J01G) accounted for 3% and 1% of total DIDs, respectively. The consumption of other beta-lactams (J01D) accounted for 1% of total DIDs. Subgroups such as glycopeptides were very rarely used.

The proportions of antimicrobial consumption in 2018 were not very different from 2019. However, notable changes in consumption were observed from 2017 to 2018. In 2017, the proportion of the penicillin group of beta-lactams (J01C) was 59% while that of tetracyclines (J01A), and sulfonamides and trimethoprim (J01E) were 15% and 13%, respectively. Figure 3 shows consumption of various groups of antimicrobials by ATC class for the three consecutive years.

Consumption of broad-spectrum antibiotics reserved for serious infections

Broad-spectrum antimicrobials including piperacillin-tazobactam, meropenem and polymixin B are made available only on a named-patient basis, and are mainly used in the three referral hospitals (based in Thimphu, Mongar and Sarpang).

In 2019, the DIDs of piperacillin-tazobactam and meropenem nationally were 0.027 and 0.021, respectively. Consumption of polymixin

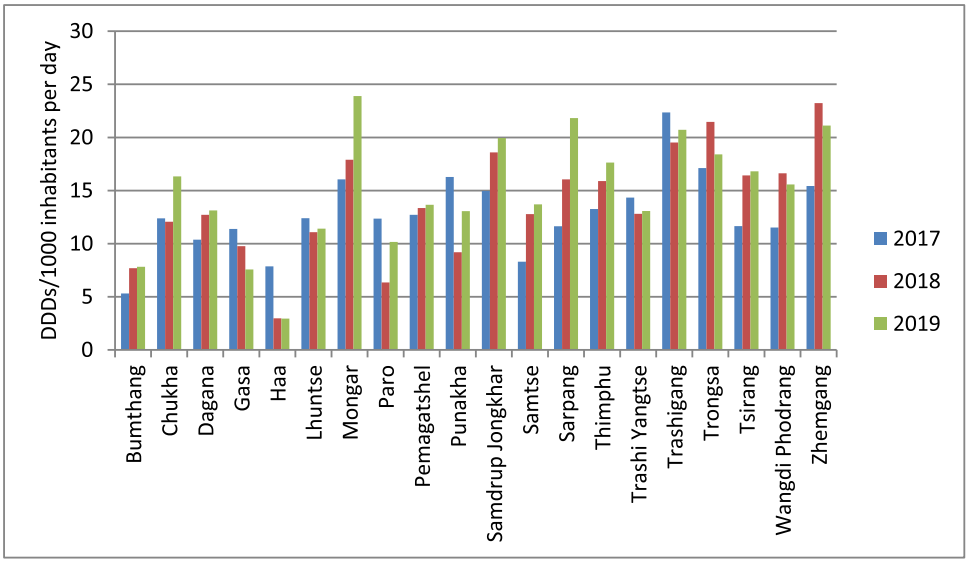

Figure 1. Consumption of antimicrobials (World Health Organization Anatomical Therapeutic Chemical Classification System subgroup J01) by Dzongkhag in defined daily doses (DDDs) per 1000 inhabitants per day.

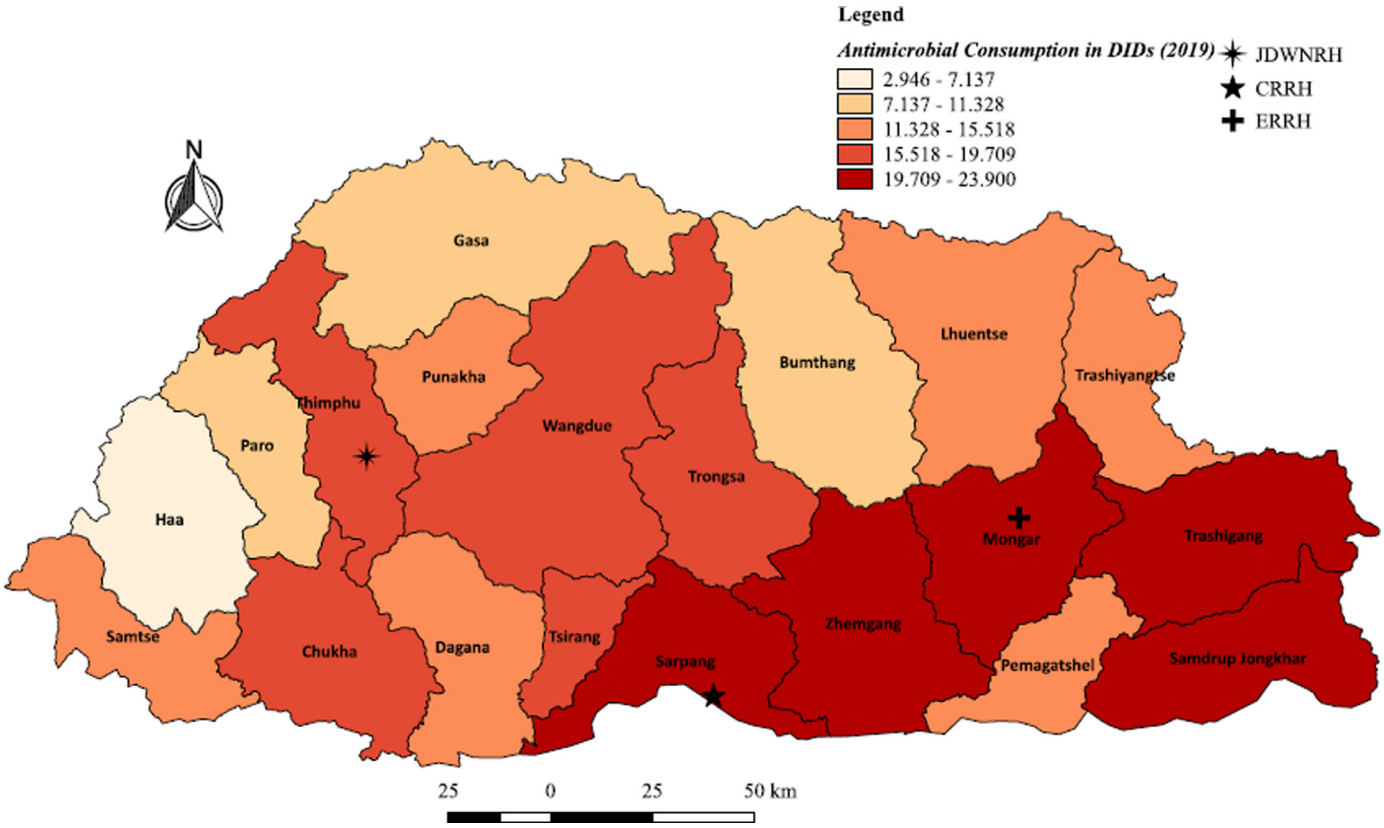

Figure 2. Map of Bhutan showing antimicrobial consumption in defined daily doses per 1000 inhabitants per day (DIDs) by dzongkhag for 2019.

B in 2019 was 0.001 DIDs only. Trends in national consumption of piperacillin-tazobactam and meropenem are shown in Figure 4. Furthermore, trends in consumption of piperacillin-tazobactam and meropenem in the three dzongkhags within which the referral hospitals are located are shown in Figures 5 and 6, respectively.

Consumption of antimicrobials by AWaRe category

In 2019, 88.21% of the total DDDs of antimicrobials consumed were from the Access group of AWaRe categories, while 11.78% were from the Watch group. Only 0.01% of the antimicrobials consumed were from the Reserve group. Figure 7 shows the proportion of antimicrobials consumed by AWaRe category.

Discussion

Similar to other countries in the region, the focus of surveillance to date in Bhutan has been on AMR. Surveillance of antimicrobial consumption has not been undertaken, despite ready access to information on antimicrobial consumption and use in hospitals, in the absence of a surveillance system for antimicrobial consumption in the country. Antimicrobial consumption in Bhutan is largely restricted to the public

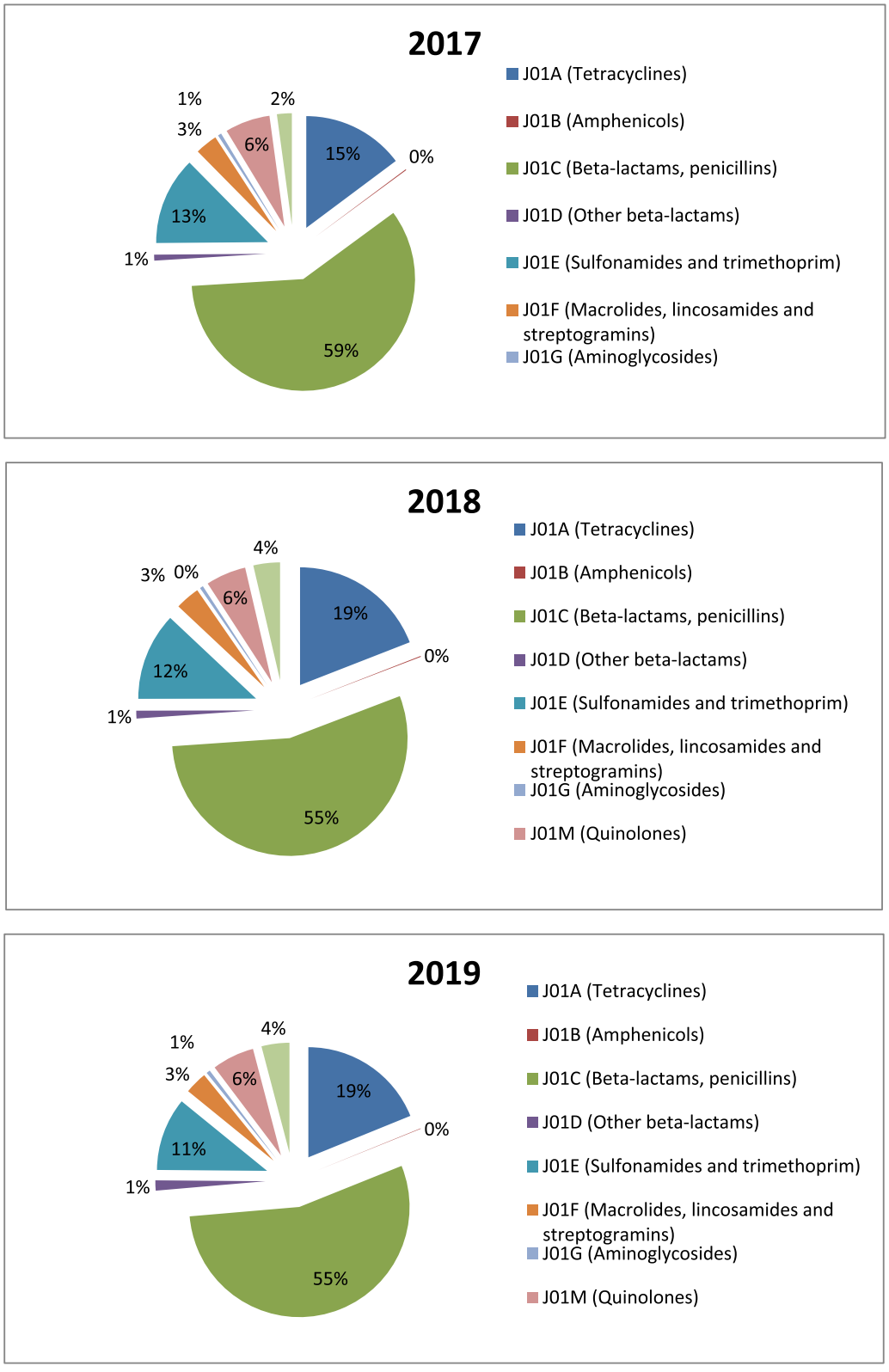

Figure 3. Proportions of antimicrobials consumed by World Health Organization Anatomical Therapeutic Chemical Classification System subgroup from 2017 to 2019.

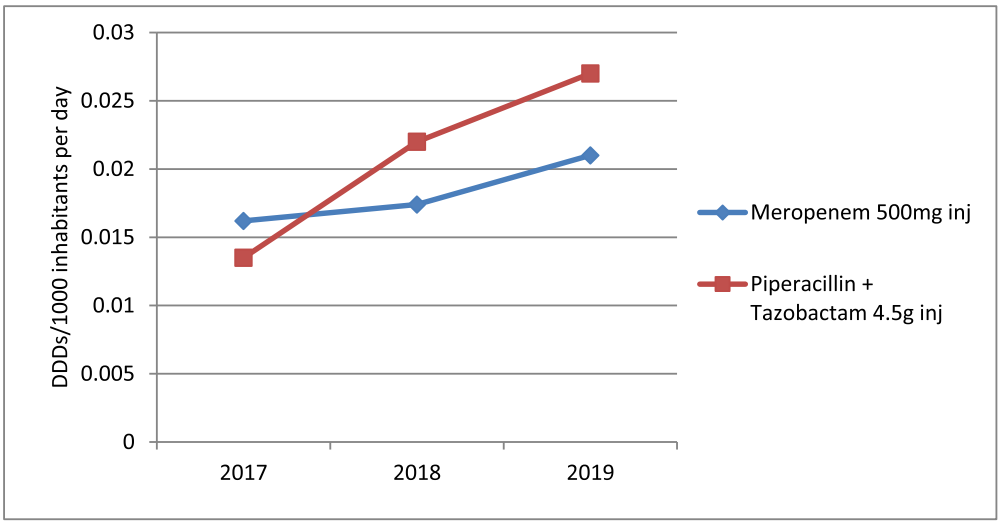

Figure 4. Trends in consumption of piperacillin-tazobactam and meropenem from 2017 to 2019. DDDs, defined daily doses.

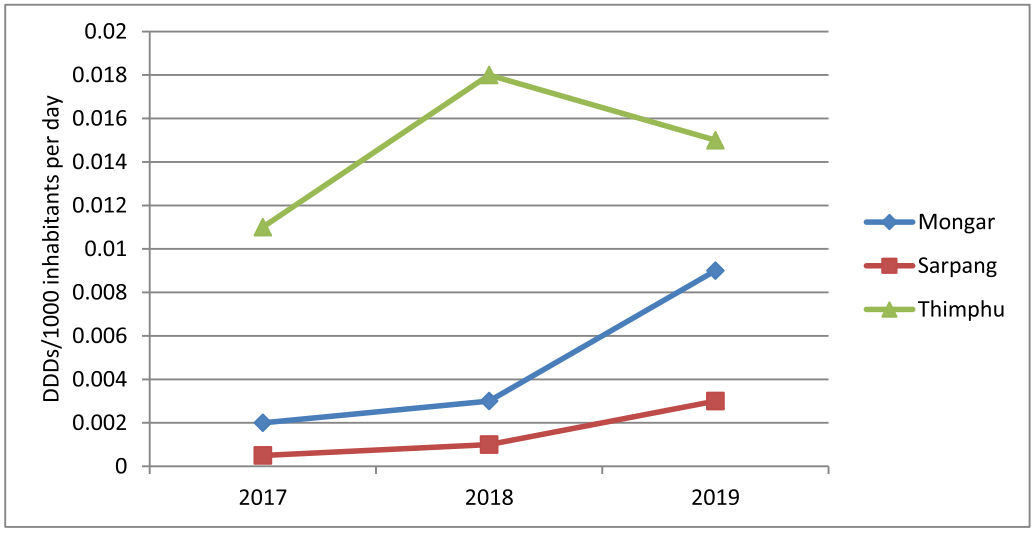

Figure 5. Trends in consumption of piperacillin-tazobactam injection in the three dzongkhags with referral hospitals from 2017 to 2019. DDDs, defined daily doses.

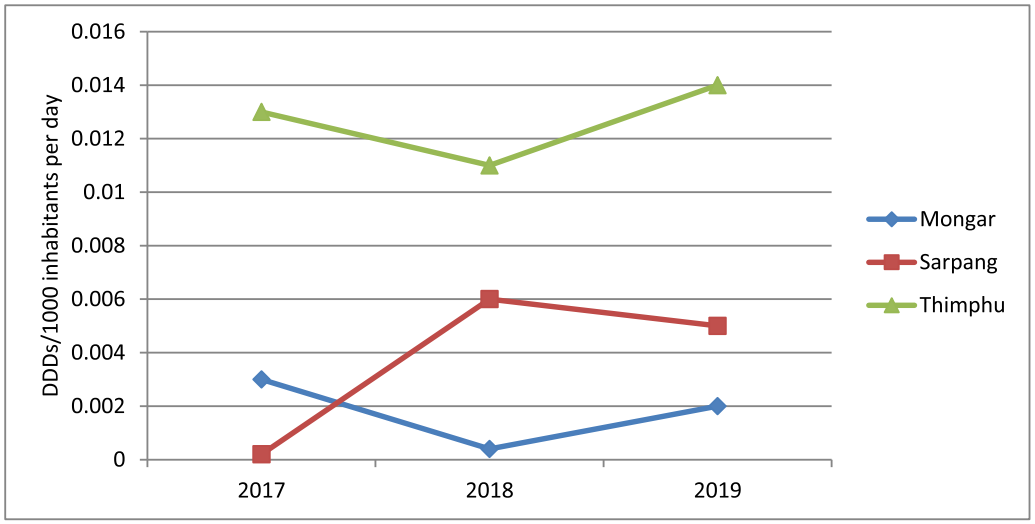

Figure 6. Trends in consumption of meropenem in the three dzongkhags with referral hospitals from 2017 to 2019. DDDs, defined daily doses.

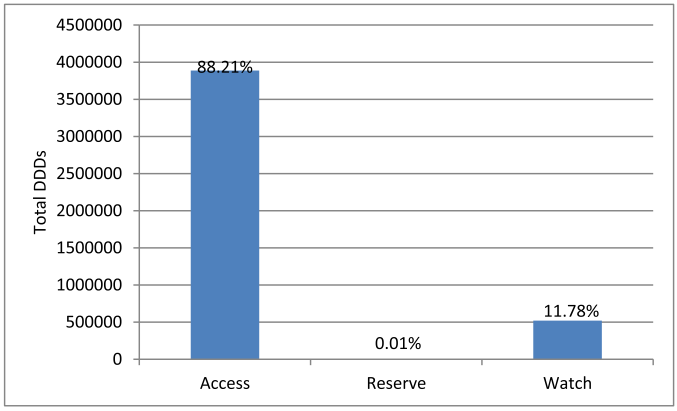

Figure 7. Proportion of antimicrobials (World Health Organization Anatomical Therapeutic Chemical Classification System subgroup J01) consumed by AWaRe category in 2019. DDDs, defined daily doses.

healthcare sector, and should, therefore, be representative of national consumption. Antimicrobials for use in public healthcare facilities are procured centrally and distributed to the healthcare facilities. Therefore, the record of distribution of antimicrobials to the healthcare facilities was found to be the most reliable source of data for the analysis of antimicrobial consumption at national level. Consumption of antimicrobials from private pharmacies and military hospitals was excluded from this study due to the lack of a reliable data source. In addition, the contribution of sales from private pharmacies to national antimicrobial consumption is considered to be negligible.

The availability of antimicrobials depends on the level of the healthcare facility and is restricted by formulary. Broad-spectrum beta-lactams and carbapenems are excluded from the NEML, and are provided only on a named-patient basis. These antimicrobials are used primarily in the three referral hospitals, and this should, therefore, be considered representative of consumption for the whole country.

In Bhutan, national antibiotic consumption in 2019 was 16.29 DIDs. This is lower than the European Union and European Economic Area (EU/EEA) average of 19.4 DIDs (community and hospital consumption combined) for the same year (European Centre for Disease Prevention and Control, 2020). It is also lower than the DIDs for most Eastern European countries and some countries in the Western Pacific region, including Mongolia and New Zealand (Versporten et al., 2014; World Health Organization, 2018). While direct comparison could not be drawn with consumption patterns from other countries in the same region due to a lack of comparable data, a consumption study undertaken in India based on the import data from 2008 to 2012 showed a similar pattern (Farooqui et al., 2018). While the current DID for overall antibiotic consumption in Bhutan is lower compared with many other countries around the world, the rate at which consumption has been increasing is a concern.

A wide variation in DIDs for overall antimicrobial consumption was observed between the dzongkhags. This could be attributed to prevailing differences in prescribing practices between the dzonghags. Doctors in Bhutan undergo their medical education in neighbouring countries and are exposed to varying prescribing practices. Therefore, despite the availability of national antibiotic guidelines, adherence to these guidelines is unknown. Another factor that could have contributed to the variation is the difference in prevalence and rate of infections in dzongkhags due to differing climatic conditions. Dzongkhags in the northern part of Bhutan, which are generally alpine areas, had low DIDs in general (Bumthang, Haa and Gasa), while dzongkhags in the southern belt with subtropical climatic conditions (Chukha, Samdrup Jongkhar, Sarpang and Zhemgang) had higher DIDs. The dzongkhags with a high population density and a large urban population also had significantly higher DIDs for antimicrobial consumption. On the other hand, the dzongkhags with a low population density and a smaller urban population had low DIDs, as exemplified by Haa and Gasa. The three dzongkhags with referral hospitals (Mongar, Sarpang and Thimphu) had high DIDs, as people likely travelled to these areas for more complex care.

Increases in DIDs were observed for Mongar, Sarpang, Thimphu, Samtse and Samdrup Jongkhar from 2017 to 2019. Gasa was the only dzongkhag which had a decrease in DIDs over the 3-year study period. The DIDs of other dzongkhags generally remained consistent.

The patterns of consumption by antimicrobial subgroup in Bhutan were similar to EU/EEA average consumption in the community (European Centre for Disease Prevention and Control, 2020). The penicillin group of beta-lactam antibacterials (J01C) was the most commonly used antimicrobial subgroup. This was due to the overwhelming use of oral amoxicillin in healthcare facilities in Bhutan. Amoxicillin remains the antimicrobial of choice for many indications, mainly in the outpatient setting, such as treatment of upper respiratory tract infections and periodontal infections.

Despite doxycycline being the only tetracyline available on the NEML, J01A was the second most commonly consumed antimicrobial subgroup. Doxycycline is available across health facilities, and is increasingly being used empirically for the treatment of rickettsial diseases (which are common in Bhutan in the southern and central dzongkhags), gynaecological infections and dermatological indications.

Consumption of other beta-lactam antibacterials (J01D) accounted for just 1% of total antibacterial consumption, which is much lower than the EU/EEA average (European Centre for Disease Prevention and Control, 2020). This is because third-generation cephalosporins, including ceftriaxone and cefotaxime are available only at the referral hospitals in Bhutan, and meropenem, the sole carbapenem in use, is available only on a named-patient basis. The consumption of sulphonamides and trimethoprim (J01E) in Bhutan was similar to the EU/EAA average, but consumption of macrolides (J01F) was much lower. This low consumption could be attributed to unavailability of higher-generation macrolides. Erythromycin was the only macrolide available for use during the study period, and is not generally preferred over other available antimicrobials.

Compared with the EU/EEA average consumption of carbapenems (in the hospital sector) of 0.04 DIDs, 0.021 DIDs of meropenem (which corresponds to total carbapenem consumption) for Bhutan could be considered low (European Centre for Disease Prevention and Control, 2020). However, the gradual increase seen over the 3-year study period is a concern. There has been an overall increase in consumption of both piperacillin-tazobactam and meropenem from 2017 to 2019. The findings may correlate well with the increased incidence rates of ESBL-producing organisms in the country. Antimicrobial stewardship interventions would be required to help optimize the use of this restricted group of antibiotics.

In Bhutan, 88.21% of antimicrobials consumed were from the Access group of AWaRe categories, which is much higher than what have been reported elsewhere (Nguyen et al., 2020; Pauwels et al., 2021). This indicates that these common antimicrobials are being used to treat infections without having to resort to other critical broad-spectrum antimicrobials.

This study only gives a very broad snapshot of antibiotic consumption in Bhutan. Qualitative studies looking at the indications and appropriateness of use are required for further understanding of antimicrobial usage behaviours in Bhutan.

Conclusion

Overall consumption of antimicrobials in Bhutan, as measured by DIDs, does not appear to be high when compared with the EU/EEA average and other countries in the region, despite the lack of structured antimicrobial stewardship programmes in the country. Nevertheless, it should be noted that antimicrobial consumption increased steadily over the 3-year study period. A wide variation in antimicrobial consumption

was found between the dzongkhags, indicating possible variation in prescribing practices. Studies to assess appropriate use of antimicrobials, including adherence to the national antibiotic guidelines, are needed. While the DIDs of broad-spectrum antimicrobials are low compared with those in other countries, their consumption increased over the 3-year study period in Bhutan. Their use should be monitored further, and appropriate stewardship interventions should be implemented accordingly. It is encouraging to see that the antimicrobials used in Bhutan are overwhelmingly from the Access group of AWaRe categories and this should be sustained. With the recent piloting of antimicrobial stewardship programmes in hospitals in Bhutan, it is expected that the consumption of antimicrobials will be better understood and efforts will be made to ensure that use is optimized.

Acknowledgements

The authors wish to thank the Healthcare and Diagnostics Division, Department of Medical Services, Ministry of Health, Royal Government of Bhutan for granting access to the distribution records of Medicines for 2016–2017, 2017–2018 and 2018–2019; Named-patient Medicines Unit, Department of Pharmacy, JDWNR Hospital for providing access to records of issue of broad-spectrum antibiotics made to hospitals; and Dr. Ugyen Namgay, National Centre for Animal Health, Royal Government of Bhutan for helping to illustrate antimicrobial consumption on a map of Bhutan.

Conflict of interest statement

None declared.

Funding

This study was performed in partial fulfilment of Fellowship in Antimicrobial Consumption from the Fleming Fund, UK.

Ethical approval

This study did not require approval from the Research Ethics Board of Health, Ministry of Health as it did not involve the use of patient data. Administrative clearance was obtained from the Ministry of Health, Royal Government of Bhutan.

References

European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA – Annual Epidemiological Report 2019. Stockholm: ECDC; 2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/Antimicrobial-consumption-in-the-EU-Annual-Epidemiological-Report-2019.pdf (accessed 12 October 2021).

Farooqui HH, Selvaraj S, Mehta A, Heymann DL. Community level antibiotic utilization in India and its comparison vis-à-vis European countries: evidence from pharmaceutical sales data. PLoS One 2018;13:1–11.

Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005;365:579–87.

Manchanda V, Sinha S, Singh N. Multidrug resistant Acinetobacter. J Glob Infect Dis 2010;2:291.

National Statistics Bureau of Bhutan. Population and Housing Census of Bhutan 2017. Thimphu: National Statistics Bureau of Bhutan; 2018 Available at: https://www.nsb.gov.bt/publications/census-report/ accessed 12 October 2021.

Nguyen NV, Do NTT, Nguyen CTK, Tran TK, Ho PD, Nguyen HH, et al. Community-level consumption of antibiotics according to the AWaRe (Access, Watch, Reserve) classification in rural Vietnam. JAC Antimicrob Resist 2020;2:1–8.

Office of the Census Commissioner. Results of Population and Housing Census of Bhutan 2005. Thimphu: Office of the Census Commissioner; 2005.

Pauwels I, Versporten A, Drapier N, Vlieghe E, Goossens H. Hospital antibiotic prescribing patterns in adult patients according to the WHO Access, Watch and Reserve classification (AWaRe): results from a worldwide point prevalence survey in 69 countries. J Antimicrob Chemother 2021;76:1614–24.

Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health 2015;109:309–18.

Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S, et al. The global threat of antimicrobial resistance: science for intervention. New Microb New Infect 2015;6:22–9.

US Center for Disease Control and Prevention. CDC: 1 in 3 antibiotic prescriptions unnecessary. Atlanta, GA: CDC; 2016 Available at: https://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html accessed 12 October 2021.

Versporten A, Bolokhovets G, Ghazaryan L, Abilova V, Pyshnik G, Spasojevic T, et al. Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. Lancet Infect Dis 2014;14:381–7.

Vilaichone R, Yamaoka Y, Shiota S, Ratanachu-ek T, Tshering L, Uchida T, et al. Antibiotic resistance rate of Helicobacter pylori in Bhutan. World J Gastroenterol 2013;19:5508–12.

WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2020. 23rd edn. Oslo: WHOCC; 2019.

WHO Collaborating Centre for Drug Statistics Methodology. ATC index with DDDs. Oslo: WHOCC; 2020 Available at: https://www.whocc.no/atc_ddd_index/ accessed 12 October 2021.

World Health Organization. Antimicrobial resistance – global report on surveillance. Geneva: WHO; 2014a.

World Health Organization. WHO methodology for a global programme on surveillance of antimicrobial consumption. Geneva: WHO; 2014b Available at: http://www.who.int/medicines/areas/rational_use/WHO_AMCsurveillance_1.0.pdf accessed 12 October 2021.

World Health Organization. Global action plan on antimicrobial resistance. Geneva: WHO; 2015.

World Health Organization. Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: WHO; 2017 Available at: https://apps.who.int/iris/bitstream/handle/10665/258965/WHO-EMP-IAU-2017.11-eng.pdf;sequence=1 accessed 12 October 2021.

World Health Organization. WHO report on surveillance of antibiotic consumption: 2016–2018 early implementation. Geneva: WHO; 2018 Available at: http://apps.who.int/iris%0Ahttps://apps.who.int/iris/bitstream/handle/10665/277359/9789241514880-eng.pdf accessed 12 October 2021.

World Health Organization. The 2019 WHO AWaRe classification of antibiotics for evaluation and monitoring of use. Geneva: WHO; 2019.