THE ANTIBIOTIC FOOTPRINT ANALYSIS

Antibiotic Consumption by Human and Animal Health Sectors in Pakistan during 2019

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List of Acronyms

AAI	Antimicrobial Active Ingredient
AF	Antibiotic Footprint
AFA	Antibiotic Footprint Analysis
AMC	Antimicrobial Consumption
AMR	Antimicrobial resistance
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical
AWaRe	Access, Watch, and Reserve
CIA	Critically Important Antimicrobials
DDD	Defined Daily Dose
DHIS	District Health Information Systems
DID	Defined Daily Dose per 1000 inhabitants per day
DIS	Drug Information System
DRAP	Drug Regulatory Authority Pakistan
EBAP	Estimated Budget of Antimicrobial Purchases
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EXIM	Pakistan Import Export Database
FA	Feed additives
FPP	Finished Pharmaceutical Product
GDP	Gross Domestic Product
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GP	Growth promoter
GW	Gross Weight
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information Systems
IDIS	Integrated Disease Information System
IGM	Import General Manifest

INN	International Non-proprietary Name
JPMC	Jinnah Postgraduate Medical Centre
KG	Net Weight
KP	Khyber Pakhtunkhwa
LMIC	Low- and Middle-Income Country
MIA	Medically important antibiotics
MT	Metric Tonnes
NW	Net Weight
OIE	Organization for Animal Health
PCU	Population Correction Unit
PIMS	Pakistan Institute of Medical Sciences
PP	Package Proportion
PPA	Public Purchases of Antimicrobials
PPS	Point Prevalence Study
PPW	Percent packaging weight
PRM	Pharmaceutical raw material
PTI	Pak Trade Info
SF	Substandard and Falsified
TNW	Total Net Weight
UD	Unit Dose
UTI	Urinary Tract Infection
WHO	World Health Organization

1 Background

Antimicrobial Resistance (AMR) is a global health emergency.[1,2] In 2019, it is estimated that AMR was associated with ~5 million deaths globally (1.27 million deaths directly attributed to AMR).[3] While evolutionary in bacterial development, AMR is driven by anthropogenic factors including the inappropriate use of antibiotics.[4] The burden of AMR requires concerted global yet region-specific efforts at containment.

Measuring antibiotics – the core subgroup of a broader group of antimicrobial therapeutic agents comprising antivirals, antifungals, and others – consumption and use is essential for the development of stewardship efforts, including use reduction, aimed at AMR containment. Methods for measuring or estimating – as measuring includes systematic and rigorous protocols not available to all – national-level antibiotic consumption in the literature include the use of Point Prevalence Studies, pharmaceutical sales volume, insurance data, import data, procurement data, farm records, household surveys, and dispensing records – depending on the sector.

The Antibiotic Footprint, modelled after the carbon footprint (which seeks to create public awareness of the negative environmental impact of greenhouse gases such as carbon dioxide), was conceptualized as a tool to communicate the need for antibiotic use reduction across One-Health sectors to contain AMR.[5] In 2021, a multi-disciplinary team of researchers representing pharmacy, public health and biomedical engineering at Boston University was commissioned to provide technical advice to the Fleming Fund, Pakistan, for a comprehensive (One-Health) national antibiotic consumption analysis employing the antibiotic footprint concept.

As a concept, the Antibiotic Footprint (AF) is an advocacy tool both to create public awareness on antibiotic consumption and the link with AMR, and to provide evidence for policies aiming to affect use reduction in practice. It relies on data aggregation and simple comparative visualization for effectiveness. Its focus is on simplified comparative data visualization using aggregated antibiotic consumption data. The major limitation in the use of this concept is its reliance on systematically collected antibiotic consumption data. Most Low- and Middle-Income Countries (LMICs) do not have the capacity for the routine, systematic collection of data, and, thus, are not represented in the public-facing AF tool.[6]

Pakistan, currently classified as lower-middle-income, is the world's 5th most populous country.[7] There are 221 million people, according to 2020 estimates[8] and over 1.5 billion livestock, comprising cattle and poultry among others. Livestock contributes around 11% to its GDP, emphasizing the role of agriculture in its economy.[9] Health services delivery is decentralized. In June 2018, Pakistan devolved its healthcare

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[1] WHO. Global Action Plan on Antimicrobial Resistance [Internet]. 2015 [cited 2019 Dec 25]. Available from: https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1

[2] Toner E, Adalja A, Gronvall GK, Cicero A, Inglesby TV. Antimicrobial resistance is a global health emergency. Health Security. 2015;13(3):153–5.

[3] Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis - The Lancet [Internet]. [cited 2022 Apr 23]. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext

[4] WHO. AWaRe Policy Brief [Internet]. 2019 [cited 2020 Nov 15]. Available from: https://adoptaware.org/assets/pdf/aware_policy_brief.pdf

[5] Limmathurotsakul D, Sandoe JAT, Barrett DC, Corley M, Hsu LY, Mendelson M, et al. 'Antibiotic footprint' as a communication tool to aid reduction of antibiotic consumption. J Antimicrob Chemother. 2019 Aug 1;74(8):2122–7

[6] Antibiotic Footprint - Main Page [Internet]. [cited 2022 May 27]. Available from: https://www.antibioticfootprint.net/infobox.aspx?pageID=101&lang=en-GB

[7] World Bank Country and Lending Groups – World Bank Data Help Desk [Internet]. [cited 2022 May 27]. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

[8] World Bank. Population, total - Pakistan | Data [Internet]. 2022 [cited 2022 Mar 30]. Available from: https://data.worldbank.org/indicator/SP.POP.TOTL?locations=PK

[9] FAO. FAOSTAT [Internet]. 2021 [cited 2021 Sep 26]. Available from: http://www.fao.org/faostat/en/#data/QCL

system.[10] This devolution also affected vertical programs, including health. Health service is delivered through a mix of public, private, and vertical programs. Challenges in health service delivery are similar to other LMICs, with more patients, 70%, procuring health services from the private sector – with a high Out-of-Pocket expenditure[11]; as well unrestricted access to antibiotics over the counter.[12] From December 2018 into 2019, the prices of medicines increased.[13] The increase was brought about by a devaluation of its currency and prevailing broader economic circumstances.[14]

There is a high burden of AMR, as in other Southeast Asian and African countries, in Pakistan.[15] For example, using 2019 World Health Organization (WHO) Global Antimicrobial Resistance and Use (GLASS) data, the prevalence of *E. coli* resistance to ciprofloxacin was 85.3% (n=746) in bloodstream infections and 72% (n=11, 384) in Urinary Tract Infections (UTIs). This was similar for UTIs in Bangladesh at 89.7% (n=376) but higher than for the United Kingdom at 11.5% (n=822,931).[16] Recognizing the challenges of AMR, the government committed to a National Action Plan on AMR in 2017.[17] Benchmarked against other countries with a similarly large veterinary sector, there are important gaps that need attention.[18] Overall, these gaps exist across One-Health dimensions according to the Global Health Security Index for 2021.[19]

1.1. Literature Review

To identify any previous national-level study providing data on antibiotic consumption in Pakistan, a systematic literature review was performed on four databases. Out of 7 retrieved records, there were 3 putatively national-level studies.[20] However, none of these 3 covered both the human and animal sectors, and all 7 were either sector- or province-specific (Table 1).

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[10] Government of Pakistan FD. Pakistan Economic Survey 2020-2021 [Internet]. 2021 [cited 2021 Sep 26]. 556 p. Available from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwib7_n7ipzzAhX_A2MBHTsqAkkQFnoECAMQAQ&url=https%3A%2F%2Fpc.gov.pk%2Fuploads%2Fcpec%2FPES_2020_21.pdf&usg=AOvVaw38c4KBkZEmRktykmI7D2Ym

[11] Khalid F, Raza W, Hotchkiss DR, Soelaeman RH. Health services utilization and out-of-pocket (OOP) expenditures in public and private facilities in Pakistan: an empirical analysis of the 2013–14 OOP health expenditure survey. BMC Health Serv Res. 2021 Feb 25;21(1):178.

[12] Home Office, UK. Country Policy and Information Note Pakistan: Medical and healthcare provisions [Internet]. 2020 Sep p. 50. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/924029/Pakistan_Medical_and_Healthcare_issues_-_CPIN.pdf

[13] Junaidi I. Recent increase in drug prices capped at 75pc [Internet]. DAWN.COM. 2019 [cited 2022 Apr 23]. Available from: https://www.dawn.com/news/1482743

[14] Pakistan's consumer sector earnings dip 26% in 2019 [Internet]. The Express Tribune. 2020 [cited 2022 Apr 23]. Available from: http://tribune.com.pk/story/2178962/2-pakistans-consumer-sector-earnings-dip-26-2019

[15] Situational-Analysis-Report-on-Antimicrobial-Resistance-in-Pakistan.pdf [Internet]. 2018 [cited 2020 Jul 8]. Available from: https://cddep.org/wp-content/uploads/2018/03/Situational-Analysis-Report-on-Antimicrobial-Resistance-in-Pakistan.pdf

[16] WHO. GLASS_Report 2021_supplementary material [Internet]. Google Docs. 2021 [cited 2021 Jun 16]. Available from: https://docs.google.com/spreadsheets/d/1Ej0a-av4V5uoFw19DfZoDvcLpdvHTscfXoqJgozGiwc/edit?usp=embed_facebook

[17] Ministry of National Health Services, Regulation & Coordination, Government of Pakistan. Antimicrobial Resistance National Action Plan Pakistan. 2017

[18] Orubu ESF, Sutradhar I, Zaman MH, Wirtz VJ. Benchmarking national action plans on antimicrobial resistance in eight selected LMICs: Focus on the veterinary sector strategies. 2020;10(2):10.

[19] Global Health Security Index 2021: Pakistan Country Score Justifications and References [Internet]. John Hopkins Center for Health Security, the Nuclear Threat Initiative, and the Economist Intelligence Unit; 2021 Dec [cited 2021 Apr 23] p. 108. Available from: https://www.ghsindex.org/wp-content/uploads/2021/12/Pakistan.pdf

[20] Mohsin M, Boeckel TPV, Saleemi MK, Umair M, Naseem MN, He C, et al. Excessive use of medically important antimicrobials in food animals in Pakistan: a five-year surveillance survey. Glob Health Action. 2019 Dec 13;12(sup1):1697541; Malik F, Figueras A. Analysis of the Antimicrobial Market in Pakistan: Is It Really Necessary Such a Vast Offering of "Watch" Antimicrobials? Antibiotics. 2019 Dec;8(4):189; Saleem Z, Hassali MA, Versporten A, Godman B, Hashmi FK, Goossens H, et al. A multicenter point prevalence survey of antibiotic use in Punjab, Pakistan: findings and implications. Expert Rev Anti Infect Ther. 2019 Apr;17(4):285–93.

Date	Study	Study design	Sector	Patient group	Facility	Scope/location	Data source
2019	Saleem et al	PPS, multicentre	Human	In-patients	Hospitals	Punjab	Hospital records
2019	Malik & Figueras	IQVIA	Human	All	Hospitals & pharmacies	National	IQVIA
2020	Saleem et al	IQVIA (tablets & capsules)	Human	All	Hospitals & Pharmacies	National	IQVIA
2016	Shaikh et al	Prescription analysis	Human	Out-patients	Hospitals & PHC	Sindh/Khairpur District	Prescriptions
2018	Sarwar et al	PPS, multicentre	Human	All	PHC	Punjab	Prescription and inpatient records
2021	Umair et al	PPS	Poultry	Broilers	Commercial farms	Punjab & KP	Questionnaire
2019	Mohsin et al	Surveillance (5-year)	Poultry	Broilers	Commercial farm	The single-farm study used to estimate national AMC in broilers	Farm records

Table 1. Literature review of peer-reviewed studies on antibiotic consumption in Pakistan

Additionally, Pakistan did not report consumption data to either the WHO GLASS report on human antibiotic consumption or the Organization of Animal Health (OIE) report on veterinary antibiotic consumption. There is, thus, an urgent need for data on national-level antibiotic consumption across human and animal health sectors in Pakistan.

1.2. Aim and Objectives

The aim of this activity was to generate, analyse, and visualize national-level antibiotic consumption data for human and animal use for Pakistan in 2019 as an inception year for future exercises. The objectives were two-fold: first, to develop a method for estimating animal antimicrobial consumption from import data; secondly, to estimate and evaluate total and relative human and animal antimicrobial consumption.

2 Methods

2.1 Human Sector

2.1.1 Data Source

Three data sources were used to estimate antibiotic use in the human sector. These were: (i) pharmaceutical sales volume to private pharmacies and hospitals as obtained from IQVIA at the level of manufacturers and distributors, comprising 85% of the pharmaceutical market[21]; (ii) antibiotic import for vertical programs by international agencies and (iii) a survey by IQVIA for public sector procurement of

[21] Rieth M. IQVIA Quality Assurance. 2019;137.

antibiotics provided data for the remaining 15%. The rationale for these data sources is largely the availability of data (**Annex 1**).

2.1.2 Data Coverage/Scope

The IQVIA data consisted of the ATC J01 class (antimicrobials for systemic use). This ATC class comprises antibacterial only, excluding those for the treatment of tuberculosis. There were 70 antibiotics as individual International Non-proprietary Names (INN), or generics, presented in sales units of packs of tablets, capsules, injections or ampoules/infusions or vials, suspensions/oral powders for suspension and oral drops of different dosage form strengths in the database. In total, they were 3,229 individual antibiotic agents or formulations.

2.1.3 Data Management and Analysis

The IQVIA dataset was reclassified into 2019 ATC codes, and based on a preliminary analysis of sale volumes, recategorized into six therapeutic groups: (I) J01A, tetracyclines, (II) J01C, beta-lactams, penicillins, (III) J01D, other beta-lactams comprising cephalosporins, monobactams and carbapenems, (IV) J01F, macrolides including azithromycin and similar, (V) J01M, quinolones such as ciprofloxacin, and (VI) "Others", consisting of eight sub-groups or individual antibiotics: aminoglycosides such as amikacin and gentamicin; amphenicols such as chloramphenicol; sulfonamides; glycopeptides comprising injectable vancomycin and teicoplanin; colistin; fusidic acid; fosfomycin; and linezolid.

Consumption was analysed according to the Anatomical Therapeutic Chemical/ Defined Daily Dose (ATC/DDD) methodology.[22] This method of estimating medicines consumption is well-established and accepted.[23] Antibiotic use was also assessed by the WHO Access Watch Reserve (AWaRe) classification scheme. This scheme categorizes over 180 antibiotics into three groups: Access, Watch and Reserve, based on their potential to induce AMR and on clinical use indications with the intent to provide a tool for antibiotic stewardship. The fourth category of Not Recommended consists of antibiotic combinations regarded as without evidence-based indications, whose use is discouraged.[24]

Antibiotic consumption was analysed and expressed as Defined Daily Doses (DDD) per 1,000 population per day, DID, for all J01 antibiotics.[25] The DDD for each substance, defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults", was obtained from the ATC-DDD index. Combination substances such as sulfamethoxazole-trimethoprim with DDD as Unit Doses (UD) or tablets were converted to DDD in mg by dividing one UD with the tablet strength of the active pharmaceutical substances. Substances without DDD were excluded from the analysis. The DDD used was formulation-specific depending on the route of administration – some substances had different DDD for tablets/capsules meant for oral administration and injections/infusions meant for parenteral administration. DDDs were 2019 values.

[22] WHOCC - ATC/DDD Index [Internet]. [cited 2020 Jun 7]. Available from: https://www.whocc.no/atc_ddd_index/

[23] WHO | 7. Sources of Drug Utilization Data [Internet]. WHO. World Health Organization; [cited 2020 Jul 2]. Available from: http://www.who.int/medicines/regulation/medicines-safety/toolkit_sources/en/; Li G, Jackson C, Bielicki J, Ellis S, Hsia Y, Sharland M. Global sales of oral antibiotics formulated for children. Bull World Health Organ. 2020 Jul 1;98(7):458–66.

[24] World Health Organization. The 2019 WHO AWaRe classification of antibiotics for evaluation and monitoring of use [Internet]. World Health Organization; 2019 [cited 2020 Jul 2]. Report No.: WHO/EMP/IAU/2019.11. Available from: https://apps.who.int/iris/handle/10665/327957

[25] World Health Organization. WHO report on surveillance of antibiotic consumption: 2016-2018 early implementation [Internet]. 2018 [cited 2019 Dec 25]. Available from: https://www.who.int/medicines/areas/rational_use/who-amr-amc-report-20181109.pdf?ua=1

The formula used for calculating antibiotic consumption can be written as:

$$1000MQP/DPN$$

Equation 1. A general form of the formula for the calculation of antibiotic consumption in DID units

[where M=Mass, or strength, of antibiotic expressed in grams (g); Q=Number of dosage units (tablet, capsule, vial, or ampoule) in a pack; and P = sales volume, or a number of packs sold, per antibiotic agent; D = Defined Daily Dose, DDD, in g; P=Population; N=Number of days (365 days for 2019).

Or equivalently, as:

$$This\ study\ aimed\ \frac{\text{Total sales amount in the year (mg) x 1000}}{\text{DDD (mg) x days in the year x study population}}\ (68,69);$$

Equation 2. An alternative formula for calculating antibiotic consumption in DID units

where total sales amount = (antibiotic dosage form strength (mg or g) x unit pack-size x units sold); and unit pack-size is the number of doses, or standard units, per pack. One standard unit was a tablet, capsule, vial, or ampoule. For oral suspensions or syrups meant for use in children, the standard unit was 5 ml.[26] For example, the unit pack-size for an oral liquid substance presented as a 60 ml bottle was 60/5, or 12 standard units per bottle. With drops, the standard unit was adopted as 1. Thus, a dropper of 10 ml volume had a unit pack size of 10. Population for 2019 was the World Bank's estimate of 216, 565, 317.[27]

The analysis is presented both as consumption (aggregated totals), and as use – consumption patterns by route of administration, therapeutic/pharmacological sub-group, or ATC codes and WHO AWaRe categories. Thus, results are stratified as follows:

1. Total consumption in DID and kg of antibiotic or active pharmaceutical ingredient (API)
2. Proportions (%) of total consumption in DID by therapeutic/ATC sub-group
3. Oral and parenteral consumption as percentages of total consumption (DID)
4. Consumption by WHO AWaRe categories (DID)

For government sector purchases, collected through survey data, estimated share of antimicrobial drugs (for each of oral & parenteral drug groups) in overall drug purchase budgets was obtained through interviewing government procurement officials in different territories i.e., Khyber Pakhtunkhwa (KP), Baluchistan, Punjab, Sindh and Federal. Total budget estimates (including drug purchase allocations) were taken from different audit and financial reports published by each provincial/territorial authority. Based on total budgets allocated to antimicrobial drugs, an average price of antimicrobial drugs (for each group of drugs taken by oral and parenteral route) was taken from the available list of approved drugs (shared by a survey participant) used in Sindh. The underlying assumption for average pricing being the same for all provinces/territories is the fact that since the suppliers (distributors/pharma companies) submit tender bids in all provinces/territories using the same (or with minimal differences) pricing methodology that allows them to remain profitable. Based on the average pricing identified for each of the antimicrobial drug group i.e., Oral, and parenteral, an estimated volume of purchases by public sector (PPA) in each province/territory was calculated using the following formula:

[26] Li G, Jackson C, Bielicki J, Ellis S, Hsia Y, Sharland M. Global sales of oral antibiotics formulated for children. Bull World Health Organ. 2020 Jul 1;98(7):458–66.
[27] Population, total - Pakistan | Data [Internet]. [cited 2020 Jul 16]. Available from: https://data.worldbank.org/indicator/SP.POP.TOTL?locations=PK

$$PPA\,Volume = \frac{EBAP\ oral\ category}{Average\ price\ (oral)} + \frac{EBAP\ parenteral\ category}{Average\ price\ (parenteral)}$$

2.2 Animal Sector

2.2.1 Data Source

The data source for estimating antibiotic consumption in the animal sector was import data obtained from the Pakistan Export Import Database (EXIM).[28] The database lists imports of goods to and from Pakistan for the years 2015 onwards. The information captured in Pakistan EXIM Trade Info is based on International Shipping records. Among the goods are also antimicrobials, either as Antimicrobial Active Ingredient (AAI) or as Finished Pharmaceutical Product (FPP). This approach using import data is one of several alternatives available in the literature[29] and was chosen for the relative ease of access to data (**Annex 2**).[30]

The protocol for estimating antibiotic consumption using this import database consisted of three discrete procedures comprising 10 steps and is summarized in Figure 1 and detailed in sections 2.2.2 to 2.2.4.

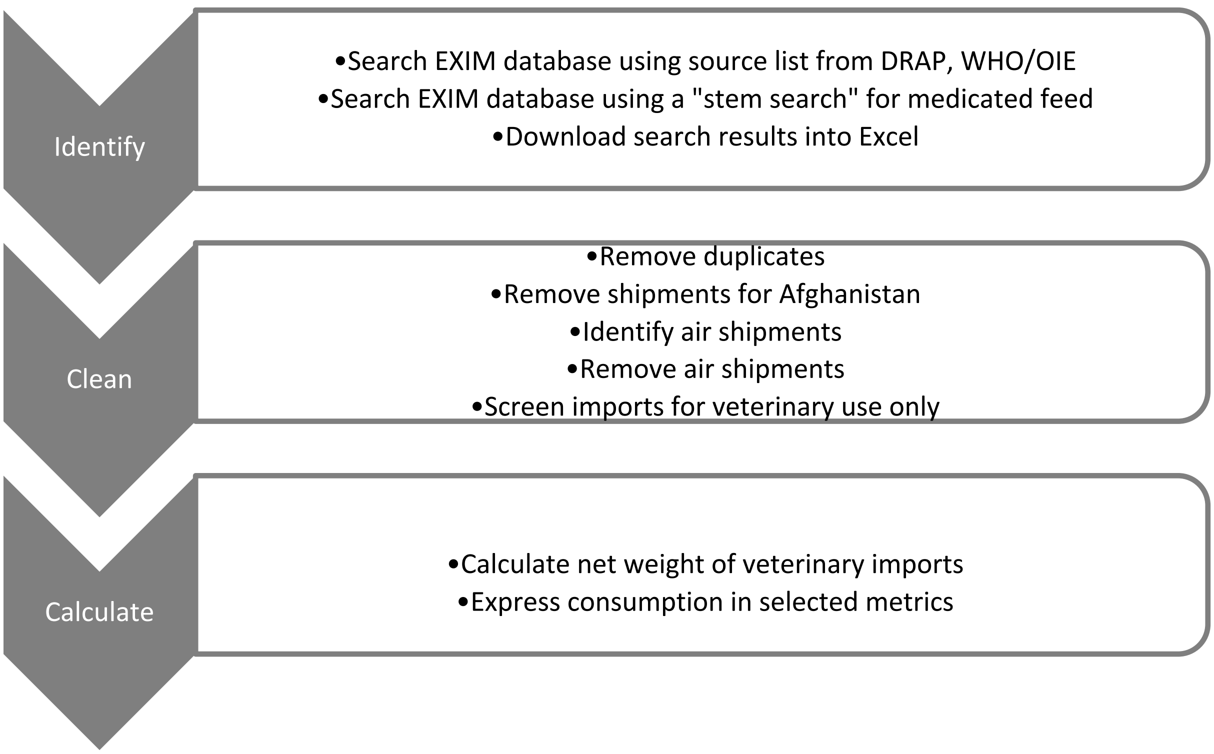

Figure 1. Schematic for the general protocol for estimating or calculating antibiotic consumption in the veterinary sector using antibiotic import data on the Pakistan EXIM database.

[28] https://pak.eximtradeinfo.com/

[29] Mouiche MMM, Moffo F, Betsama JDB, Mapiefou NP, Mbah CK, Mpouam SE, et al. Challenges of antimicrobial consumption surveillance in food-producing animals in sub-Saharan African countries: Patterns of antimicrobials imported in Cameroon from 2014 to 2019. J Glob Antimicrob Resist. 2020 Sep; 22:771–8; Kanu JS, Khogali M, Hann K, Tao W, Barlatt S, Komeh J, et al. National Antibiotic Consumption for Human Use in Sierra Leone (2017-2019): A Cross-Sectional Study. Trop Med Infect Dis. 2021 May 13;6(2):77; Abilova V, Kurdi A, Godman B. Ongoing initiatives in Azerbaijan to improve the use of antibiotics; findings and implications. Expert Rev Anti Infect Ther. 2018 Jan;16(1):77–84.

[30] Note: In the veterinary sector, the broader term of antimicrobials is used to include anti-parasitic agents used, for example, in medicated feeds

There was a verification step in between the Identify and the Clean steps where the data from EXIM was compared against another database using select antibiotics to confirm import volumes.

2.2.2 Data Identification, Verification and Extraction

A "master list" of antimicrobial products (by API/INN) for use in animals with valid market authorization provided by the Drug Regulatory Authority of Pakistan (DRAP) – the federal medicines regulatory body for Pakistan responsible for licensing all medicines in Pakistan – was used to identify all antimicrobials in the animal sector through a comprehensive search on the Pakistan EXIM Trade Info database (**Annex 3**).

This list was cross-referenced against several information sources both to identify AAI to be used as Pharmaceutical Raw Materials (PRM) for secondary manufacturing purposes and FPP for animal use as well as differentiate between manufacturers of human and animal products. The sources used for verification were:

1. The list of manufacturers that are known to produce antibiotics used in animals in Pakistan (**Annex 4**). The list includes 113 manufacturers, with several overlaps between manufacturers of human and veterinary only products, depending on the product in question. That is, some of these 113 manufacturers produce products for both the human and animal sectors.
2. The WHO/OIE list of Medically Important Antibiotics (**Annex 5**) with 125 active ingredients.
3. The DRAP list of all manufacturers (both human and animal sectors) licensed in 2019.
4. An online Drug Information System (DIS) containing licensed human medicines in Pakistan as well as manufacturers.[31]
5. Product catalogues on manufacturers' websites, or other online sources including social media (Facebook; LinkedIn) information that is publicly available.

These 5 sources were used to identify, verify, and extract all antibiotic products meant for use in animals only imported into Pakistan in 2019, as detailed:

- Using the "master list" from DRAP (**Annex 3**), the EXIM database was searched for the API for the period from January 1, 2019, to December 31, 2019. The name of the base API was used instead of the salt form to retrieve all salt forms. For example, "colistin" rather than "colistin sulphate". Sulpha drugs were also searched using the alternative sulpha prefix. Import records for 104 products on the DRAP's "master list" were found on the EXIM database. These 104 records were then extracted onto an Excel sheet for consumption analysis.
- To ensure completeness, the DRAP Master list was compared against the WHO/OIE list to identify products/INN not captured by the DRAP list that may have been imported into Pakistan. Firstly, the WHO/OIE listed products (**Annex 5**) were searched for on the EXIM database to identify those imported in 2019. Next, the products/INN on the WHO/OIE list that were imported were then compared with the DRAP list to identify "missing" products on the DRAP list. These "missing products" were then downloaded from the EXIM database and processed for analysis, or verified, as for other APIs. That is, "missing products" are antimicrobial imports for animal use not on the DRAP list.

[31] http://www.druginfosys.com

- Imports were rigorously screened against the DIS, DRAP list of manufacturers, and product catalogues both to identify antimicrobials for animal use only and to quantify import volumes for APIs for animal and human use imported by manufacturers that produce both human and animal products. Where the manufacturer product catalogue shows that the API in question is used only for animal products, that API is assigned as wholly for animal use by that manufacturer. Where the manufacturer product catalogue shows that the API is used for both human and animal medicines, the import volume of the API in question for that manufacturer was averaged to quantify its use for animal only products (see also section 2.2.3 on data cleaning).

Imports on the DRAP and WHO/OIE lists that were veterinary Feed Additives/Growth Promoters (FAs/GPs) products were identified from the Item Description column/field in the EXIM database. To ensure that FAs/GPs are not missed where these are imported by names other than the APIs, a "stem search" was performed on the EXIM database using the following terms: "feed", "growth promoter", "premix" and "granular". All these shipments were then downloaded onto Excel followed by data cleaning.

2.2.3 Data Cleaning

Data cleaning involved several steps to ensure the computation of animal-only data. Data cleaning was necessary to exclude shipments in transit through Pakistan, specifically those bound for Afghanistan as expressly stated in shipment information. Screening for veterinary-only use avoided double accounting with antimicrobials used also in human medicines. This cleaning step represents a potential confounding step in the subsequent calculations, due to the lack of complete information for all antimicrobials.

This comprised the following sequential steps:

a. Removal of imports determined to be for human use by screening imports against the DIS, manufacturer's product catalogues or social media posts, and the list of veterinary manufacturers,

b. Removal of duplicate entries,

c. Exclusion of products imported into Pakistan but meant for Afghanistan,

d. Exclusion of dud entries, for example, "Index Cancelled", where this represents a "self-detected" repeat.

2.2.4 Data Verification

To ensure accuracy of the import data on the EXIM database, import volumes for selected antimicrobials on the EXIM database were compared against those on the PakTradeInfo database – an alternative similarly subscribed service holding import and exports for Pakistan.[32]

The selected antimicrobials were: ceftiofur, colistin, enrofloxacin, neomycin, and tylosin.

2.2.5 Data Analysis

2.2.5.1 Estimation of antibiotic consumption from import volume

Consumption as quantities in kg of API was obtained from import volumes through the calculation of net weight. In the EXIM database, each shipment records the item imported in an Item Description column, as well as Gross Weight (GW), and other shipping information including Buyer, Supplier, and Port of

[32] http://www.paktradeinfo.com

departure, among others – with the relevant variable being the GW. The derivation of the net weight, or quantities in kg of API, from each shipment, depended on the nature in which the product was imported – whether as PRM or FPP; the number of ingredients per product; the presence or absence of a stated net weight in the product's Item Description; importation route – whether by sea or by air; and intended use – either as medicines or as medicated feeds (as detailed in subsections 2.2.5.2 and 2.2.5.3 below). Consumption was the total net weight across import volumes for all shipments of APIs in the DRAP list and "missing products" from the WHO/OIE determined to be for animal use only and medicated feed.

The estimation protocol for imports as veterinary antibiotic medicines – PRM and FPP – is described in section 2.2.5.2 and for feed additives, or medicated feed, in section 2.2.5.3. Consumption analysis, as total and relative consumption, is presented in sections 2.2.5.4-7.

2.2.5.2 APIs imported as Antimicrobial Active Ingredients (AAI) or Finished Pharmaceutical Products (FPP)

For antibiotics imported either as an AAI/FPP – that is on a named INN based as presented in the Item Description column in the EXIM database, sea shipments were separated from air shipments. The rationale for the exclusion of air freights is the inconsistency in recorded GWs (**Annex 6**). For these sea shipments or vessel shipping, the recorded GW includes the AAI/FPP net weight plus the packaging weight. The packaging weight depends on the packaging material, and was thus, variable.

The protocol used to calculate net weights included several approaches, depending on the nature of the import, number of AAI per product, and/or the packaging material used in shipping, for example drums or bags or package type (and for FPP, whether in vials). The study, therefore, used a combination of methods to derive net weight:

(i) Moving Averages – Here, the average package weight of the shipping material was calculated using only "single-item" shipments with stated net weights. That is determining a "shipping package weight proportion" using the difference between the sum of the gross weight of these "single-item" shipments containing only the INN/API of interest and the stated net weight for that shipment. This was performed severally for different APIs/INNs as the exact value used depended on the API.

(ii) Packages – This approach estimated an overall shipping package weight proportion for each type of shipping package – drums, cartons, bags, or "packaging", where a "package" for a sea shipment refers to one of several different types such as cartons and drums. This packages approach to estimating shipping package weight proportion was applied to estimate the net weight for shipments without stated net weights.

(iii) Modified packages – This used the primary package of the shipment rather than the shipping package to estimate/calculate net weights. This was applied mostly to imports in vials; but also, to all imports where the Item Description column of the import record provided the net weight of the API/substance.

The applications of the moving average and packages methods are as detailed:

Moving averages: All sea shipments with API/FPP net weights available in the Item Description column were considered to calculate a Percent Packaging Weight (PPW) (**Equation 3**). For shipments of single-item products, the stated gross weight is applied. For combined products, that is with more than one API/FPP item, and no net weights available in the item description, the item gross weights were distributed equally over the number of items in that shipment (for example, for shipments of two products enrofloxacin HCl and oxytetracycline HCl with a gross weight of 609 kg, the average gross weight (609/2), or 304.5 kg was considered in the calculation of enrofloxacin's net weight – when this was the API of interest).

Where there is no net weight in the Item Description, an adjusted net weight (AdjNW) was calculated by subtracting the PPW from each shipment (**Equation 4)**.

The cumulative Total Net Weight (TNW) across each API/INN imported as a pharmaceutical raw material (PRM) for secondary processing or as medicine was calculated by adding PRM AdjNW and the net weight of all the shipments with net weights available in the item description (**Equation 5)**.

$$PPW = \left[\frac{\sum_{m=1}^{M}(NW)_m}{\sum_{m=1}^{M}(GW)_m} \times 100\right] - 100$$

Equation 3. Formula for calculation of total net weight for single item shipments with given net weights

$$PRM_{AdjNW} = \sum_{n=1}^{N}(GW - PPW)_n$$

Equation 4. Formula for the net weight calculation for imports without stated net weights

$$PRM_{TNW} = PRM_{AdjNW} + \left[\sum_{m=1}^{M}(NW)_m\right]$$

Equation 5. Formula for net weight calculations

(Where NW is net weight, GW is gross weight, M is the total number of shipments with PRM net weight available, and N is the total number of remaining shipments).

Packages: Where there is no information on the net weight, assumptions were made. Based on preliminary work with 7 antibiotics, a 13% packaging weight proportion was assumed for sea shipments (which are usually packed in drums). However, this could vary from about 10-15%. The package approach thus aggregated sea shipments by package type to provide an estimate: cartons = 2kg; drums (as well as other package types) = 3.5kg. Under the packages approach, the estimated individual package weight is applied to the quantity of the respective package type and then subtracted from the stated gross weight of the shipment to estimate the net weight for shipments without stated net weights.

2.2.5.3 Medicated feeds/feed additives

For feed additives, only the weights of the AAIs were used in the estimation rather than the stated total GW since these products include substances other than the API of interest. Usually, the feed additives' Item Description would include an indication of the per cent strength in grams of the API in the shipped item. All other calculations are as described above using the moving average and packages methods. (See also **Annex 7**).

The amounts of AAI for each FA/GP product were calculated from product strengths and volumes imported according to Equation 6.

$$\boldsymbol{AAI} = \%\,\boldsymbol{strength} \times \boldsymbol{Package\ NW} \times \boldsymbol{Tot.Packges\ Imported}_{\boldsymbol{NW}}$$

(Where NW is net weight)

Equation 6. Formula for calculating the net weight of medicated feeds

2.2.5.4 Consumption in mg/PCU

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) protocol was adapted to estimate total veterinary antibiotic consumption in mg of active ingredient or API/Population Correction Units (PCU).[33] The PCU calculates an estimated weight at the point of antibiotic treatment across all veterinary animals in a given period. It is the residual of the sum of the products of slaughtered animals and livestock animals and their estimated respective weights at treatment, per animal species, accounting for both imports and exports, expressed in kg.

With this protocol, total veterinary antimicrobial consumption was expressed as mg/PCU, where mg is the weight of all antimicrobials included in the DRAP and WHO/OIE lists that were found in the EXIM database as well as all identified veterinary feed additives – excluding those identified by brands with indications for use in specific animal species – imported into Pakistan in 2019. The PCU across all species in this study – asses, cattle, poultry, buffalo, camels, sheep, goats, horses, mules, and ducks – which are the livestock or livestock products in Pakistan – was estimated using the online ESVAC tool.[34] To account for animal species in the study that are not included in the ESVAC methodology and tool, certain assumptions were made as listed below (see also Table 2, section 2.2.5.5):

1. Asses, buffaloes, camels, and mules were treated as horses
2. Slaughtered buffaloes and camels were treated as slaughtered bullocks and bulls, respectively
3. The population of all living cattle were used in place of living dairy cows
4. Living goats were combined with living sheep

The population data of slaughtered and living animals used for the calculation of PCU were obtained primarily from FAOSTAT.[35] Overall, the rationale for these assumptions is the widespread or indiscriminate use of antimicrobials in the community. However, it is understood that they may, in turn, by increasing the value of the denominator used to normalize consumption, result in an underestimation of consumption values in mg/PCU units.

The PCU is equivalent to the animal biomass, in that 1 PCU =1 kg of animal biomass. The online tool simultaneously computes biomass across the animal species in this study. The biomass, as defined in the 5th OIE annual report, is “the total weight of the live domestic animals in a given population and year, used as a proxy to represent those likely exposed to the quantities of antimicrobial agents reported”.[36] The computed PCU was used as a denominator to normalize the total consumption in mg of active ingredients to obtain consumption in mg/PCU units.

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[33] EMA. European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) [Internet]. European Medicines Agency. 2018 [cited 2022 May 25]. Available from: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/european-surveillance-veterinary-antimicrobial-consumption-esvac

[34] EMA. Ibid

[35] FAO. FAOSTAT [Internet]. 2021 [cited 2021 Sep 26]. Available from: http://www.fao.org/faostat/en/#data/QCL; Government of Pakistan FD. Pakistan Economic Survey 2020-2021 [Internet]. 2021 [cited 2021 Sep 26]. 556 p. Available from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwib7_n7ipzzAhX_A2MBHTsqAkkQFnoECAMQAQ&url=https%3A%2F%2Fpc.gov.pk%2Fuploads%2Fcpec%2FPES_2020_21.pdf&usg=AOvVaw38c4KBkZEmRktykmI7D2Ym

[36] Fifth OIE Annual Report on Antimicrobial Agents Intended for Use in Animals [Internet]. OIE - World Organisation for Animal Health. [cited 2022 May 23]. Available from: https://www.oie.int/en/document/fifth-oie-annual-report-on-antimicrobial-agents-intended-for-use-in-animals/

2.2.5.5 Consumption in mg/kg of active ingredient used and in metric tonnes

To allow for cross comparison with other countries and regions that do not use the mg/PCU units, antimicrobial consumption in the animal sector was also estimated in mg of total antimicrobial consumed per kg of live animals, or mg/Kg units (Table 2). The total liveweight of the animal population in 2019 was 49,722,368,000 kg.

To allow for comparison with human consumption, total consumption of veterinary antimicrobials was also expressed as kg, or Metric Tonnes (MT) of imports of all veterinary medicines and medicated feeds.

S. No	Production animal	Population, 2019	Average weight, kg	Total weight
1	Asses	5417000	400	2,166,800,000
2	Buffalo	40002000	425	17,000,850,000
3	Camel	1090000	600	654,000,000
4	Cattle	47821000	425	20,323,925,000
5	Chicken	1321000000	1	1,321,000,000
6	Duck	3843000	1	3,843,000
7	Goat	76143000	75	5,710,725,000
8	Sheep	30859000	75	2,314,425,000
9	Horses	371000	400	148,400,000
10	Mules	196000	400	78,400,000
				49,722,368,000

Table 2. Total weights of production animals, Pakistan 2019

Notes:

1. The population of production animals was obtained from FAOSTAT.[37]
2. Average weights are obtained from the ESVAC and OIE Reports.[38]
3. The average weights of asses and mules were made equal to that of horses.
4. The average weight of buffalo was made equal to that of cows (both bovines).

2.2.5.6 Stratification

Total consumption for AAIs listed by DRAP or WHO/OIE was stratified by antibiotic class and by WHO MIA categorization. Antibiotic class categories were obtained from the 5th OIE annual report.[39]

[37] FAO. FAOSTAT [Internet]. 2021 [cited 2021 Sep 26]. Available from: http://www.fao.org/faostat/en/#data/QCL
[38] EMA. European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) [Internet]. European Medicines Agency. 2018 [cited 2022 May 25]. Available from: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/european-surveillance-veterinary-antimicrobial-consumption-esvac ; Fifth OIE Annual Report on Antimicrobial Agents Intended for Use in Animals [Internet]. OIE - World Organisation for Animal Health. [cited 2022 May 23]. Available from: https://www.oie.int/en/document/fifth-oie-annual-report-on-antimicrobial-agents-intended-for-use-in-animals/
[39] Fifth OIE Annual Report on Antimicrobial Agents Intended for Use in Animals.

Medicated feed was stratified by animal species using licensing information obtained from brand labels and from global licensing information. Additionally, the total net weight of antimicrobials in feed additives imported was determined and expressed as a proportion of the total veterinary import volumes.

3 Results

3.1 Human Health Sector

3.1.1 Total Consumption

The total consumption in kg of API and in DID by API and ATC group is presented in Table 3.

The total antibiotic consumption in the human sector using IQVIA sales data to the private sector was estimated in the two selected metrics as:

1. DID: The total consumption of systemic antibiotics in humans for 2019 in Pakistan was 18.60 DID.
2. Kg of API: The total estimated antibiotic consumption for 2019 was 1,651,908.96 kg (1,652 MT).

The antibiotic use pattern in the human sector in DID per ATC group is presented in Figure 2 (see also section 3.1.2)

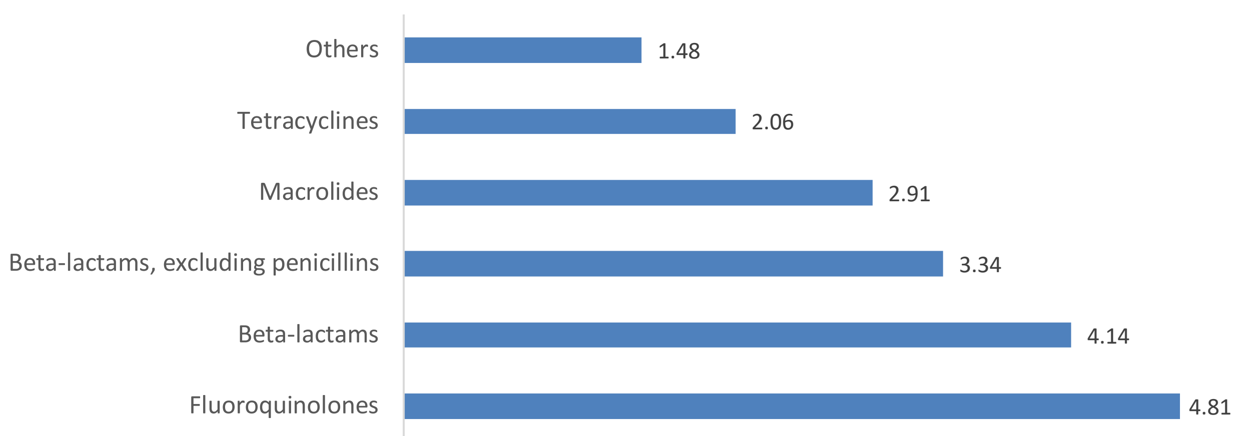

Figure 2. Human antibiotic use pattern, Pakistan (DID, 2019)

The ATC J01M class of fluoroquinolones was the most consumed, followed by the J01B class of beta lactams cephalosporins followed by the penicillins.

ATC group	API	Sales volume	DDD	DID	Kg
J01A	Doxycycline	1,769,076	0.1g	2.0087	15,889.63
Tetracyclines	Minocycline	144,352	0.2g	0.0091	144.35
	Oxytetracycline	111,222	1g	0.0339	7,555.79
	Tetracycline	15,070	1g	0.0047	373.67
		2,039,720		**2.056**	23,963
J01C					

Penicillins	Amoxicillin	22,099,614	1.5/3g	1.3776	163,647.37
	Amoxicillin-clavulanic acid	75,376,827	1.5/3g	2.2266	270,355.14
	Amoxicillin-cloxacillin	571	2g	0.0000	5.71
	Amoxicillin-flucloxacillin	8,229	-	0.0000	70.03
	Amoxicillin-pivsulbactam	97,485	1.5/3g	0.0028	334.34
	Amoxicillin-sulbactam	83,092	1.5/3g	0.0005	107.93
	Ampicillin	373,441	2/6g	0.0322	6,341.04
	Ampicillin-cloxacillin	3,501,824	2g	0.4871	77,108.44
	Ampicillin-sulbactam	29,860	6g	0.0000	26.96
	Bacampicillin	2	-	0.0000	0.01
	Piperacillin-tazobactam	1,650,585	14g	0.0108	6,301.59
		103,221,530		**4.1377**	524,298.57
J01D					
Other beta lactams	Cefaclor	7,669,871	1g	0.1596	10,554.84
	Cefadroxil	7,346,208	2g	0.1757	27,515.98
	Cefalexin	5,771,043	2g	0.0965	14,475.50
	Cefapirin	1,211	4g	0.0000	1.21
	Cefazolin	405,359	3g	0.0013	301.56
	Cefepime	1,891,437	4g	0.0030	951.58
	Cefixime	51,776,486	0.4g	1.8907	59,975.04
	Cefoperazone	3,044	4g	0.0000	5.17
	Cefoperazone-sulbactam	5,759,981	4g	0.0273	8,637.36
	Cefotaxime	23,046,431	4g	0.0351	11,108.54
	Cefpirome	19,148	4g	0.0000	14.07
	Cefpodoxime proxetil	2,959,135	0.4g	0.0629	1,988.63
	Cefradine	26,526,308	2g	0.5223	84,655.95
	Ceftazidime	7,844,744	4g	0.0111	3,619.58
	Ceftizoxime	990,666	4g	0.0014	450.30
	Ceftriaxone	66,376,544	2g	0.3002	43,178.13
	Cefuroxime	1,536,657	0.5/3g	0.0030	1,145.51
	Cefuroxime axetil	639,267	0.5/3g	0.0514	2,031.75
		210,563,540		**3.341**	270,610.70
J01F					

Macrolides	Azithromycin	15,168,766	0.3/0.5g	1.174	27,872.33
	Clarithromycin	15,639,821	05/1g	0.924	35,824.18
	Clindamycin	735,535	1.2/1.8g	0.025	2,687.07
	Erythromycin	1,603,797	1g	0.275	21,770.24
	Lincomycin	8,881,622	1.8g	0.222	43,732.16
	Roxithromycin	253,744	0.3g	0.143	345.06
		42,283,285		**2.763**	132,231.044

ATC group	API	Sales volume	DDD	DID	Kg
J01M	Ciprofloxacin	48,033,114	1/0.8g	1.974	242,524.21
Fluoroquinolones	Enoxacin	236,354	-	0.000	1,890.83
	Gemifloxacin	267,059	0.32g	0.023	590.68
	Levofloxacin	19,779,071	0.5g	2.127	92,499.50
	Moxifloxacin	6,870,807	0.4g	0.383	81,810.71
	Norfloxacin	553,916	0.8g	0.049	3,100.98
	Ofloxacin	3,196,849	0.4g	0.219	8,068.35
	Perfloxacin	12,677	0.8g	0.001	50.71
	Sparfloxacin	95,841	0.2g	0.006	95.84
		79,045,688		**4.782**	**430,631.806**
Others	Cloxacillin	50,005	2g	0.000	12.50
	Penicillin G	966,162	6mu (3.6g)	0.000	-
	Penicillin G Streptomycin	15,006	-	0.000	15.01
	Amikacin	6,196,161	1g	0.034	2,802.88
	Gentamicin	2,379,054	0.24g	0.039	1,045.54
	Kanamycin	735,922	1g	0.098	2,273.92
	Kanamycin Penicillin G	608	-	0.000	0.49
	Tobramycin	376,731	0.24g	0.001	21.53
	Cilastatin Imipenem	433,925	2g	0.001	313.05
	Doripenem	2,559	1.5g	0.000	1.28
	Ertapenem	19,643	1g	0.000	19.64
	Meropenem	1,381,580	3g	0.004	1,015.13

	Colistin	15791	9mu (0.72g)	0.000	1.26
	Fosfomycin	2,371,376	3/8g	0.032	7,665.18
	Fosfomycin trometamol	253,797	3/8g	0.003	152.28
	Fusidic acid	49,385	1.5g	0.002	244.99
	Linezolid	1,522,308	1.2g	0.066	56,374.04
	Teicoplanin	30,259	0.4g	0.000	7.47
	Tigecycline	24,883	0.1g	0.000	1.24
	Vancomycin	462,344	2g	0.002	306.29
	Chloramphenicol	33,801	3g		351.62
	Sulfamethoxazole trimethoprim	17,203,657	1.92g	1.313	197,548.07
		TOTAL		**18.67**	**1,651,908.96**

Table 3. Antibiotic consumption in kg of API and DDD per 1000 inhabitants per day and pharmaceutical sale volumes of systemic antibacterial for human use by ATC groups for 2019 in Pakistan

Notes:

1. There is no DDD for the following APIs: amoxicillin-flucloxacillin, enoxacin, penicillin G streptomycin, and kanamycin penicillin G
2. Where a DDD is x/y, x = the DDD for the oral form and y = DDD for the parenteral form
3. ATC sub-totals not included in the calculation of the grand total in kg

3.1.2 Relative Consumption (Proportions of Total Consumption) by ATC Sub-group

The two largest groups, in DID proportions (%), were fluoroquinolones (26% of total consumption) and the beta-lactams (22%).

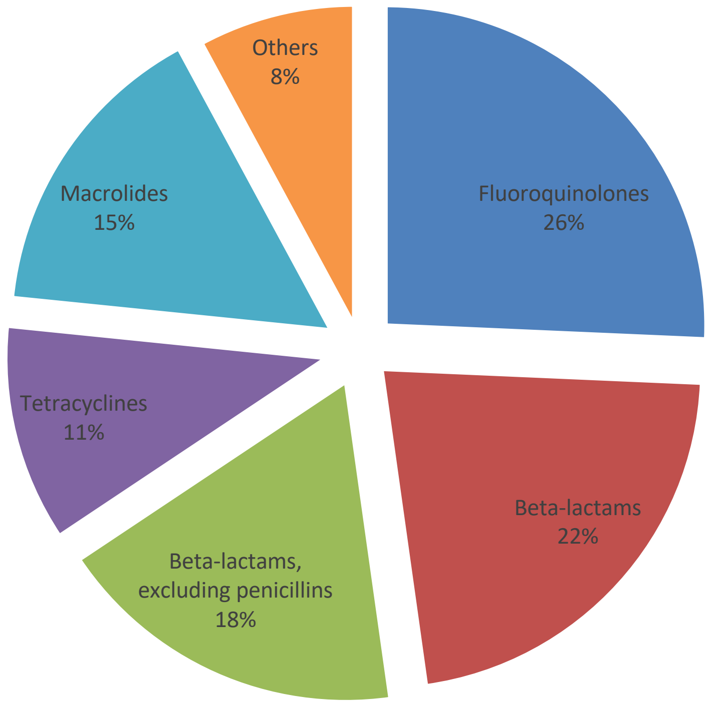

Figure 3. Antibiotic consumption by therapeutic sub-group/ATC sub-groups

3.1.3 Oral vs Parenteral Antibiotic Consumption (DID)

Consumption in DID was dominated by products for oral administration (Figure 2). The two ATC groups with parenteral consumption greater than 1% of total consumption were other beta lactams, J01C, comprising the cephalosporins, at 12.4%, and others, comprising mostly the aminoglycosides, at 2.2%.

Of all 6 ATC groups, beta-lactam, others, comprising mostly the cephalosporins was overall the most frequently administered (~80%) by injection, in keeping with the fact that most of this antibiotic group consisting of members such as ceftriaxone, are available as parenteral formulations. Even though, in DID terms, this was a small fraction (14%, 0.42/2.93) of the total consumed group of the Beta-lactams ATC J01D group of antibiotics.

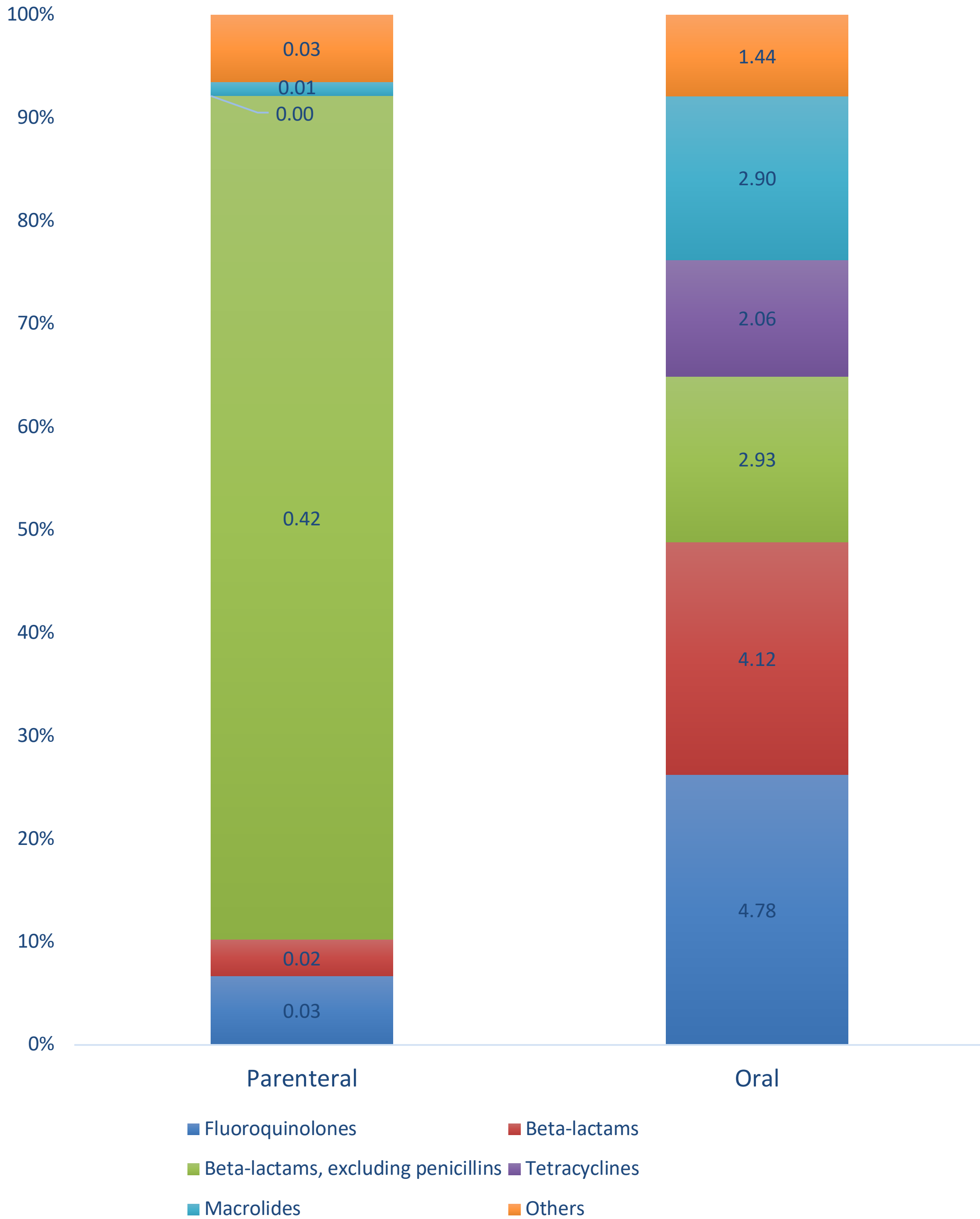

Figure 4. Relative antibiotic consumption by route of administration - oral and parenteral, DID[40]

[40] Note there is no parenteral tetracycline product licensed for human use in the dataset

3.1.4 AWaRe Categories

The watch group of antibiotics were the most common consumed, with 44 APIs comprising 63% of all systemic antibiotics (Figure 5).

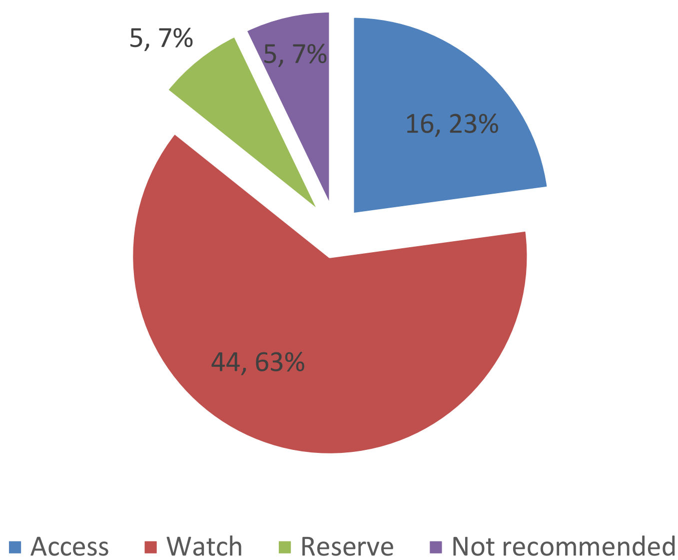

Figure 5. AWaRe classification of commercially available antibiotics for systemic use in the community in Pakistan, 2019

However, expressed by DID, the Access and Watch groups were the most consumed, together comprising about 50% of total consumption (Figure 6).

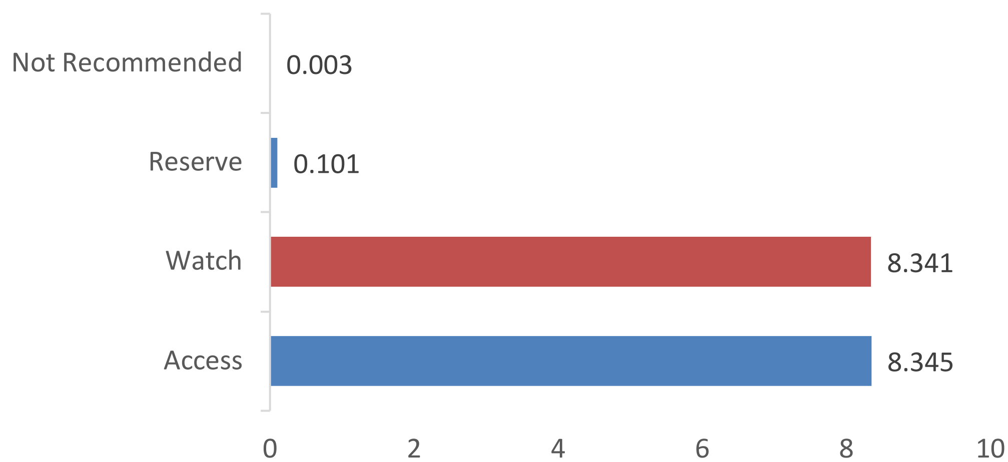

Figure 6. Consumption by AWaRe categories, DID

3.1.5 Public Sector Purchases (Primary Survey)

Various segments within the public sector have a share in total antimicrobial consumption:

Segments	Share in total antimicrobial consumption
Tertiary Care Institutions	~60%
Non-Tertiary Care Institutions (Includes all primary & secondary health institutions)	~25%
Disease Programs (Anti-TB etc.)	~7%
Armed Forces Health Institutions	~7%
Total	**100%**

Table 4. Segments with share in antimicrobial consumption

Some of the top tertiary care hospitals contributing to high consumption of antimicrobials in each province/territory as identified in the survey interviews are as below:

Institutions	Governing Authority
Civil Hospital, Karachi	Sindh Government
Jinnah Post Graduate Medical Centre (JPMC), Karachi	Federal Government
DOW University Hospital, Karachi	Sindh Government
Mayo Hospital, Lahore	Punjab Government
General Hospital, Lahore	Punjab Government
Pakistan Institute of Medical Sciences (PIMS), Islamabad	Federal Government
Rawalpindi Medical University, Rawalpindi	Punjab Government
Mayo Hospital, Lahore	Punjab Government
Bolan Medical Complex, Quetta	Baluchistan Government
Civil Hospital, Quetta	Baluchistan Government
Hayatabad Medical Complex, Peshawar	Khyber Pakhtunkhwa Government
Cantonment General Hospital, Peshawar	Khyber Pakhtunkhwa Government

Table 5. List of Hospitals contributing to the consumption of antimicrobial

Purchase decision-making at tertiary healthcare institutions is also independent with no purchase data sharing protocols in place with the provincial or central authorities. Hence estimation of antimicrobial consumption at large/tertiary level institutions is only possible based on assumptions unless data is collected directly from the institute. For primary & secondary care institutions, however, the purchase is mainly centralized at the provincial level.

The sizing methodology & assumptions of antimicrobials in the public sector was based on demand estimates as below (Figure 7):

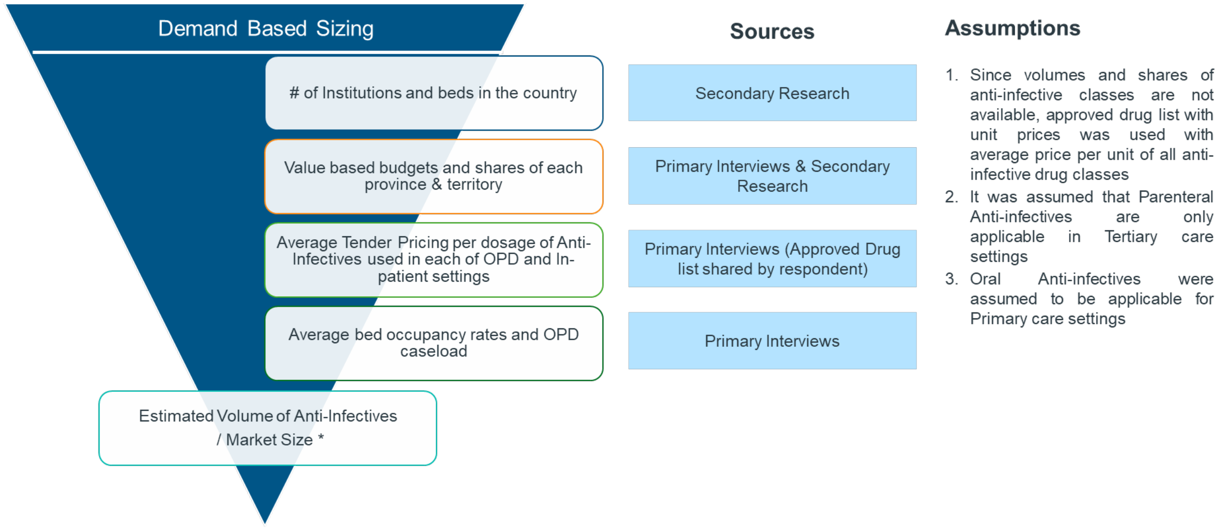

Figure 7. Demand-based sizing methodology of PPA

Based on the parameters used and collected through secondary research and survey participants, the number of antimicrobial doses disbursed in the public sector in 2021 is estimated to be in the range of 230 – 260 million with ~75% share being of oral antimicrobials (Figure 8):

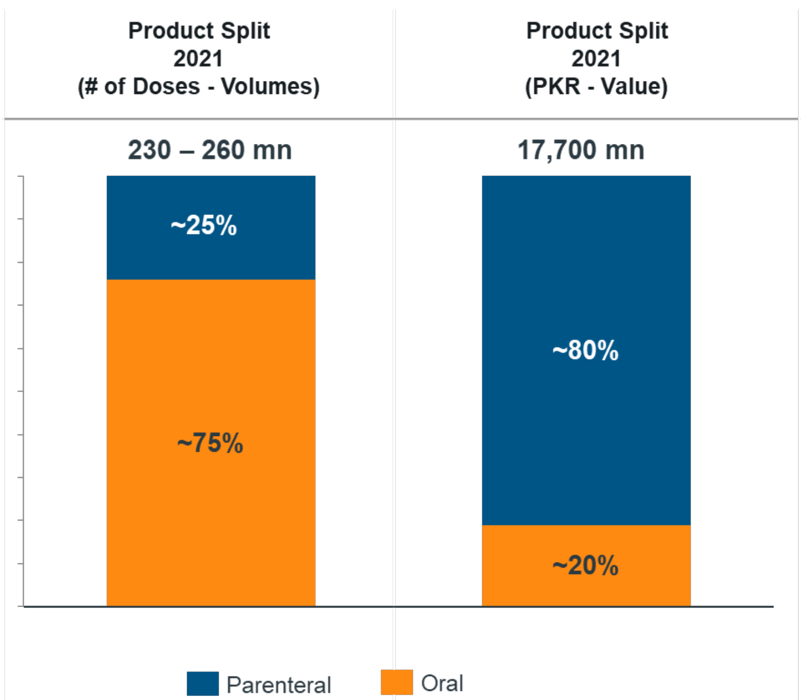

Figure 8. Sizing estimates of PPA

It is important to note that while having a significantly high share of oral antimicrobial doses in PPA, they are still insufficient to fulfil the prescriptions generated at public institutions and are either partially fulfilled from private retail pharmacies or result in discontinuation of treatment, hence contributing to further aggravation of AMR in the population.

The survey participants also mentioned that due to insufficient budgets, a higher priority is given to parenteral antimicrobials since they are meant to be used by in-patients mainly for emergency/critical case

3.2 Animal Health Sector

3.2.1 Imports on the DRAP "Master List" – APIs/INNs Used as Pharmaceutical Raw Materials

There were 148 licensed antimicrobials for animal use on the DRAP list. Of these, 104 were identified on the EXIM database as imported between January 1-December 31, 2019, and included in the consumption analysis. Forty-four APIs, including 32 determined to be either repeat (with alternative names, as for sulfonamides/sulphonamides for example); or not antimicrobials, or with no evidence for import for animal use – several cephalosporins for example – were excluded (See **Annex 5** for the full list of antibiotics included and excluded from the DRAP master list).

The 104 were imported in 4,030 shipments in 2019. Following data cleaning, 1,714 shipments (42.5%) were determined to be imported for veterinary use (or imports by veterinary manufacturers, importers, or feed mills) only. Exclusions were INNs determined to either be solely for human use, in transit to Afghanistan or air shipments.

3.2.2 Additional Imports from the WHO/OIE Listed Items, not on the DRAP List

To ensure that items for veterinary use not listed on the DRAP list were not missed, a separate search of items on the WHO/OIE list was performed on the EXIM database. This search identified a further 18 APIs (amikacin, avilamycin, cefazolin, ciprofloxacin, framycetin, fusidic acid, gramicidin, maduramycin, nalidixic acid, oxolinic acid, polymyxin, rifampicinm, roxarsone, sulfadoxine, tetracycline, ticarcillin, and tobramycin).

However, 83%, 15/18 of these antimicrobials are also used in humans. A few used exclusively in animals (avilamycin, maduramycin and roxarsone) are available as medicated feeds which are not under the control of DRAP. Two of these – avilamycin and maduramycin, as well as other medicated feeds not on any of these two lists - are captured as described in section 3.2.4 on veterinary feed additives.

3.2.3 Data Verification

There are differences between the EXIM and PakTradeInfo (PTI) datasets. Initially, eyeballing the data on both the EXIM database and the second database used for verification, the PTI, showed a complete match for neomycin (five imports). However, a more detailed analysis shows this not to be the case. Thus, these two datasets are not "superimposable". These differences are in:

a. The "import" dates used in each database

b. Entries for air imports

c. The measurement unit for gross weight

Notwithstanding, these differences do not result in significant differences in computations. Variations, in terms of the number of imports retrieved, ranged from 4-12% for the 5 INNs that were used for validation: ceftiofur, colistin, enrofloxacin, neomycin and tylosin (Table 4). That aside, where items matched, the GW was the same in both databases for ship shipments (but they were different for air shipments).

	Database	No. imports	Variation, %	Notes
Ceftiofur	EXIM	9	12	1
	PTI	9		
Colistin	EXIM	110	6	2
	PTI	113		
Enrofloxacin	EXIM	140	4	3
	PTI	144		
Neomycin	EXIM	147	4	4
	PTI	151		
Tylosin	EXIM	194	6	5
	PTI	200		

Table 6. Variations between the veterinary import data source, EXIM, against the PTI database used for verification

Notes

1. One shipment by Nawan not captured. This one shipment was captured instead as a repeat for Shams Enterprises. The Nawan shipment was an air freight for 8 packages with a stated weight of 109.
2. There are 3 mismatches and 3 missing values in the EXIM database, compared to PTI.
3. The observation of the mismatch in dates and hence in datasets as seen with colistin also apparent with enrofloxacin. Out of 140 imports using date of arrival, there were 4 mismatches, or a 3% variance. In total, the PTI dataset contained 144 entries to the EXIM dataset with 140.
4. Variation of 4% (6/147) comprising 2 unique values and 4 "missing entries" for EXIM compared to PTI database.
5. Variation of 6% all told. 6 unique values and 6 "missing values", for 12/194.

Further Notes:

1. The rationale for testing with these 6 is that they are only used in animals (tylosin, enrofloxacin) and or are among the most used/consumed according to our calculations (enrofloxacin, neomycin, and tylosin).
2. Datasets not a complete match in both databases. One reason for this might be that while one database lists entries or imports by arrival date, the other lists imports by an Import General Manifest (IGM) date and these two dates do not necessarily coincide. Thus, on extracting imports during a period, in this case, in 2019, it is likely that different datasets are picked. However, the two datasets match in most cases. A scrutiny of the discrepancy for colistin reveals that there could be up to a month of more at the start or end of the calendar year differences in the data that is retrieved using the IGM and arrival dates in the two databases - with the IGM date being

the earlier. Adopting the date of arrival, as the IGM date precedes arrival, there is a 6% variation (6/107) for colistin - this includes mismatch or missing data, of which there are three each.

3. With respect to air shipments, the PTI database does not expressly state the unit of measure of its gross weight. Thus, while these differ from the EXIM database in value, it is hard to tell the unit of measure.

3.2.4 Veterinary Feed Additives/Medicated Feed

Identification

Thirty medicated feed AAIs comprising 24 unique INNs were identified from Item Descriptions on the EXIM database for products on the DRAP "master list" or WHO/OIE list and from the "stem search":

1. Twelve INNs, out of the 104 on the DRAP list, imported as AAIs, FPPs or FAs (Table 5); and
2. Eighteen INNs from the "stem search" (Table 6), including six among the 12 INNs on the DRAP and WHO/OIE lists. Thus, there were 24 distinct INNs imported as veterinary FAs in 2019 into Pakistan.

Stratification by clinical indication

The animal species for which the identified FAs are clinically indicated are detailed in Tables 5 & 6.

Quantities imported & clinical indications

The quantities of imported AAIs, used either as PRM or as FAs, as contained in the DRAP list in 2019, are shown in Table 5. For these, the estimated amounts are included in the consumption analysis for the respective APIs presented in Table 8. On the other hand, the import quantities of the 18 INNs identified from the stem search were 361.76 MT (Table 6).

	INN	Animal species[41]	FA/GP (MT)
1	Clopidol[42]	Poultry	9.5
2	Colistin[43]	Poultry, cattle, etc.	2.44
3	Diclazuril[44]	Poultry, rabbits, etc.	0.71
4	Enramycin[45]	Poultry & pigs	15.3
5	Florphenicol[46]	Cattle	0
6	Lincomycin[47]	Poultry & pigs	8.966
7	Neomycin[48]	Poultry, cattle, etc.	19.92

[41] Substances listed as indicated for poultry & pigs/rabbits are considered for use in poultry only in Pakistan.
[42] NCATS Inxight Drugs — CLOPIDOL [Internet]. [cited 2022 May 28]. Available from: https://drugs.ncats.io/drug/8J763HFF5N
[43] NCATS Inxight Drugs — DICLAZURIL [Internet]. [cited 2022 May 28]. Available from: https://drugs.ncats.io/drug/8J763HFF5N
[44] NCATS Inxight Drugs — DICLAZURIL. Ibid
[45] Enramycin Premix | AdvaCare Pharma [Internet]. [cited 2022 May 28]. Available from: https://www.advacarepharma.com/en/veterinary/enramycin-premix
[46] Possibly one PRM/FPP in air shipment, which was excluded from the calculation for reasons stated earlier.
[47] LINCOMIX® 50(lincomycin) [Internet]. [cited 2022 May 28]. Available from: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=c402bfe3-9ceb-4a47-9bfe-55ffd84fc743&type=display
[48] New Animal Drugs for Use in Animal Feeds; Oxytetracycline; Neomycin [Internet]. Federal Register. 2009 [cited 2022 May 28]. Available from: https://www.federalregister.gov/documents/2009/08/13/E9-19414/new-animal-drugs-for-use-in-animal-feeds-oxytetracycline-neomycin

8	Salinomycin[49]	Chicken, cattle, pigs, rabbit	35.41
9	Tiamulin[50]	Poultry & pigs	6.87
10	Tilmicosin[51]	Cattle, sheep	52.52
11	Tylosin[52]	Cattle, poultry, etc.	112.00
12	Zinc bacitracin[53]	Poultry & pigs	0.956

Table 7. Estimated antimicrobial consumption in 2019 and animal species indicated for 12 INNs available as pharmaceutical forms and/or medicated feeds on the DRAP list.[54]

	Group	INN	Animal species	Brand	Import volume (MT)
1	**Aminoglycosides**	Spectinomycin	Cattle, sheep, poultry	Bio-Spectin	
2	**Ionophores**	Maduramycin	Poultry	Sacox	4.07
				Yumamycin	0.49
				Maducarb	
		Salinomycin[55]	Poultry	Coxistac	10.32
		Monensin[56]	Cattle	Rumensin	
3	**Lincosamides**	Lincomycin	Poultry & pigs	B-Linovit	24.82
				Linco 4.4	
				Karlincomix	
				Lincograin	
				Lincozag	
4	**Macrolides**	Tylosin	Cattle, poultry, etc.	Karitylo	6.19
				Tylomax	
				Tylovet	
				Tylozag	3.25

[49] Government of Canada CFIA. Salinomycin sodium (SAL) – Medicating Ingredient Brochure [Internet]. 2012 [cited 2022 May 28]. Available from: https://inspection.canada.ca/animal-health/livestock-feeds/medicating-ingredients/salinomycin-sodium/eng/1331066179898/1331066230292
[50] PubChem. Tiamulin [Internet]. [cited 2022 May 28]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/656958
[51] PubChem. Tilmicosin [Internet]. [cited 2022 May 28]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/5282521
[52] Tylosin - an overview | ScienceDirect Topics [Internet]. [cited 2022 May 28]. Available from: https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/tylosin
[53] Government of Canada CFIA. Bacitracin (as zinc bacitracin) (BACN-Z) – Medicating Ingredient Brochure [Internet]. 2012 [cited 2022 May 28]. Available from: https://inspection.canada.ca/animal-health/livestock-feeds/medicating-ingredients/bacitracin/eng/1330990393761/1330990470561
[54] Blanks under the AAI/FPP column means the INN is only available/imported as medicated feed premixes.
[55] Coxistac 12% Granular | Bio Agri Mix [Internet]. [cited 2022 May 28]. Available from: https://www.bioagrimix.com/products/coxistac-12-granular
[56] https://www.trustedbygenerations.com/?gclid=EAIaIQobChMI39Goj6mD-AIVWf3jBx3tjA8ZEAAYASAAEgJfWfD_BwE [Internet]. [cited 2022 May 28]. Available from: https://www.trustedbygenerations.com/?gclid=EAIaIQobChMI39Goj6mD-AIVWf3jBx3tjA8ZEAAYASAAEgJfWfD_BwE

				Furamax	13.13
		Tylvalosin[57]	Poultry & pigs	Aivlocin	29.99
5	**Orthomycins**	Avilamycin[58]	Chicken, rabbits, & pigs	Maxus 100	4.5
		Virginamycin[59]	Poultry & pig	Stafac 500	2.7
6	**Pleuromutilins**	Tiamulin	Poultry & pigs	Tiamax	5.69
				Tiazin	
7	**Polypeptides**	Bacitracin/BMD	Poultry & pigs	Sinomd	44.57
				Zambac MD100	
				Sinobac	51.65
				Umavila 10	
		Colistin	Poultry, cattle, etc.	Pro PS Coli	
				Sinocol	1.28
8	**Other - Triazines**	Diclazuril	Poultry, rabbits, etc.	Nuoqiu	0.23
	Other - Carbanilides	Nicarbazine	Poultry	Nicarmix	7.05
				Marxiban	
				Nicamad	
	Other	Nicarbazine[60] + Maduramycin[61]	Poultry	MNGrow	4.38
	Other	Furazolidine		Furamax	13.13
	Other	Flavomycin[62]	Poultry	Flavopak 80	1.02
					228.46

Table 8. Import volumes of veterinary feed additives by brand name as identified from the stem search in 2019[63]

Notes:

The brands captured here do not represent an exhaustive listing of the medicated feed in Pakistan. This information was not available for this study.

[57] Safeguard Your Flock with Tyvalosin. [Internet]. Zamira Australia. [cited 2022 May 28]. Available from: https://www.zamira.com.au/product/zamityl-soluble-antimicrobial/
[58] NCATS Inxight Drugs — AVILAMYCIN [Internet]. [cited 2022 May 28]. Available from: https://drugs.ncats.io/drug/720WDX56D3
[59] Stafac® 500 (Virginiamycin) TYPE A MEDICATED ARTICLE [Internet]. [cited 2022 May 28]. Available from: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6e136d64-2fc7-4921-bb9c-7575455b2389&type=display
[60] NCATS Inxight Drugs — NICARBAZIN [Internet]. [cited 2022 May 28]. Available from: https://drugs.ncats.io/drug/11P9NUA12U
[61] Maduramicin - an overview | ScienceDirect Topics [Internet]. [cited 2022 May 28]. Available from: https://www.sciencedirect.com/topics/medicine-and-dentistry/maduramicin
[62] ASIA POULTRY FEEDS (PVT) LTD Trade Records [Internet]. TAJIR. [cited 2022 May 28]. Available from: https://tahjir.com/companies/imp/992559/asia-poultry-feeds-pvt-ltd/
[63] The quantities here are distinct from those of identical INNs contained in Table 5. Essentially, the quantities captured in Table 6 would have been lost if the DRAP list were the only data source consulted.

3.2.5 Total consumption in the Animal Sector

The estimated total consumption of medicines and medicated feed in the veterinary sector was 1,481.78 kg. Total consumption comprised of 1,253.52 kg as APIs and 228.46 kg of medicated feed.

Total consumption in mg/PCU, or biomass, was estimated at 22.94 mg/Kg (Table 8). [Normalized across the large population of animals in Pakistan, including those in which antimicrobials may not be used, means that this figure underestimates consumption among animal production systems, for example, poultry, where antimicrobials are heavily used].

The ratio of consumption of medicated feed to medicines was 0.2. That is, for every 1 MT of antimicrobials intended for use in animals imported into Pakistan in 2019, 0.2 MT of antimicrobials were also imported as medicated feed.

3.2.6 Veterinary Antimicrobial Consumption Pattern/Stratification by Antimicrobial Groups

The consumption pattern of antimicrobials imported as AAIs/FPP in the veterinary sector, by antimicrobial groups, is shown in Figure 9. The top 3 most consumed antimicrobials in mg/kg animal weight by antimicrobial groups were: aminoglycosides (197.52), macrolides (171.10), and tetracyclines (167.02).

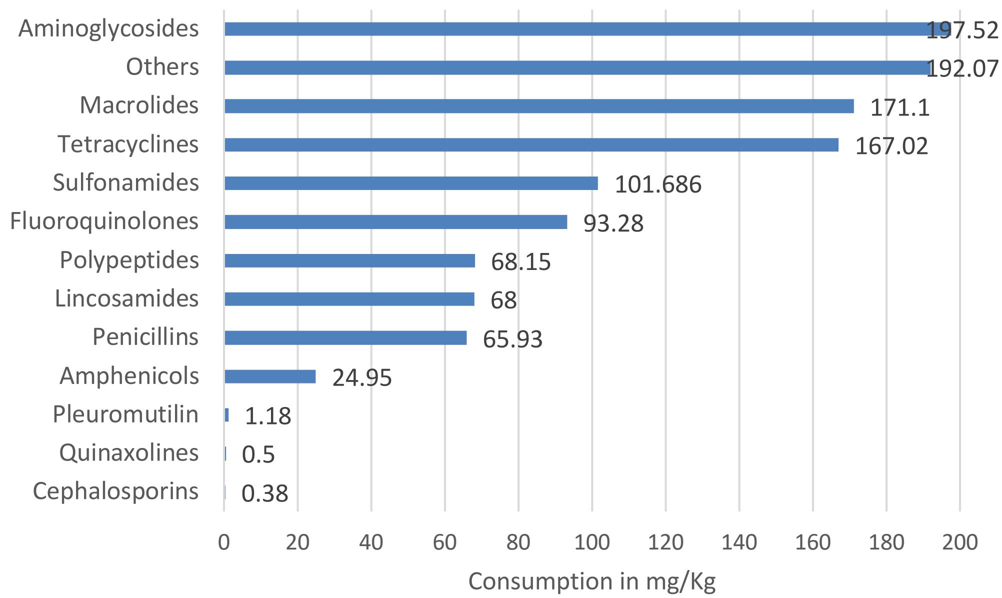

Figure 9 Consumption by antimicrobial groups in the veterinary sector, Pakistan (2019 estimate; mg/kg animal weight)

Note:

1. The Others group was a mixed group of several different antimicrobial classes and individual agents; thus, it is not included in the ranking of the three topmost consumed veterinary antimicrobials.
2. This categorization does not include antimicrobials imported as medicated feed in 2019.

	Antibiotic group	INN/API/Feed premix	No. imports	No. assessed as being for veterinary use	Import volume, 2019 (MT)	Consumption mg/Kg
1	Aminoglycoside	Dihydrostreptomycin	14	14	6.3	0.13
		Gentamicin	13	0	See Gentamycin	
		Gentamycin	54	31	7.46	0.15
		Kanamycin	5	0	Human?	
		Neomycin	147	120	110.63	2.22
		Spectinomycin	33	29	4.95	0.10
		Streptomycin	46	40	68.18	1.37
					197.52	**3.75**
2	Amphenicols	Florfenicol	114	64	24.95	0.50
		Thiamphenicol	1	0	Air Import	
					24.95	**0.50**
3	Cephalosporin	Cefalexin	1	0	Human?	
		Ceftiofur	9	5	0.38	0.01
		Cefuroxime	31	0	Human?	
		Cephalexin	15	0	Human?	
					0.38	0.01
4	Fluoroquinolone	Enramycin	27	25	12.8	0.26
		Enrofloxacin	140	139	78.1	1.57
		Moxifloxacin	113	0	0	0.00
		Norfloxacin	60	8	2.38	0.05

		Ofloxacin	78	0		0.00
		Pefloxacin	2	0		0.00
					93.28	**1.88**
5	Lincosamides	Lincomycin	173	45	**68**	**1.37**
	Antibiotic group	**INN/API/Feed premix**	**No. imports**	**No. assessed as being for veterinary use**	**Import volume, 2019 (MT)**	**Consumption mg/Kg**
6	Macrolide	Azithromycin dihydrate	335	0		0.00
		Erythromycin	74	17	2.84	0.06
		Spiramycin	14	11	1.72	0.03
		Spiramycin Adipate				0.00
		Tilmicosin	90	80	52.52	1.06
		Tylosin	194	180	114.02	2.29
					171.1	**3.44**
7	Penicillin	Amoxicillin	63	5	2.35	0.05
		Ampicillin	42	23	41.56	0.84
		Benzathine Penicillin G (as Benzathine Penicillin)	3	3	0.4	0.01
		Benzyl penicillin	10	9	2.7	0.05
		Cloxacillin	3	0		0.00
		Penicillin G Procaine	6	6	3.04	0.06
		Penicillin G Sodium	5	5	2.56	0.05
		Phenoxymethylpenicillin	5	1	0.61	0.01
		Procaine Penicillin	27	22	12.71	0.26
		Procaine Penicillin G	12	0		0.00

					65.93	**1.33**
8	Pleuromutilin	Tiamulin	4	4	1.18	0.02
		Tiamulin Hydrogen Fumarate				0.00
					1.18	**0.02**
9	Polypeptides	Colistin	357	99	11.12	0.22
		Zinc bacitracin	17	15	57.03	1.15
					68.15	**1.37**
	Antibiotic group	**INN/API/Feed premix**	**No. imports**	**No. assessed as being for veterinary use**	**Import volume, 2019 (Tonnes)**	**Consumption mg/Kg**
10	Quinoxalines	Olaquindox	1	1	**0.5**	0.01
11	Sulfonamides	Clotrimazole	21	1	0.096	0.00
		Sulfadiazine	18	8	12.65	0.25
		Sulfadimethoxine	1	1	0.2	0.00
		Sulfadimidine	5	5	7.75	0.16
		Sulphadimidine	51	49	49	0.99
		Sulfamerazine	4	3	0.36	0.01
		Sulfamethazine (as Sulphamethazine)	5	0		0.00
		Sulfamethoxypyridazine	1	1	0.1	0.00
		Sulfaquinoxaline	5	3	2.19	0.04
		Sulfoxide	28	0		0.00
		Sulphachloropyridazine	3	3	2.29	0.05
		Sulphaclozine	1	1	0.48	0.01

		Sulphaguanidine	7	7	5.69	0.11
		Sulphamethoxazole (as sulfamethoxazole)	2	0		0.00
		Sulfamethoxypyridazine	1	1	0.1	0.00
		Sulphamethoxypyridazin e	6	6	1.25	0.03
		Sulphanilamide	2	0		0.00
		Sulphaquinoxaline	10	10	4.22	0.08
		Sulphaquinoxaline Sodium				0.00
		Trimethoprim	70	47	15.31	0.31
					101.69	**2.05**
	Antibiotic group	**INN/API/Feed premix**	**No. imports**	**No. assessed as being for veterinary use**	**Import volume, 2019 (Tonnes)**	**Consumption mg/Kg**
12	Tetracycline	Chlortetracycline Hydrochloride	31	31	12.16	0.24
		Doxycycline	264	154	98.1	1.97
		Oxytetracycline	135	43	56.76	1.14
		Oxytetracycline HCl				0.00
					167.02	**3.36**
13	Others - Benzimidazoles	Albendazole	54	35	20.03	0.40
	Others - Benzimidazole	Fenbendazole	10	7	1.52	0.03
	Others - Benzimidazole	Mebendazole	14	1	0.24	0.00
	Others - Benzimidazole	Oxfendazole	38	30	9.66	0.19
	Others - Benzimidazole	Thiabendazole	1	0		0.00

	Others - Benzimidazole	Triclabendazole (anti-parasitic)	29	27	9.55	0.19
	Others - Triazinetrione	Toltrazuril	17	13	0.75	0.02
	Others	Abamectin	74	0	N/A	
	Others	Amprolium	44	44	23.08	0.46
	Others	Boric Acid	122	1	5	0.10
	Others	Buparvaquone	2	0	Air freights	
	Others - Phosphonic acid derivatives	Calcium Fosfomycin	1	0	Air freights	
	Others	Clavulanic Acid	3	0		0.00
	Others - salicylanilides	Clonastel/Closantel	22	0		0.00
	Others	Clopidol	1	1	9.5	0.19
	Others	Clorsulon (anti-parasitic)	7	3	0.3	0.01
	Others - salicylanilides	Closantel (anti-parasitic)	22	15	5.05	0.10
	Others - Nitroimidazole	Dimetridazole	1	0		0.00
	Others - Phenyhydrazines	Diminazene	6	3	0.37	0.01
	Antibiotic group	**INN/API/Feed premix**	**No. imports**	**No. assessed as being for veterinary use**	**Import volume, 2019 (Tonnes)**	**Consumption mg/Kg**
	Others - Avermectins	Doramectin (anti-parasitic)	8	0		0.00
	Others	Ethopabate (anti-parasitic)	1	0		0.00
	Others - Phosphonic acid derivatives	Fosfomycin	43	2	1.1	0.02
	Others - Carbanilides	Imidocarb	4	4	0.1	0.00
	Others - Avermectins	Ivermectin	55	17	1.14	0.02

	Others - Imidazothiazoles	Levamisole (anti-parasitic)	53	42	27.31	0.55
	Others	Methenamine	1	1	2.92	0.06
	Others	Metronidazole	239	14	3.37	0.07
	Others - Benzanilides	Niclosamide	4	2	1.5	0.03
	Others - salicylanilides	Oxyclozanide (anti-parasitic)	60	40	33.95	0.68
	Others - Tetrahydropyrimidines	Pyrantel pamoate	1	1	0.29	0.01
	Others - salicylanilides	Rafoxanide	3	2	0.44	0.01
	Others	Rifaximin	33	0		0.00
	Others - Ionophores	Salinomycin Sodium	16	14	29.8	0.60
	Others - Imidazothiazoles	Tetramisole HCl (anti-parasitic)	6	5	3.03	0.06
	Others	Chlorpheniramine Maleate				0.00
	Others	Colistimethate Sodium				0.00
	Others	Diaveridine	8	8	1.97	0.04
	Others	Diclazuril	7	7	0.1	0.00
	Others	Trichlorfon	11	0		0.00
					192.07	**3.86**
					1151.77	**22.94**

Table 9. Consumption in mg/PCU and mg/Kg units and import quantities of all AAIs assessed as being for veterinary only use

Notes:

1. Blanks for salts, examples tiamulin hydrogen fumarate, indicates that computations were made for the base and salts forms and included under the base form, in this case, under tiamulin.

4 One-Health Antibiotic Consumption for Pakistan, 2019

4.1 Antibiotic footprint: Pakistan's National One-Health Footprint

The estimated combined antibiotic consumption across sectors for 2019 in Pakistan was 3,072 MT[64]. Human antibiotic consumption contributed 54% (Figure 10). The relative consumption in both sectors, as proportions of total antimicrobial consumption, or import volumes, is shown in Figure 11.

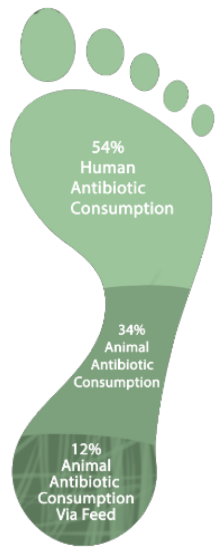

Figure 10. Footprint - total antimicrobial consumption by human and animal sectors (MT)

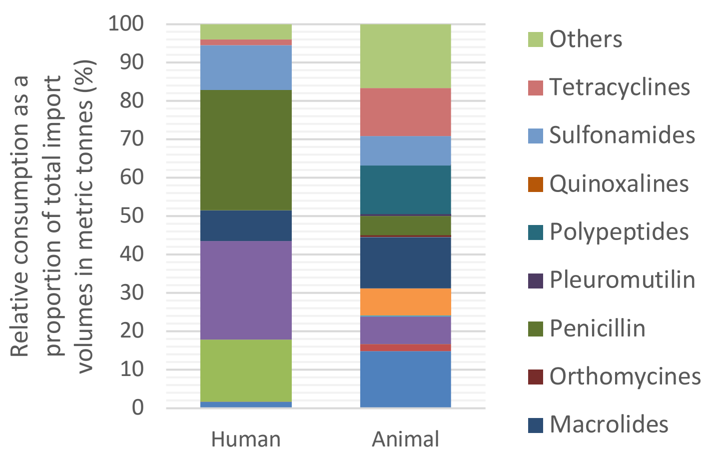

Figure 11. Relative consumption by antimicrobial group in humans and animals (%, MT)

4.2 One Health Indicators of Antibiotic Use in Pakistan

The estimated values of the 10 selected indicators of antimicrobial use in Pakistan are summarized in Table 13.

[64] This excludes the 10% public sector antibiotic consumption.

	Indicator	Target	Value
	Human sector		
1	Total consumption in DID	Reduce	18.7
2	Ratio of broad-spectrum to narrow-spectrum antibiotics in DID	Minimize	5
3	Total consumption in DID (% Access)	60	45
4	Top 10 antibiotic consumption in DID (% Watch)	-	50
	Animal sector		
1	Total consumption, mg/PCU	50	30 - 90
2	Import of 3rd/4th cephalosporins in mg/PCU	Reduce	0.38[1]
3	Import of fluoroquinolones in mg/PCU, %	Reduce	7[1]
4	Sale of polymyxins/polypeptides in mg/PCU, % of total	Reduce	17[1]
5	Total consumption in Metric Tonnes of HP CIAs	Restrict	497
6	Stratification in MT by animal species & medicines/feed ratio	-	0.36[2]

Table 10. Estimated values and targets for selected indicators of antimicrobial use in humans and animals in Pakistan

Notes:

1. As the value of these indicators depend critically on the precision with which the value is derived, they are included here as illustrative. Uncertainty of the precision with which they were derived from import data means that they are not exact as intended. Secondly, in this study, the Metric Tonnes unit of measure was adapted because of the specified mg/PCU metric because of the degree of uncertainty in computing the mg/PCU metric.
2. Only the ratio of medicines to medicated feed is included here. Stratification by animal species could not be performed for all active antimicrobial agents. In this activity, only partial stratification by animal species was performed for medicated feed imported in 2019 into Pakistan.
3. There are no targets for indicator no.4 in the human sector on percentage Watch of the top 10 antibiotic consumption and indicator no.6 on stratifications in the animal sector. These indicators are only descriptive.

The values from other indicators used in this study were:

- Relative consumption as ratio of oral to parenteral formulations which was estimated as 99.97%.

5 Discussion

Antimicrobial consumption analysis lays down the base for initiation, monitoring and evaluation of interventions addressing AMR through antimicrobial stewardship, or antimicrobial use reduction. Using established and novel methods, this activity employed the Antimicrobial Footprint concept to aggregate, analyse, and visualize consumption in the human and animal sectors in Pakistan.

The activity made four important contributions in providing evidence for policy on AMR.

Firstly, it elaborated a method for estimating animal antimicrobial consumption for both medicines and medicated feed from import data. Secondly, it generated an Antimicrobial Footprint; or an aggregate national-level One-Health antimicrobial consumption both in terms of total consumption as well as consumption patterns, across the human and animal sectors, in Pakistan for the year 2019, providing baseline data for evidence.

Thirdly, by stratifying human and animal antimicrobial consumption by antimicrobial groups and evaluating these against the WHO's and WHO/OIE'S use recommendations, respectively, it highlighted potentially inappropriate antimicrobial uses for stewardship actions. Fourthly, it mapped data sources for estimating antimicrobial consumption in the human and animal sectors, directing the government's effort to address the gaps in data collection. The findings from this activity provides a set of policy recommendations that could aid the government's efforts to contain AMR in Pakistan.

The analysis developed a method to calculate the volume of antimicrobials imported for use in the animal sector. The methods section of the report provides ways to use import data to estimate consumption a road map on how to proceed. However, for training purposes it is suggested to develop a manual that describes each step in more detail. In addition, an Excel workbook that users can populate would be helpful. Such manual and workbook could be used for training purposes of stakeholders including DRAP. Unfortunately, the website that is used to obtain custom data has been deregistered. Future work will need to identify custom data sources, ideally non-proprietary sources. DRAP has a key responsibility to make import data available. It should support the Fleming Fund and other institutions with the access to import data.

One key finding was that data on market authorization of antimicrobials for animal use was incomplete – as DRAP currently does not provide oversight functions on medicated feed. If the activity had focused exclusively on data provided by DRAP, it would have underestimated antimicrobial use in the animal sector for the study period by ~40%. This means that cross referencing several data sources is necessary. The supply-chain data-sources maps can guide the identification of alternative data sources. Further research is needed to develop validation methods for antimicrobial consumption data in Pakistan. Apart from import data and its use to estimate antimicrobial consumption, further work is needed to improve data on livestock in Pakistan to ensure that the denominator (biomass) is estimated accurately. This includes work such as that being undertaken by the Fleming Fund on the survey of farms.

It was also noted that over the past couple of years several organizations in Pakistan have made great strides to improve data collection of antimicrobial consumption. DRAP representatives, industry experts, federal and local government officials as well as researchers stated that they are working hard to gather consumption data in the human and animal sector. However, one recurrent theme that all of them mention is that there is a lack of data sharing agreement between institutions. This lack of data governance makes it very hard to collaborate between institutions and organizations. It was noticed from several key informants that institutions are in the process of building such data governance structures including establishing ways to safely share data between institutions. However, currently such structures are not in place which hinders advancement on a variety of issues including the estimation of national consumption level. The interviews conducted did not inquire about the necessary incentives that would need to be in place to establish such data sharing agreement. This should be studied further to enhance the chances for successful data sharing in the future. Leadership from the highest level in Pakistan is needed to make progress on such essential area of data transfer and infrastructure.

5.1 Aggregate One-Health Antimicrobial Consumption, Evaluation of Consumption Patterns, and Implications

Antibiotic consumption was estimated for the human and animal sectors using pharmaceutical sales volume and import data, respectively, and measured in metric tonnes (MT) and the normalized DID metrics for the human sector, and as MT, mg/kg live weight, and mg/PCU in the animal sector. The total antibiotic consumption for 2019, in the tonnage metric, was estimated as 3,072 MT in 2019, comprising 1,652 MT (53.8%) human consumption and 1,420 MT (46.2%) animal consumption. This means that documenting the animal sector consumption is extremely relevant as it contributes about one half of all consumption in Pakistan. Aggregated, this consumption estimate is comparable with Vietnam, another Southeast Asian country for which a similar study estimating total antibiotic consumption has recently become available, with an antibiotic consumption across the human and animal sectors, including aquatic animals, of 3,838 MT.[65] However, it is higher than for all other countries in different geographical regions with data on the Antibiotic Footprint database except for the USA.

5.2 Human Antibiotic Consumption and Implications for AMR

Antibiotic use is prevalent and relatively high in the community in Pakistan. The estimated total human antibiotic consumption was 18.70 Defined Daily Doses per 1,000 inhabitants per day (DID) in Pakistan for 2019. At this rate, Pakistan had a below-median consumption among countries that participated in the WHO global surveillance of antibiotic consumption for 2019 which saw countries reporting the consumption of systemic antibiotics between 4 and 64 DID. However, an earlier 2015 study suggested that Pakistan consumed more antibiotics (7.138 DID) than regional neighbours China (3.060 DID) and India (4.950 DID), even when data coverage for Pakistan was limited to the retail sector, but to both the retail sector and hospitals for the other two countries.[66] The DID metric normalizes antibiotic consumption across different population sizes, allowing for direct cross-country comparisons. This 2015 estimate, thus, meant that for every 1,000 persons in each of these countries – even though India and China were more populous with >1 billion people each in 2015 – 7 persons would consume an antibiotic every day in 2019 in Pakistan, as against 3 in China and 5 in India. That is, human antibiotic use was more prevalent in Pakistan than in India and China in 2015. This consumption rate had even been estimated in another study as high as 19.2 DID. Altogether, the 2019 estimate from this study of 18.70 DID is in order with the higher 2015 consumption analysis that also ranked Pakistan 3rd among 76 LMICs with an antibiotic consumption estimate of about 20 DID.[67]

Consumption was dominated by oral antibiotic formulations suggesting ambulatory use in the community. Oral antibiotics accounted for over 97% of total consumption in DID, similar to the consumption pattern of oral and parenteral formulations in other studies. For example, in the WHO surveillance of antibiotic consumption in the community or retail sector in the Western Pacific Region, Brunei, Lao, Hong Kong, Japan, and the Philippines reported ≥90% of total antibiotic consumption being oral formulations.[68]

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[65] Didem Torumkuney, Subhashri Kundu, Giap Van Vu, Hoang Anh Nguyen, Hung Van Pham, Praveen Kamble, Ngoc Truong Ha Lan, Nergis Keles, Country data on AMR in Vietnam in the context of community-acquired respiratory tract infections: links between antibiotic susceptibility, local and international antibiotic prescribing guidelines, access to medicines and clinical outcome, *Journal of Antimicrobial Chemotherapy*, Volume 77, Issue Supplement_1, September 2022, Pages i26–i34, https://doi.org/10.1093/jac/dkac214

[66] ResistanceMap - Antibiotic Use [Internet]. [cited 2022 Apr 2]. Available from: https://resistancemap.cddep.org

[67] Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase, and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci. 2018 Apr 10;115(15): E3463–70

[68] World Health Organization, Regional Office for the Western Pacific. Antimicrobial consumption in the WHO Western Pacific Region: early implementation of the Western Pacific Regional Antimicrobial Consumption Surveillance System (WPRACSS). [Internet]. 2021 [cited 2022 Jun 20]. Available from: https://apps.who.int/iris/handle/10665/351130

There was a high-use pattern of antibiotics which are targets of antimicrobial stewardship. Consumption is dominated by quinolones, which make up slightly more than a quarter (26%) of total consumption, in DID. This finding is consistent with other consumption analyses for Pakistan. The fluoroquinolones, as a class, are known to be among the most potent inducers of resistance in bacteria – able to induce resistance even with a single use. In 2019, Malik and Figueras reported a quinolone consumption of 4.77 DID in 2018. In this present study, a consumption of 4.81 DID for the quinolone class was reported – apparently continuing an annual rise in quinolone consumption from 2014. The high use, and consistent rise in the use, of fluoroquinolones in Pakistan could be both a cause or/and consequence of the reported high rates of antibiotic resistance in Pakistan.[69] For example, the 2021 WHO GLASS report showed a 100% resistance to ciprofloxacin in *N. gonorrhea*. This is, interestingly though, the same for India and Indonesia, but slightly different from Japan with 75% resistance.[70] Overall, resistance in *E. coli* to the fluoroquinolones is moderate to high in several Asian countries – 50% in China, 69% in Pakistan, and 89% in India.[71]

Overall, community use of the WHO Watch antibiotics – which are antibiotics whose use should be curtailed – was high at about 50%. This places Pakistan about the middle of the pack alongside the United Arab Emirates and South Korea among 76 LMICs in the proportion of use of Watch antibiotics.[72] The WHO introduced the AWaRe categorization of antibiotics both as a tool to measure consumption and to promote antimicrobial stewardship in the efforts to contain AMR. It sets a target of 60% use of the access group of antibiotics by 2023. To meet this target, Pakistan would need to reduce the use of Watch antibiotics. However, how feasible this would be would depend on the prevailing rates of AMR.

These findings, taken together, illustrate – by the combined human total consumption in DID and ranking among 76 LMICs, as well as the use of fluoroquinolones and other Watch antibiotics – a high, and likely inappropriate, consumption of antibiotics in the human sector in Pakistan. While not considered in this report, the prevalence of substandard and falsified (SF) medicines – which is a factor in the spread of AMR, and how this intersects with the high and inappropriate use of antibiotics, needs to be factored into policies seeking to address AMR in Pakistan.

5.3 Animal Antimicrobial Consumption and Implications for AMR

Asia accounts for the largest regional consumption of veterinary antimicrobials.[73] However, Pakistan's contribution to veterinary antimicrobial consumption in the Asia region is poorly documented. This activity provides data on veterinary antimicrobial consumption in 2019 for Pakistan and can help fill this data gap.

This study estimated a total import of veterinary antimicrobials or consumption of 1,471 MT. A study notes a comparatively high consumption of an estimated 658 MT in the poultry sector alone in Pakistan.[74]

Animal antimicrobial consumption was dominated by Medically Important Antibiotics (MIAs). The top-5 antibiotics used in the animal sector are critically important antibiotics. All but lincomycin belong to the

[69] Malik F, Figueras A. Continuous rise in cephalosporin and fluoroquinolone consumption in Pakistan: a 5-year analysis (2014–18). JAC-Antimicrob Resist. 2019 Dec 1;1(3): dlz063.

[70] WHO. GLASS_Report 2021_supplementary material [Internet]. Google Docs. 2021 [cited 2021 Jun 16]. Available from: https://docs.google.com/spreadsheets/d/1Ej0a-av4V5uoFw19DfZoDvcLpdvHTscfXoqJgozGiwc/edit?usp=embed_facebook

[71] ResistanceMap - Antibiotic Resistance [Internet]. [cited 2022 Apr 2]. Available from: https://resistancemap.cddep.org/

[72] Klein EY, Milkowska-Shibata M, Tseng KK, Sharland M, Gandra S, Pulcini C, et al. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: an analysis of pharmaceutical sales data. Lancet Infect Dis. 2021 Jan 1;21(1):107–15.

[73] Tiseo K, Huber L, Gilbert M, Robinson TP, Van Boeckel TP. Global Trends in Antimicrobial Use in Food Animals from 2017 to 2030. Antibiotics. 2020 Dec 17;9(12):918.

[74] Mohsin M, Boeckel TPV, Saleemi MK, Umair M, Naseem MN, He C, et al. Excessive use of medically important antimicrobials in food animals in Pakistan: a five-year surveillance survey. Glob Health Action. 2019 Dec 13;12(sup1):1697541.

Critically Important MIA subgroup, with lincomycin itself being Highly Important. These antibiotics are all useful arsenals for infection control in humans and ought not to be used indiscriminately in the veterinary sector. Their use in feed, as this report and other studies have showed, should be actively discouraged.

The excessive consumption of antimicrobials in animals, either through therapeutic uses or via feed for preventive or meat-production purposes is associated with an increase in AMR in humans. This has been demonstrated across Europe.[75] Thus, it is important that the use of antimicrobials in animals is curtailed and carefully controlled, to prevent the unintended consequence of animals serving as reservoirs of resistance with its implication for public health.[76] As with the human sector, there is also the need to control the prevalence and use of SF veterinary antimicrobials in an effort to contain AMR.[77]

5.4 Standards for Human and Animal Antimicrobial Consumption

Globally, there is yet no standard, or target, against which to measure total antimicrobial consumption in all One-Health sectors – humans, animals, agriculture, and the environment – across nations beyond the use of the comparative DID and mg/PCU metrics in the human and animal sector, respectively. In 2015, the O'Neill's Commission on AMR had proposed reducing antimicrobial consumption in the animal sector to a theoretical maximum of 50 mg/kg of livestock per year, based on data from livestock production in the Scandinavian countries.[78] This call has been supported by other authors who similarly argue that using less than this number of antimicrobials would reduce AMR.[79] This animal use target of ≤ 50 mg/kg/year of farm animal production has been used to track progress in antimicrobial stewardship efforts in the United Kingdom for example. Over two years, from 2014-2016, the United Kingdom reported a 27% drop in veterinary antimicrobial consumption from 62 mg/kg to 45 mg/kg.[80]

Human antimicrobial use standards are less specific. Human antimicrobial consumption analyses employ the WHO's target of a 60% national consumption of the Access group of antibiotics to evaluate appropriate use. For Pakistan in 2019, Access antibiotics comprised an estimated 45% of total consumption in DID.

The joint European Medicines Agency (EMA), European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) proposal uses 8 indicators to assess standards of antimicrobial use.[81] The two primary "standards" in this proposal have been covered in the report. These are the overall level of consumption in both human and animal sectors. These overall consumption in DID and mg/PCU metrics have also been presented and discussed. Selected secondary standards of the relative use of broad spectrum to narrow spectrum antibiotics in the community, and ratio of sales – imports in this study – of fluoroquinolones and polymixins which are Medically Important Antibiotics were also evaluated. With

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[75] EMA. Analysis of antimicrobial consumption and resistance ("JIACRA" reports) [Internet]. European Medicines Agency. 2018 [cited 2022 Apr 29]. Available from: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/analysis-antimicrobial-consumption-resistance-jiacra-reports

[76] Chris Dall CIDRAP News. Antibiotic resistance in farm animals tied to global hot spots [Internet]. CIDRAP. [cited 2022 Apr 29]. Available from: https://www.cidrap.umn.edu/news-perspective/2019/09/antibiotic-resistance-farm-animals-tied-global-hot-spots

[77] Clifford K, Desai D, Prazeres da Costa C, Meyer H, Klohe K, Winkler AS, et al. antimicrobial resistance in livestock and poor-quality veterinary medicines. Bull World Health Organ. 2018 Sep 1;96(9):662–4.

[78] O'Neill J. Antimicrobials in agriculture and the environment - Reducing unnecessary use and waste.pdf [Internet]. 2015 [cited 2019 Dec 25]. Available from: https://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf

[79] Van Boeckel TP, Glennon EE, Chen D, Gilbert M, Robinson TP, Grenfell BT, et al. Reducing antimicrobial use in food animals. Science. 2017 Sep 29;357(6358):1350.

[80] Oct 31 CD| NR| CN|, 2017. Report: Veterinary antibiotic sales, use in UK falling [Internet]. CIDRAP. [cited 2022 Jun 8]. Available from: https://www.cidrap.umn.edu/news-perspective/2017/10/report-veterinary-antibiotic-sales-use-uk-falling

[81] European Food Safety Authority. ECDC, EFSA and EMA Joint Scientific Opinion on a list of outcome indicators as regards surveillance of antimicrobial resistance and antimicrobial consumption in humans and food-producing animals | EFSA [Internet]. 2017 [cited 2022 Jun 9]. Available from: https://www.efsa.europa.eu/en/efsajournal/pub/5017

these "standards", a country attempts to achieve a temporal reduction in total consumption with time. Additionally, the desired objective is to reduce the consumption of broad-spectrum antibiotics in favour of narrow spectrum antibiotics in the human sector and the elimination of the use of MIAs for non-therapeutic uses in animals. These indicators are supplemented by similar standards by the WHO. The WATCH categorization is one such standard in the human sector. The Medically Important Antibiotics, or Critically Important Antimicrobials (CIAs) classification, is the equivalent standard in the animal sector. Both prioritize antibiotics for stewardship.

Across the human and animal sectors, the primary target or goal is, thus, to reduce the consumption of certain classes of antibiotics and to reduce the overall level of total antibiotic consumption.

5.5 Mapping Data Sources for Human and Animal Antimicrobial Estimation or Surveillance

The mapping of data sources onto the antimicrobial supply chains for the human and animal sector can help regulators and other relevant stakeholders to identify channels that are currently not routinely monitored and to develop a system for routine surveillance. This roadmap should be refined and updated regularly. The maps are visual advocacy tools that the Fleming Fund can use to make its case on areas where more investment in surveillance is needed.

5.6 Policy Implications, Proposals, and Suggestions – Way Forward

Targets for Use Reduction: While Pakistan's National Action Plan on antimicrobial resistance containment makes provision for antimicrobial consumption measurement, it sets no targets for use reduction. This contrasts with Thailand's, for example, that targets a 30% reduction in antimicrobial consumption by 2030.[82] This can be a consideration in the iteration of the National Action Plan.

Establishment of a Surveillance System for Antimicrobial Consumption: Establishing regional and federal structures for surveillance of antimicrobial use and resistance in Pakistan is an urgent need. Among other requirements, such structures require data sharing agreements between institutions. The analysis identified DRAP as a key organization within Pakistan that ought to have a responsibility to make data on antimicrobial imports available in a timely manner. It also has a key responsibility to publish up-to-date information on manufacturers and products with valid market authorization. Though, Minutes of Meetings in which DRAP deliberates on licensing of products are public records[83], aggregating and indexing the import and production of antimicrobials would be useful. This would enable appropriate standards to be set against which progress on reducing antimicrobial consumption can be evaluated. Some other policy considerations are provided in Orubu et al, 2020.[84] In this regard, the present study might represent one source for establishing a baseline antimicrobial consumption level and pattern across the human and animal sectors.

In 2022, IQVIA was commissioned to analyse antibiotic consumption in the public sector.[85] Their study revealed numerous challenges in data collection across the different provinces in Pakistan: lack of standardization of data collection and storage procedures, a large number of stakeholders who would

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[82] Ministry of Public Health, Ministry of Agriculture and Cooperatives. National Strategic Plan on Antimicrobial Resistance 2017-2021 Thailand: At a glance [Internet]. [cited 2019 Dec 26]. Available from: http://www.fda.moph.go.th/sites/drug/Shared%20Documents/AMR/05.pdf

[83] Drug Regulatory Authority of Pakistan. Partial Minutes of 317th Meeting of Registration Board – Drug Regulatory Authority of Pakistan [Internet]. [cited 2022 Jun 20]. Available from: https://www.dra.gov.pk/publications/meeting_minutes/registration_board/partial-minutes-of-317th-meeting-of-registration-board/

[84] Orubu ESF, Sutradhar I, Zaman MH, Wirtz VJ. Benchmarking national action plans on antimicrobial resistance in eight selected LMICs: Focus on the veterinary sector strategies. 2020;10(2):10.

[85] IQVIA. Anti-infectives consumption study report. Karachi: IQVIA. June 2022.

need to be on board to agree to data harmonization efforts and the absence of enforcement capacities of harmonization efforts.

Mandating Manufacturers and Importers to Report Sales: Mandating manufacturers, importers, and other demand points providing antimicrobials for use to report sales of human and veterinary antimicrobials and medicated feed would allow tracking of the use of all antimicrobial products. These reports could then be evaluated against specified benchmarks, or temporarily analysed, to monitor the impact of policies promoting antimicrobial use reduction or judicious use. Sales data have been widely employed in the European Union to measure and monitor antimicrobial use with reported improvements in use.[86] IQVIA's June 2022 confirms that manufacturers are currently unwilling to share either volume or value of antibiotics sold to government institutions arguing that this would compromise their competitiveness.[87]

Community-based Surveillance Systems: Community-based surveillance systems could also be established to simultaneously create awareness and monitor antimicrobial consumption among both industrial and backyard farmers in Pakistan. This system is in use in Bangladesh, for example, where the Department of Livestock Services collaborates with the Food and Agriculture Organization as part of an *Upazila* to Community (U2C) Initiative to sensitize small-scale livestock farmers and collect information on antimicrobial use in food producing animals.

Regulating Medicated Feed: Particularly important is the need for the design and implementation of policies to regulate the use of medicated feed. This study suggests that a significant amount (~30%) of veterinary antimicrobials imported into Pakistan are used in livestock production in the form of feeds. The need to prohibit the use of CIAs in medicated feed has been reiterated by the Global Action Group on AMR.[88] Overall, the five call-to-action points suggested by this group may be relevant for further policy developments on AMR in Pakistan.[89] These are: placing the use of antimicrobials in the animal sector under veterinary oversight; enforcing prescription-only sales of antimicrobials; improving hygiene and biosecurity measures; ensuring access to quality antimicrobials and alternatives in livestock production; and eliminating the use of CIA-containing feed products.

Routine Evaluation of Consumption Patterns: Finally, there may be the need for a more systematic evaluation of access and misuse of antimicrobials in the context of AMR in Pakistan. A lean and rapid means of providing a rapid situation analysis to identify actionable gaps for targeted intervention might be that proposed by Orubu et al, 2021, which uses 16 indicators to assess gaps for policy and practice interventions.[90]

5.7 Limitations

There are strengths and limitations with this work. Firstly, IQVIA provides the most comprehensive sales data of antimicrobials for human use in the private sector. However, data coverage is limited to only systemic antibiotics. In LMICs, this may not reflect the complete picture, as this methodology, used widely in other studies, do not include other antimicrobials such as antivirals, and antimalarials. Thus, in countries

[86] EMA. 10th ESVAC report shows continued decrease in sales of veterinary antibiotics [Internet]. European Medicines Agency. 2020 [cited 2022 Jun 20]. Available from: https://www.ema.europa.eu/en/news/10th-esvac-report-shows-continued-decrease-sales-veterinary-antibiotics
[87] IQVIA. Anti-infectives consumption study report. Karachi: IQVIA. June 2022.
[88] Bangladesh U2C Initiative Farm assessment and monitoring report
[89] CIDRAP. Global group urges limits on antimicrobials in food production [Internet]. CIDRAP. [cited 2022 Jun 9]. Available from: https://www.cidrap.umn.edu/news-perspective/2021/08/global-group-urges-limits-antimicrobials-food-production
[90] WHO. World leaders and experts call for significant reduction in the use of antimicrobial drugs in global food systems [Internet]. 2021 [cited 2022 Jun 9]. Available from: https://www.who.int/news/item/24-08-2021-world-leaders-and-experts-call-for-significant-reduction-in-the-use-of-antimicrobial-drugs-in-global-food-systems

with high burdens of HIV, for example, it may underestimate actual antimicrobial consumption. However, this may not apply to Pakistan. A second limitation with the ATC-DDD method is that it applies only to adults (of an average weight of 70 kg) and not to children. In this study, an approach used by other studies was adopted to correct for this limitation, which involves the conversion of a bottle of medicine into units similar to tablets.[91] Thirdly, the IQVIA dataset covers only 85% of the market for pharmaceuticals in Pakistan, thus, this study may underestimate actual consumption. It is hoped that data would soon be available from an extension of this activity to enable analysis for 100% of the market to allow for a more comprehensive assessment. Longitudinal data collection from Point Prevalence Studies (PPS) could help bridge the data gap in the human health sector.

In the animal sector, there is no data provider comparable to IQVIA. This report used a novel method to calculate animal sector consumption using import data. On one hand, this method has several advantages: assuming that there is little domestic production of API, import volumes can be collected efficiently using customs records. Asking manufacturers and wholesalers to share their sales data can be difficult and very labour intensive. Although collecting consumption data from farmers would be ideal, as it captures the amount used, sampling farms is inherently difficult in the absence of any sample frame. There is no census of farms in Pakistan.

On the other hand, limitations with the use of import data in the estimation of antibiotic consumption include data quality or reliability, double-accounting, and other risks for overestimation. Poor data quality precluded the use of imports by air for calculations for veterinary antimicrobial consumption, potentially leading to under-estimation. Double accounting, which is a double or multiple counting of an antimicrobial used in both the human and animal sector, leads to overestimation and misleading figures for antimicrobial consumption. A multipronged strategy has been adopted to screen imports for human use and other non-animals uses from animals uses – implemented as earlier described in the Data Cleaning section under Methods. This approach is expected to minimize the risk of double accounting. Overestimation could also arise from the fact that not all imports may be intended to be used in the year of import. In addition, not excluding any subsequent export would lead to overestimation for the year under consideration. In not factoring in possible non-concurrent use (use in a subsequent year different from the year of import, 2019) and any export, the results in the animal antibiotic consumption are likely to be overestimated. Also, an inability to make a fine-grained distinction between animal production systems introduces an error in the estimate of animal consumption in mg/PCU units, as not all the imported AAI are used across all animal species. Greater data availability in both the human and animal sectors could help prevent these errors in subsequent exercises/projects.

6 Conclusion

This activity performed a national-level One-Health antibiotic consumption analysis for 2019 in Pakistan. The high proportions of WHO Watch antibiotic consumption in the human health sector and of WHO Medically Important Antibiotics in the animal health sector point to the urgent need for antimicrobial stewardship in Pakistan. The high proportion of import of medicated feed not under the regulation of the medicines regulatory agency suggests the need for policy innovation in the regulation of veterinary feed additives. Visualizing the estimated consumption provides an antibiotic footprint that can easily be compared against other countries and used in the public communication of the need to reduce consumption overall, as a means of containing antimicrobial resistance.

[91] Li G, Jackson C, Bielicki J, Ellis S, Hsia Y, Sharland M. Global sales of oral antibiotics formulated for children. Bull World Health Organ. 2020 Jul 1;98(7):458–66.

The work on developing the methodology of the AFA and the results show the critical bottleneck to any reliable antibiotic consumption in Pakistan: high-quality data availability and accessibility. There is an urgent need for policy reform to make reporting of antimicrobial sales data for human and animal consumption mandatory so that researchers and policymakers can identify specific, contextual, and implementable policies to tackle AMR. Many countries, including Thailand, have made this a requirement. The greater data availability should go hand in hand with capacity building in data use for decision-making.

7 Annexes

7.1 Annex 1: Human Medicines Supply Chain and Associated Potential Data Sources for Estimating Consumption

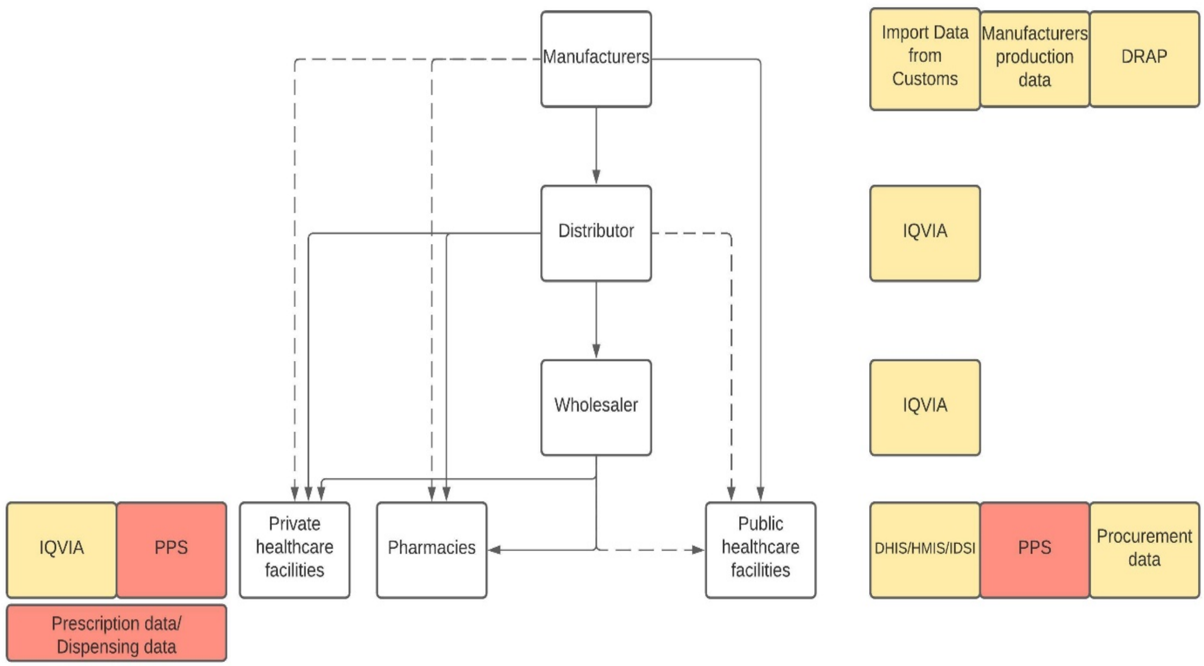

Figure 7. Schematic of the supply chain for human medicines and data sources on antimicrobial consumption at each level of the supply chain for Pakistan.[92]

Notes:

1 The boxes in light yellow indicate data sources that are available while the boxes in light red indicate data sources that are not available. Some levels of the supply chain have potentially multiple sources of consumption data. For example, at the level of the manufacturer, there are 3 possible data sources – customs' import data, manufacturers' production data, and DRAP-held data. Similarly, at the level of the public health facilities, there are several possible data sources, including data from the District Health Information Systems (DHIS) or Health Management Information Systems (HMIS) at the provincial levels and the Integrated Disease Information System (IDIS) at the Federal level. Some of these data sources overlap, while some are unique. Overlapping data sets include those from DRAP and Customs.

2. IQVIA sources pharmaceutical sales data at the level of manufacturers and distributors. These supply chain elements largely supply medicines to the private healthcare facilities and pharmacies, hence do not cover all distribution points for the supply of medicines to the public.

3. The schematic does not include vertical programs.

[92] Source of the human medicines supply chain elements: Adapted from Atif et al., 2019doi: 10.1136/BMJ open-2018-027028. Data source elements inserted by Boston University.

7.2 Annex 2: Animal Medicines Supply Chain and Associated Potential Data Sources

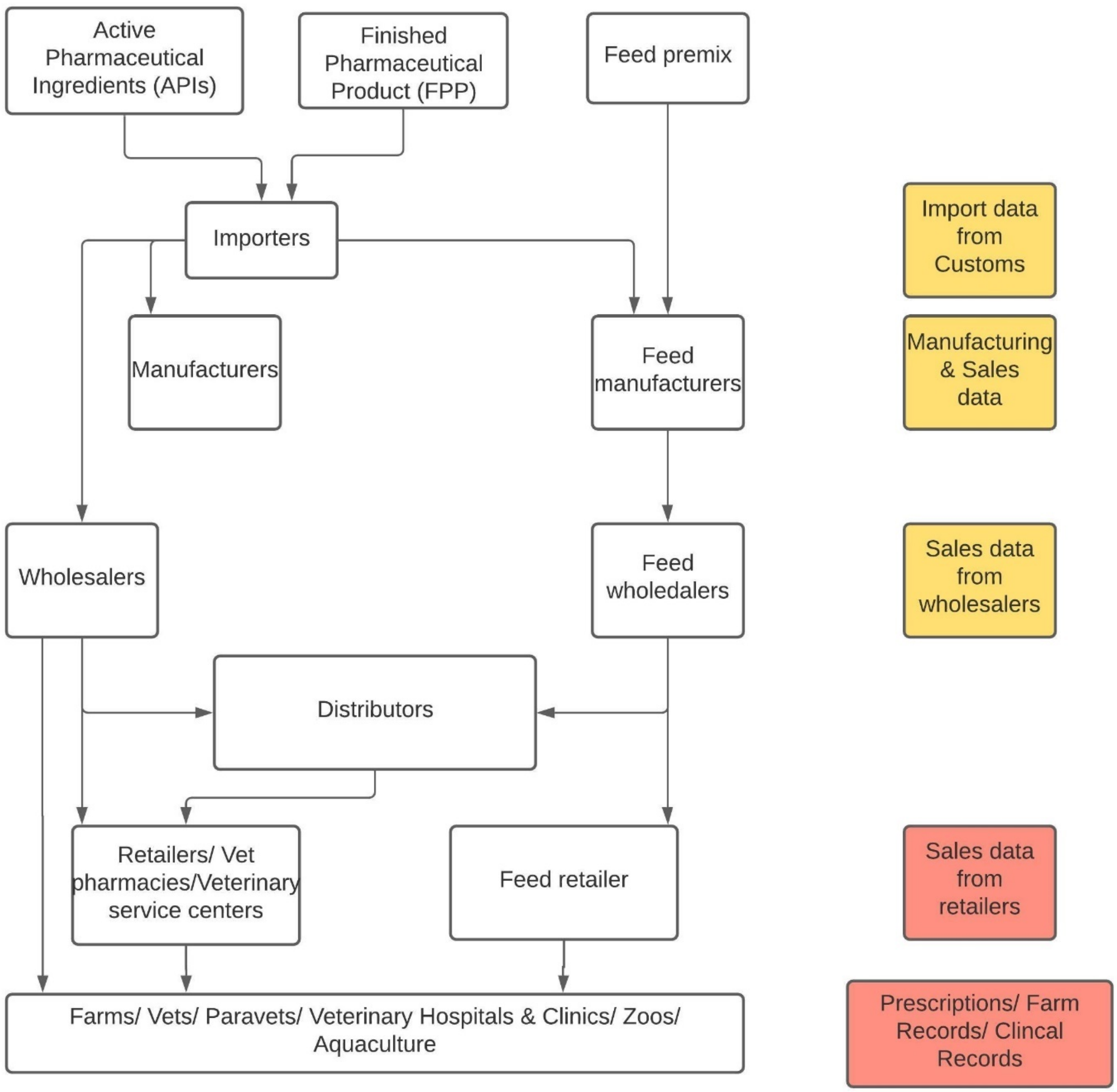

Figure 10. Pharmaceutical supply chain for the veterinary sector and associated consumption data sources for Pakistan. Boxes in light yellow indicate available data sources, while boxes in light red indicate data not available.[93]

[93] Adapted from the OIE AMU Workshop Report as prepared by Fleming Fund, March 2020. Data source elements inserted by Boston University.

7.3 Annex 3: The Status in the Pakistan Export Import Database (EXIM) of the DRAP List of the Antimicrobials registered for Veterinary Use in Pakistan

(1=Listed: 2=Not Listed in EXIM)

	Name of molecule/ formulation	STATUS In Pakistan EXIM Trade Info 2019*
1	Abamectin	1
2	Albendazole	1
3	Amoxicillin trihydrate	1
4	Ampicillin sodium	1
5	Amprolium	1
6	Azithromycin dihydrate	1
7	Benzathine Penicillin G **(Benzathine Penicillin found)**	1
8	Benzyl penicillin	1
9	Benzyl Penicillin Procaine	2
10	Bithionol Sulfoxide	2
11	Boric Acid	1
12	Buparvaquone	1
13	Calcium Fosfomycin	1
14	Cefalexine Monohydrate	2
15	Cefapirin	2
16	Cefquinome (as cefquinome sulphate)	2
17	Ceftiofur	1
18	Cefuroxime as axetil	1
19	Cenfloxacin	2
20	Cenoxine	2
21	Cephalexin	1
22	Cetrimide	2
23	Chlorpheniramine Maleate	1
24	Chlortetracycline Hydrochloride	1
25	Cinoxin	2
26	Clavulanic Acid	1
27	Clonastel (As Sodium) (**Closantel found**)	1
28	Clopidol	1
29	Clorsulon (anti-parasitic)	1

30	Closantel (anti-parasitic)	1
31	Clotrimazole	1
32	Cloxacillin	1
33	Colistimethate Sodium	1
34	Colistin Sulphate	1
35	Danofloxacin Mesylate	2
36	Diaveridine Hcl (anti-parasitic)	2
37	Diclazuril	1
38	Dihydrostreptomycin Sulphate	1
39	Dimetridazole	1
40	Diminazene Diaceturate	1
41	Disodium Arsono-Acetate	2
	Name of molecule/ formulation	**STATUS In Pakistan EXIM Trade Info 2019***
42	Dodecyl Dimethyl-2-Phenoxyethyl Ammonium Bromide	2
43	Doramectin (anti-parasitic)	1
44	Doxycycline Hyclate	1
45	Enramycin	1
46	Enrofloxacin	1
47	Erythromycin	1
48	Ethopabate (anti-parasitic)	1
49	Febantel (anti-parasitic)	2
50	Fenbendazole	1
51	Florfenicol	1
52	Flumequine	2
53	Fosfomycin Calcium	1
54	Gentamycin Sulphate	1
55	Haloxon (anti-parasitic)	2
56	Imidocarb Dipropionate	1
57	Ivermectin	1
58	Josamycin	2
59	Kanamycin Sulphate	1
60	Levamisole Hydrochloride (anti-parasitic)	1
61	Lincomycin	1
62	Marbofloxacin	2

63	Marek's disease vectored IBD recombinant	2
64	Mebendazole	1
65	Methenamine	1
66	Methenamine Hexamethylene Tetramine	2
67	Methenamine Mandelate	2
68	Methyl Parahydroxybenzoate	2
69	Metronidazole	1
70	Monensin as sodium	2
71	Moxifloxacin HCl	1
72	Neomycin Sulphate	1
73	Niclosamide (anti-parasitic)	1
74	Nitrovin	2
75	Nitroxinil (anti-parasitic)	2
76	Novobiocin Sodium	2
77	Ofloxacin	1
78	Olaquindox	1
79	Oxfendazole	1
80	Oxibendazole (anti-parasitic)	2
81	Oxyclozanide (anti-parasitic)	1
82	Oxytetracycline Dihydrate	1
83	Oxytetracycline HCl	1
84	Pefloxacin	1
85	Penicillin G Procaine	1
	Name of molecule/ formulation	**STATUS In Pakistan EXIM Trade Info 2019***
86	Penicillin G Sodium	1
87	Phenoxymethylpenicillin	1
88	Phtalyl Sulphathiazole	2
89	Praziquantel (anti-parasitic)	2
90	Procaine Benzylpenicillin	2
91	Procaine Penicillin	1
92	Procaine Penicillin G	1
93	Pyrantel pamoate	1
94	Rafoxanide	1
95	Rifaximin	1

96	Salinomycin Sodium	1
97	Spectinomycin Sulphate	1
98	Spiramycin	1
99	Spiramycin Adipate	1
100	Streptomycin	1
101	streptomycin (as sulphate)	2
102	Streptomycin (Base)	2
103	Streptomycin 2Hcl	2
104	Sulfa benzylpyridine	2
105	Sulfachloropyridazine Sodium Monohydrate	2
106	Sulfaclozine Sodium Monohydrate	2
107	Sulfadiazine Sodium	1
108	sulfadimerazine sodium	2
109	Sulfadimethoxine	1
110	Sulfadimethoxine Sodium	2
111	Sulfadimidine sodium	1
112	Sulfamerazine	1
113	Sulfamethazine (as **Sulphamethazine**)	1
114	Sulfamethoxypyridazine	1
115	Sulfaquinoxaline	1
116	Sulfathiazole	2
117	Sulfoxide	1
118	Sulphabenz Pyrazine	2
119	Sulphachloropyrazine Sodium Monohydrate	2
120	Sulphachloropyridazine	1
121	Sulphaclozine sodium	1
122	Sulphadimirazine	2
123	Sulphaganilamide	2
124	Sulphaguanidine	1
125	Sulphamethoxazole (as **sulfamethoxazole**)	1
126	Sulphamethoxypyridazine Sodium	2
127	Sulphamonomethoxine	2
128	Sulphanilamide	1
129	Sulphaquinoxaline	1

	Name of molecule/ formulation	STATUS In Pakistan EXIM Trade Info 2019*
130	Sulphaquinoxaline Sodium	1
131	Tetramisole HCl (anti-parasitic)	1
132	Thiabendazole	1
133	Thiamphenicol	1
134	Tiamulin	1
135	Tiamulin Hydrogen Fumarate	1
136	Tilmicosin Phosphate	1
137	Toltrazuril	1
138	Trichlorfon	1
139	Trichlorfon/Metrifonate (anti-parasitic) **(Trichlorfon)**	2
140	Triclabendazole Martindale	2
141	Triclabendazole (anti-parasitic)	1
142	Trimethoprim	1
143	Tulathromycin	2
144	Tylosin	1
145	Tylosin base (as Tartrate)	2
146	Veratryl Pyrimidine (anti-parasitic)	2
147	Virginiamycin	2
148	Zinc Bacitracin	1

Table 11. List of Antimicrobials Registered for Veterinary Use in Pakistan

*1= Present; 2= Absent

7.4 Annex 4. Manufacturers with License to Produce Products for Animals[94]

Sr#	Company	Area*	Operation
1	A & K Pharmaceuticals	Veterinary	Manufacturer
2	Aims Traders	Veterinary	Manufacturer
4	Al Asar Enterprises	Veterinary	Manufacturer
5	Al-Hamd Poultry & Livestock Services	Veterinary	Importer
6	Alina Combine Pharmaceuticals	Veterinary	Manufacturer
7	Amarant Pharma	Veterinary	Manufacturer
8	Amster Laboratories	Veterinary	Manufacturer
9	Ani Cure Veterinary Services	Veterinary	Importer
10	Aptly Pharmaceuticals	Veterinary	Manufacturer
12	Attabak Pharmaceuticals	Veterinary	Manufacturer
13	Avicenna Laboratories	Veterinary	Manufacturer
14	Baariq Pharmaceuticals	Veterinary	Manufacturer
15	Baxter Pharmaceuticals	Veterinary	Manufacturer
16	Better Traders International	Veterinary	Importer
17	Bin Sadiq International	Veterinary	Importer
18	Bio Vision Corporation	Veterinary	Importer
20	Biogen Pharma	Veterinary	Manufacturer
21	Bio-Labs	Veterinary	Manufacturer
22	Bio-Oxime Pharmaceuticals	Veterinary	Manufacturer
23	Biorific Pharma	Veterinary	Manufacturer
24	Breeze Pharma	Veterinary	Manufacturer
25	Cherished Pharmaceuticals	Veterinary	Manufacturer
26	Cherry Pharmaceutica	Veterinary	Importer
27	Decent Pharma	Veterinary	Manufacturer
28	Delux Chemical Industries	Veterinary	Manufacturer
29	D-Haans Pharmaceuticals	Veterinary	Manufacturer
30	Divine Pharmaceuticals	Veterinary	Manufacturer
31	D-Maarson Pharmaceuticals	Veterinary	Manufacturer
32	Elegance Pharmaceuticals	Veterinary	Manufacturer

[94] The list of manufacturers that are known to produce antibiotics used in animals was shared by Health Security Partners Consultant Dr Mashkoor Mohsin.

33	Elko Organization	Veterinary	Manufacturer
35	Evergreen Pharmaceuticals	Veterinary	Manufacturer
36	Farm Aid	Veterinary	Manufacturer
37	Fizi Pharmaceutical and Chemical Laboratories	Veterinary	Manufacturer
38	Ghazi Brothers	Veterinary	Importer
39	Grand Pharmaceuticals	Veterinary	Manufacturer
40	Guyton Pharmaceuticals	Veterinary	Manufacturer
41	Hassan Brothers	Veterinary	Importer
42	Hawk Bio Pharma	Veterinary	Manufacturer
43	Hilton Pharma	Veterinary	Manufacturer
44	Huzaifa International	Veterinary	Importer
45	ICI Pakistan	Veterinary	Manufacturer
46	Inshal Pharma	Veterinary	Manufacturer
47	International Chempharma	Veterinary	Importer
48	International Pharma Labs	Veterinary	Manufacturer
49	Intervac Pharma	Veterinary	Manufacturer
50	ISIS Pharmaceuticals	Veterinary	Manufacturer
51	Izfaar Pharmaceuticals	Veterinary	Manufacturer
52	Jfrin Pharmaceuticals	Veterinary	Manufacturer
53	Kailgon Agro Industries	Veterinary	Manufacturer
54	Kohinoor Industries	Veterinary	Manufacturer
55	Kotila Corporation	Veterinary	Importer
56	LDS (Pvt) Ltd.	Veterinary	Importer
57	Leads Pharma	Veterinary	Manufacturer
58	Lexicon Pharmaceuticals	Veterinary	Manufacturer
59	Majestic Pharma	Veterinary	Manufacturer
60	Mallard Pharmaceuticals	Veterinary	Manufacturer
61	Manhattan Pharmaceuticals	Veterinary	Manufacturer
62	Mediexcel Pharmaceuticals	Veterinary	Manufacturer
64	Medi-Vet Animal Health	Veterinary	Manufacturer
65	Mehran International	Veterinary	Importer
66	Moreno Iglisias Research Laboratories	Veterinary	Manufacturer
67	Morgan Chemicals	Human + Veterinary	Manufacturer
68	MTI Medical	Veterinary	Manufacturer

70	Mustafa Brothers	Veterinary	Manufacturer
71	Mylab Pharma	Veterinary	Manufacturer
72	Myrtle Pharma	Veterinary	Manufacturer
73	N.B. Sons	Veterinary	Manufacturer
74	Nawal Pharmaceuticals	Veterinary	Manufacturer
75	Nawan Laboratories	Veterinary	Manufacturer
76	Noa Hemis pharmaceuticals	Veterinary	Manufacturer
77	Noble Pharma	Veterinary	Manufacturer
78	Orient Animal Health	Veterinary	Importer
79	Orient Traders	Veterinary	Importer
80	Pantex Pharmaceutica	Veterinary	Importer
82	Prix Pharmaceutica	Veterinary	Manufacturer
83	Ras Pharma	Veterinary	Manufacturer
84	Regent Laboratories	Veterinary	Manufacturer
86	Rotex Pharmaceuticals	Veterinary	Manufacturer
87	Saadat International	Veterinary	Importer
88	Samara Store	Veterinary	Importer
89	Sanna Laboratories	Veterinary	Manufacturer
90	SB Pharmaceuticals	Veterinary	Manufacturer
91	Schiwo Pakistan	Veterinary	Importer
92	Selmore Pharmaceuticals	Veterinary	Manufacturer
93	Shepherd Transnational Pharmaceutical	Veterinary	Manufacturer
94	Shine Laboratories	Veterinary	Manufacturer
95	SS Associates	Veterinary	Importer
96	Star Laboratories	Veterinary	Manufacturer
97	Symans Pharmaceuticals	Veterinary	Manufacturer
99	UM Enterprises	Veterinary	Importer
100	Univet Pharmaceuticals	Veterinary	Manufacturer
101	Vantage Pharmaceuticals	Veterinary	Manufacturer
102	Vet Line International	Veterinary	Importer
103	Vetcon Pharmaceuticals	Veterinary	Manufacturer
104	Vetec Laboratories	Veterinary	Manufacturer
105	Vetnocare Pharmaceutical	Veterinary	Manufacturer
106	Vetz Pharmaceuticals	Veterinary	Manufacturer

108	Welldone Marketing	Veterinary	Importer
109	Westmont Pharma	Veterinary	Manufacturer
110	Wimits Pharmaceuticals	Veterinary	Manufacturer
111	Zakfas Pharma	Veterinary	Manufacturer
112	Zoic International	Veterinary	Manufacturer
113	Zumars Pharma	Veterinary	Manufacturer

Table 12. List of Manufacturers

*There is a substantial overlap of manufacturers producing antimicrobials for both human and veterinary use.

7.5 Annex 5: WHO Medically Important Antibiotics in the EXIM Database 2019

World Health Organization Medically Important Antibiotics (MIA)	STATUS In Pakistan EXIM Trade Info 2019*
Spectinomycin	1
Streptomycin	1
Dihydrostreptomycin	1
Kanamycin	1
Neomycin	1
Framycetin	1
Gentamicin	1
Tobramycin	1
Amikacin	1
Thiamphenicol	1
Rifampicin	1
Rifaximin	1
Roxarsone	1
Cefalexin	1
Cefazolin	1
Cefuroxime	1
Cefoperazone	1
Ceftiofur	1
Ceftriaxone	1
Fusidic acid	1
Maduramycin	1
Salinomycin	1
Lincomycin	1
Erythromycin	1
Spiramycin	1
Tilmicosin	1
Tylosin	1
Avilamycin	1
Benzylpenicillin	1
Benzylpenicillin procaine/Benzathine penicillin	1
Amoxicillin	1

Ampicillin	1
Amoxicillin + Clavulanic Acid	1
Ticarcillin	1
Phenoxymethylpenicillin	1
Cloxacillin	1
Fosfomycin	1
Tiamulin	1
Enramycin	1
Gramicidin	1
Bacitracin	1
Colistin	1
Polymixin	1
Nalidixic acid	1
World Health Organization Medically Important Antibiotics (MIA)	**STATUS In Pakistan EXIM Trade Info 2019***
Oxolinic acid	1
Ciprofloxacin	1
Enrofloxacin	1
Norfloxacin	1
Ofloxacin	1
Olaquindox	1
Sulfadiazine	1
Sulfadimethoxine	1
Sulfadimidine	1
Sulfadoxine	1
Sulfaguanidine	1
Sulfamerazine	1
Sulfaquinoxaline	1
Sulfamethoxypyridazine	1
Trimethoprim	1
Chlortetracycline	1
Doxycycline	1
Oxytetracycline	1
Tetracycline	1

Novobiocin	2
Paromomycin	2
Apramycin	2
Fortimycin	2
Florphenicol	2
Nitarsone	2
Bicozamycin	2
Cefacetrile	2
Cefalotin	2
Cefapyrin	2
Cefalonium	2
Cefquinome	2
Lasalocid	2
Monensin	2
Narasin	2
Semduramicin	2
Pirlimycin	2
Oleandomycin	2
Gamithromycin	2
Tulathromycin	2
Carbomycin	2
Josamycin	2
Kitasamycin	2
Mirosamycin	2
Terdecamycin	2
Tildipirosin	2
Tylvalosin	2
World Health Organization Medically Important Antibiotics (MIA)	**STATUS In Pakistan EXIM Trade Info 2019***
Sedecamycin	2
Benethamine penicillin	2
Penethamate (hydroiodide)	2
Mecillinam	2
Hetacillin	2

Ampicillin + Sulbactam	2
Tobicillin	2
Aspoxicillin	2
Phenethicillin	2
Dicloxacillin	2
Nafcillin	2
Oxacillin	2
Valnemulin	2
Flumequin	2
Miloxacin	2
Danofloxacin	2
Difloxacin	2
Marbofloxacin	2
Orbifloxacin	2
Sarafloxacin	2
Carbadox	2
Sulfachlorpyridazine	2
Sulfafurazole	2
Sulfadimethoxazole	2
Sulfamethoxine	2
Sulfamonomethoxine	2
Sulfanilamide	2
Sulfapyridine	2
Phthalylsulfathiazole	2
Ormetoprim+ Sulfadimethoxine	2
Trimethoprim+ Sulfonamide	2
Baquiloprim	2
Ormetoprim	2
Virginiamycin	2
Nosiheptide	2

Table 13. WHO Medically Important Antibiotics

7.6 Annex 6: Discrepancies in the capture of packaging and gross weight information for air import

	IGM Date	BL No	Item Description	Buyer Name	Weight Gross	Packaging	Vessel/Flight	Data source
	Enrofloxacin							
1	12/9/2019	99972522074	ENROFLOXACIN BASE	HILTON PHARMA PVT LTD	553	20 PACKAGES	CA-945; PAKISTAN INTERNATIONAL AIRLINE	PTI
2	2019-12-10	99972522074	ENROFLOXACIN BASE	HILTON PHARMA PVT LTD	553	553 PACKAGES	CA-945	EXIM
	Moxifloxacin							
1	12/24/2019	23554301295	PHARMACEUTICAL RAW MATERIAL MOXIFLOXACIN	SAMI PHARMACEUTICALS PVT LIMITED	489	18 PACKAGES	TK-708; GERRYS DNATA (PVT.) LIMITED	PTI
2	2019-12-24	23554301295	PHARMACEUTICAL RAW MATERIAL MOXIFLOXACIN	SAMI PHARMACEUTICALS PVT LIMITED	489	489 PACKAGES	TK-708	EXIM
3	12/19/2019	99972522262	MOXIFLOXACIN HCL	TABROS PHARMA PVT LTD	112	4 PACKAGES	CA-945; PAKISTAN INTERNATIONAL AIRLINE	PTI
4	2019-12-19	99972522262	MOXIFLOXACIN HCL	TABROS PHARMA PVT LTD	112	112 PACKAGES	CA-945	EXIM
5	1/23/2019	3269293322	MOXIFLOXACIN EP/BP	AMSON VACCINES & PHARMA (PVT) LTD.	1	1 PACKAGES	EK-614; GERRYS DANTA (PRIVATE) LIMTIED	PTI
6	2019-01-24	3269293322	MOXIFLOXACIN EP/BP	AMSON VACCINES & PHARMA (PVT) LTD.	1	1	EK-614	EXIM

	Neomycin							
1	4/2/2019	15752122906	NEOMYCIN SULPHATE	P D H LABORATORIES PVT LTD	29	1 PACKAGES	QR-620; M/S ROYAL AIRPORT SERVICES (PVT)	PTI
2	2019-04-03	15752122906	NEOMYCIN SULPHATE	P D H LABORATORIES PVT LTD	29	PACKAGES	QR-620	EXIM
	Tylosin							
1	3/28/2019	99954401686	TYLOSIN TARTRATE GRANULAR	ORIENT ANIMAL HEALTH PVT LTD	1837	10 PACKAGES	CA-945; PAKISTAN INTERNATIONAL AIRLINE	PTI
2	2019-03-29	99954401686	TYLOSIN TARTRATE GRANULAR	ORIENT ANIMAL HEALTH PVT LTD	1837	1873 PACKAGES	CA-945	EXIM
3	1/16/2019	99953176126	TYLOSIN TARTRATE	HILTON PHARMA PVT LTD	560.6	24 PACKAGES	CA-945; PAKISTAN INTERNATIONAL AIRLINE	PTI
4	2019-01-17	99953176126	TYLOSIN TARTRATE	HILTON PHARMA PVT LTD	560.6	560.6 PACKAGES	CA-945	EXIM
5	1/18/2019	99953176126	TYLOSIN TARTRATE	HILTON PHARMA PVT LTD	23.4	1 PACKAGES	CA-945; PAKISTAN INTERNATIONAL AIRLINE	PTI
6	2019-01-19	99953176126	TYLOSIN TARTRATE	HILTON PHARMA PVT LTD	23.4	23.4 PACKAGES	CA-945	EXIM
	Ceftiofur							
1	12/24/2019	78442504011	CEFTIOFUR HCL	INTERNATIONAL PHARMA LABS	34	3 PACKAGES	CZ-6017; GERRYS DNATA (PVT.) LIMITED	PTI

2	2019-12-24	78442504011	CEFTIOFUR HCL	INTERNATIONAL PHARMA LABS	34	34 PACKAGES	CZ-6017	EXIM
3	12/21/2019	99973155143	CEFTIOFUR HCL	S. J&G. FAZUL ELLAHIE PVT LTD	32	4 PACKAGES	CA-945; PAKISTAN INTERNATIONAL AIRLINE	PTI
4	2019-12-22	99973155143	CEFTIOFUR HCL	S. J&G. FAZUL ELLAHIE PVT LTD	32	32 PACKAGES	CA-945	EXIM
5	3/23/2019	99953561491	CEFTIOFUR HCL	NAWAN LABORATORIES PVT LTD	55	4 PACKAGES	CA-945; PAKISTAN INTERNATIONAL AIRLINE	PTI
6	2019-03-24	99953561491	CEFTIOFUR HCL	NAWAN LABORATORIES PVT LTD	55	55 PACKAGES	CA-945	EXIM
7	4/15/2019	99955503582	CEFTIOFUR HCL MICRONIZED	NAWAN LABORATORIES PVT LTD	109	8 PACKAGES	CA-945; PAKISTAN INTERNATIONAL AIRLINE	PTI
	Colistin							
1	8/29/2019	60345668162	COLISTIN SODIUM	PHARMASOL PVT LTD	15	3 PACKAGES	UL-185; M/S ROYAL AIRPORT SERVICES (PVT)	PTI
2	2019-08-30	60345668162	COLISTIN SODIUM	PHARMASOL PVT LTD	15	15 PACKAGES	UL-185	EXIM
3	3/22/2019	60782749310	COLISTIN SODIUM	PHARMASOL PVT LTD	14	3 PACKAGES	EY-243; GERRYS DNATA (PVT.) LIMITED	PTI
4	2019-03-22	60782749310	COLISTIN SODIUM	PHARMASOL PVT LTD	14	14 PACKAGES	EY-243	EXIM

Table 14. Details of discrepancies

7.7 Annex 7. Import data protocol for estimating net weight illustrated with selected APIs

APIs and Feed

Data extraction and cleaning

1. The import data for colistin from January 1, 2019, to December 31, 2019, was downloaded from the database and saved as an Excel file.
2. Data cleaning was performed to remove duplicates and dud entries. Air freights, for which packaging information is often incomplete, were identified by port of entry, and excluded.
3. Human sector-only importers were identified from an online search and removed.
4. Companies for which no information as to whether they were human, or animal manufacturers were treated as companies dealing solely with the animal sector
5. Imports/products not for use in the human or animal sectors but for research purposes by universities or laboratories were identified from the item descriptions and/or by name of the importer and removed.
6. Shipments identified as "samples" were removed.
7. Shipments with importers based in Afghanistan, as identified from their addresses; and or for which the Item Description column in the EXIM database identified as being in transit to Afghanistan was excluded
8. All multicomponent items/imports of colistin were identified as feed and treated separately.

Data analysis (colistin used here as an example)

9. For imports identified as APIs, net weights were calculated as follows:
    a. Imports with stated net weights of colistin were identified and summed to obtain an average package weight, expressed in KG units and as a proportion of the stated gross weights as the Package Proportion (PP)
    b. The calculated Package Proportion (PP) was then applied to APIs without net weight information using Equation 1:
        i. Net weight (KG) = Gross weight (MT) *1000 (1-PP) Equ. 1
10. For imports identified as feeds, the steps in 7 were repeated, with the following provisions:
    a. Incomplete entries where the number of components in the feed mix were seen to be incomplete – entry errors leading to truncation of words – were excluded
    b. Conversion of colistin expressed in IU units to KG units. (5,000,000 IU colistin sulphate = 0.244g)
    c. For feed imports where colistin's weight was expressly stated, this weight was used without calculating a PP; or using the PP to estimate net weight
    d. For feed imports where there was no stated quantity of colistin, the number of components in the mixture, n, was used to estimate colistin by dividing Equ. 1 by "n".

- Where the n components were “quantified” by the number of drums, this proportion was used instead of “n” (as stated in 10d above).

The steps for metronidazole, imported also an FPP in vials, are presented below:

Data cleaning

1 Duplicates removed = 15

2 Human manufacturers*' shipments = 179

3 Air shipments = 24

4 Afghanistan imports = 4

5 Duds, or "Index cancelled" = 2

* Screening followed 5 sequential steps: (i) Identification of manufacturers of metronidazole for human use on the Drug Information System; (ii) Website or product catalogues searches for the remaining manufacturers; (iii) Website searches of the exporter to understand if they manufacture for the animal or human sector or both; (iv) Identification as a manufacturer on the DRAP List; (v) Identification as a veterinary manufacturer using Mohsin's list.

Of note is the fact that only ISIS is the veterinary manufacturer identified by Mohsin's list.

Ningbo Nuobai list metro injection without stating whether for human or animal use

Calculation: Proportional based on vials/bottles (Method B)

Notes

1 Each vial assumed to contain 500mg/100ml of metronidazole

2 Net wgt is: 500mg x # of vials, or bottles - if given

Feed additive

Net weight computation for zinc bacitracin used as a medicated feed follows the same formula described for metronidazole vial, with the stated percentage of the API applied as a percentage to convert the total net weight of the feed to the net weight of zinc bacitracin.

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