CAPTURA Country Report:

Kingdom of Bhutan

February 2023

CAPTURA
Capturing data on Antimicrobial resistance Patterns and Trends in Use in Regions of Asia

MOTT MACDONALD

UKaid
from the British people

The Fleming Fund
Regional Grants

Contributions

The team involved in the CAPTURA work for Bhutan includes (in alphabetical order), Ahmed Taha Aboushady, Emmanuel Eraly, Kevin Chi, Patrick Gallagher, Marianne Holm, Hea Sun Jenny Joh, William MacWright, Kien Duc Pham, Nimesh Poudyal, Kristi Prifti, Raghunath Sharma, John Stelling, Julhas Sujan, Benjamin Taylor, Tshokey Tshokey, Sonam Wangda, Pema Yangzom and Corin Yeats.

Coordinating authors for this report: Nimesh Poudyal, Patrick Gallagher, Hea Sun Jenny Joh, Kristi Prifti, Emmanuel Eraly, Kevin Chi, William MacWright & Marianne Holm

Design by Grace Jun (IVI)

CAPTURA consortium executive group:
Florian Marks (Project Director) & Nimesh Poudyal (Technical Lead), International Vaccine Institute
William MacWright (Public Health Surveillance Group)
John Stelling (WHONET, Brigham & Women's Hospital, Harvard Medical School)
David M Aanensen (Big Data Institute, University of Oxford)

CAPTURA Consortium

The CAPTURA consortium is led by the International Vaccine Institute (IVI), and includes as partners, the Public Health Surveillance Group (PHSG), Harvard Medical School's Brigham & Women's Hospital (BWH) and Oxford University's Big Data Institute (BDI).

Acknowledgements

The Fleming Fund is a £265 million UK aid investment to tackle antimicrobial resistance in low- and middle-income countries around the world. The program is managed by the UK Department of Health and Social Care, in partnership with Mott MacDonald, the Fleming Fund Grants Management Agent. This work was supported by the Fleming Fund Regional Grants (grant numbers FF10-135 and FF11-139).

CAPTURA extends sincere gratitude to our country coordinator, consultant microbiologist and entire team for supporting data collection and effective liaison with in-country stakeholders. We are also grateful to the entire Fleming Fund Project team at Department of Medical Services, Ministry of Health, Royal Government of Bhutan for close engagement and support extended for implementation of the project in the country.

Use of Document

This is the final report that summarises CAPTURA engagements and activities conducted in Bhutan. It is written to help inform planning future investments in combatting AMR in the Asian Region and beyond. As such, it is aimed at any individual or organization interested and/or active in the field of antimicrobial resistance (AMR) surveillance and research, funding of AMR initiatives including policy and regulatory decision-making, and infectious disease prevention and control programs in Bhutan, the Asian region and beyond. This covers sectors such as academia, government, philanthropy, the private sector, supranational organizations, and the general public.

The findings presented in this report have been generated based on data collected directly as part of the CAPTURA project as well as on previously generated original data shared based on the agreement between Department of Medical Services, Ministry of Health, Royal Government of Bhutan and the International Vaccine Institute. The use and/or reproduction of data or other report contents without agreement of the International Vaccine Institute and the Royal Government of Bhutan (as relates to original data contents) is not permitted.

Suggested citation: Final Report Kingdom of Bhutan, Capturing Data on Antimicrobial Resistance Patterns and Trends in Use in Regions of Asia, 2022, International Vaccine Institute, Seoul, South Korea

Executive Summary

As part of the large Fleming Fund (FF) portfolio of grants funded by the Government of the United Kingdom and established as a response to the global problem of AMR, in 2019 the CAPTURA project was awarded with the specific objective of expanding the volume of historical data on antimicrobial resistance (AMR), consumption (AMC), and use (AMU) in the human health care sector across 12 countries in South and Southeast Asia, including Bhutan.

AMR context in Bhutan

AMR is a growing threat for Bhutan with high level resistance to commonly used antimicrobials in the country. The AMR-National Action Plan (2018-2022) has identified several challenges to be addressed for achieving its objectives to guide various sectors to ensure a coherent, multi-sectoral approach towards combatting AMR. Though the country is yet to establish a formal AMR surveillance system, efforts are already in place for sharing AMR data generated from laboratories around the country at the global level. Progress is also being made towards establishment of an AMR surveillance network under coordination of the National Referral Laboratory for both human and animal sectors.

Free, universal health care is exclusively provided and regulated by the Bhutan government with no private health care providers in the country. Ministry of Health, Royal Government of Bhutan along with multinational agencies and external partners in the country are working closely to upgrade the existing infrastructures and technologies to generate standardized quality data and are also providing trainings to prepare future leaders to champion the AMR containment efforts in the country.

The authority to regulate production, import, sales and prescription of antimicrobials in the country lies with the Drug Regulatory Authority of Bhutan Government. The government has thus been able to ban over-the-counter sales of antibiotic and use in animal feed, and centrally procures drugs required for national distribution. Although consolidated antimicrobial procurement and distribution data is available, it is not collected in a systematic way. With Bhutan joining the GLASS-AMC, establishing future collection following the GLASS methodology for surveillance will help enable the country to analyze, use, and share AMC data at both the local and global levels in coming years.

To generate data on antimicrobial use, antimicrobial audits are currently being piloted at Jigme Dorje Wangchuck National Referral Hospital and is planned to be extended across the major hospitals in the country.

Continued collection of national AMR/C/U data will allow the country to further establish their national surveillance system as well as to implement evidence-based approaches for treatment and management of infectious diseases, tracking AMR trends and formulate AMR containment strategies.

CAPTURA experience

CAPTURA's early engagement with the AMR stakeholders and subsequent effective coordination between project team and MOH led to expedited approval and work initiation in the country. Although early progress was slowed down by the COVID pandemic, CAPTURA was able to successfully achieve its objectives of identifying, mapping and assessing existing microbiology capacity, as well as collecting and analysing retrospective AMR and AMC data. Numerous WHONET trainings were also provided to technical laboratory staff from both the human and animal health sectors. Further, a subset of AMU data was collected and analysed as part of a piloting exercise to introduce hospital-based AMU surveillance.

CAPTURA findings

CAPTURA activities in Bhutan have enabled capacity building within data management and analysis for future AMR, AMC and AMU surveillance efforts. In this report we present a summary of findings from the scoping and analytical work conducted by CAPTURA in collaboration with DMS, MOH, Bhutan since 2019. The data content of this final report has been selected after discussion with CAPTURA in-country team and AMR stakeholders at MOH, Bhutan. Comprehensive analytical outputs and visualization tools will be shared with the National AMR program, DMS before the closure of the project.

The main utility of the retrospective data collected through CAPTURA project is to establish a preliminary data baseline. It is our hope it can be a useful contribution to planning future investments in combatting AMR in Bhutan and the Asian region.

Table of Contents

Executive Summary 3

Table of Contents 4

Acronyms 5

SECTION 01

CAPTURA Overview 6

Introduction 7

AMR Context 8

SECTION 02

CAPTURA Experience 10

Planning and Implementation 11

Capacity Building Activities 12

SECTION 03

CAPTURA Findings 13

Results 14

AMR data findings 20

AMC data findings 31

AMU data findings 32

SECTION 04

Conclusion 35

SECTION 05

Appendix 38

1. CAPTURA's data definitions 39

2. Metadata methodology 40

3. Contents of CAPTURA's WHONET AMR reports for facilities 42

4. AMC Methodology 43

Acronyms

AMC	Antimicrobial Consumption
AMR	Antimicrobial Resistance
AMU	Antimicrobial Use
AST	Antimicrobial Susceptibility Test
AWaRe	Access, Watch and Reserve
CAPTURA	Capturing data on Antimicrobial resistance Patterns and Trends in Use in Regions of Asia
CG	Country Grant
CIP	Country Implementation Plan
CLSI	Clinical & Laboratory Standards Institute
CONS	Coagulase Negative Staphylococci
DD	Disk Diffusion
DMS	Department of Medical Services
DoMSHI	Department of Medical Supplies and Hospital Infrastructure
DRA	Drug Regulatory Authority
DTAC	Drug Technical Advisory Committee
EQA	External Quality Assurance
FF	Fleming Fund
GLASS	Global Antimicrobial Resistance Surveillance System
HAI	Hospital Acquired Infection
IQC	Internal Quality Control
JDWNRH	Jigme Dorje Wangchuck National Referral Hospital
MIC	Minimum Inhibitory Concentration
MOH	Ministry of Health
MRSA	Methicillin Resistant Staphylococcus aureus
NAP	National Action Plan
NCAH	National Centre for Animal Health
NCC	National Coordinating Center
NEML	National Essential Medicine List
NRL	National Reference Laboratory
PPS	Point Prevalence Survey
RCDC	Royal Center for Disease Control
REBH	Research Ethics Board of Health
RGOB	Royal Government of Bhutan
RIS	Resistant Intermediate Susceptible
RLQA	Rapid Laboratory Quality Assessment
SOP	Standard Operating Procedure

SECTION

01

CAPTURA Overview

Introduction

The Capturing data on Antimicrobial resistance Patterns and Trends in Use in Regions of Asia (CAPTURA) consortium was awarded the Fleming Fund (FF) Regional Grants Round 1 for the South and Southeast Asian regions. These FF grants, funded by the Government of the United Kingdom, were established as a response to the global problem of AMR, and the aims of Round 1 grants were to expand the volume of historical and current data on antimicrobial resistance (AMR), consumption (AMC) and use (AMU) data from the human health sector.

The CAPTURA project takes place in 12 countries - 6 in both South and Southeast Asia. The project includes collecting four years' worth of de-identified retrospective AMR/C/U data, assessing the quality of datasets and laboratories where data were collected, and analyzing data within a central database, which then can be used by the countries to make evidence-based policies and practices.

Additionally, collaborative efforts with country stakeholders can foster capacity building opportunities and strengthen advocacy for improved data quality and submission to regional and/or national repositories. It is our hope that the CAPTURA project can assist in improving surveillance, containment, and awareness of AMR in local, regional, and global contexts.

The CAPTURA project was executed in several phases in Bhutan (Figure 1).

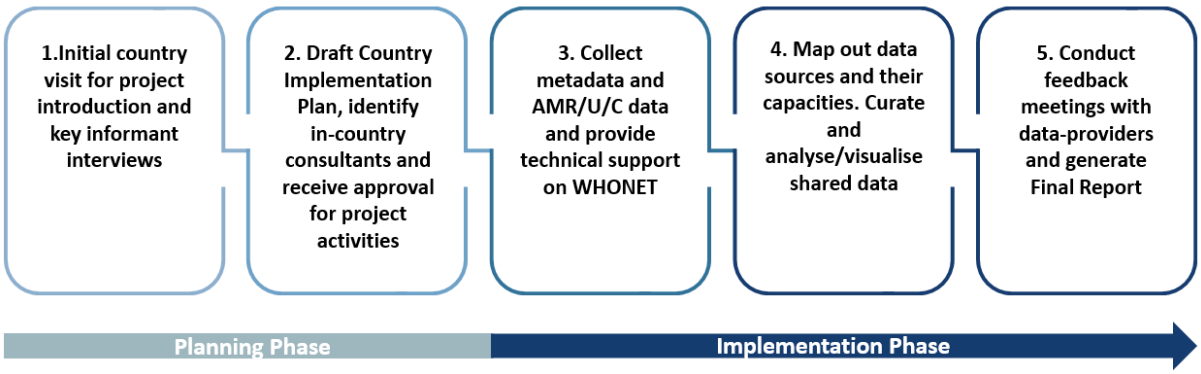


Figure 1. CAPTURA's scope of work in Bhutan

AMR Context

Bhutan, a country of nearly 800,000 inhabitants is situated in the Himalayan mountains with difficult terrains. Healthcare service is provided free of cost by the government. The country has made remarkable achievement in health systems performance, but communicable diseases remain a substantial burden.[1]

AMR is a growing threat in the country, especially given its location in South Asia. Hospital based data on isolation of human pathogens with high level resistance to commonly used antimicrobials is available[2], but current AMR trends at a national level is unknown. To tackle this emerging issue Bhutan developed and endorsed its AMR National Action Plan [AMR-NAP (2018-2022)] in 2017. The NAP has identified several AMR challenges: suboptimal governance structures and plans; less than rational use of antimicrobials; weak surveillance and monitoring of AMR and AMU; insufficient education and awareness among specialists and the public; insufficient AMR research; weak internal as well as external collaboration; and insufficient regulation of pharmaceuticals across sectors.[3]

The National AMR program at Ministry of Health (MOH) functions as the AMR National Coordinating Center (NCC) and two National Referral Laboratories (NRLs) for human health [Jigme Dorje Wangchuck National Referral Hospital (JDWNRH) and Royal Center for Disease Control (RCDC)] have been designated. Though formal AMR surveillance is not yet fully established, Bhutan has been able to contribute to Global Antimicrobial Resistance Surveillance System (GLASS)[4] 2020 data call with three facilities from the human health sector contributing data. The country is currently drafting an AMR surveillance guideline and is proposing to include all existing human health and animal health labs performing antimicrobial susceptibility testing (AST) as potential AMR surveillance sentinel sites under coordination of the designated NRL's.[5] Understanding the current capacity of existing laboratories, the quantity and quality of AST data being generated can help the country to identify gaps and prioritize areas for improvement for successful roll out of the planned surveillance program in the country.

Other key stakeholders in the country also support AMR containment efforts led by MOH and includes external partners like WHO and FF providing technical and financial assistance to upgrade laboratory infrastructures and technologies. The FF has specifically invested in laboratory enhancement, training of technical human resources to lead future AMR initiatives and building knowledge among clinicians on rational prescription use. Fourteen Fleming fellowships covering AMR, AMU, and AMC surveillance and policy across human and animal health have been supported by the Doherty Institute, Australia.

In terms of antimicrobial consumption surveillance and control efforts, the Drug Technical Advisory Committee (DTAC) has been identified to function as the National Steering Committee for AMR. The Drug Regulatory Authority (DRA) is authorized to regulate production, distribution, sale, and prescription of antimicrobial agents in the country. Over-the counter sale of antibiotics is banned and use in animal feed is restricted.[6] Point prevalence surveys (PPS) enabling oversight of prescription patterns have been conducted and feasibility studies of introducing antimicrobial stewardship programmes across hospitals is currently being carried out.[7] A recent report suggests overall consumption of antimicrobials in Bhutan to be lower compared to other countries in the region, but with a noticeable increase in consumption from 2017 to 2019. [8]

[1] Thinley S, Tshering P, Wangmo K, Wangmo K, Wangchuk N. et al. (2017(. The kingdom of Bhutan health system review. World Health Organization. Regional Office for South-East Asia. https://apps.who.int/iris/handle/10665/255701

[2] Adeep, M., Nima, T., Kezang, W. *et al.* A retrospective analysis of the etiologic agents and antibiotic susceptibility pattern of uropathogens isolated in the Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan. *BMC Res Notes* **9,** 54 (2016). https://doi.org/10.1186/s13104-015-1728-1

[3] Bhutan National Action Plan on Antimicrobial Resistance (2018-22) (https://www.flemingfund.org/wp-content/uploads/bc4ead8018642e9793ff86c34dde4a96.pdf).

[4] 9789240005587-eng.pdf (who.int)

[5] AMR surveillance guideline bhutan v1 CRL - basic Pathology - BCP101 - - StuDocu

[6] The Kingdom of Bhutan Health System Review. Health System in Transition; vol 7 no 2 2017 available at 9789290225843-eng.pdf (who.int)

[7] antimicrobial-resistance-bulletin-september-2019.pdf (who.int)

[8] Tshering T, Wangda S, Buising K. Trends in antimicrobial consumption in Bhutan. IJID Regions:1 (2021);67-71 https://doi.org/10.1016/j.ijregi.2021.09.009

Nonetheless, a trend on total consumption and appropriateness of antimicrobial use in the country will be unknown in absence of formal AMU/C surveillance mechanisms. An important early step taken by the local government was the revision of Bhutan's National Essential Medicine List (NEML) in 2017 to include antimicrobials grouped into the AWaRe (Access, Watch and Reserve) categories.

Though strong commitment has been shown by the government and enormous efforts have been made over the last few years for containment of AMR in the country, the progress needs to be continued with coordinated actions to meet the objectives outlined in the NAP is required.

SECTION

02

CAPTURA Experience

Planning and Implementation

CAPTURA's engagement with Bhutanese AMR stakeholders started with a workshop in Nepal followed by a visit to Bhutan to further discuss collaborations in June 2019. The workshop and face-to-face meetings were helpful to learn about the country's ongoing efforts to strengthen AMR surveillance in the country. Key informant interviews with AMR stakeholders at MOH, JDWNRH, DRA and RCDC served to provide background information on the available AMR/U/C data from the past 3 (or more) years and their relevance to understanding the AMR situation in Bhutan.

After the initial country visit, Bhutan FF Program at Department of Medical Services (DMS) assigned a team including a country coordinator and consultant microbiologist to support CAPTURA activities locally. The CAPTURA team then created a Country Implementation Plan (CIP) in August 2019 which outlined the proposed scope, objectives, and timeline of the work in Bhutan. The CIP was presented to the MOH for review and approved in October 2019. MOH also issued formal administrative clearance and the Research Ethics Board of Health (REBH) provided exemption from ethics review in November 2019. With all the approvals in place, CAPTURA's in-country activities started in early 2020.

Though in-country activities were unavoidably delayed several times due to the COVID-19 pandemic, implementation proceeded smoothly overall. MOH quickly reviewed approval requests, and the Bhutan-based team gathered metadata and AMR/U/C data.

A summary of the timeline for CAPTURA implementation is provided in Figure 2 below.

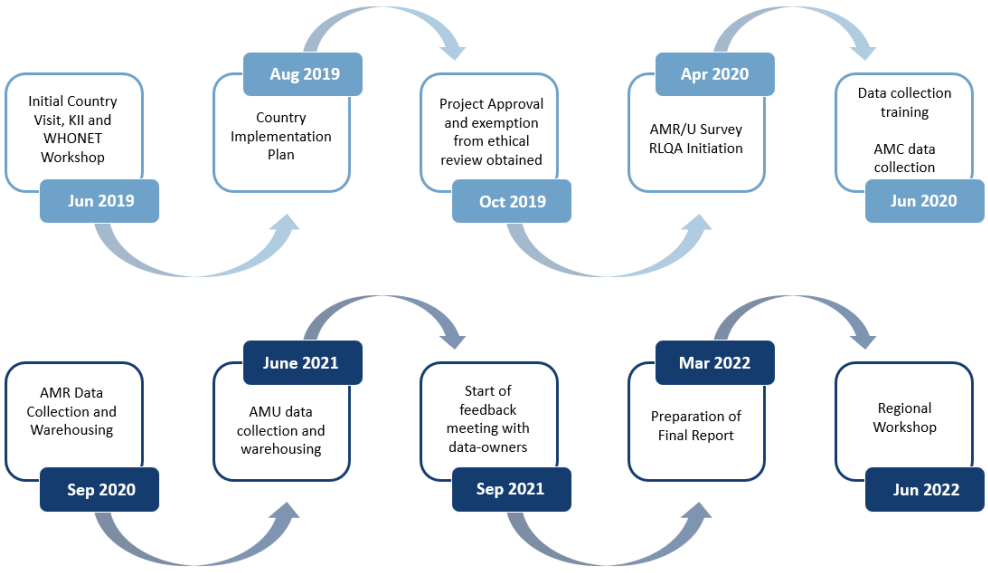


Figure 2. Timeline of activities in Bhutan

Capacity Building Activities

WHONET Training

WHONET is a free Windows-based multilingual database software developed for the management and analysis of microbiology laboratory data with a special focus on the analysis of AST results. The software is primarily used to enhance the local use of data for local needs: clinical decision support, AMU policy, infection control and outbreak detection, identifying laboratory test performance, and characterization of local microbial and resistance epidemiology. Additionally, it is used to promote local, national, regional, and global collaborations through the exchange of data and sharing of experiences.

CAPTURA supported numerous WHONET trainings (On-site and Virtual) in Bhutan (Table 1). Laboratory staff at all the sites selected for AMR data sharing were trained in using WHONET to manage their microbiology data. Subsequently, they were involved in data digitization and processing prior to sharing the data with CAPTURA. The following number of trainings were provided to in-country stakeholders in Bhutan.

Table 1. List of WHONET Training

Participating Facilities	Training date
Laboratory staff from clinical Microbiology laboratories RCDC stakeholders National Center for Animal Health (NCAH) staff	June 2019
CAPTURA in-county stakeholders	Sept 2019
CAPTURA in-county stakeholders	April 2021
CAPTURA in-county stakeholders	May 2021

Development of AMU data collection tool

CAPTURA facilitated and supported workshops for development of an EpiCollect based AMU data collection tool in August 2021 to be used for prospective AMU data collection in Bhutan. The developed tool was initially piloted through collection of retrospective data from in-patients' hospital records, which was analysed by CAPTURA (presented later in this report). The country has also completed piloting the tool for prospective data collection at JDWNRH and has plans to roll out in two additional regional hospitals for routine audit of AMU.

SECTION

03

CAPTURA Findings

Results

In the following section we present a summary of findings from the scoping and analytical work conducted by CAPTURA in Bhutan since 2019.

Most of the analysis and visualizations for the project are done using electronic visualization tools. The data presented in this report are primarily excerpts from these.

Comprehensive analytical outputs and visualization tools will be shared directly with stakeholders at MOH, Royal Government of Bhutan (RGOB). The data content of this final report has been selected after discussion with the AMR technical working group and relevant technical staff considering reliability in terms of data quality and value of data sharing.

Data Types

To identify the relevant data holding facilities and to ensure evaluation of data quality, detailed assessments of facilities were conducted through facility questionnaires and visits before actual data sharing agreements were made and source data collated. As a result, two levels of information are available and presented here:

1) CAPTURA metadata which constitutes all the information collected directly by and as part of the CAPTURA project from questionnaires and interviews
2) CAPTURA AMR/U/C data are the identified retrospective source data generated in facilities between Jan 1, 2016, and Dec 31, 2019 (and sometimes beyond), see also definition section and appendix for more detailed description.

The overall approach to the selection of facilities and collation and analysis of different data sources is illustrated below (Figure 3). See Appendix for more detailed information on methods.

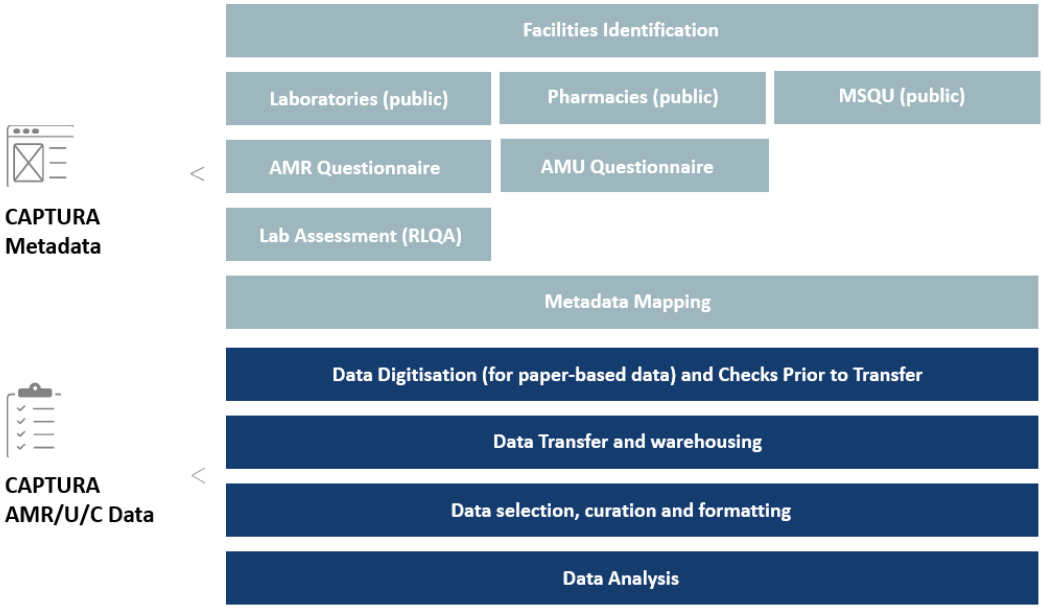


Figure 3. Approach to data identification and mapping

Facility Identification

In Bhutan, RGOB exclusively provides all types of health care (preventive, curative, traditional) to the population. There are no private entities providing health care including laboratory services in the country. During the initial scoping we identified six (6) hospital-based laboratories generating microbiology data in the country. Two laboratories, one associated with Royal Bhutan Army Hospital, another a public health laboratory not generating routine AST data were excluded due to complexities in reaching data sharing agreement and unavailability of AMR data, respectively. The remaining four labs were included for further assessments through AMR survey and Rapid Laboratory Quality Assessments (RLQA).

Each national, regional and district level hospital have their own pharmacies with manual antibiotic dispensing records. Based on the knowledge of availability of antimicrobial dispensing data records and recommendation of the in-country CAPTURA team, six pharmacies were selected for AMU survey. See table 2 for an overview of facilities.

MOH centrally procures all essential medicines to be distributed to health care facilities throughout the country and this procurement is managed by Department of Medical Supplies and Health Infrastructure (DoMSHI) of DMS. CAPTURA in-country team engaged with DoMSHI for sharing the national antimicrobial procurement data for analysis.

A map of all facilities identified and evaluated are included in page 17.

Table 2. Overview of facilities surveyed on data availability

Name of Hospitals	AMR Questionnaire	AMU Questionnaire	Rapid Laboratory Quality Assessment
Jigme Dorje Wangchuk National Referral Hospital	✓	✓	✓
Eastern Regional Referral Hospital	✓	✓	✓
Central Regional Referral Hospital	✓	✓	✓
Phuntsholing General Hospital	✓	✓	✓
Trongsa Hospital	-	✓	-
Samdrup Jongkhar General Hospital	-	✓	-
Royal Center for Disease Control	n/a	n/a	n/a
Royal Army Hospital	n/a	n/a	n/a

AMR Metadata

All four targeted facilities completed the AMR questionnaires in April 2020. Based on the survey, all four laboratories performed Microbiology culture and susceptibility testing, and were hospital-based facilities serving as national referral/regional/district level service providers. Four different types of clinical specimens (Blood, Soft tissue & Bodily Fluids, Stool and Urine) were primarily processed for bacteriological culture and susceptibility testing in all four labs, while two of them also processed respiratory specimens. Disk Diffusion was the method used for AST by all facilities, while limited MIC determination of isolates was done on a routine basis. Two facilities were noted to record and manage AST data manually. One facility mentioned to exclusively use an electronic data entry system, whereas one laboratory used both electronic and manual system for record keeping of the same AST database. The laboratories using an electronic data recording system responded to have maintained 3-10 years of AST records. The facilities were not sharing isolate level AMR data externally.

The rapid laboratory quality assessment was completed in all four facilities by June 2020. In general, all the laboratories were equipped and staffed for performing basic Microbiology assays, with the national referral laboratory at JDWNRH being the one with the most functional equipment and bench staff. A basic set of in-house prepared media was noted to be in use by most of the laboratories. Standard Operating Procedure (SOPs) for microbiological processes were in place at all laboratories and the in-country CAPTURA team further confirmed existing practice of using control strains for internal quality control in all labs however, only one laboratory participated in EQA for pathogen identification and AST. Gaps in provision of refresher training on blood culture was observed in two of the laboratories.

Since most of the laboratory data was available only in paper format (recorded and stored in logbooks), it was decided to digitize recent (2017-2019) historical data into the WHONET software. Hardware installation and subsequent *ad hoc* trainings and troubleshooting sessions with staff were conducted to digitize and analyse data.

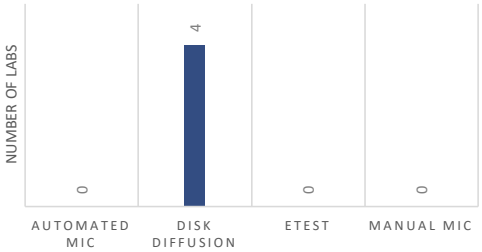
AMU Metadata

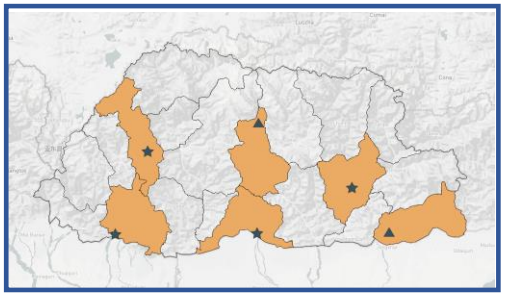
All six surveyed pharmacies were dispensing antimicrobials to outpatients. Three pharmacies also catered to the emergency department, while only two supplied to the in-patient department. The number of registered pharmacists were disproportionately distributed between the six with some having only 1 while others had 10 in one facility.

Every pharmacy received antimicrobial agents from MoH, RGOB and five of them noted to dispense and stock drugs following available guidelines. Respondents from three of the five pharmacies with guideline in place, indicated absence of periodic training on use of guidelines. Five of the pharmacies were recording antimicrobials dispensed in paper-based format (no pharmacy had software in place for electronic record keeping). Five out of six pharmacies required prescriptions for dispending antibiotics and noted to have patient diagnosis on prescriptions. All pharmacies indicated preparation of reports on drugs dispensed, but with reporting frequency ranging from monthly to annually. Only one pharmacy noted to analyse their data using EXCEL sheets, but none mentioned to share data with other facilities/entities.

AMR Metadata

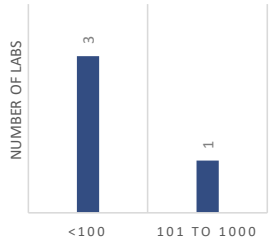
METHOD OF ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST)





Indicated as stars are 4 facilities where both AMR and AMU Questionnaires were collected. Indicated as triangles are 2 additional facilities where AMU Questionnaires were collected. In total there were 4 AMR Questionnaires and 6 AMU Questionnaires collected in Bhutan.

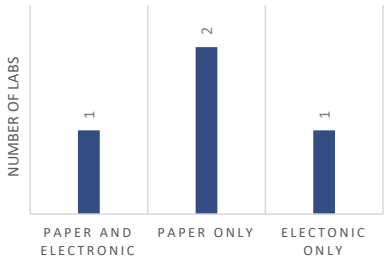
AST PER MONTH



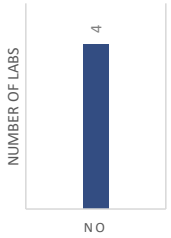
AVAILABLE AMR DATA VARIABLES IN LABORATORIES

	BT01L	BT02L	BT03L	BT04L
Date of Birth	✓	✓	✓	✓
Sex	✓	✓	✓	✓
Patient Location	✓	✓	✓	✓
Admission Date	✓	✓	✓	✓
Date of Visit	✓	✓	✓	✓
Specimen Date	✓	✓	✓	✓
Specimen Type	✓	✓	✓	✓
Culture Result	✓	✓	✓	✓
AST Interpretation (R,I,S)	✓	✓	✓	✓
AST Measurement	✓	✓	✓	✓
Antibiotic Prescription	✓	✓	✓	✓
Diagnosis	✓	✓	✓	✓
Patient Outcome	✓	✓	✓	✓
Date/cause of Death	✓	✓	✓	✓
Other Infections	✓	✓	✓	✓
Other Patient Information	✓	✓	✓	✓

FORMAT OF DATA

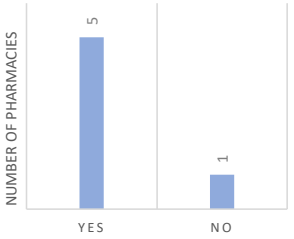


DATA SHARED EXTERNALLY

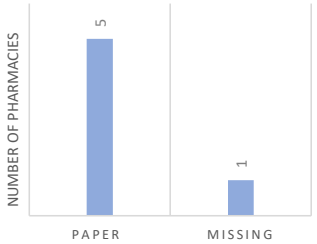


AMU Metadata

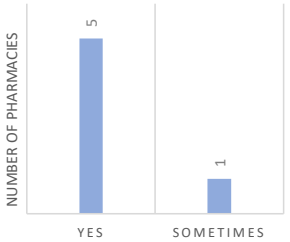
DISPENSARY DATA RECORDED



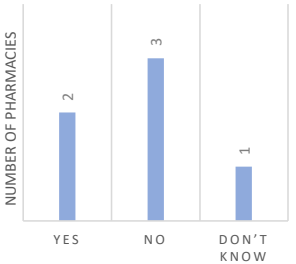
FORMAT OF DATA



PRESCRIPTION REQUIRED



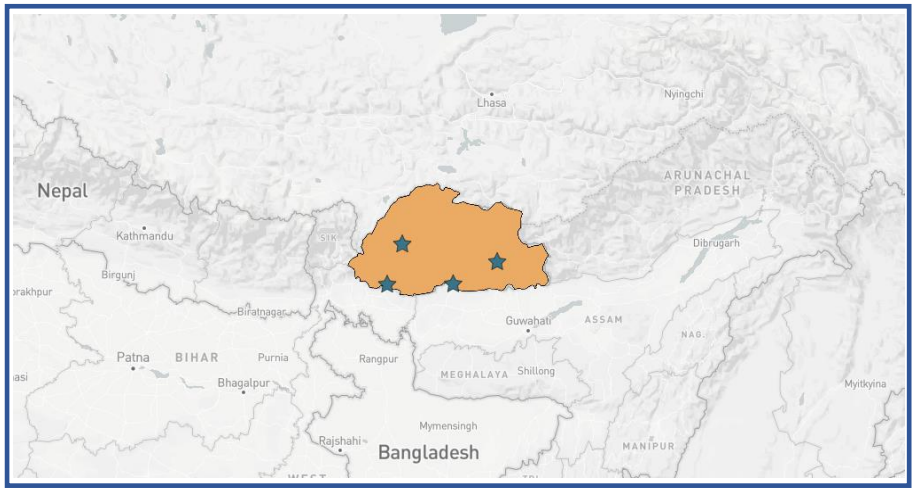
TRAINING ON DISPENSING



AVAILABLE AMU DATA VARIABLES IN PHARMACIES

	BT01P	BT02P	BT03P	BT04P	BT05P	BT06P
Patient Sex	✓	✓	✓	✓	✓	✓
Patient Age	✓	✓	✓	✓	✓	✓
Type of Drug (Drug Class)	x	✓	✓	x	✓	✓
Production Name	x	✓	✓	x	✓	✓
Daily Defined Doses (DDD)	x	✓	✓	x	✓	✓
Formulation Type	✓	✓	✓	✓	✓	✓
Pack Size/Doses	x	✓	x	x	✓	✓
Date of prescription	✓	✓	✓	✓	✓	✓
OPD, IPD, Emergency	✓	✓	✓	✓	✓	✓
Route of Administration	✓	✓	✓	✓	✓	✓
Strength of Drug	✓	✓	✓	✓	✓	✓
Ingredients	✓	x	x	✓	✓	✓
Manufacturer	x	✓	✓	x	✓	✓
ATC Codes	x	x	x	x	x	x
Indication	x	✓	✓	x	x	x
MDR Risk	x	✓	✓	x	x	x
Previous Prescriptions	x	✓	✓	x	x	x
Product Origin	x	✓	✓	x	x	x
Brand Name or Generic	x	✓	✓	x	x	x
Change to Initial Therapy	x	✓	✓	x	x	x

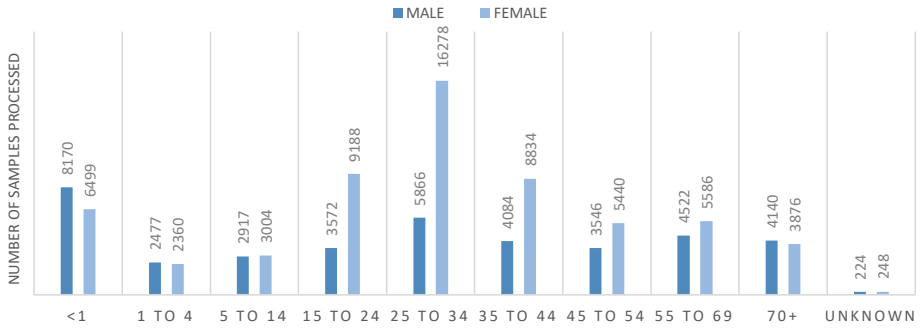
Bhutan - AMR Data Findings I



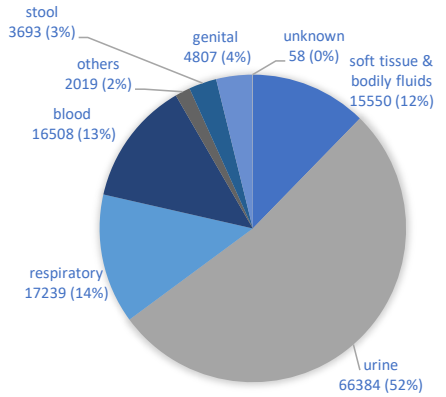
Kingdom of Bhutan | 780,000 | JDWNRH, CRRH, ERRH, PGH

Total # records = 126259

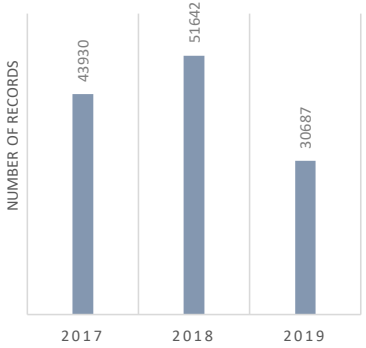
NUMBER OF PATIENTS BY AGE AND GENDER



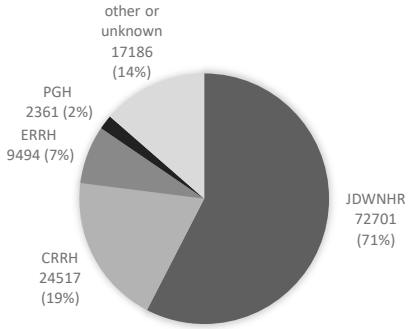
ALL RECORDS BY SPECIMEN TYPES



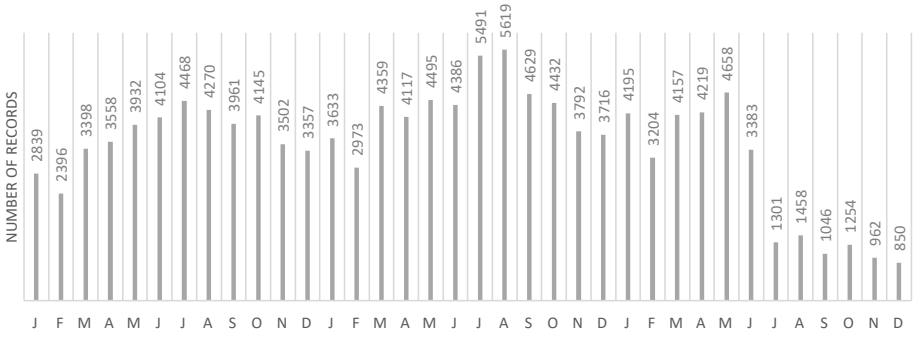
DATA VOLUME BY YEAR



DATA VOLUME BY FACILITY



DATA VOLUME BY MONTH



Bhutan - AMR Data Findings II

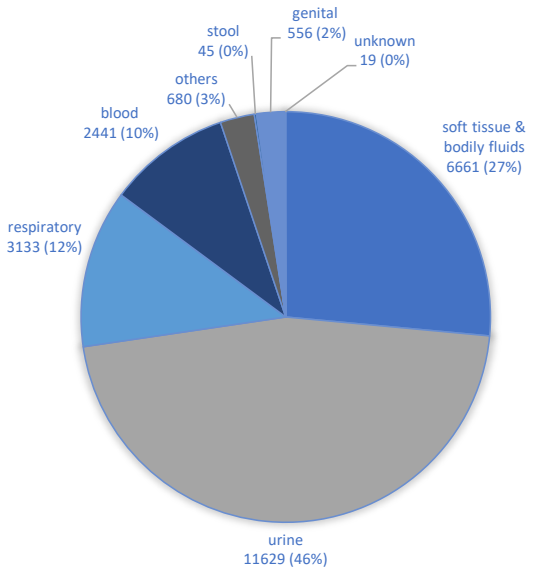
Total # of records = 126259

EXCLUDED: Negative and null/missing values

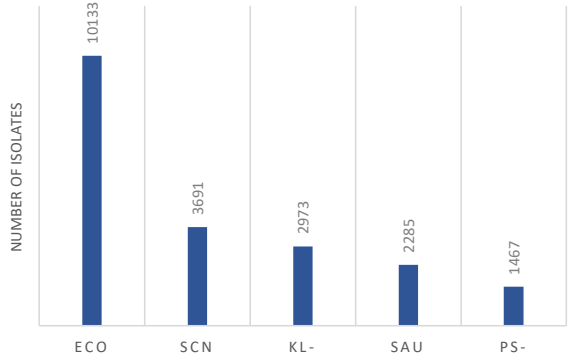
Number of positive culture results = 25164

Organism code	Organism
ac-	Acinetobacter sp.
aer	Aeromonas sp.
can	Candida sp
eco	Escherichia coli
ent	Enterococcus sp.
Kl-	Klebsiella sp.
ps-	Pseudomonas sp.
sal	Salmonella sp.
sau	Staphylococcus aureus ss. aureus
scn	Staphylococcus, coagulase negative
shb	Shigella flexneri
shd	Shigella sonnei
str	Streptococcus sp.
tva	Trichomonas vaginalis

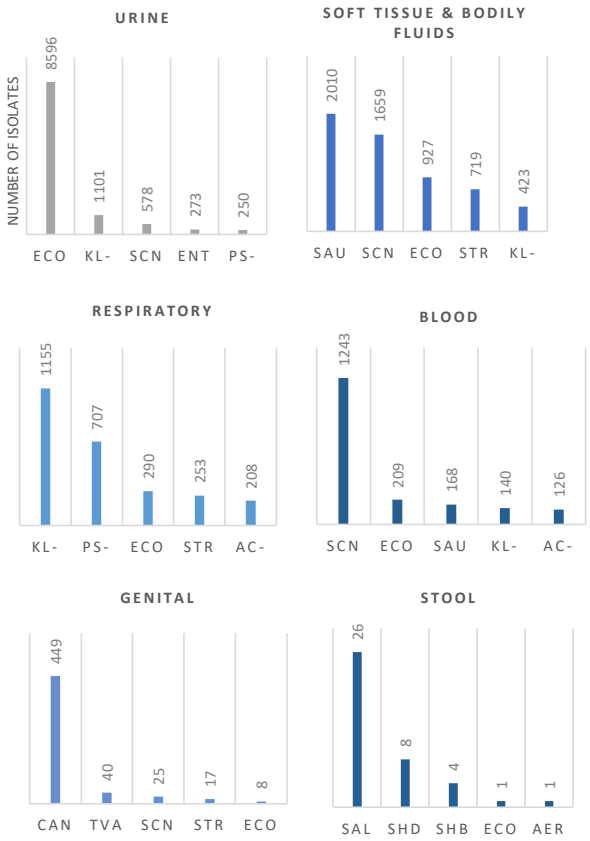
POSITIVE CULTURE RESULTS BY SPECIMEN TYPES

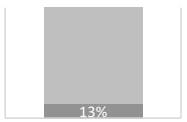


FIVE MOST COMMON ORGANISMS (FROM ALL SPECIMEN)



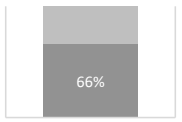
FIVE MOST COMMON ORGANISMS BY SPECIMEN





METHICILLIN-RESISTANT SAU IN BLOOD

(BASED ON 138 PATIENTS)



ECO RESISTANT TO 3RD GEN. CEPHALOSPORIN

(BASED ON 174 PATIENTS)

AMR data findings

Epidemiology

Bhutan provided results for 126,259 samples collected between 2017 and 2019 from four laboratories including both positive (n=49,608; true pathogens isolated: 25,164 and mix flora/contaminants: 24,444 samples) and negative results. A descriptive data summary is presented on page 18-19, which includes details on the number of samples processed, number of isolates as well as patient and sample demographics.

Organism statistics**:**

The most common findings from the data shared with CAPTURA showed samples with bacterial growth as 'normal flora/mixed bacterial growth/no significant growth' etc. (nearly 27% of samples with growth). These were reported mostly in respiratory, urine and stool specimens (>80%). This is a common observation in microbiology labs processing samples which are mixed with normal flora, and generally pose a challenge to microbiologists to correctly identify pathogens if supporting patient clinical details are not available. Additionally, the most common bacterial pathogen isolated from the samples was *Escherichia coli* (~40.27%). The other commonly detected organisms are coagulase negative Staphylococci (CONS), followed by *Klebsiella spp., Staphylococcus aureus* and *Pseudomonas species*. Even though CONS can cause true infections, especially healthcare-associated infections (HAI), it is important to note that this organism was primarily isolated in 'blood' and 'soft tissue and fluids' specimens in Bhutan dataset. Given their pervasive presence on the skin, isolation of these may therefore indicate contamination during sampling.

From 2017 to 2019 there were statistically significant increases in isolation of *E. coli* and *Enterococcus spp.* This increase is most likely due to increased testing volume rather than specific disease patterns. Nevertheless, a true increase in frequency of pathogen associated with hospital associated infections requires close monitoring as they are mostly associated with high level of antimicrobial resistance.

Antimicrobial results:

Detailed analyses of resistance profiles on the isolated pathogens including Gram-positive and Gram-negative antibiograms have been generated and will be shared with all the four labs. Resistance rates were also determined for WHO Global priority list of resistant bacteria and the WHO GLASS pathogens, including the two SDG indicators for blood isolates of *Staphylococcus aureus* (%MRSA) = 13%) and *Escherichia coli* (%third-generation cephalosporin resistance) = 66%). However, it is important to note the limited number of patients these prevalence estimates are based on.

Multidrug resistance profiles are valuable for outbreak detection, treatment guidelines, characterization of resistance mechanism, and recognition of possible errors in laboratory testing. See Table 3 for summary of organisms and specimens relevant for WHO GLASS reporting.

While resistance rates and profiles are valuable in monitoring resistance trends over time and in developing treatment guidelines, policymakers must be aware of laboratory test quality and types of biases (due to patient presentation, sampling practices, and laboratory test practices).

Table 3. Patients with specimen and organisms relevant for WHO GLASS in Bhutan

Specimen Type	Pathogen	Number of Patients
Blood	*Acinetobacter spp.*	124
Blood	*Klebsiella pneumoniae*	116
Blood	*Salmonella spp.*	70
Blood	*Staphylococcus aureus*	138
Blood	*Streptococcus pneumoniae*	29
Blood	*Escherichia coli*	181
Genital	*Neisseria gonorrhoeae*	3
Stool	*Salmonella spp.*	26
Stool	*Shigella spp.*	11
Urine	*Klebsiella pneumoniae*	843
Urine	*Escherichia coli*	7808

A small number of isolates with high-priority resistance finding or multidrug resistance profiles were reported. However, these finding require retesting or further confirmation. See also description of these findings in the 'isolate alerts' section below.

Test practices and quality report
This section addresses the issue of "quality" from several perspectives. The analyses include several indicator metrics that may be used to identify priority areas for improvement, monitor improvement over time, and compare results from different laboratories.

- Data entry and data management: Completeness and accuracy of data entry, antibiotic configuration, use of recommended WHONET codes
- Laboratory results: Organism identification, antimicrobial susceptibility test practices, quality control results

Data entry:
Data completeness of the core data variables was excellent (86%). The primary deficiency was the absence of a patient identification number in 51% at JDWNRH. This identification number is valuable for tracking and counting individuals with repeated samples over time. It is a recommendation to use quality control strains at a regular interval to ensure the reliability of test results and maintaining of such records is a part of good documentation practice. Though, CAPTURA in-country team confirmed existing practice of routine use of control strains for IQC but the IQC data was not recorded into WHONET software; the dataset received by CAPTURA team for analysis did not include any information related to testing of quality control strains, thus CAPTURA team was unable to verify the practice of testing quality control strains as a part of routine IQC for the shared dataset. It is generally recommended to maintain IQC records with laboratory AMR data for data verification and validation.

Organism identifications**:**
The laboratories in Bhutan were able to speciate 79% of isolated organism to species level while nearly 100% of *Klebsiella* were identified up to genus level. There were several identifications of fastidious organisms, which is an indicator of the laboratory's capacity to receive, process, isolate, and identify samples with special growth characteristics or reagent needs.

AST practices:
All laboratories performed disk diffusion testing alone following CLSI guidelines.

Antimicrobials were not consistently tested. Nearly 92% of *S. aureus* isolated was regularly tested against only 3 core antimicrobials while 73% of *E. coli* isolated were tested against seven different antimicrobials.

We would recommend adopting a set of standard antimicrobials to be promoted within and among laboratories. The set of standard antimicrobials can then support routine clinical decision and improve comparability of findings over time and between facilities.

There were results provided for several antimicrobials for which validated breakpoints do not exist. This may be either because the lab is testing incorrect antimicrobials or there is a mistake in laboratory configuration of WHONET. In both circumstances, corrective action is indicated. If there is a mistake in the WHONET or BacLink configuration, this should be corrected. If the laboratory is performing incorrect testing, then education and review of purchasing and test practices would be indicated.

Test interpretations (RIS) were recorded while inhibition zone diameters were missing. In the future, we would recommend recording disk diffusion zone diameters, in order to improve the assessment of data quality and recognition and tracking of microbial sub-populations. Moreover it would enable data reanalysis if breakpoints change.

Isolate alerts:
WHONET generated a number of isolate-level alerts. From a public health perspective, some of the more important ones include high-priority important species: *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Salmonella* Typhi.

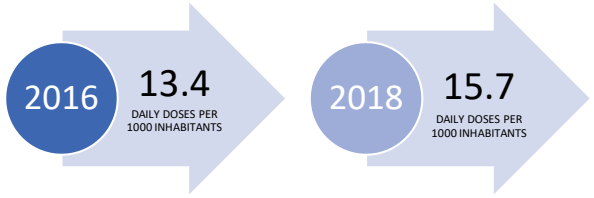
There were several quality control alerts, especially among *Enterobacteriaceae* that are typically ampicillin resistant found to test as ampicillin susceptible. While this is occasionally a correct finding, such results should not be reported to clinicians without a thorough confirmation of the species identification and ampicillin result, to avoid a clinician choosing an antimicrobial to which the patient's pathogen is resistant.

In summary, several problems in susceptibility test practices were noted: the testing of antimicrobials for which there are no validated Clinical Laboratory Standard Institute (CLSI) interpretative criteria, the inconsistency in antimicrobial susceptibility test practices (such that only three antimicrobials were tested >80% of the time for *S.* aureus while five others were only tested against 40-60% of the isolates) and the absence of disk diffusion zone diameters. As

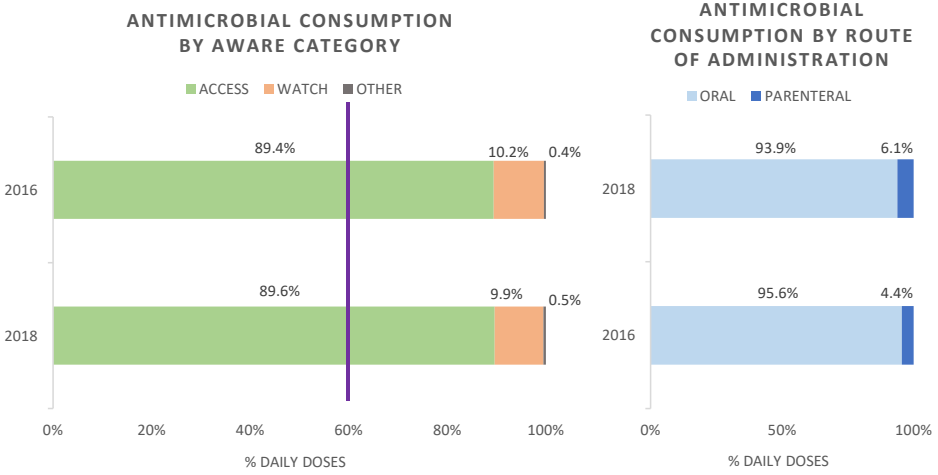
recording zone diameters would offer a number of benefits for reliability of clinical reports, quality assessment, and epidemiological monitoring, it is strongly recommended.

Bhutan - AMC Data Findings I

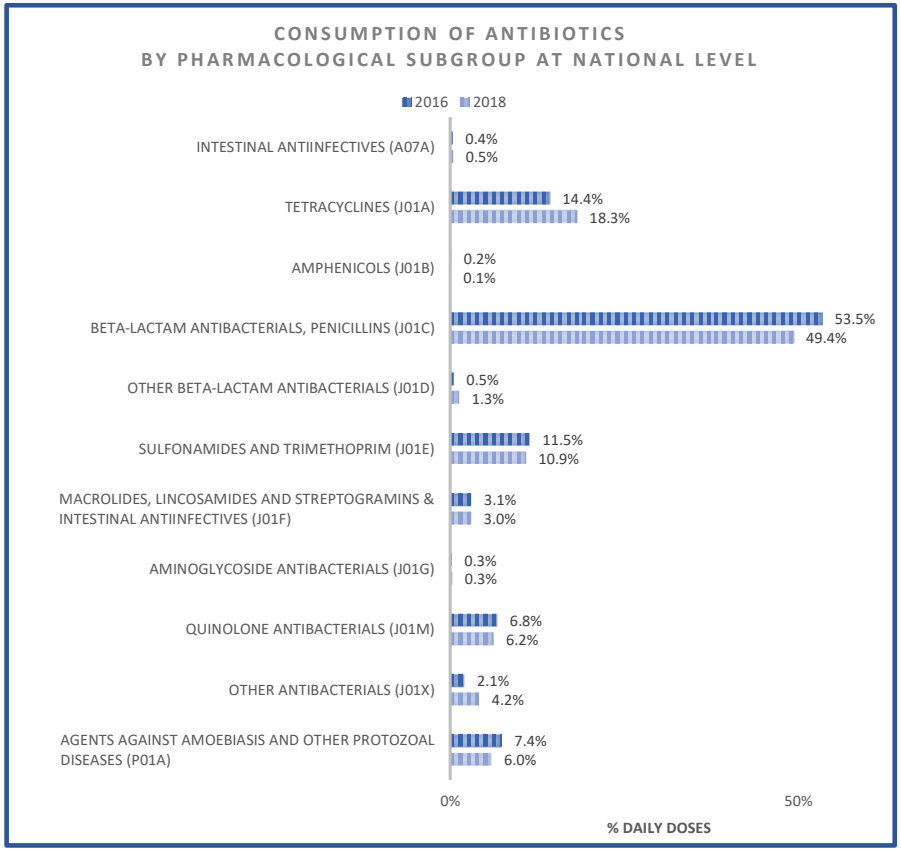
Data Source	Provider	Estimated Coverage	Limitation
Distribution records to provinces	Ministry of Health (MSQU)	Nationwide covering public sector	AMC monitoring system under development



DID increased from 2016 to 2018, suggesting an increase in consumption of antibiotics



Access antibiotics are predominantly used
Bhutan is meeting the WHO's global target of 60% of total antibiotics in the Access category
Relatively small consumption of Watch antibiotics have been recorded

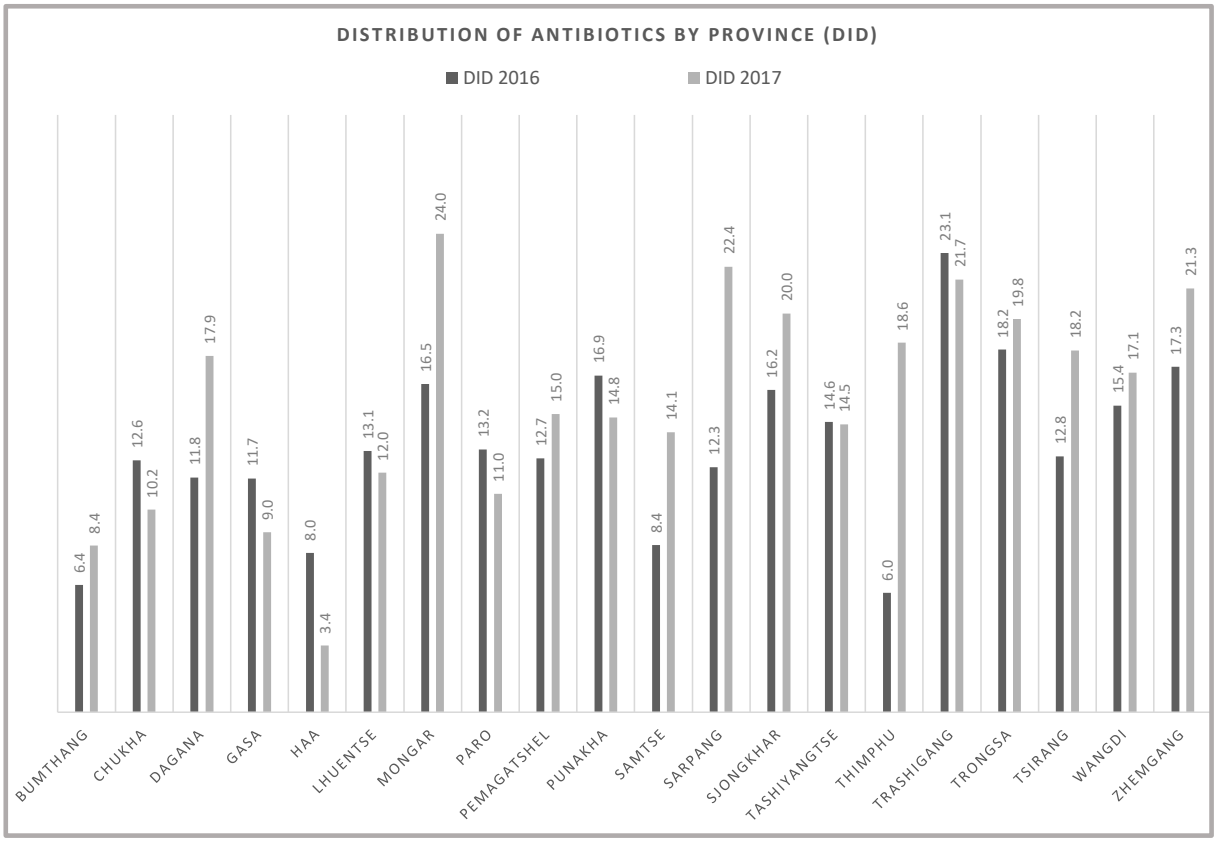


Bhutan - AMC Data Findings II

	Antimicrobial	% out of total ORAL consumption (2018)	AWaRE
1	amoxicillin	42.0%	Access
2	doxycycline	19.4%	Access
3	sulfamethoxazole and trimethoprim	11.6%	Access
4	metronidazole	6.4%	Access
5	cloxacillin	5.7%	Access
6	ciprofloxacin	5.4%	Watch
7	nitrofurantoin	4.2%	Access
8	erythromycin	3.2%	Watch
9	norfloxacin	0.8%	Watch
10	cefalexin	0.5%	Access

	Antimicrobial	% out of total PARENTERAL consumption (2018)	AWaRE
1	procaine benzylpenicillin	49.3%	Access
2	ampicillin	12.1%	Access
3	ceftriaxone	9.6%	Watch
4	cloxacillin	6.5%	Access
5	benzylpenicillin	4.6%	Access
6	gentamicin	4.2%	Access
7	metronidazole	4.0%	Access
8	cefazolin	3.0%	Access
9	ciprofloxacin	2.2%	Watch
10	benzathine benzylpenicillin	1.8%	Access

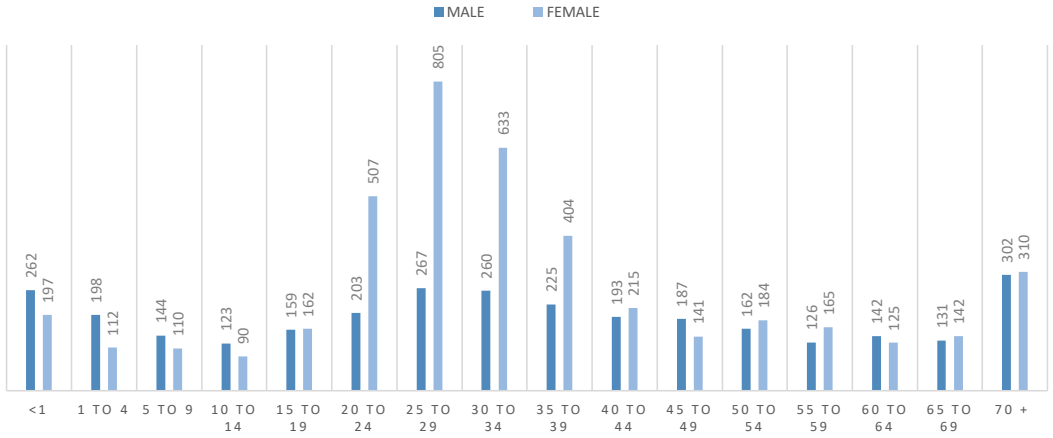
Top 10 oral and parenteral consumption/distribution of antimicrobials in 2018



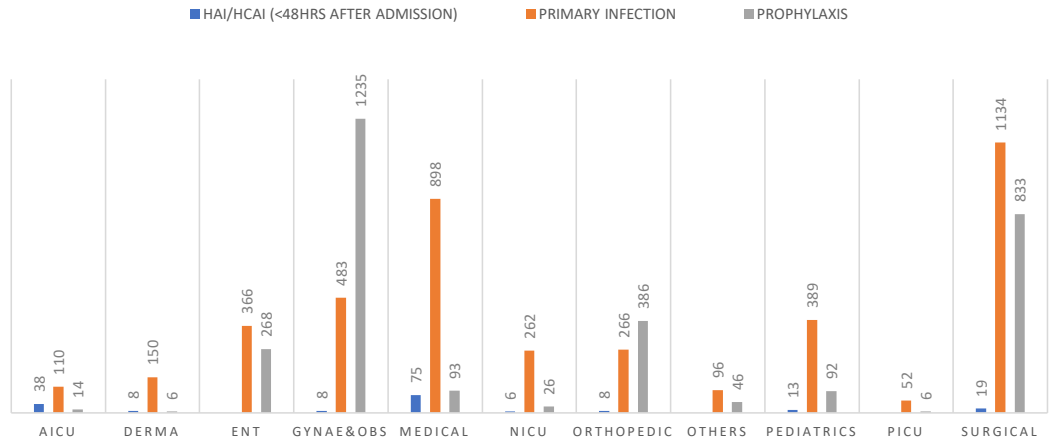
Bhutan - AMU Data Findings I

Data Source	Provider	Estimated Coverage	Limitation
Antimicrobial use data was extracted from paper based Medical Records of admitted in-patients	Jigme Dorji Wangchuk National Referral Hospital (tertiary facility)	7,386 prescriptions to 3,651 patients; Select months of 2019 (May – December)	Pilot dataset shared for preliminary analysis

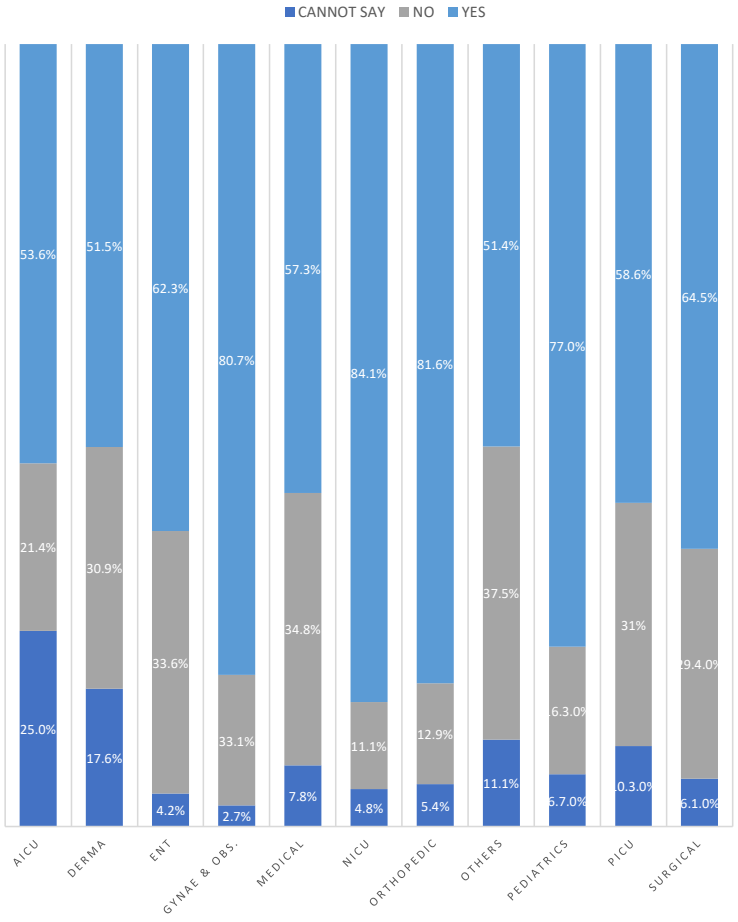
NUMBER OF PRESCRIPTION BY PATIENT'S AGE AND GENDER



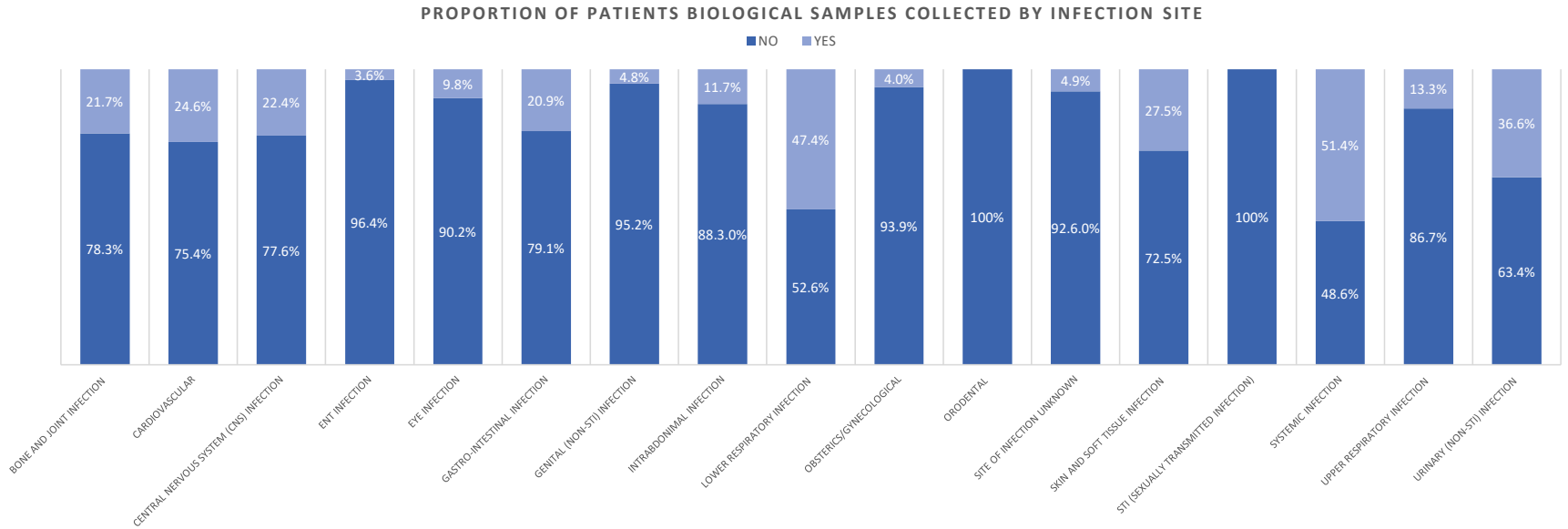
NUMBER OF PRESCRIPTIONS BY INDICATION AND WARD

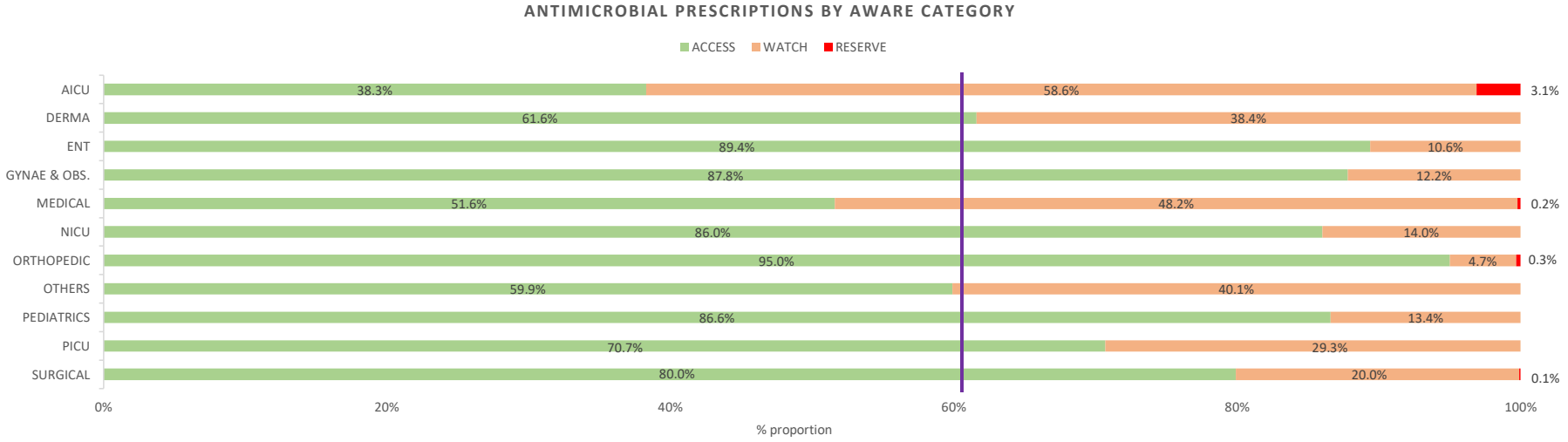


PROPORTION OF TREATMENT APPROPRIATENESS BY WARD



Bhutan - AMU Data Findings II





AMC data findings

The antimicrobial consumption data presented in this report were collated by CAPTURA by applying the WHO protocol on surveillance of antimicrobial consumption[9] to datasets provided by Bhutan. CAPTURA uses the Anatomical Therapeutic Chemical (ATC) classification system[10] to classify antimicrobial substances and the number of DDDs as a measurement metric. A more detailed description of the AMC data analyses methods can be found in Appendix 1. See summary of AMC data analyses on page 22-23.

Data sources:
Consumption data was retrieved by CAPTURA from distribution records managed by Bhutan's Ministry of Health Medical Supplies Quantification Unit (MSQU). The data sources cover distribution of essential medicines records to 20 districts in Bhutan. Bhutan does not have a national production capacity of antimicrobials and therefore all the antimicrobials are imported. MSQU noted there are some antimicrobials available in the country which are not captured in the distribution list to districts, but the volumes of these are limited. The denominator (population size) was obtained from the respective years (2016-2017; 2018-2019) using UNFPA population data as there is no recent population data available publicly for Bhutan. Internally, Bhutan uses a different denominator, which might help to explain some minor discrepancies in the findings of CAPTURA and Bhutan's own internal analysis.

Here CAPTURA presents preliminary results of 2016-2017 and 2018-2019 data on national consumption of antibiotics for systemic use from imported and locally produced antibiotics in Bhutan.

Total Consumption of Antibiotics:
Antibiotic consumption was determined by means of Defined Daily Doses (DDD) per 1000 inhabitants (DID). Estimation of the antibiotic consumption by DIDs indicated that overall consumption of antibiotics in Bhutan increased from 2016-2017 to 2018-2019. Given that this is the first time Bhutan is undertaking an AMC analysis it is difficult to assess if this increase represents an actual rise in the use of antibiotics or is the result of programmatic factors such as for example different procurement or import patterns.

Consumption of oral antibiotics:
The proportion of oral antibiotics out of the total volume of antibiotics dropped in 2018, but well over 90% of antimicrobials are consumed orally. This finding is in line with what is commonly observed in other Low- and Middle-Income Countries (LMIC).

Consumption of antibiotics by pharmacological subgroup:
The most frequently used antibiotic in Bhutan is amoxicillin (Access) across all selected years. Ciprofloxacin is the most used antibiotic in the Watch category.

Comparing 2016-2017 to 2018-2019 data, Bhutan reported an increase in the use of tetracyclines (predominantly due to increased use of doxycycline). It is noted that while the proportion of beta-lactam antibacterial out of the total consumption decreased in 2018-2019, there was a minor increase in the consumption of antibiotics such as cloxacillin and amoxicillin.

Classification in AWaRE categories:
The WHO AWaRe classification was employed by CAPTURA to describe overall antibiotic use as assessed by the variation between use of Access, Watch and Reserve antibiotics for the observed years. Relative consumption of antibiotics as a percentage of total consumption by AWaRe categories (Access, Watch and Reserve) was estimated. The percentage of Access and Watch antibiotics is relatively stable across the period of analysis (2016-2019). The Access group antibiotics comprised approximately 90% of antibiotic consumption for the entire reporting period. As such, Bhutan already meets the global target that by 2023 60% of all antibiotics consumed must come from Access category. However, it is also important to note that the absolute national may cover different scenarios including potential lack of access to antibiotics in some areas. No use of Reserve antimicrobials was observed in Bhutan based on the national AMC data records.

[9] World Health Organisation. WHO methodology for a global programme on surveillance of antimicrobial consumption v1.0
[10] WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2020. 2019

Subnational Analysis:
The availability of data by district enabled CAPTURA to analyze antimicrobial consumption across 20 districts. The preliminary analysis by district showed quite significant differences across districts and also within. In a particular district, the consumption changed significantly from 2016-2017 to 2018-2019. A case in point is Thimphu district which has a DID of just over 6 DID in the first year of reporting, but then has a sharp increase to 18 DID. Most likely supply management issues can help to explain such differences. However, differences in disease outbreak patterns may also be contributing.

AMU data findings

The antimicrobial usage data in this report was collected through a piloting exercise of a template created in collaboration between CAPTURA and the in-country team. The exercised was based on both the WHO protocol on surveillance of antimicrobial consumption[11] as well as adaptations from the WHO protocol on Point prevalence Surveys[12]. Since the initial dataset generated from this pilot is limited, the analysis presented in this report are preliminary and primarily meant to serve as an initial evaluation of the collection tool before further development and broader implementation. All curation, analysis and visualizations were performed using R statistical software. See summary of AMU data on page 24-25.

Data sources:
Antimicrobial use data was extracted from paper based Medical Records of admitted in-patients at JDWNRH hospital in Thimphu for selected months of the years 2018 (June, July, October, December) and 2019 (May – December). The data was downloaded from the Epicollect5 software and personal patient information, such as patient ID and age over 70, were encrypted.

It is important to note, that the antimicrobial use in JDWNRH is likely higher than in other hospitals as it is a central referral hospital catering to more serious cases or patients requiring more specialized treatment often necessitating prescribing more and broader spectrum antimicrobials than in other settings and therefore cannot be generalized to the entire country.

Data overview

Before curation:
It is important to study the data and gain insights on the structure, completeness and perform some basic visualizations and descriptive statistics. This was achieved by using the Data Explorer package in R Studio. It was noted that exemplar data collected for 2018 was very limited and therefore it was decided to only perform analysis for 2019.

An overview of the raw numbers of variables/observations and key missing data profile can be found on Table 4 and Table 5, respectively. Each Row represents one unique patient. Columns contained information on prescriptions such as: antibiotic name, strength, form, route of administration, frequency, therapy start and stop date, infection site, treatment indication as well as specimen collection and microbiology laboratory data for the subset of patients (n=561) where a microbiology sample was taken. A variable recording 'appropriateness of antimicrobial prescribing' according to available country guidelines in terms of choice, dose, frequency, and duration was also recorded.

Table 4. Raw data Profile

	Raw Data (2019)
Rows/ Observations	3,901
Columns/Variables	109
Missing Columns	17

Table 5. Basic data statistics

Variable	Basic Statistic	Missing/Other
Age (mean)	33	14
Gender	Female (60.7%)	Others (0.2%)
Indication	Prophylaxis (50.7%)	UNK (1.1%) Other/NA (0.8%)
Ward	N=13 wards 1st Gynae & Obs. (28.5%)	
Sample Taken	Yes (15.4%)	28 (0.7%)
Route of Admin	Parenteral (69%)	7

[11] World Health Organisation. WHO methodology for a global programme on surveillance of antimicrobial consumption v1.0

[12] (WHO) World Health Organisation. WHO Methodology for Point Prevalence Survey on Antibiotic Use in Hospitals v1.1. Geneva, 2018.

Table 6. Curation Steps

Variable	Action towards analysis
COUNTRY	N/A
MONTH_of_DATA	N/A
YEAR_of_DATA	N/A
DISTRICT	N/A
HOSPITAL	N/A
DEPARTMENT	N/A
WARD	Recoded "Dental" and "Opthal" into "Others"
PATIENT_ID	N/A
AGE_in_YEAR	Merged into one variable named AGE (expressed in years) Recoded into AGE_GROUPS from Under 1 to Over 70 in 5-year increments Removed patients with no age information
AGE_in_MONTH	
AGE_in_DAY	
GENDER	Removed "Others" (n=8)
WEIGHT	N/A
DRUG_GENERIC_NAME 1-5	Transformed into long form and renamed as "name". Removed missing values.
ATC 1-5	Removed missing values.
FORM 1-5	Removed missing values.
ROUTE_ADMIN 1-5	Recoded "Oral" = "O" | "IV" & "IM" = "P". Assigned route of administration to the respective formulation when value missing. Removed "Inhalation" and "Nasogastric" and any missing values without respective formulation.
STRENGTH 1-5	Turned all into grams
STRENGTH_UNIT 1-5	Turned all into grams
DOSE 1-5	N/A
DOSE_UNIT 1-5	N/A
FREQ 1-5	N/A
FREQ_UNIT 1-5	N/A
START_DATE 1-5	Recoded as Character (There were formatting issues and was not used for analysis)
STOP_DATE 1-5	Recoded as Character (There were formatting issues and was not used for analysis)
INDICATION	Recoded "Unknown" to "other/NA" & spell checked
INFECTION_SITE	Missing variable recoded as Unknown
DIAGNOSES	N/A. Entered as free text
SAMPLE_TAKEN	Removed UNK & Missing
SAMPLE_TYPE 1-3	N/A
CUTURE_RESULT 1-3	N/A
ORGANISM 1-3	N/A
AST_PERFORMED	N/A
ASTR 1-10	N/A
ANTIBIOTIC_PANEL 1-10	N/A
TREATMENT_REVIEWED	N/A
APPROPRIATENESS	N/A

Curation:

Table 6 gives an overview of the curation work for each variable. After initial curation, 3,651 patients were retained (individual observations were retained). As expected, some patients had more than one antibiotic prescribed, thus the total number of records of prescriptions was 7,386 of which 58.2% (n=4,302) were prescribed to women. The majority (n=2,349) of antimicrobial prescriptions were given to women between 20-39 years old. This pattern is commonly seen and indicative of women of childbearing age being the most frequent recipients of antibiotics in association with urinary tract infections and/or pregnancies and childbirth. The most prescribed antibiotic group (n= 3,438, 46.5%) was other beta lactams (carbapenems and cephalosporins), followed by beta-lactams and penicillin's (1,894, 25.6%).

Over half of the patients (52.2%) were given an antibiotic treatment as a prophylaxis and most often in surgical specialties such as Obstetrics/Gynecological (n=870, 82.5%), General Surgery (n=427, 51.5%), Orthopedic surgery (n=299, 72.9%), which reflects the standard practice of giving prophylaxis prior to delivery and/or surgeries, respectively.

In terms of antimicrobial prescriptions per ward, the majority of wards gave out prescriptions for primary infections besides Obstetrics/Gynecological, Orthopedics. The surgical unit had a high level of antimicrobial prescription for management of primary infections (n=1134, 57.1% of their total prescriptions), followed by the medical ward (n=898, 84.2% of their total prescriptions) and NICU (n=262, 89.1% of total prescriptions of the ward). The highest number of prescriptions given on the indication of a hospital acquired infection were seen in the AICU and medical ward (n=38, 23.5% & n=75, 7% of their total, respectively).

Overall, antimicrobial prescription was highest in the surgical ward (26.9%) closely followed by gynecology and obstetrics ward (23.4%), medical (14.4%) and orthopedic surgery (8.9%). Antibiotics in the 'other beta-lactam' subgroups comprise the majority of antibiotics prescribed in most wards, with particularly high numbers prescribed in the surgical, orthopedic and OBGYN wards. Among patients that had samples taken (n=561) most frequently samples were taken from patients admitted to the medical ward (32.4%).

When looking at proportion of samples taken by infection site (among patients prescribed antibiotic), lower respiratory, urinary (non-STI) and systemic infections were the most common infections where patients had biological samples collected (28.7%, 15.2% and 13.5%, respectively). In more than half of the cases where antimicrobials were prescribed a biological sample was never obtained for testing.

Although these finding require further investigation and validation, they could likely inform focus areas of stewardship interventions in the facility.

As noted above, the AMU findings presented here are preliminary and mainly meant to be used for informing updates to the prospective data collection and analyses efforts planned in JDWNRH and other hospitals in Bhutan.

Table 7. Top Ten Antibiotics by route of administration and WHO AWARE Categorization

No	Oral	Parenteral
1.	Amoxicillin	Cefazolin
2.	Cephalexin	Ampicillin
3.	Doxycycline	Ceftriaxone
4.	Metronidazole	Metronidazole
5.	Azithromycin	Gentamicin
6.	Ciprofloxacin	Ciprofloxacin
7.	Cloxacillin	Cloxacillin
8.	Trimethoprim/sulfamethoxazole	Meropenem
9.	Nitrofurantoin	Piperacillin/tazobactam
10.	Erythromycin	Amikacin

When looking at the relative distribution of antimicrobial prescriptions according to AWaRe categories as indicated by WHO, there was some variation but across most departments the proportion of Access antimicrobials prescribed was well above 60 %. The Medical and Adult ICU awards were the only wards that did not meet the global target of 60% of antibiotic prescriptions to come from the Access category, however this is not unexpected in such wards in a tertiary facility. The AICU was also the department with the highest prescription of reserve antibiotics (3.1%). Of note, this finding conflicts with the national AMC data where no consumption of Reserve antimicrobials was recorded. An antimicrobial consumption analysis was not conducted in the absence of appropriate denominator data and will be explored later in collaboration with the country team.

Evaluation of the appropriateness of prescriptions deemed more than 80% of antimicrobial prescriptions in Neonatal ICU, Orthopedic and Gynecology/obstetrics department appropriate, while the least number of prescriptions deemed appropriate (below 60%) was seen in the Dermatology, Adult ICU and Medical units of the hospital. A relatively large proportion of cases where appropriateness was uncertain were also seen across these departments.

SECTION

04

Conclusion

This final country report serves to summarize the experiences made through in-country implementation of CAPTURA activities in Bhutan between June 2019 and March 2021 and presents the summary findings from the initial AMR and AMC/U data identification, assessment, and analysis.

As noted above, most of the analysis and visualizations for the project are done using electronic visualization tools. Comprehensive analytical outputs and the visualization tools will be shared. The final data content of this report has been selected after discussion with and feedback from data owners and relevant technical staff in the country considering both reliability in terms of data quality as well as value of data sharing.

It is important to note that the main utility of the data collected on AMR, AMC and AMU through CAPTURA project in Bhutan is to help establish a preliminary data baseline. We believe CAPTURA activities have primarily enabled and fostered capacity building within data management and analysis for future AMR surveillance efforts.

AMR – limitations and recommendations

CAPTURA's findings demonstrates availability of bacteriological culture and AST capacity at four different Hospital for diagnosis of infection caused by bacteria. Some gaps in testing and data management capacity were observed. Hence, there is a need to further enhance the capacity and quality of microbiology diagnostic services across the country.

It is observed that laboratory staff are maintaining AST data where it is available. Through CAPTURA the technical staff involved in data generation and management have been trained on further use of WHONET. Additionally, standardized testing procedures are in place and designated NRLs are regularly providing training on common testing protocol. Therefore, it is now imminently feasible for the country to formally establish an AMR surveillance network to start monitoring and tracking of AMR in the country as well as to share the findings at both local and international level.

A process to digitize AMR data with support of CAPTURA has been initiated, which can be continued prospectively by the country for proper data recording and management for future use. The laboratory currently functioning as the NRL is capable of processing different types of samples and specimens. It can also continue to maintain electronic records of AMR and support other facilities in the country to do the same. Though it is not an absolute necessity, recording AST findings with zone diameters should help use the data in future if the susceptibility breakpoints changes overtime. Further, we would recommend the adoption of a set of standard antimicrobials to be promoted among laboratories - both to support routine clinical decision and to improve comparability of findings over time within and between facilities. Equally important is to have uninterrupted supplies of reagents at the laboratory to ensure quality controlled outcomes and results.

Though not verified by CAPTURA, it is encouraged to maintain quality control strain test results to validate the AST data generated by each laboratory. Further development and implementation of a more robust Quality Management System (QMS) for ensuring consistent quality performance should be prioritized. Similarly, regular participation in an EQA program by the NRL is encouraged. Upon establishment of microbiology capacity at referral sites, establishment of a national proficiency testing program for bacterial culture, pathogen identification and AST is also recommended.

AMC – limitations and recommendations

Monitoring of antimicrobials consumption has not been done in a systematic manner in Bhutan and it is therefore important to acknowledge that this initial analysis by CAPTURA should be seen as an important learning opportunity to guide the country to build AMC surveillance capacity in the future. Bhutan is encouraged to establish, collect, and compare data across several years through their surveillance systems to monitor antibiotic consumption over time. Specifically, it would be advisable for Bhutan to ensure future data collection is done using templates that follow the WHO methodology and particularly ensuring the relevant formats that would facilitate easy collation and analysis. CAPTURA has developed a freely available data template and visualization tool following WHO methodology that could be useful for such effort. This would allow monitoring of trends and eventually contribute more systematic and quality data on AMC to GLASS AMC module and detect changes to antibiotic consumption patterns early on that merit further exploration, and which may have policy implications and/or lead to stewardship interventions.

AMU – limitations and recommendations

Similar to CAPTURA's experience across other countries in the region, in Bhutan very limited information were readily available on antimicrobial use at the patient level. The obtained antimicrobial use data was limited to piloting collection of digitized prescriptions and medical record data from JDWNRH. Although limited in amount, the AMU data collected from Bhutan was unique in that it allowed for more detailed analysis at the individual patient level, which is crucial to inform and evaluate antimicrobial stewardship interventions. If such data can be prospectively gathered across multiple facilities in a standardized manner incl. consistent linkage to clinical and AMR data, it will truly represent a distinctive example of national AMU surveillance in the region. To further enable the establishment of this system, CAPTURA supported Bhutan in conducting a national workshop for development of AMU data collection tools, which can hopefully be expanded across all hospitals throughout the country. For this purpose, CAPTURA specifically recommends that:

1) hospitals prioritize electronic prescription data capture wherever possible;

2) ensure that prescriptions include information on:

- basic patient and department demographics,
- treatment duration and indication
- link to clinical diagnosis (and outcomes) as well as relevant lab information.

This will allow more granular assessment of use quantities and, most importantly, assessment of appropriateness of antimicrobial use.

SECTION

05

Appendix

1. CAPTURA's data definitions

Project metadata constitutes all the information collected directly by and as part of the CAPTURA project. This data includes:

- information collected by landscape- and desktop-reviews, and from interviews on the names, function, and location of facilities etc.
- information collected to identify, quantify, and prioritize data sources
- information collected to assess the quality and relevance of data sources or facilities generating data

Most of the project meta-data is collected by questionnaires generated for the purpose of and administered by the CAPTURA project.

Project facility data is the actual retrospective source data from the identified facilities, which has been identified and prioritized for collection. This data includes historical AMR, AMU or AMC data already collected in the facilities.

Antimicrobial resistance (AMR):
AMR data refers to microbiology laboratory data with a special focus on antimicrobial susceptibility test results of WHO priority pathogens[21] (excl. TB). This data may or may not include characteristics of the person from whom the sample was drawn. Examples of AMR data may be isolate level test results from microbiology labs or aggregate data on AMR testing from hospitals such as antibiograms.

To ensure consistency in categorization of identified AMU/C data sources during the project, the following definition of AMU/C is used:

Macro Antimicrobial consumption (AMC):
Macro AMC refers to antimicrobial consumption statistics such as total sales, import or export in a country or region. Examples of Macro AMC data, for the purpose of CAPTURA project, include data on import and export of antibiotics and national distribution obtained from country's drug regulatory authorities and similar.

Micro Antimicrobial consumption (AMC):
Micro AMC refers to records of antibiotic procurement/supply/distribution at district or facility level, but which does not hold data on individual dispensing. This data is often the only data available on antimicrobial use at a more granular level and hence often used as a proxy for antimicrobial use. Examples of Micro AMC data, for the purpose of CAPTURA project, include procurement or inventory records from individual facilities (e.g., hospital pharmacies).

Antimicrobial use (AMU):
AMU data refers to records of dispensed antibiotics to individual patients (e.g., prescription data including patient information and potentially also information on indication or diagnoses). Examples of AMU data, for the purpose of CAPTURA project, include pharmacy-level records on dispensed antibiotics to patients/customers and hence differentiated into the individual prescription level.

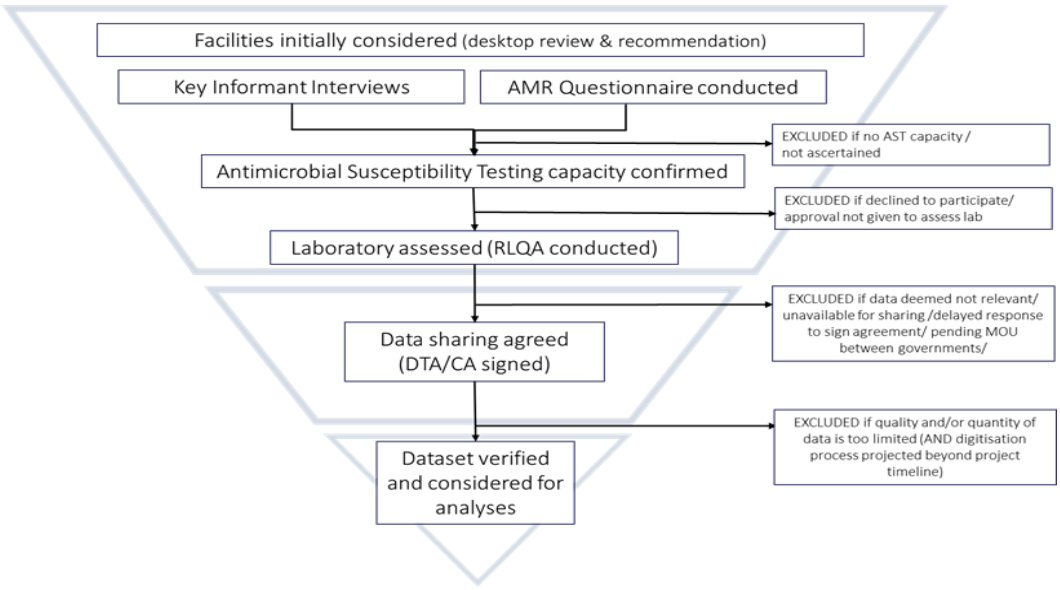
2. Metadata methodology

The AMR Questionnaire assisted CAPTURA and MoH to collect information on AMR data available at each facility, the methods used to collect it, format of the stored data, and additional indicators prior to collection of AMR datasets from each laboratories selected (see overview of variables in the next page).

A 'Rapid Laboratory Quality Assessment Tool for AMR' (RLQA) was used to rapidly assess selected quality indicators of laboratories' pathogen identification and antibiotic susceptibility testing for the past 3 years. The information was collected from a person who had access to the historical records, necessary information regarding the laboratory and adequate knowledge about the microbiology processes done at the laboratory for at least the past three years.

The RLQA assesses seven sections: Equipment, Staffing, Media, Pathogen Identification, Antimicrobial Susceptibility Testing (AST), Internal Quality Control (IQC), and External Quality Assurance (EQA). It is important to note that the RLQA tool and the associated scores do not represent a comprehensive and validated microbiology lab assessment.

The AMU Questionnaire assisted CAPTURA and MoH to understand the antimicrobial use (AMU) data available at each facility, the methods used to collect it, format of the stored data, and additional indicators in prioritizing the facilities to be considered for future AMU surveillance (see overview of variables in the next page).



CAPTURA AMR Metadata and Priority Variables
Metadata
Facility Location
Public or private facility
Type of culturing conducted
Ability to conduct Antimicrobial Susceptibility Testing (AST)
How AST performed (automated or manual)
Average number of AST per month
AST data format (paper or electronic)
Number of years of available AST data
Presence of Laboratory Information System
Presence of internet connectivity at facility
Priority and Specialised Variables
Sample Origin (Human/Animal/Food)
Date of Birth/ Age
Sex
Patient Location (ward/clinic)
Healthcare Facility Admission Date (if inpatient)
Healthcare Facility Date of Visit (if outpatient)
Specimen Date
Specimen Type
Culture Result (organism isolated)
AST Interpretation (R, I, S)
AST Measurement (disk diffusion zone diameter/MIC value)
Antibiotics Prescribed After Specimen Collection
Diagnosis (after laboratory results provided)
Patient Outcome
Date and Cause of Death (if applicable)
Additional/Recurrent Isolates/Infections
Additional Patient Information (e.g., change in initial therapy, date of discharge, comorbidities, date of discharge, etc.)

CAPTURA AMU Metadata and Priority Variables
Metadata
Facility Location
Public or private facility
Located within a hospital/health centre
In-patient ward, Out-patient ward, Emergency Department
Number of staff working at facility and qualifications
Source of antimicrobials
Antimicrobial distribution data format (public or private)
Number of years of recorded data
Data format (e.g., paper or electronic)
Type of software used
Prescription linked to patient diagnosis
Ability to conduct data analysis
Presence of internet connectivity at facility
Priority and Specialised Variables
Patient Age
Patient Sex
Date of Prescription
Department (OPD, IPD, ED)
Type of Drug (Drug Class)
Ingredients
Strength of Drug
Formulation Type
Route of Administration
Product Name
Manufacturer
Pack Size Unit /Number of Doses Distributed
Daily Defined Doses (DDD)
Indication for Prescription / Diagnosis
MDR Risk
Product Origin
Brand Name or Generic
Previous Antimicrobial Prescriptions
Change to Initial Therapy

3. Contents of CAPTURA's WHONET AMR reports for facilities

Epidemiology Report
1. Data volume
2. Patient and sample details
2.1 Patient demographics
2.2 Location details
2.3 Sample details
3. Organism statistics
3.1 Organism frequencies
3.2 Organism frequencies by specimen categories
3.3 Organism trends
4. Antimicrobial statistics
4.1 Gram-positive and Gram-negative antibiograms
4.2 Isolate alerts - Important resistance
4.3 Multidrug resistance: ECDC definitions of MDR/XDR/PDR
4.4 Multidrug resistance: Resistance profiles
5. Reporting to the World Health Organization and the United Nations
5.1 WHO Global Priority List of Antibiotic-Resistant Bacteria
5.2 WHO GLASS results
5.3 United Nations Sustainable Development Goals
6. Cluster detection
6.1 Cluster detection by species
6.2 Cluster detection by resistance profile
Appendix A. Antibiograms
Test practices and quality report
1. Data entry and management
1.1 Data volume
1.2 Completeness and validity of data entry
2. Quality control testing
3. Organism results
3.1 Capacity for organism identification
3.2 Capacity for the isolate of fastidious organisms
3.3 Blood culture results
4. Antimicrobial susceptibility test practices
4.1 Antibiotic Configuration
4.2 Antibiotic tests without validated breakpoints
4.3 Regularity of antimicrobial testing
4.4 Antimicrobial susceptibility test measurements
5. Quality control alerts

4. AMC Methodology

The consumption data in this report were collated by CAPTURA by applying the WHO protocol on surveillance of antimicrobial consumption[13]

CAPTURA uses the Anatomical Therapeutic Chemical (ATC) classification system[14] to classify antimicrobial substances and the number of DDDs as a measurement metric. The DDD is the assumed average maintenance dose per day of an antimicrobial substance(s) used for its main indication in adults and is assigned to active ingredients with an existing ATC code. As a rule, the DDDs for antimicrobials are based on treatment for infections of moderate severity. To adjust for population size, the consumption is usually presented as number of DDDs per 1000 inhabitants per day. The 2019 ATC/DDD version is used by CAPTURA to present the data for all reporting years.

Antibiotic consumption is presented using the following key indicators:

- Quantity of antibiotics as DDD per 1000 inhabitants per day for total consumption and by pharmacological subgroup (ATC3);
- Relative consumption of antibiotics as a percentage of total consumption by route of administration (oral, parenteral) and AWaRe categories (Access, Watch and Reserve)[15];
- List of the most frequently used antibiotic substances comprising 75% of the total consumption, stratified by route of administration-Drug Utilization 75 (DU75).

AWaRe Categorization

Antibiotics of the WHO Model List of Essential Medicines List are grouped in three AWaRe categories: Access, Watch and Reserve. The AWaRe classification covers 177 commonly used antibiotics with the aim of supporting antibiotic monitoring and stewardship activities. The Access category includes first and second choice antibiotics for the empirical treatment of common infectious syndromes and they should be widely available in health care settings. Antibiotics in the Watch category have a higher potential for resistance to develop and their use as first and second choice treatment should be limited. Finally, the Reserve category includes “last resort” antibiotics whose use should be reserved for specialized settings and specific cases where alternative treatments have failed. In this report the consumption data grouped according to the WHO AWaRe categorization, revised in 2019 are presented.

DATA visualization

CAPTURA has designed and engineered a tool to enable visualization of the AMC data collected as part of the project. The tool is a pre-coded template, which can be used by individual facilities/countries to build their own, individually tailored, and interactive AMC dashboard files.

The template including guidance on how to use it is freely available on: https://captura.ivi.int/

[13] World Health Organisation. WHO methodology for a global programme on surveillance of antimicrobial consumption v1.0

[14] WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2020. 2019

[15] World Health Organisation. WHO 2019 AWaRe Classification Antibiotics https://www.who.int/medicines/news/2019/WHO_releases2019AWaRe_classification_antibiotics/en