



# An investigation into antibiotic consumption and use for a better understanding of antibiotic resistance on the island of Mauritius

Lovena Veerapa-Mangroo

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**Université de la Réunion**

École doctorale "Sciences, Technologies et Santé" E.D. 542

**Pour l'obtention du grade de**

**DOCTEUR DE L'UNIVERSITE DE LA REUNION, UFR SCIENCES ET TECHNOLOGIES**

**Spécialité : Épidémiologie**

**AN INVESTIGATION INTO ANTIBIOTIC CONSUMPTION AND USE  
FOR A BETTER UNDERSTANDING OF ANTIBIOTIC RESISTANCE  
ON THE ISLAND OF MAURITIUS**

**UNE ENQUETE SUR LA CONSOMMATION ET L'UTILISATION D'ANTIBIOTIQUES  
POUR UNE MEILLEURE COMPREHENSION DE LA RESISTANCE AUX ANTIBIOTIQUES  
SUR L'ILE MAURICE**

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## ABBREVIATIONS

ABR	Antibiotic Resistance
ALEA	Animal Level of Exposure to Antimicrobials
AMC	Antimicrobial Consumption
AMR	Antimicrobial Resistance
AST	Antibiotic Susceptibility Testing
ATC	Anatomical Therapeutic Chemical
BSH	Brown Sequard Hospital
BSI	Blood Stream Infections
CDCU	Communicable Disease Control Unit
CHL	Central Health Laboratory
CIRAD	French Agricultural Research Centre for International Development
CLSI	Clinical and Laboratory Standards Institute
CRE	Carbapenem Resistant Enterobacteriaceae
CSD	Central Supply Division
DDD	Defined Daily Dose
DID	Defined Daily Dose per 1000 Inhabitants per Day
DHS	Director Health Services
ECDC	European Centre for Disease Prevention and Control
ESBL	Extended Spectrum Beta Lactamase
GBD	Global Burden of Diseases, Injuries, and Risk Factors Study
GLASS	Global Antimicrobial Resistance and Use Surveillance System
HAI	Hospital-acquired Infection
ICU	Intensive Care Unit
IOC	Indian Ocean Commission
IPC	Infection Prevention and Control
MCR	Mobilized colistin resistance
MDR	Multi Drug Resistant
MDRO	Multi Drug Resistant Organisms
NAP	National Action Plan
NDM-1	New Delhi Metallo B-lactamase-1



NICU	Neonatal Intensive Care Unit
WOAH	World Organization for Animal Health
PCU	Population Correction Unit
PPS	Point Prevalence Survey
PVC	Peripheral Vascular Catheter
RPHS	Regional Public Health Superintendent
SBE	Subramanian Bharati Eye Hospital
SEGA	Surveillance Epidémiologique et Gestion des Alertes
SSI	Surgical Site Infections
SWIO	South West Indian Ocean
WHO	World Health Organization

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Antibiotic Use**

## Short Abstract (English)

Antibiotic resistance (ABR) presents a great global threat and Mauritius, an upper middle-income country situated in the Southwest of the Indian Ocean, has not been spared. In order to comprehend the factors contributing to the high rate of resistance in the country, this thesis sheds light on antibiotic consumption, usage, and resistance by determining: 1) the distribution of antibiotic consumption in the different sectors in Mauritius, 2) the pattern of antibiotic consumption and use in public institutions of Mauritius, 3) the prevalence of Multi Drug Resistant (MDR) and Carbapenem resistant bacteria in the public healthcare institutions of Mauritius. The consumption of antibiotics in kilograms, Defined Daily Dose will be explored as well as the AST results of *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. A Point Prevalence study on antibiotic use explores the use of antibiotics in hospital settings.

It is observed, that in contrast to the global trend, the consumption of antibiotics in the human healthcare institutions of Mauritius (11 500 kg in 2017), plays a more valuable role in the selection pressure, as opposed to the animal sector (700 kg in 2017). Furthermore, the Defined Daily Dose per 1000 inhabitants per day (DID) of antibiotics (21.7 DID in 2017), including carbapenems (0.02 DID in 2017), is not elevated when compared to other African and European countries. Another noteworthy discovery is the substantial consumption of WATCH group of antibiotics in the private human healthcare sector.

Regarding the use of antibiotics in hospital settings, it is observed that a proportion (33-48%) of patients were receiving antibiotics for surgical prophylaxis, and more than 60% of them were administered multiple doses of antibiotics over multiple days, contrary to the guidelines recommended by the World Health Organization (WHO). Additionally, around 75% of all antibiotic prescriptions consisted of third generation cephalosporins (ceftriaxone or cefotaxime), amoxicillin, metronidazole, and ciprofloxacin). Another concern is the low percentage (16%) of antimicrobial susceptibility testing (AST) conducted prior to prescribing antibiotics.

It is to be noted that data on antibiotic consumption and usage is being presented for the first time in Mauritius.

The data on antibiotic resistance shows a decrease susceptibility of *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* to the WATCH and RESERVE antibiotics from 2015 to 2023. It is alarming to note that the susceptibility of the above bacteria to meropenem has decreased from 2015 to 2023, from 98% to 94%, 83% to 53%, 45% to 28% and 63% to 47% respectively.

Furthermore, the proportion of Multi-Drug Resistant (MDR) pathogens in Mauritius is comparable to that of India and Malawi but high compared to Europe.

This thesis highlights important information and identifies gaps that need to be addressed in the country's efforts to combat antibiotic resistance. The findings provide valuable information on misuse of antibiotics and decreasing antibiotic sensitivity, which can eventually help in the formulation of an antibiotic stewardship program. In addition, to tackle the complex issue of bacterial resistance, Mauritius needs to adopt a One Health approach that considers the interplay of humans, animals, and the environment. It offers insights, specific to the local context of Mauritius, which should be incorporated into the National Action Plan on Antimicrobial Resistance 2024-2029.

## Résumé court (français)

La menace de la résistance aux antibiotiques est une menace mondiale et Maurice, un pays situé dans le sud-ouest de l'océan Indien, n'a pas été épargné. Afin de comprendre les facteurs contribuant au taux élevé de résistance dans le pays, cette thèse met en lumière la consommation, l'utilisation et la résistance aux antibiotiques en déterminant : 1) la répartition de la consommation d'antibiotiques dans les divers secteurs, 2) le schéma de consommation et d'utilisation des antibiotiques, 3) la prévalence des organismes multi-résistants (MR) et carbapénèmes résistants dans les établissements de santé de Maurice. La consommation d'antibiotiques en kilogrammes, les doses quotidiennes définies sont explorées ainsi que la sensibilité d'*Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* et *Pseudomonas aeruginosa*. De plus, une étude de prévalence ponctuelle explore l'utilisation des antibiotiques dans les hôpitaux.

Il est observé, contrairement à la tendance mondiale, que la consommation d'antibiotiques dans les établissements de santé humaine à Maurice (11 500 kg en 2017) joue un rôle plus significatif dans la pression de sélection, par opposition au secteur animal (700 kg en 2017). De plus, la dose quotidienne définie pour 1000 habitants par jour (DID) d'antibiotiques (21,7 DID en 2017), y compris les carbapénèmes (0,02 DID en 2017), n'est pas significativement élevée par rapport à d'autres pays africains et européens. Une autre découverte notable est la consommation substantielle d'antibiotiques du groupe WATCH dans le secteur privé.

En ce qui concerne l'utilisation des antibiotiques dans les établissements hospitaliers, il est observé qu'une proportion significative (33-48 %) des patients recevaient des antibiotiques pour prophylaxie chirurgicale, et plus de 60 % d'entre eux ont reçu plusieurs doses d'antibiotiques sur plusieurs jours, contrairement aux directives recommandées par l'Organisation mondiale de la santé (OMS). De plus, environ 75 % de toutes les prescriptions d'antibiotiques étaient constituées de céphalosporines de troisième génération, amoxicilline, métronidazole et ciprofloxacine. Un autre point important est le faible pourcentage (16 %) de tests de sensibilité aux antimicrobiens réalisés avant la prescription d'antibiotiques.

Il convient de noter que les données sur la consommation et l'utilisation des antibiotiques sont présentées pour la première fois à Maurice.

Les données sur la résistance aux antibiotiques montrent une diminution de la sensibilité d'*Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* et *Pseudomonas*

*aeruginosa* aux antibiotiques WATCH et RESERVE de 2015 à 2023. La sensibilité de ces bactéries au méropénem a diminué de 2015 à 2023, passant respectivement de 98 % à 94 %, de 83 % à 53 %, de 45 % à 28 % et de 63 % à 47 %.

De plus, la proportion de pathogènes multirésistants (MDR) à Maurice est comparable à celle de l'Inde et de Malawi, mais élevée par rapport à l'Europe.

Cette thèse met en évidence des informations importantes et identifie les lacunes à combler dans les efforts du pays pour lutter contre la résistance aux antibiotiques. Ces résultats fournissent des informations sur le mésusage des antibiotiques et la diminution de la sensibilité aux antibiotiques, ce qui peut contribuer à l'élaboration d'un programme de gestion des antibiotiques. De plus, Maurice doit adopter une approche "One Health". Elle offre des perspectives significatives, spécifiques au contexte local de Maurice, qui devraient être intégrées dans le Plan d'action national sur la résistance aux antimicrobiens 2024-2029.



## Résumé étendu (français)

### Introduction

La résistance aux antibiotiques (ABR) est la résistance des bactéries aux antibiotiques. Elle représente une menace majeure à l'échelle mondiale. Les infections causées par des bactéries résistantes aux antibiotiques ont été liées à des taux de mortalité plus élevés, des séjours prolongés à l'hôpital et des dépenses de santé accrues.

L'ABR est une partie importante d'un problème plus large connu sous le nom de résistance aux antimicrobiens (AMR), qui englobe la résistance de divers micro-organismes, y compris les bactéries, les virus, les champignons et les parasites, aux traitements antimicrobiens.

L'AMR est une pandémie silencieuse qui affecte chaque pays du monde. Jim O'Neill (2016) a estimé qu'en 2050, le nombre de décès annuels attribués à l'AMR augmentera à 10 millions par rapport aux 700 000 décès actuels par an.

Maurice est un pays à revenu intermédiaire supérieur situé dans l'océan Indien, avec une population d'environ 1,2 million d'habitants. Comme d'autres pays, Maurice n'a pas été épargnée par la menace posée par l'AMR. Plusieurs études ont montré une forte prévalence de l'ABR parmi les agents pathogènes dans les institutions de santé publique de Maurice.

Maurice est l'un des cinq pays membres de la Commission de l'océan Indien (COI). L'Unité de Contrôle des Maladies Transmissibles du ministère de la Santé et du Bien-être à Maurice collabore avec le Réseau One Health SEGA (Surveillance Épidémiologique et Gestion des Alertes/Unité de Surveillance Épidémiologique et de Réponse) de la COI, ainsi qu'avec le Centre de Recherche Agricole pour le Développement International (CIRAD) de l'île de la Réunion. Cette collaboration vise à adopter une approche "One Health" pour lutter contre la résistance aux antibiotiques. Cette thèse a été réalisée dans le cadre de cette collaboration, avec le précieux soutien et l'expertise de ces agences.

### ÉNONCÉ DU PROBLÈME

Dans cette thèse, l'accent est principalement mis sur la consommation, l'utilisation et la résistance aux antibiotiques à Maurice.

Le processus de planification a conduit à un certain nombre de questions qui ont été soulevées concernant a) comment obtenir des données sur la consommation et l'utilisation des antibiotiques comme moyen de comprendre la ABR, b) mesurer la consommation

d'antibiotiques dans le secteur humain et animal, c) la consommation d'antibiotiques localement par rapport à d'autres pays, d) la consommation d'antibiotiques dans les institutions de santé humaine publiques et privées, e) la consommation d'antibiotiques par les institutions de santé publique à Maurice, f) l'utilisation d'antibiotiques dans les milieux hospitaliers de Maurice, g) la prévalence d'*Escherichia coli* multirésistant, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* qui sont des pathogènes prioritaires selon GLASS-WHO, h) la prévalence de bactéries résistantes aux carbapénèmes dans les institutions de santé publique de Maurice. Plus précisément, ces préoccupations majeures nous ont amenés aux trois questions de recherche suivantes énoncées dans cette thèse :

- Quelle est la répartition de la consommation d'antibiotiques dans les différents secteurs de Maurice ? Cela a été réalisé en comparant la consommation d'antibiotiques en kilogrammes pour les secteurs humain et animal et en Dose Journalière Définie (DDD) pour les secteurs humains public et privé.
- Quel est le schéma de consommation et d'utilisation d'antibiotiques dans les institutions de santé publique de Maurice ? La consommation d'antibiotiques par les institutions de santé a été déterminée en DDD par patient externe et en DDD par admission. Une étude de prévalence ponctuelle a été réalisée pour explorer la distribution des antibiotiques dans les milieux hospitaliers.
- Quelle est la prévalence des bactéries multirésistantes (MDR) et résistantes aux carbapénèmes dans les institutions de santé publique de Maurice ? La proportion de d'*Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* sensible à plusieurs antibiotiques, y compris les carbapénèmes, a été déterminée dans les milieux hospitaliers. La prévalence d'*Escherichia coli* multirésistant, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* a également été déterminée, ainsi que leur répartition par service.

En ce qui concerne l'utilisation des antibiotiques dans les hôpitaux, la principale préoccupation est d'obtenir plus d'informations sur les mauvais usages des antibiotiques. Cela aidera les autorités à mettre en place et à mettre en œuvre un programme d'optimisation des antibiotiques approprié dans le pays. De plus, quelques études ont

indiqué que Maurice connaît une forte prévalence de bactéries résistantes aux carbapénèmes chez les patients hospitalisés ou les patients venant de Maurice.

La thèse vise à estimer la charge de la consommation, de l'utilisation et de la résistance aux antibiotiques à Maurice. Les résultats guideront à leur tour la formulation de recommandations basées sur des preuves et le développement de stratégies dans le prochain Plan d'action national sur la résistance aux antimicrobiens 2024-2028 à Maurice.

## Résultats

Il est observé, contrairement à la tendance mondiale, que la consommation d'antibiotiques dans les établissements de santé humaine à Maurice (11 500 kg en 2017) joue un rôle plus important dans la pression de sélection, par opposition au secteur animal (700 kg en 2017). De plus, la dose quotidienne définie pour 1000 habitants par jour (DID) d'antibiotiques (21,7 DID en 2017), y compris les carbapénèmes (0,02 DID en 2017), n'est pas significativement élevée par rapport à d'autres pays africains et européens. Une autre découverte notable est la consommation substantielle d'antibiotiques du groupe WATCH dans le secteur privé.

En ce qui concerne l'utilisation des antibiotiques dans les établissements hospitaliers, il est observé qu'une proportion significative (33-48 %) des patients recevaient des antibiotiques pour prophylaxie chirurgicale, et plus de 60 % d'entre eux ont reçu plusieurs doses d'antibiotiques sur plusieurs jours, contrairement aux directives recommandées par l'Organisation mondiale de la santé (OMS). De plus, environ 75 % de toutes les prescriptions d'antibiotiques étaient constituées de céphalosporines de troisième génération, amoxicilline, métronidazole et ciprofloxacine. Un autre point important est le faible pourcentage (16 %) de tests de sensibilité aux antimicrobiens réalisés avant la prescription d'antibiotiques.

Il convient de noter que les données sur la consommation et l'utilisation des antibiotiques sont présentées pour la première fois à Maurice.

Une autre constatation alarmante est la proportion d'isolats sensibles au méropénem, à la céfétriaxone et à la ciprofloxacine qui a été observée en baisse de 2015 à 2023. La sensibilité d'*E. coli*, de *Klebsiella pneumoniae*, d'*Acinetobacter baumannii* et de *Pseudomonas aeruginosa* au méropénem a diminué de 2015 à 2023, passant respectivement de 98% à 94%, de 83% à 53%, de 45% à 28% et de 63% à 47%. De 2015 à 2023, la sensibilité d'*E. coli* et de *K. pneumoniae* à la céfétriaxone a diminué de 55% à 39% et de 37% à 22% respectivement. Cette augmentation de la résistance d'*E. coli* et de *K. pneumoniae* aux carbapénèmes a également

été observée en moyenne dans les pays européens, selon le rapport ECDC 2021. Cette augmentation de la résistance aux antibiotiques de dernier recours est alarmante car elle limite les options de traitement disponibles pour les patients malades, qui peuvent développer une défaillance multiviscérale, des complications et décéder. La situation est donc critique et il est urgent que les autorités prennent des mesures urgentes pour résoudre ce problème.

De plus, les résultats ont montré que plus de 50% des souches de *Klebsiella pneumoniae* et d'*Acinetobacter baumannii* résistantes au méropénem ont été isolées dans les unités de soins intensifs des hôpitaux régionaux de Maurice. Une autre étude réalisée en 2020 dans l'USI d'un hôpital a montré une prévalence similairement élevée. Il a été observé que ces organismes résistants aux carbapénèmes entraînaient une augmentation de l'utilisation d'antibiotiques et prolongeaient le séjour à l'hôpital. Cependant, bien que plus de 50% des souches résistantes aux carbapénèmes aient été identifiées en soins intensifs, les autres 50% ont été détectées dans les autres services de l'hôpital. Il est donc important de prendre des mesures appropriées telles que le renforcement des mesures de prévention et de contrôle des infections pour prévenir la propagation.

La proportion de souches MDR à Maurice a été comparée à celle du rapport 2017 du Centre européen de prévention et de contrôle des maladies (ECDC) ainsi qu'à celles de l'Inde (2014) et du Malawi (2016). La proportion de *Klebsiella pneumoniae* MDR était de 50 à 60% des bactéries isolées à Maurice contre 15,5% en Europe, 44% en Inde et 92% au Malawi. La proportion d'espèces d'*Acinetobacter* MDR était de 50 à 60% des bactéries isolées à Maurice contre 43,2% en Europe et 89% en Inde. De plus, la proportion d'*E. coli* MDR était de 25 à 41% à Maurice, 7,3% en Europe, 9% en Inde et 69% au Malawi. En ce qui concerne les isolats de *Pseudomonas aeruginosa* MDR, la proportion était de 25 à 41% à Maurice, 4% en Europe et 30% au Malawi. Les taux de MDR à Maurice sont comparables à ceux de l'Inde et du Malawi mais élevés par rapport à l'Europe. Le choix des échantillons en Europe pourrait expliquer ces données, car les échantillons collectés dans le rapport de l'ECDC incluaient du liquide céphalorachidien ainsi que du sang, tandis que pour cette étude à Maurice, seuls des échantillons de sang ont été inclus. Des études supplémentaires devraient être réalisées pour suivre la tendance des bactéries MDR et déterminer le taux de mortalité dû à la AMR dans les hôpitaux de Maurice.

Cependant, il est important de noter que de 2015 à 2023, la proportion d'*Acinetobacter baumannii* et de *Pseudomonas aeruginosa* MDR a encore augmenté, passant de 58% à 74% et de 33% à 45% respectivement. Certaines raisons expliquant cette augmentation de la résistance et la forte prévalence de la résistance peuvent être un mauvais contrôle de l'infection dans les hôpitaux, un mauvais usage des antibiotiques, le non-respect de la posologie des antibiotiques prescrite par le médecin traitant, l'importation d'animaux porteurs de bactéries résistantes, le fort flux de touristes dans le pays ou le choix des patients chez qui une culture sanguine a été effectuée.

### Perspectives et conclusions

Cette étude fournit des informations importantes qui doivent être intégrées dans le Plan d'action national sur la résistance aux antimicrobiens 2024-2028. L'objectif principal de cette thèse est de comprendre l'incidence de la consommation, de l'utilisation et de la résistance aux antibiotiques à Maurice. Les recherches menées dans le cadre de cette thèse ont mis en lumière l'épidémiologie de la résistance aux antibiotiques (ABR) ainsi que le schéma de consommation et d'utilisation des antibiotiques. Ces résultats ont fourni des informations précieuses sur les forces ainsi que les lacunes et les faiblesses de la situation de l'ABR à Maurice.

Il révèle également que des efforts supplémentaires doivent être déployés pour lutter contre ce problème de l'ABR à Maurice. Cette thèse nous amène à approfondir les questions de recherche suivantes : quel est le rôle du secteur animal et de l'environnement dans l'émergence et la propagation de l'ABR ? Y a-t-il une transmission de gènes de résistance entre les différents secteurs ? Quels sont les autres facteurs affectant l'ABR à Maurice ? La résistance aux antibiotiques diminuera-t-elle si la consommation et l'utilisation d'antibiotiques sont réduites à Maurice ? Quel est le rôle de la prévention et du contrôle des infections dans les établissements hospitaliers ? Quel est le rôle des voyages dans la propagation de l'ABR à Maurice ? Ces aspects nécessitent d'être explorés davantage.

L'importance de l'approche One Health en matière d'ABR a été largement discutée précédemment dans cette thèse. Il est donc essentiel d'adopter une approche One Health pour comprendre l'interaction de l'ABR chez les humains, les animaux et l'environnement. Des recherches supplémentaires doivent être menées pour déterminer l'épidémiologie de l'ABR,

la consommation et l'utilisation d'antibiotiques chez les animaux, les plantes et l'environnement.

De plus, pour déterminer l'interaction entre les secteurs humain, animal et environnement, il serait intéressant de produire un arbre phylogénétique des ESBL-Ec dans les différents secteurs de Maurice. Compte tenu de la prévalence élevée des pathogènes multirésistants dans le pays, il a été supposé que la pression de sélection fût également élevée. Cependant, une découverte intrigante de l'étude est que la consommation d'antibiotiques exprimée en termes de dose quotidienne définie par 1000 habitants par jour n'était pas élevée par rapport à d'autres pays. Les données sur la consommation d'antibiotiques suggèrent que des études supplémentaires sont nécessaires pour comprendre cette résistance élevée aux antibiotiques à Maurice. Une diminution de la sensibilité de certains pathogènes a été observée dans les hôpitaux mauriciens de 2015 à 2023. Il est donc urgent d'explorer les facteurs contribuant à la forte présence de bactéries multirésistantes et de bactéries résistantes aux carbapénèmes dans le pays. Le mouvement mondial des individus, des animaux et des marchandises facilite la transmission transfrontalière de bactéries résistantes aux antibiotiques. Par conséquent, il serait intéressant de mener d'autres recherches sur le microbiote des patients médicaux ou des voyageurs revenant à Maurice en provenance de pays présentant des taux élevés de résistance, tels que l'Inde, la Thaïlande, entre autres. De plus, nous avons observé que le secteur privé consomme davantage d'antibiotiques d'importance critique, notamment des céphalosporines, des tétracyclines, des macrolides et des aminoglycosides. Des informations supplémentaires sont nécessaires sur l'utilisation des antibiotiques dans le secteur privé. Dans les hôpitaux publics également, il est crucial de développer et de mettre en œuvre un programme de gestion des antibiotiques. Il est particulièrement important de traiter cette question car la mise en œuvre d'un programme de gestion des antibiotiques par les médecins des secteurs public et privé exigera des changements importants. Une session de réflexion au ministère de la Santé et du Bien-être et au Conseil de la pharmacie est essentielle pour trouver des solutions à ce problème.

Enfin, il est impératif que l'ABR soit une priorité pour les parties prenantes au niveau ministériel. L'engagement politique est crucial si le pays veut lutter contre l'ABR. Une équipe dédiée des différents ministères devrait travailler sur cette question pour assurer la mise en œuvre du Plan d'action national sur la résistance aux antimicrobiens 2024-2028.

Après avoir travaillé sur ces questions, Maurice pourra élaborer des stratégies efficaces pour lutter contre la résistance aux antibiotiques et atténuer son impact sur la santé publique. En combinant des pratiques de prescription responsables avec des politiques publiques robustes, nous pouvons commencer à aborder le problème complexe de la résistance bactérienne. Cette stratégie globale vise à freiner la sélection et la propagation de bactéries résistantes, à préserver l'efficacité des antibiotiques et à protéger la santé humaine et animale. Ce n'est qu'à travers des efforts collectifs et une approche multifacette que nous pourrons espérer atténuer la menace posée par la résistance aux antibiotiques et garantir un avenir durable pour nos systèmes de santé.

## GENERAL INTRODUCTION



Antibiotic Resistance (ABR) is the resistance of bacteria to antibiotics. It presents a major global threat (WHO Antibiotic Resistance, 2020). Infections caused by antibiotic-resistant bacteria have been linked to higher mortality rates, prolonged hospital stays and increased healthcare expenses (WHO Antibiotic Resistance, 2020). A study conducted in 2019 estimated that 1.27 million deaths worldwide were attributable to antibiotic resistance that year (Murray *et al.*, 2022).

ABR is a major subset of a larger concern known as Antimicrobial Resistance (AMR), which encompasses the resistance of various microbes, including bacteria, viruses, fungi, and parasites, to antimicrobial treatments (WHO Action Plan AMR, 2015).

AMR is a silent pandemic that affects every country in the world (MacIntyre and Bui, 2017). Jim O'Neill (2016) made an estimation that by 2050, the number of annual deaths attributed to AMR will increase to 10 million as compared to the actual 700,000 deaths per year (*Review AMR Jim O'Neill*, 2016).

Although AMR is a natural occurrence, the extensive selection pressure caused by the misuse and overuse of antimicrobials all over the world is accelerating the process (Alfredo, Brian and C, 2012; Oz *et al.*, 2014a; Van Boeckel *et al.*, 2014; *World's Antibiotics*, 2021). As AMR is today a pressing concern, it is crucial for all countries to implement strict policy measures to curb the rise of AMR and consequently ABR.

Mauritius is an upper middle-income country located in the Indian Ocean, with a population of about 1.2 million (*Tourism in Republic of Mauritius*, 2020; MOHW, 2022) Like other countries, Mauritius has not been spared to the threat posed by AMR. Several studies have shown a high prevalence of ABR among pathogens in the public health institutions of Mauritius (Issack, Yee Kin Tet and Morlat, 2007; Issack *et al.*, 2012; Khurshid Mungloo-Rujubali, Issack and Jaufeerally-Fakim, 2013; Nuckchady and Boolaky, 2020a).

In this battle against AMR, the Ministry of Health and Wellness of Mauritius developed a National Action Plan on AMR implemented from 2017 to 2022 (*Republic of Mauritius NAP AMR 2017-2022*, 2017). A few measures have been taken, namely registration with the Global Antimicrobial Resistance and Use Surveillance System (GLASS) and entering AMR data on

WHONET, among others. However, there is still much work to be done, and several questions need to be addressed before drafting the next action plan for the period 2024 to 2028.

Today, with the One Health approach, we are becoming more and more conscious that bacteria do not distinguish between human and animal sectors. Numerous studies have shown the horizontal transfer of resistant genes across different species and the environment (Smillie *et al.*, 2010; Baker *et al.*, 2018; Sun, 2018; Liu, Thomsen and Olsen, 2022) Moreover, the private healthcare industry is growing in Mauritius. Hence it is crucial to compare the consumption of antibiotics in the public and private human sectors. This leads to our first question, which is: 'What is the distribution of antibiotic consumption in the different sectors of Mauritius?' Consequently, our first aim is to determine the consumption of antibiotics in both the human and animal sectors to understand the impact the selection pressure in Mauritius.

One of the main drivers of antibiotic resistance is the misuse and overuse of antibiotics in the public healthcare institutions of Mauritius (Oz *et al.*, 2014a). This gives rise to our next research question which is: 'What is the pattern of antibiotic consumption and use in the public healthcare institutions of Mauritius?' Currently, no data on antibiotic consumption is available in the country. The first major concern of this study therefore is to assess the extent of antibiotic consumption and use in Mauritius.

Another important consideration is the limited research conducted on Multi-Drug Resistant Organisms (MDRO) in Mauritius (Nuckchady and Boolaky, 2020a) Patients infected with MDRO have limited access to effective treatments, as only a few antibiotics remain effective against these organisms. Without proper investigation and intervention, this problem will continue to worsen, leading to a steady decrease in treatment options and an increase in mortality and morbidity due to resistance. So far, three studies have indicated a high incidence of Carbapenem-resistant bacteria in Mauritius (Holman *et al.*, 2017; Gay *et al.*, 2020a; Nuckchady and Boolaky, 2020a). Carbapenems are considered as last-resort antibiotics that should be preserved for critically ill patients. The high incidence of Carbapenem-resistant bacteria in Mauritius poses a threat to the successful treatment and eventually to the life of these patients. This leads eventually to the third research question which is: 'What is the prevalence of MDR and carbapenem resistant bacteria in the healthcare institutions in Mauritius? '

This survey is of great significance as it highlights both the weaknesses and strengths of the Mauritian health system. It will serve as a guide for establishing an efficient surveillance system for monitoring antibiotic consumption, usage, and resistance, employing a One Health approach. It emphasizes the importance of collaboration and coordination among various Ministries. The findings and recommendations identified in this thesis will be communicated to the country's leaders for integration into the National Action Plan on AMR.

This work also emphasizes the importance of understanding the burden of ABR in the local context of Mauritius. The findings from this survey will facilitate the development of a robust antibiotic stewardship program in the country. This understanding will enable health authorities to make evidence-based recommendations to address this public health issue more effectively.

Mauritius is one of the five-member countries of the Indian Ocean Commission (IOC) (*SEGA - One Health - IOC*, 2023). The Ministry of Health and Wellness's Communicable Disease Control Unit in Mauritius collaborates with the SEGA One Health Network (Surveillance Epidemiologique et Gestion des Alertes/ Epidemiologic Surveillance and Response Unit) of the IOC, as well as the French Agricultural Research Centre for International Development (CIRAD) in Reunion Island (*Republic of Mauritius NAP AMR 2017-2022*, 2017; *CIRAD*, 2023; *SEGA - One Health - IOC*, 2023). This collaboration aims to adopt a One Health approach to tackling antibiotic resistance. This thesis has been conducted within the framework of this collaboration, with the valuable support and expertise of these agencies.

### **Framework of study**

This thesis explores antibiotic consumption, use and resistance in Mauritius. The introduction gives an overview of the importance of addressing the problem concerning ABR in the country. The literature review provides the global, regional, and local history of AMR as well as the evolution, and relevant aspects of antibiotic consumption, usage, and resistance. It also examines the healthcare system in Mauritius in relation to ABR. The results on antibiotic consumption, use and resistance in Mauritius are presented through published articles or articles submitted for publication. The thesis ends with an overall discussion which includes a general analysis of the Mauritian situation concerning ABR, followed by a few recommendations to reduce ABR prevalence.

## LITERATURE REVIEW

## Introduction on ABR

### Bacterium and the discovery of microorganisms

Bacteria are microscopic organisms that exist ubiquitously on Earth (O'Malley, 2007). They can be found in various environments, both inside and outside living organisms (Von Graevenitz, 1977; O'Malley, 2007; H. Wang *et al.*, 2018; Vitorino and Bessa, 2018). According to several scientists, bacteria are believed to have been among the first organisms to inhabit the planet's surface (Oschmann, Grasshof and Gudo, 2002; Zavarzin, 2008; Forterre, 2010). They have demonstrated remarkable survival abilities and adaptability through genetic mutations (Oschmann, Grasshof and Gudo, 2002; L, 2003).

While there are countless types of bacteria, only a small fraction of them is harmful to humans and animals (Von Graevenitz, 1977; H. Wang *et al.*, 2018). These harmful bacteria, known as pathogens, can cause diseases and infections in living organisms, leading to complications and even death (Von Graevenitz, 1977; H. Wang *et al.*, 2018). On the other hand, many bacteria play crucial roles in human survival (Von Graevenitz, 1977; H. Wang *et al.*, 2018). For example, bacteria in the digestive system aid in food digestion, while those in the vaginal passage prevent the colonization of pathogens and assist in environmental waste cleanup (Von Graevenitz, 1977; H. Wang *et al.*, 2018).

While bacteria are an integral part of the world and are present everywhere, their existence were not known until the 17th century. The discovery of microorganisms marked a significant breakthrough in understanding the causative agents of infections and the mechanisms involved in treating them. Many scientists and numerous research have made invaluable contributions in the field of microbiology, enabling the progress and advancements in medicine (Aryal, Karki and Pandey, 2015; Von Graevenitz, 1977; O'Malley, 2007; Zavarzin, 2008; Aminov, 2010; Forterre, 2010; H. Wang *et al.*, 2018; Vitorino and Bessa, 2018).

Antonie van Leeuwenhoek, a Dutch scientist in the 17th century, played a crucial role in the early observation and documentation of bacteria under a microscope (Zwick and Schmidt, 2014; Zuidervaart and Anderson, 2016; Cocquyt, 2022). His pioneering work laid the foundation for further research and has contributed to the understanding of these microscopic organisms.

Louis Pasteur, a French chemist, and microbiologist in the 19th century, made groundbreaking discoveries that revolutionized medicine (Bennett, 1989; 'SIC volume 8 issue 2 Cover and Back

matter', 1995; Schwartz, 2001; Bordenave, 2003). He demonstrated the role of microorganisms in fermentation and spoilage, leading to the development of pasteurization techniques to prevent the growth of harmful bacteria in food and beverages (Pasteur, 1881; 'SIC volume 8 issue 2 Cover and Back matter', 1995; Schwartz, 2001; Bordenave, 2003; Masters, 2008; Aminov, 2010; Blevins and Bronze, 2010)(Pasteur, 1881; 'SIC volume 8 issue 2 Cover and Back matter', 1995; Schwartz, 2001; Bordenave, 2003; Masters, 2008; Aminov, 2010; Blevins and Bronze, 2010).

Robert Koch, a German physician, further advanced the field in the late 19th century by establishing the connection between specific bacteria and infectious diseases (Bennett, 1989; Münch, 2003; Masters, 2008; Blevins and Bronze, 2010)(Bennett, 1989; Münch, 2003; Masters, 2008; Blevins and Bronze, 2010) . His work on identifying the causative agents of diseases like tuberculosis and cholera laid the groundwork for medical microbiology and the development of effective treatment strategies.

#### Discovery of antibiotics

An antibiotic is a medication that can kill (bactericidal) or stop the growth and proliferation (bacteriostatic) of bacteria ('Antibiotic \_ Medical dictionary', 2023. Antibiotics are used as chemotherapeutic agents in the treatment of infectious diseases ('Antibiotic\_ Medical dictionary', 2023).

Before the discovery of antibiotics, several methods were used by traditional healers to cure infections. One such method was the use of molds and plant extracts in ancient Egypt, China, Serbia, Greece, and Rome (Clardy, Fischbach and Currie, 2009; Aminov, 2010; Jeśman, Młodzik and Cybulska, 2011; Mohr, 2016; Kourkouta L and Plati P, 2018).

The accidental discovery of penicillin by Alexander Fleming in 1928 is a breakthrough in the history of medicine (Bennett and Chung, 2001; Clardy, Fischbach and Currie, 2009; Jeśman, Młodzik and Cybulska, 2011; Tan and Tatsumura, 2015; Mohr, 2016; Kourkouta L and Plati P, 2018). The history of antibiotics is incomplete without including Selman Waksman, a Ukrainian-American inventor who coined the word 'antibiotic' and discovered more than 20 antibiotics. His technique involved studying the soil microflora to identify antibacterial properties in soil microbes (Kresge, Simoni and Hill, 2004; Aminov, 2010; Lewis, 2012; Kourkouta L and Plati P, 2018). These discoveries revolutionized the treatment of bacterial infections and saved countless lives.

In over only 100 years, the discovery and use of antibiotics have changed modern medicine. However, since the year 2000, there has been a scarcity in the discovery of new classes of antibiotics (Clardy, Fischbach and Currie, 2009; Aminov, 2010; Jeśman, Młodzik and Cybulska, 2011; Mohr, 2016; Kourkouta L and Plati P, 2018; Hutchings, Truman and Wilkinson, 2019). Discovering and developing a new antibiotic can take 10-15 years and may cost over \$1 billion. It is a challenging task. While several substances have been found that kill bacteria, it is still harder to find such substances that can eliminate bacteria but at the same time, be non-toxic to humans. Nevertheless, each year, several drugs move into clinical trials to determine their safety and effectiveness.

The current economic model for developing new antibiotics is failing. Companies invest huge amounts of money to bring a new drug to market but cannot recover their costs or make a profit (Clardy, Fischbach and Currie, 2009; Aminov, 2010; Lewis, 2012; Kourkouta L and Plati P, 2018). New antibiotics are seen as 'drugs of last resort' against dangerous bacteria. So, to limit the development of antibiotic resistance, they need to be used sparingly – and not sold in large volumes. The combination of low sales and low prices limits the amount of money companies can make. Without financial incentives, many large pharmaceutical companies have started to pull out of the field (Clardy, Fischbach and Currie, 2009; Aminov, 2010; Lewis, 2012; Mohr, 2016; Kourkouta L and Plati P, 2018). Hence, the need to respond quickly to ensure the protection of modern medicine against the increasing threat of drug-resistant infections while there is still time.

#### [What causes antibiotic resistance and what are the resistance mechanisms?](#)

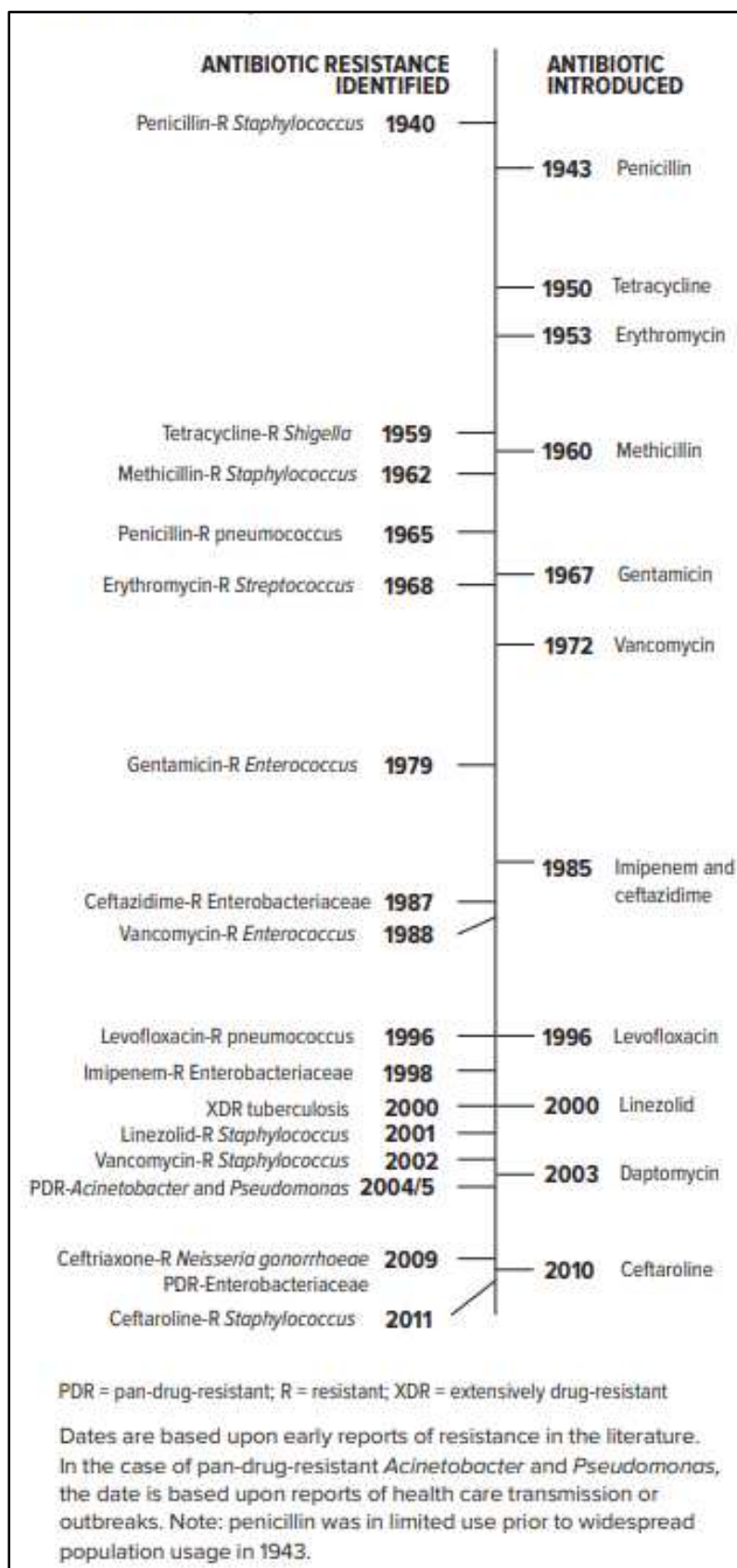
In order to understand the problem of antimicrobial resistance, it is useful to discuss some relevant concepts. Bacteria possess a remarkable ability to adapt and respond to various environmental challenges, including the presence of antibiotics that pose a threat to their survival. This genetic plasticity enables them to develop mechanisms to counteract the effects of antibiotic molecules (Julian and Dorothy, 2010; Lee Ventola, 2015; Lin et al., 2015; Uddin et al., 2021)) Antimicrobial resistance is ancient and it is the expected result of the interaction of many organisms with their environment (Pasteur, 1881; D'Costa *et al.*, 2011; Alam *et al.*, 2019; Uddin *et al.*, 2021). Bacteria that coexist in the same environment as antimicrobial-producing organisms have developed ancient methods of resisting the harmful effects of antibiotics. This defense mechanisms known as intrinsic resistance allows them to thrive even when exposed

to these antibiotic molecules. There is strong evidence indicating that the "environmental resistome" serves as a significant reservoir for antibiotic resistance genes, which can be acquired by clinically relevant bacteria. This genetic exchange has been linked to the widespread dissemination of resistance to commonly used antibiotics.

Moreover, while resistance in bacteria is a natural and evolutionary process, the intense selection pressure exerted by the use of antibiotics accelerates this process, driving bacteria to evolve and mutate in order to protect themselves. This phenomenon is not solely a natural occurrence but is a consequence of human intervention in the natural world. It serves as a compelling example of the principles of selection and survival proposed by Darwin (Baquero, Alvarez-Ortega and Martinez, 2009; Julian and Dorothy, 2010; MacLean and San Millan, 2019; Uddin *et al.*, 2021)

Following the massive manufacture and success of antibiotics, there has been a rapid emergence of strains that are resistant to these drugs as shown in figure 1 (Clardy, Fischbach and Currie, 2009; Aminov, 2010; Lee Ventola, 2015; Mohr, 2016; Kourkouta L and Plati P, 2018; Hutchings, Truman and Wilkinson, 2019; Uddin *et al.*, 2021). Sulfonamide was first discovered in the 1930s, and the development of resistance mechanisms was observed few years later (Bennett and Chung, 2001; Jeśman, Młodzik and Cybulska, 2011; Lee Ventola, 2015; Lin *et al.*, 2015). In the case of streptomycin, introduced in 1944 for the treatment of tuberculosis, mutant strains of *Mycobacterium tuberculosis* resistant to therapeutic concentrations of the antibiotic were found to arise during patient treatment sometime later. As other antibiotics have been discovered and introduced into clinical practice, a similar course of events has ensued as illustrated in figure 1 ((Lee Ventola, 2015; Lin *et al.*, 2015; Mohr, 2016; Hutchings, Truman and Wilkinson, 2019; Uddin *et al.*, 2021).

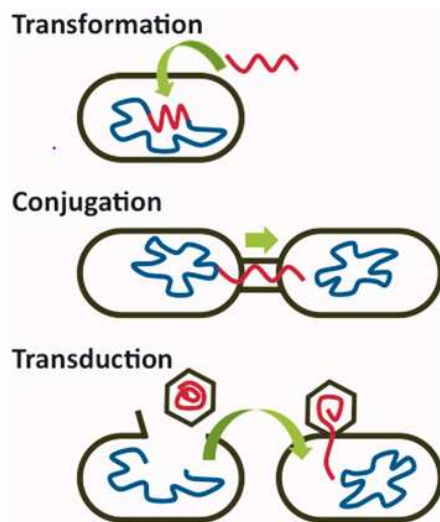




**Figure 1: Timeline of key events on introduction of antibiotics and identification of their resistance** (Lee Ventola, 2015)

From an evolutionary perspective, bacteria use two major genetic strategies to adapt to the antibiotic “attack”, *i*) mutations in gene(s) often associated with the mechanism of action of the compound, and *ii*) acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer (HGT) (Kurland, Canback and Berg, 2003; Baquero, Alvarez-Ortega and Martinez, 2009; Boto, 2009; Julian and Dorothy, 2010; Lee Ventola, 2015; Lin *et al.*, 2015; Soucy, Huang and Gogarten, 2015; MacLean and San Millan, 2019; Uddin *et al.*, 2021). Horizontal gene transfer (HGT) refers to the transfer of genetic material between different organisms. HGT is significant in the evolution of bacteria, as it allows them to acquire antibiotic resistance and virulence. There are several methods through which foreign DNA can be introduced into cells; transformation, transduction, conjugation, and transfection (Figure 2) (Kurland, Canback and Berg, 2003; Keeling and Palmer, 2008; Boto, 2009; Baltrus, 2013; Burmeister, 2015; Soucy, Huang and Gogarten, 2015).

During transformation, bacteria incorporate foreign DNA from their surroundings into their own genetic material. In conjugation, bacteria directly transfer genetic material between bacterial cells. This transfer occurs through a physical connection between the two cells. Transduction is a process where bacteriophages, which are viruses that infect bacteria, carry genes from one bacterial cell to another.



**Figure 2: Mechanisms of bacterial horizontal gene transfer** (Burmeister, 2015)

Bacteriophages can pick up genes from an infected cell and transfer them to another cell during the next infection cycle (de la Cruz and Davies, 2000; Thomas and Nielsen, 2005; Burmeister, 2015; Soucy, Huang and Gogarten, 2015; Arnold, Huang and Hanage, 2022).

Following their transfer, pathogens continue to proliferate and undergo evolution, causing a surge in antibiotic resistance and the development of new resistance mechanisms. Examples of bacterial mutations are the development of enzymes in bacteria as the ESBL, NDM-1 that confer resistance to several antibiotics or the carbapenemases and *mcr* genes that confer resistance to the last resort antibiotics (Julian and Dorothy, 2010; Lee Ventola, 2015; MacLean and San Millan, 2019)(Julian and Dorothy, 2010; Lee Ventola, 2015; MacLean and San Millan, 2019). As a result, the prevalence of MDRO that are resistant to the last resort antibiotics are increasing drastically all over the world (de la Cruz and Davies, 2000; Thomas and Nielsen, 2005; Harris et al., 2010; Lindsay, 2013; McCarthy et al., 2014; Soucy, Huang and Gogarten, 2015; Stanczak-Mrozek et al., 2015).

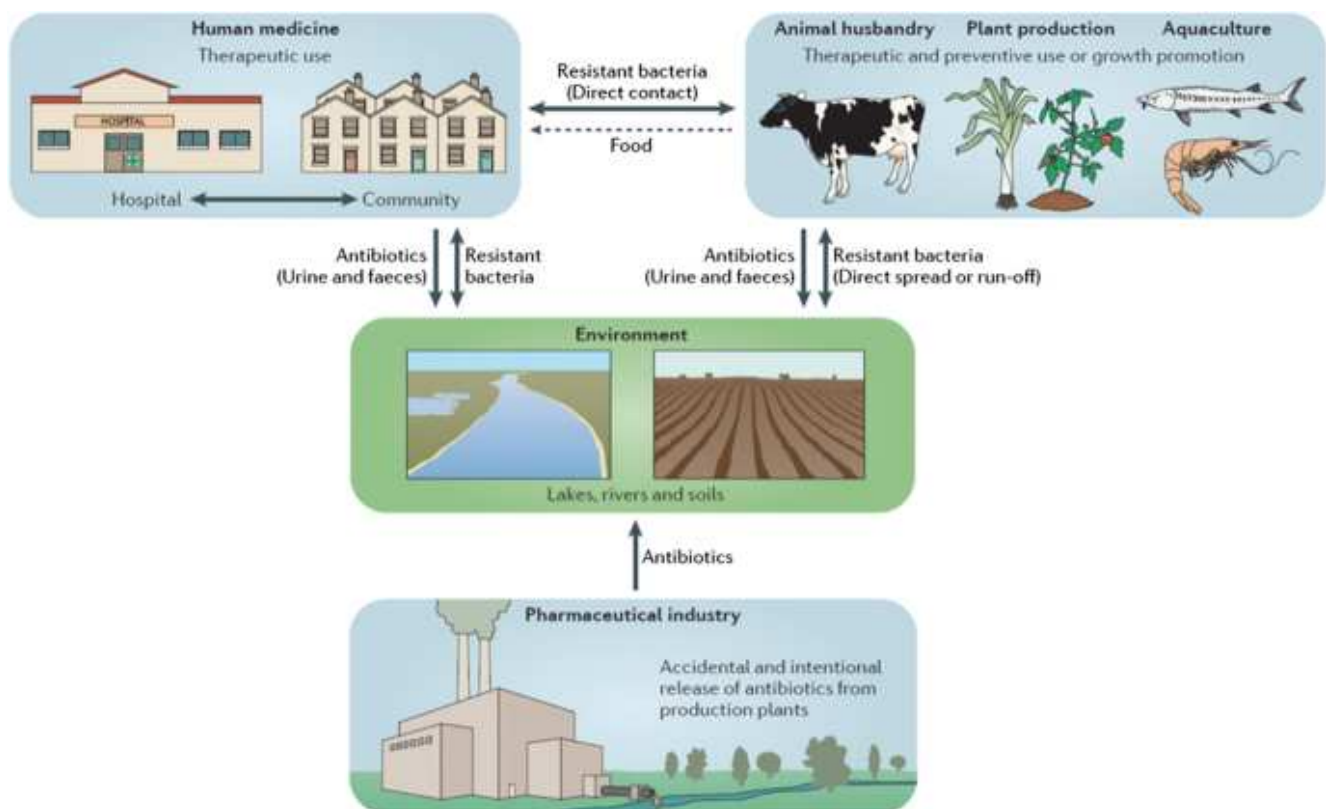
The danger is real as very few replacement antibiotics are nowadays in the pipeline (Lee Ventola, 2015). People infected with these MDR strains are more difficult to treat, have longer hospitalizations, higher healthcare cost, are at higher risk of developing complications and have higher mortality rate. Antimicrobial resistance (AMR) has today become a matter of global concern. It has been proclaimed by the World Health Organization (WHO), as one of the top 10 global public health threats (Lee Ventola, 2015).

One Health Approach: human-animal-environment interface

One-Health is defined as the “collaborative effort of multiple disciplines—working locally, nationally, and globally—to attain optimal health for people, animals, and the environment through policy, research, education, and practice” (Rubin *et al.*, 2013; Gronvall *et al.*, 2014). The concept of One Health emphasizes the interconnectedness of human health, animal health, and the environment (Figure 3). It recognizes that the well-being of humans is closely linked with the well-being of animals and the sustainability of ecosystems (Rubin *et al.*, 2013; Andersson and Hughes, 2014; Gronvall *et al.*, 2014; Wang *et al.*, 2021).

Antibiotic resistance (ABR) is a One Health challenge due to the rapid emergence and spread of resistant bacteria and genes among humans, animals, and the environment. Antibiotics are used in both humans and animals whereas the environment is a reservoir of the resistant pathogens (Walsh, 2018). Carriers of resistant genes in humans and animals release their excretions into the environment through wastewater or manure. This in turn contaminate plants and drinking water as illustrated in figure 3 (Walsh, 2018a; White and James M Hughes, 2019).

Bacteria and mobile genetic elements move easily between different environments and species (de la Cruz and Davies, 2000; Walsh, 2018; Badau, 2021). This can have significant impacts on the structure and productivity of microbiomes where antibiotic-resistant bacteria are prevalent. Conversely, any changes in these environments, such as contamination from antibiotics or antibiotic-resistant organisms, can also affect the composition of the bacterial populations associated with them. As a result, the spread of antibiotic resistance within and between these microbiomes can be influenced. It is worth noting that the transmission of resistant microorganisms is not confined to local interactions within interconnected habitats; it can occur on a larger scale, even globally. Therefore, it is essential to establish coordinated global health initiatives to effectively address this issue (Collignon, 2013; Gronvall *et al.*, 2014; Robinson *et al.*, 2016; Walsh, 2018; Durso and Cook, 2019; Badau, 2021; Kim and Cha, 2021; Wang *et al.*, 2021; Velazquez-Meza *et al.*, 2022; Cella *et al.*, 2023).



**Figure 3: Integrated ecosystem of the transfer and spread of antimicrobial resistance illustrates the critical importance of a One Health approach to the problem ((Andersson and Hughes, 2014)(Andersson and Hughes, 2014)**

In order to enhance global coordination and promote collaboration among the public health, animal health, and food safety sectors, the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE) have established a formal tripartite alliance. This alliance recognizes the interdependence of these sectors and prioritizes antimicrobial resistance (AMR) as a key area for joint action (*The FAO-OIE-WHO Collaboration animal-human-ecosystems*, 2010; 'The FAO-OIE-WHO Collaboration. A Tripartite Concept Note', 2010).

In recent years, both national and multinational strategies have been developed to address the urgent issue of AMR. These include the United States National Action Plan for combating antibiotic-resistant bacteria, the World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance, and the FAO/OIE/WHO Tripartite Collaboration (*The FAO-OIE-WHO Collaboration animal-human-ecosystems*, 2010; 'U.S.\_CDC', 2022; WHO Action Plan AMR, 2015). These strategies emphasize the critical need for a multisectoral One Health approach, recognizing the interconnectedness of human, animal, and environmental health in combating AMR.

To address this issue, it is crucial to implement comprehensive strategies that include surveillance, antimicrobial stewardship, infection prevention and control measures, and research collaborations across various sectors. By embracing a One Health approach, a more integrated and coordinated response to combat antibiotic resistance is promoted in order to preserve the effectiveness of antibiotics for current and future generations (Gronvall *et al.*, 2014; Robinson *et al.*, 2016; Walsh, 2018; White and Hughes, 2019; Kim and Cha, 2021; Velazquez-Meza *et al.*, 2022; Cella *et al.*, 2023). Similarly, this study examines the distribution of antibiotic consumption in both human and animal sector in order to better understand the causes of ABR.

Antibiotic Resistance and Consumption in the world

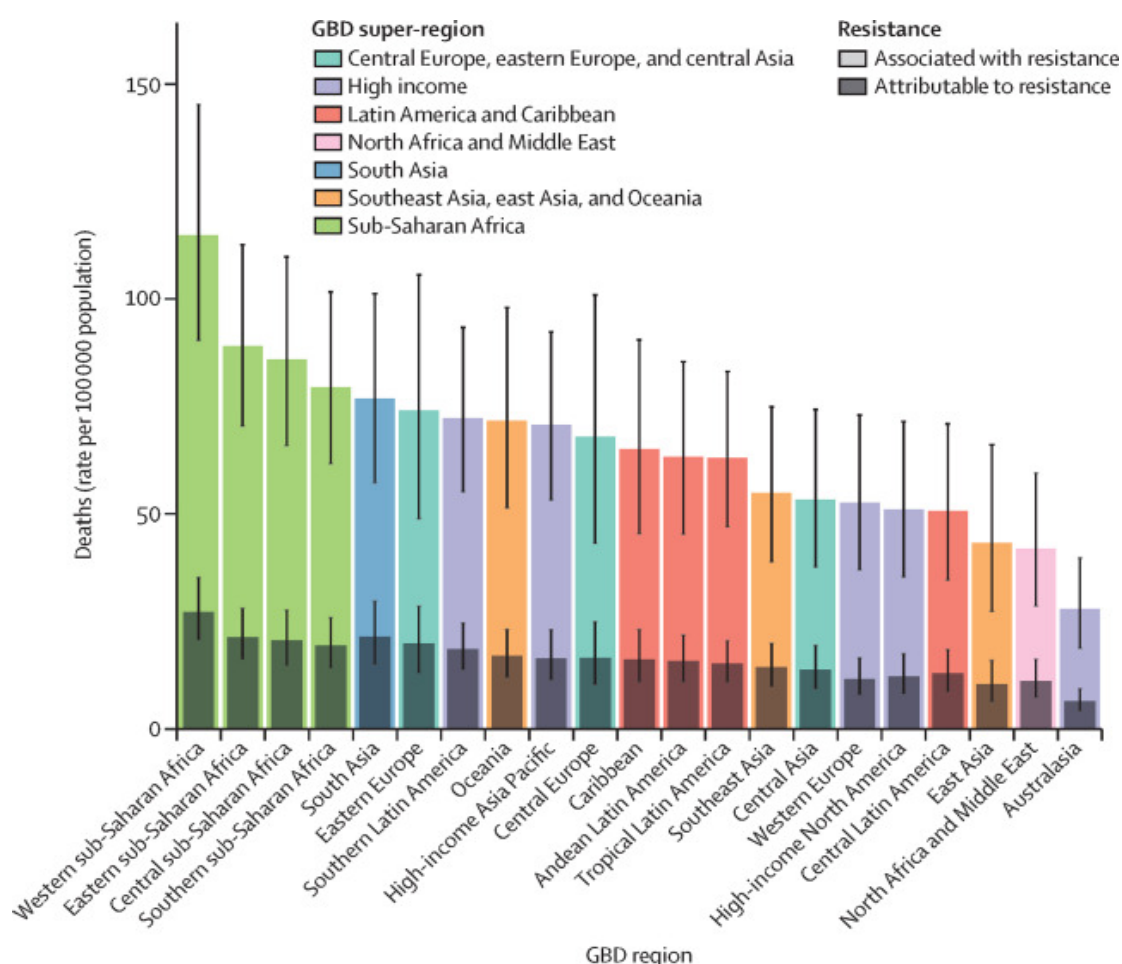
Antibiotic Resistance

Danger and consequences of Antibiotic Resistance

The rise in antibiotic resistance is a matter of great concern all over the world (Aslam *et al.*, 2018; Alam *et al.*, 2019).

Infections caused by antibiotic-resistant bacteria have been associated with higher mortality rates, longer hospitalizations, and increased healthcare costs compared to infections caused by antibiotic-susceptible bacteria. This is mainly attributed to the potential delay in initiating effective antimicrobial therapy for infections caused by antibiotic-resistant bacteria, in contrast to infections caused by bacteria that are susceptible to antibiotics (Laxminarayan *et al.*, 2013a; Prestinaci, Pezzotti and Pantosti, 2015; WHO Action Plan AMR, 2015; Shankar, Piryani and Piryani, 2017).

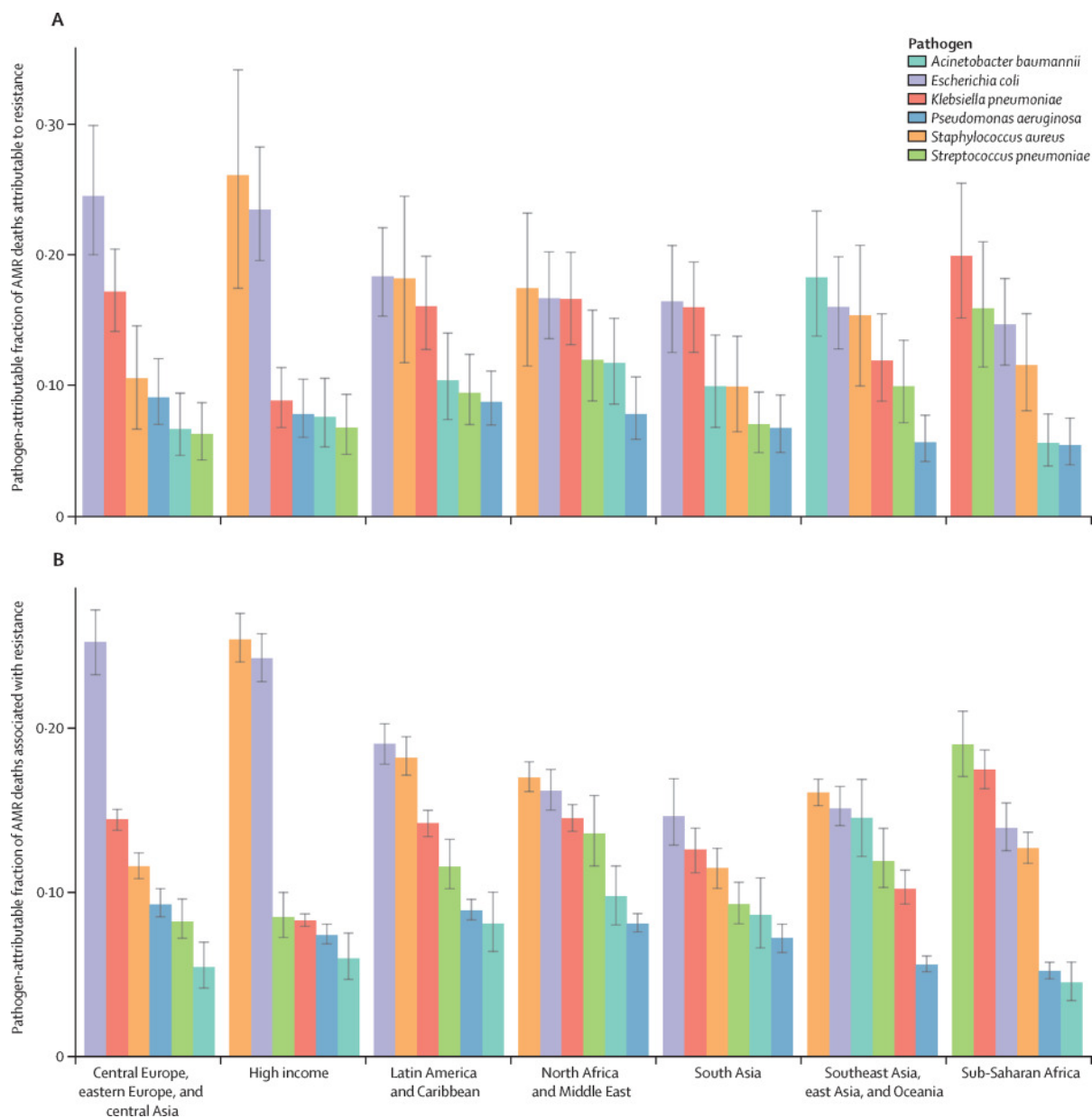
A study done in 2019, estimated global deaths attributable to resistance in 2019 to be 1.27 million; meaning 1.27 million lives could have been spared if the infections were susceptible to antibiotics instead of being resistant (Murray *et al.*, 2022). Among the different regions, Western sub-Saharan Africa had the highest deaths attributed to AMR with 27.3 deaths per 100 000 population (Murray *et al.*, 2022).



**Figure 4: All-age rate of deaths attributable to and associated with bacterial antimicrobial resistance by GBD region, 2019** (Murray *et al.*, 2022)

(GBD=Global Burden of Diseases, Injuries, and Risk Factors Study)

In 2019, the top six pathogens leading to deaths related to resistance were *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. These pathogens were responsible for a total of 929,000 deaths attributed to antimicrobial resistance (AMR) and 3.57 million deaths associated with AMR (Laxminarayan *et al.*, 2013b; Murray *et al.*, 2022).



**Figure 5: Pathogen-attributable fraction of deaths attributable to (A) and associated with (B) bacterial AMR for the six leading pathogens by GBD super-region, 2019** (Murray *et al.*, 2022)

(GBD=Global Burden of Diseases, Injuries, and Risk Factors Study)

Among the priority pathogens identified by the World Health Organization are *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*. They were identified as the topmost pathogens causing infections in 2019 (WHO Action Plan AMR, 2015; Murray *et al.*, 2022).

#### Global Antibiotic Resistance

ESBLs are primarily produced by the *Enterobacteriaceae* family of Gram-negative organisms, in particular *Klebsiella pneumoniae* and *Escherichia coli* (L and A, 2005; Dhillon and Clark, 2012). The data on ESBL-producing *Enterobacteriaceae* in the world is alarming. In India and China respectively, the prevalence of ESBL-positive strains was above 80% and 60% (Hsueh *et al.*, 2010; Sekar, 2011; ECDC, 2015). The NDM-1 gene which confer resistance to most antibiotics except for polymyxin or colistin, has been detected in more than 70 countries all over the world (Khan, Maryam and Zarrilli, 2017).

Moreover, a specific strain, known as *Escherichia coli* sequence type (ST)131 with CTX-M-15 ESBL production, has a high potential for causing epidemics and has been observed worldwide (Rossolini, D'Andrea and Mugnaioli, 2008; Livermore, 2012; D'Andrea *et al.*, 2013). These strains are now present in all continents of the world (Bonnet, 2004; Rossolini, D'Andrea and Mugnaioli, 2008; Livermore, 2012; D'Andrea *et al.*, 2013; Akova, 2016).

Each year, the EARS-Net publish reported AMR data in blood and cerebrospinal fluids from various countries of Europe. Data from EARS-Net reveals that the average resistance rate of *E.coli* and *Klebsiella pneumoniae* to third-generation cephalosporins in the European Union is 13.8% and 34.3 % respectively (ECDC AMR, 2021). From 2015 to 2021, the reported data revealed that above 50% of the *E. coli* specimens and above 33% of *K.pneumoniae* isolates were resistant to at least one class of antimicrobials (ECDC AMR, 2015, 2020, 2021). Moreover, the reported resistance of *K.pneumoniae* to carbapenems was above 10% in about a quarter of the EU countries and 18% and 38% of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* respectively were resistant to carbapenem.



Table 1 : Total number of invasive isolates tested (n) and percentage of isolates with AMR phenotype (%) in European countries (excluding United Kingdom) by bacterial species and antimicrobial group, 2017–2021 (ECDC AMR, 2021)

Bacterial species	Antimicrobial group/agent	2017		2018		2019		2020		2021		2021 EU/EEA country range <sup>a</sup>	Trend 2017–2021 <sup>b</sup>
		n	%	n	%	n	%	n	%	n	%		
<i>E. coli</i>	Aminopenicillin (amoxicillin/ampicillin) resistance	97 219	58.1	104 198	57	102 375	56.6	107 371	54.6	108 730	53.1	31.7–70.2	↓*
	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	112 659	15.6	124 043	15.7	131 325	15.6	139 057	14.9	143 180	13.8	5.5–37.3	↓*
	Carbapenem (imipenem/meropenem) resistance	110 364	0.1	120 215	0.1	127 262	0.3	135 624	0.2	137 526	0.2	0.0–1.1	↑*
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	111 377	26.9	123 358	26.4	132 015	24.7	139 372	23.8	143 253	21.9	9.6–51.6	↓*
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance <sup>c</sup>	111 049	11.6	122 147	11.2	130 984	10.8	136 101	10.9	139 435	9.6	4.1–27.0	↓*
	Combined resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides <sup>d</sup>	108 300	6.6	120 450	6.4	129 083	6.1	134 115	5.7	137 757	5.1	1.2–14.8	↓*
<i>K. pneumoniae</i>	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	27 979	34.1	33 239	34.4	36 190	34.1	39 848	33.9	43 261	34.3	3.4–81.4	-
	Carbapenem (imipenem/meropenem) resistance	27 686	8.1	32 548	8.5	35 439	9.0	39 279	10.0	42 007	11.7	0.0–73.7	↑*
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	27 615	34.7	33 154	34.3	36 315	34.0	40 066	33.9	43 136	33.6	0.0–80.0	↓
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance <sup>c</sup>	27 756	26.4	32 830	24.7	36 078	24.5	38 977	23.7	42 181	23.7	0.0–69.1	↓*
	Combined resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides <sup>d</sup>	26 837	22.9	32 381	21.6	35 622	21.5	38 331	21.0	41 590	21.2	0.0–67.4	↓
<i>P. aeruginosa</i>	Piperacillin-tazobactam resistance	13 717	18.3	16 018	18.5	16 894	18.6	19 799	18.8	21 419	18.7	0.0–47.2	-
	Ceftazidime resistance	13 801	16.0	16 327	15.5	17 328	15.7	20 122	15.5	21 750	15.8	2.3–46.0	-
	Carbapenem (imipenem/meropenem) resistance	14 274	18.9	16 473	18.8	17 496	18.1	20 517	17.9	22 267	18.1	3.5–45.9	↓
	Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	14 118	21.8	16 460	21.2	17 635	20.5	20 425	19.6	22 129	18.7	3.3–48.0	↓*
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance <sup>c</sup>	14 117	14.4	16 393	12.9	17 552	12.6	12 880	9.4	14 537	8.9	0.0–41.7	↓*
	Combined resistance to ≥ 3 antimicrobial groups (among piperacillin-tazobactam, ceftazidime, carbapenems, fluoroquinolones and aminoglycosides) <sup>d</sup>	13 022	14.1	15 514	14.1	16 289	13.5	12 041	13.6	13 684	12.6	0.0–42.1	↓
	Carbapenem (imipenem/meropenem) resistance	5 389	37.6	5 798	36.4	5 209	36.9	7 507	37.9	10 732	39.9	0.0–99.5	↑*
<i>Acinetobacter</i> spp.	Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	5 294	42.0	5 754	41.1	5 181	40.9	7 372	41.7	10 626	43.0	1.5–99.8	-
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance <sup>c</sup>	5 252	36.3	5 711	35.2	5 170	36.9	7 275	37.0	10 399	39.6	2.1–98.8	↑*
	Combined resistance to carbapenems, fluoroquinolones and aminoglycosides <sup>d</sup>	5 126	32.1	5 607	32.4	4 998	33.6	7 111	34.0	10 172	36.8	0.0–98.5	↑*
<i>S. aureus</i>	MRSA <sup>e</sup>	57 396	18.4	63 837	17.8	65 604	17.2	72 976	16.7	78 633	15.8	0.9–42.9	↓*
<i>S. pneumoniae</i>	Penicillin non-wild-type <sup>f</sup>	13 219	14.0	14 498	14.0	14 568	13.2	8 076	15.5	8 465	16.3	3.6–35.7	↑*
	Macrolide (azithromycin/clarithromycin/erythromycin) resistance	13 302	17.2	14 753	16.6	15 069	15.9	8 407	16.8	8 758	18.3	0.0–36.0	-
	Combined penicillin non-wild-type and resistance to macrolides <sup>f</sup>	12 669	9.1	14 016	8.6	14 102	8.0	7 782	8.9	8 141	9.9	0.0–28.0	-
<i>E. faecalis</i>	High-level gentamicin resistance	13 930	29.7	15 343	27.1	13 577	25.3	14 316	29.0	16 301	29.0	6.7–55.2	-
<i>E. faecium</i>	Vancomycin resistance	11 981	13.4	13 346	16.2	14 095	17.7	18 349	16.8	22 315	17.2	0.0–66.4	↑*

<sup>a</sup> Lowest and highest national AMR percentage among reporting EU/EEA countries (n=29).

<sup>b</sup> ↑ and ↓ indicate statistically significant increasing and decreasing trends, respectively, in the overall data; \* indicates confirmation in the form of a significant trend in the data that only included laboratories reporting continuously for all five years; - indicates no statistically significant trend.

<sup>c</sup> The aminoglycoside group includes only gentamicin and tobramycin from 2020 onwards.

<sup>d</sup> The aminoglycoside group includes only tobramycin from 2020 onwards.

<sup>e</sup> MRSA is based on AST results for ceftazidime or, if unavailable, oxacillin. AST results reported for cloxacillin, dicloxacillin, flucloxacillin or methicillin are accepted as a marker for oxacillin resistance if oxacillin is not reported. If no phenotypic results are available, data from molecular confirmation tests (detection of *mecA* gene PCR or a positive PBP2A-agglutination test) are accepted as a marker for MRSA.

<sup>f</sup> Penicillin results are based on penicillin or, if unavailable, oxacillin. For *S. pneumoniae*, the term penicillin non-wild-type is used in this report, referring to *S. pneumoniae* isolates reported by local laboratories as susceptible, increased exposure (I) or resistant (R) to penicillin, assuming MIC to benzylpenicillin above those of wild-type isolates (> 0.06 mg/L). The qualitative susceptibility categories (S/I/R) as reported by the laboratory are used, since quantitative susceptibility information is missing for a large part of the data. Laboratories not using EUCAST clinical breakpoints in the period 2017–2018 may have used different interpretive criteria for the susceptibility categories.

From 2017 to 2021, in Europe, the proportion of *E.coli*, *Klebsiella pneumoniae* and *Acinetobacter baumannii* resistant to carbapenems increased on average from 0.1% to 0.2%, 8.1% to 11.7%, 37.6 % to 39.9% respectively. On the other hand, the proportion of the same pathogens resistant to aminopenicillins, fluoroquinolones, aminoglycosides was seen to decrease during the same period as seen in table 1.

The reported resistance of *E. coli* isolates to three antimicrobial groups was 10% on average while the reported resistance of *K.pneumoniae* isolates to three antimicrobial classes was 21% on average in 2021. The resistance of *Pseudomonas aeruginosa* to three antimicrobial classes or more was about 10% on average while the resistance of *Acinetobacter baumannii* to three or more antibiotics was 67% on average (ECDC AMR, 2021)

Concerning ABR in animal health, MDR *E.coli isolates* reported in Europe ranged between 8.2 and 78.8% in pigs, 0–62.9% in calves, 2.4–85.2% in broilers and 4.6–90.3% in turkeys (EU AMR animal, 2021).

Globally, the proportion of *E. coli* isolates from pigs, calves, broilers and turkeys resistant to a combination of ampicillin, sulfamethoxazole, trimethoprim, and tetracycline was 41.6%, 86.9%, 41.5% and 42.2% respectively ('EU AMR animal', 2021).

In the U.S, the ABR of several pathogens has shown an improvement from 2013 to 2019 after strict measures as the implementation of antibiotic stewardship and IPC guidelines were taken by the country (Antibiotic resistance threats in the United States, 2019). A decrease of 28% in deaths caused by antibiotic resistance was observed in the hospitals of the United States as well as a reduction of carbapenem-resistant *Acinetobacter baumannii* and of MDR *Pseudomonas aeruginosa* respectively. Although these drastic measures brought about some progress in the proportion of resistance, the danger of AMR is still present (Antibiotic resistance threats in the United States, 2019).

In an Australian tertiary hospital, we note the drastic surge of the levels of *ESBL-producing E. coli* from 0.7% (95% CI = 0.0–3.8) in hospital-acquired UTIs in 2009 to 6.5% (95% CI = 3.2–11.6) in 2013 and an increase was also noted for community-acquired UTIs (0.6%; 95% CI = 0.2–1.4 in 2009 to 3.7%; 95% CI = 2.5–5.3 in 2013) (Raphael, Glymour and Chambers, 2021).

Several articles have declared India as ‘the AMR capital of the world (Taneja and Sharma, 2019; Broom and Doron, 2020). According to the 2017 AMR report of India, approximately 70% of *A. baumannii*, 57% of *K. pneumoniae*, more than 40% of *P. aeruginosa*, and more than 10% of *E. coli* were carbapenem resistant (Gandra *et al.*, 2017). Bloodstream infections caused by dual carbapenem and colistin-resistant *K. pneumoniae* in Indian patients are associated with a mortality rate of 69.3% (Kaur *et al.*, 2017). Concerning agriculture, it was found that 48 % of the Gram-negative bacilli detected in the cow and buffalo milk were ESBL producers (Das *et al.*, 2017). In a lake found in Maharashtra, it was found that 48% of the *Enterobacteriaceae* found in the gut of the tilapia fish were ESBL producers (Marathe *et al.*, 2016; Taneja and Sharma, 2019)

In the retail Indian markets of shrimps, shellfish, and crabs in Kerala, resistance of *Vibrio cholera* and *V. parahaemolyticus* to ceftazidime ranged from 67% to 96% (Sudha *et al.*, 2014). Moreover, all salmonella species isolated in broilers from Bihar and West Bengal were resistant to ciprofloxacin, gentamicin, and tetracycline (Gandra *et al.*, 2017).

In north Indian rivers, 17.4% of Gram-negative bacteria were found to be ESBL producers, with the presence of resistance genes like *bla<sub>NDM-1</sub>* and *bla<sub>OXA48</sub>* (Azam, Jan and Haq, 2016). In the south Indian river Cauvery, all 283 *E. coli* isolates were resistant to third-generation cephalosporin (Skariyachan *et al.*, 2015). Groundwater and surface water used for drinking and recreation have also shown antibiotic-resistant *E. coli*, with rates ranging from 7% to 100% in different regions of India (Kumar, Tripathi and Garg, 2013; Poonia, Singh and Tsering, 2014; Skariyachan *et al.*, 2015).

A study conducted in Kerala, India, investigated carbapenem resistance among bacterial isolates from water bodies receiving hospital effluents and nearby aquaculture farms (Kalasseril *et al.*, 2020). The study identified *Klebsiella species*, *Escherichia coli*, *Enterobacter aerogenes*, and *Acinetobacter baumannii* as the main isolates. Antibiotic sensitivity testing revealed that approximately 60% of the screened *Enterobacteriaceae* isolates were multidrug-resistant, with 16.6% showing resistance to carbapenems.

#### *Blood Stream Infections and Antibiotic Resistance*

A bloodstream infection (BSI) is a serious and potentially life-threatening condition (Bates, Pruess and Lee, 1995; NCBI Bacteremia, 2023). Bacteremia refers to the presence of live

bacteria in the bloodstream, regardless of whether it is associated with an active disease (Bearman and Wenzel, 2005; NCBI Bacteremia, 2023). When bacteria release toxins into the bloodstream, it can trigger a robust immune response known as systemic inflammatory response syndrome (SIRS). SIRS is characterized by symptoms such as rapid breathing, low blood pressure, and fever. If left untreated, SIRS can progress to sepsis, septic shock, and multiple organ dysfunction syndrome (MODS), further exacerbating the patient's health. It is crucial to promptly diagnose and treat bloodstream infections to prevent the development of these severe complications (Bearman and Wenzel, 2005; NCBI Bacteremia, 2023).

Bacteremia is a global health concern, contributing to a high burden of illness and mortality (Bates, Pruess and Lee, 1995; Bearman and Wenzel, 2005; Wilson *et al.*, 2011; Skogberg *et al.*, 2012; Goto and Al-Hasan, 2013). In England, *E. coli* accounted for 22.5% of all episodes of bacteraemia reported in 2008 (Wilson *et al.*, 2011). The estimated annual number of bloodstream infection (BSI) episodes in Europe is 1.2 million, with approximately 157,000 associated deaths (Goto and Al-Hasan, 2013).

While bacteremia can be a life-threatening condition and is a common complication in critically ill patients, the presence of ABR further threatens the prognosis for these patients, as it limits the available treatment options (Bearman and Wenzel, 2005; Seboxa *et al.*, 2015; Akova, 2016; Ergönül *et al.*, 2016; Musicha *et al.*, 2017; Tian, Zhang and Sun, 2019). If timely and appropriate antibiotic therapy is not administered to the patient with sepsis, the survival rate can be decreased. Prompt initiation of effective antibiotic therapy is essential to reduce mortality rates and improve clinical outcomes. However, choosing the most appropriate empiric antibiotic regimen can be difficult due to the widespread presence of multidrug-resistant (MDR) organisms that have developed reduced susceptibility to commonly used broad-spectrum antimicrobials (Seboxa *et al.*, 2015; Akova, 2016). Several studies have shown the higher mortality rates in those patients with BSI (Ibrahim *et al.*, 2000; Seboxa *et al.*, 2015; Ergönül *et al.*, 2016; Musicha *et al.*, 2017; Tian, Zhang and Sun, 2019).

Having country-specific data on the major pathogens responsible for bloodstream infections is crucial, especially considering the emerging patterns of resistance among commonly isolated bacteria. This information is essential for effectively addressing and managing the challenges posed by antimicrobial resistance (Ibrahim *et al.*, 2000; Seboxa *et al.*, 2015; Akova, 2016; Ergönül *et al.*, 2016; Musicha *et al.*, 2017; Tian, Zhang and Sun, 2019). Similarly, this

thesis provides recent ABR data in bloodstream infections in the hospital settings of Mauritius, orienting towards appropriate measures which should be taken.

## Antibiotic Consumption and Use

### *Tools for measuring antibiotic consumption*

#### Defined Daily Dose Indicator for antibiotic consumption in human health

In 1996, the World Health Organization (WHO) officially adopted the ATC/DDD methodology as a universally accepted standard for studying drug utilization (WHO DDD, 2023). This endorsement aimed to promote equitable access to essential medications and encourage the appropriate and rational drugs, especially in countries with limited resources. The WHO Collaborating Centre for Drug Statistics Methodology plays a central role in establishing and managing the ATC/DDD system, which has become an internationally recognized standard (WHO DDD, 2023).

Concerning antibiotic consumption, the DDD is an indicator used globally and is an important tool as it provides a standardized way of calculating and comparing DDD across countries and with time.

#### Population Correction Unit (PCU) and Animal Level of Exposure to Antimicrobials (ALEA)

The Population Correction Unit (PCU) was introduced by the European Medicines Agency (EMA) in 2009 and has been widely adopted across Europe (ANSES PCU, 2023; PCU UK, 2023). It is a conceptual unit of measurement that takes into consideration the animal population of a country over a year and factors in the estimated weight of each species at the time of antibiotic treatment. The PCU offers a standardized approach to track and evaluate antibiotic usage in animal populations, aiding in the monitoring and assessment of antibiotic consumption in veterinary medicine (ANSES PCU, 2023; PCU UK, 2023).

ALEA, which stands for Animal Level of Exposure to Antimicrobials, is a metric that quantifies the overall amount of antibiotics utilized in animal production per year, divided by the total weight of animals produced (ANSES PCU, 2023). The calculation of ALEA considers parameters such as the total weight of animals produced, the total quantity of antibiotics employed in animal production, and the bioavailability of each antibiotic (ANSES PCU, 2023). This measure

provides valuable insights into the level of antimicrobial exposure experienced by animals in the agricultural sector.

#### Global antibiotic consumption

In human health, the global antibiotic consumption rose from 11.3 to 15.7 Defined Daily Doses per 1000 people from 2000 to 2015 ((Klein *et al.*, 2018, 2021; *World's Antibiotics*, 2021)). This increase was mostly observed in low- and middle-income countries (Shankar, Piryani and Piryani, 2017; Klein *et al.*, 2018, 2021; *World's Antibiotics*, 2021). If the same trend continues, it was predicted that the global antibiotic consumption might double by 2030 (Shankar, Piryani and Piryani, 2017; *World's Antibiotics*, 2021). In 2019, the World Health Organization developed and launched the AWARE tool to monitor consumption of antibiotics and curb antibiotic resistance at global and national level ('WHO AWARE Classification', 2019). The known antibiotics were organized into three different categories: ACCESS, WATCH and RESERVE. The ACCESS group of antibiotics are the first line options that should be used for the most common infections while the RESERVE group should be used sparingly and only for infections that cannot be treated with other antibiotics. A rise was observed from 2000 to 2015 in the WATCH category of antibiotics from 2.0 to 5.3 DDDs per 1000 population while the ACCESS antibiotics increased from 6.1 to 7.8 DDDs (Klein *et al.*, 2018, 2021; *World's Antibiotics*, 2021).

On average, globally, antimicrobial consumption in the animal sector is three times that consumed in the human healthcare. The total antibiotic consumption in animals in 2013 was 131, 109 tons (95% C.I [100,812-190,492]) and was projected to increase to 200, 235 tons (95% C.I. [150,848-297,034]) by 2030 if nothing is done to curb the consumption rate (Shankar, Piryani and Piryani, 2017; *World's Antibiotics*, 2021). This increase demand is leading many farmers to use antibiotics not only to cure sick animals but also as growth promoters where antibiotics are given at a suboptimal level to improve the distribution of fat and protein in the animals (Toldrá and Reig, 2016). The high consumption in the animal protein production and aquaculture was largely driven by the BRICS countries, namely Brazil, Russia, India, China and South Africa. The animals consuming the largest amount of antibiotics were chicken and pigs (Shankar, Piryani and Piryani, 2017; *World's Antibiotics*, 2021).

### Substandard and falsified medicines

Substandard medicines refer to genuine products that do not meet the required quality standards or specifications (Report fifth meeting on substandard/spurious/falsely labelled/falsified/counterfeit medical products, 2017; Roth, Biggs and Bempong, 2019). This can be due to manufacturing errors, improper storage, or inadequate distribution practices. On the other hand, falsified medicines are counterfeit products that intentionally misrepresent their identity, composition, or source. Falsified medicines are typically produced with the intention of economic exploitation (Report fifth meeting on substandard/spurious/falsely labelled/falsified/counterfeit medical products, 2017; Roth, Biggs and Bempong, 2019). The use of substandard or falsified medicines further accelerate the emergence of resistance due to constant exposure of patient to a lower dose of antibiotics (Johnston and Holt, 2014; Theodoros and E, 2015).

### Role of travel and movement of people and animals in AMR

The rapid spread of COVID 19 across the globe is proof that the world is a global village. As a result, the role of travel in the spread of AMR is an important aspect that should not be neglected. The flux of human beings and animals across the world today can spread viruses and bacteria from one country to another (Frost *et al.*, 2019). Though measures are taken to optimize antibiotic use and limit the spread of resistant bacteria in a country, resistant genes and microorganisms can be brought from abroad through humans and animals. People travelling from one country to another can be asymptomatic carriers of resistant pathogens or genes (Frost *et al.*, 2019). The identification of resistant bacteria in persons after travel to the tropical countries in Africa and Asia has been documented in various articles (Ruppé *et al.*, 2014; Hassing *et al.*, 2015; Le Guern *et al.*, 2019; Leo *et al.*, 2019). A study stated that the risk of being colonized with ESBL was four times higher in international travelers compared to those who did not go abroad (Ruppé *et al.*, 2014). Another one has shown the carriage of the resistant pathogens to last only three months in the microbiome of humans which is largely sufficient to spread the resistant bacteria to other people and the environment (Le Guern *et al.*, 2019). Through excretions, the resistant genes are released in the environment, where they go into the ecosystem and reach the people and animals of that country as illustrated in figure 3 (Fletcher, 2015; Frost *et al.*, 2019).

Two recent instances serve as alarming examples of the emergence and rapid geographical spread of antibiotic resistance genes. The New Delhi metallo-beta-lactamase 1 (NDM-1) enzyme, which provides resistance against a broad range of antibiotics, initially appeared in the Indian subcontinent, and later spread to the UK through medical tourism, first detected in 2008 (Dongun *et al.*, 2009). Subsequently, the NDM-1 gene was found in surface and tap water samples in India in 2010, as well as in the environment in Bangladesh, indicating the potential for its environmental origin and global spread, along with its variants (Walsh *et al.*, 2011; Aminul *et al.*, 2017; Khan, Maryam, and Zarrilli, 2017). More recently, the NDM-1 gene was discovered in nutrient-rich Arctic soil in a remote Norwegian archipelago, raising concerns about potential transmission through migratory bird faeces (McCann *et al.*, 2019). Another example is the MCR-1 (mobilized colistin resistance-1) gene, which was initially identified in pigs in China in 2014, conferring resistance to colistin (Liu *et al.*, 2016). Since then, it has rapidly spread to numerous other countries (Marston *et al.*, 2016; R. Wang *et al.*, 2018). These examples highlight the urgent need for global attention and collaborative efforts to address the dissemination of antibiotic resistance genes. The saying 'No one is safe till everyone is safe' applies to AMR as well as COVID.

Like carbon emissions, even countries with effective antimicrobial stewardship programs in health and agriculture are vulnerable to the importation of AMR genes that have emerged and spread from other regions of the world (Gronvall *et al.*, 2014; Marston *et al.*, 2016; R. Wang *et al.*, 2018; Hernando-Amado *et al.*, 2019).

#### AMR in the Indian Ocean

The Indian Ocean is the third largest ocean of the world. It is surrounded by several countries including Iran, Pakistan, India, and Bangladesh in the north. To the east, it is bordered by the Malay Peninsula, the Sunda Islands of Indonesia, and Australia. In the south, it connects with the Southern Ocean, while in the west it is bounded by Africa and the Arabian Peninsula. In the southwest, it meets the Atlantic Ocean near the southern tip of Africa, and in the east and southeast, its waters blend with those of the Pacific Ocean ('Indian Ocean - Factbook', 2023; 'Bazaruto Island Marine Reserve', 2023).



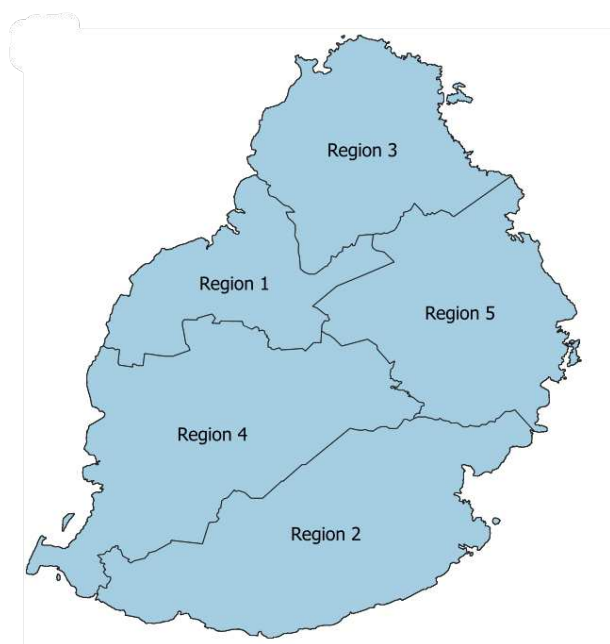
The immense load of suspended sediments from the rivers emptying into the Indian Ocean is the highest of the three major oceans, and nearly half of it comes from the Indian subcontinent alone ('Bazaruto Island Marine Reserve', 2023). Other studies demonstrate the large amount of multidrug-resistant *E. coli* and *K. pneumoniae* in the wastewater that flows from the hospital into the community sewage system, eventually reaching the Indian Ocean (Seguni *et al.*, 2023). The number of organisms and animals in the Indian Ocean are various and may be a huge reservoir of resistant genes. It would be interesting to determine the phylogenetic tree of the resistant genes and explore the possible transmission of genetic mobile elements and resistance genes between various organisms in the Indian Ocean.

Several articles have also been published portraying the prevalence of resistant bacteria in the countries of the Southwest Indian Ocean region, including Mauritius, Madagascar, Mayotte, La Reunion, and Union of Comores (Gay *et al.*, 2017; Miltgen *et al.*, 2018, 2020, 2022a).

## Introduction on Mauritius

### Demographics and Health Care System

The island of Mauritius is found in the Southwest of the Indian Ocean. It is an upper middle-income country and has a tropical climate all year round. It has a population of about 1.2 million and consists of five health regions as illustrated in figure ('Mauritius World Bank', 2023).



**Figure 6: Island of Mauritius with five health regions.**

The Mauritius healthcare system consists of a public and a private sector (MOHW, 2017, 2022).

In 2017, there were 2,927 doctors registered with the Medical Council of the Republic of Mauritius, that is 23.1 doctors per 10,000 population. 1,514 (51.7%) doctors, including 326 specialists, were employed in the public sector (MOHW, 2017). The number of qualified nurses and midwives in the public and private sectors was 4,445 of whom 4,016 were employed by the Ministry of Health and Quality of Life (MOHW, 2017). In 2021 on the other hand, there were 3775 doctors registered with the Medical Council of the Republic of Mauritius, that is, 29.9 doctors per 10,000 population. 1,681 (44.5%) doctors, including 376 specialists, were employed in the public sector. The number of qualified nurses and midwives in the public and private sectors was 4,386 of whom 3,711 were employed by the Ministry of Health and Wellness (MOHW, 2022).

Treatment in the public health sector of Mauritius including medications and laboratory tests, is completely free of charge. The public sector in Mauritius comprises of a primary healthcare level which consists of 141 health centers and 2 district hospitals, a secondary healthcare level which consists of five regional hospitals and a tertiary healthcare level which consists of eight specialized hospitals distributed all over the island. The five regional hospitals provide both outpatient and inpatient care (MOHW, 2017, 2022).

Concerning the public health department, the Communicable Disease Control Unit (CDCU) at the Headquarters of the Ministry of Health and Wellness oversees the surveillance and response of the communicable diseases in Mauritius. It is under the aegis of the Director Health Services (DHS) of public health. At the community level, the island is divided into five health regions, with the Regional Health Superintendent (RPHS) in charge of the surveillance and response in each region. The RPHS are accountable to the DHS of the public health of the Ministry of Health and Wellness and communicate with the CDCU regarding the surveillance and response of all diseases.

The Vaccination Unit forms part of the CDCU. Vaccines are provided free of charge at each health centers of the island. Moreover, the public health nursing officers carry out vaccination sessions at the government schools and follow the national vaccination schedule. Mauritius has a high vaccination coverage (MOHW, 2017, 2022; *MOHW*, 2021).

#### Animal Health care institutions

In Mauritius, the Ministry of Agro-industry oversees the use of antibiotics as well as the treatment of animals. They have an Animal Health Laboratory where AST is done in sick animals.

#### Health burden in Mauritius

The Health Statistics of Mauritius provide important data on the health burden in the country. Non-communicable diseases are responsible for most deaths (MOHW, 2017, 2022). In 2017, diabetes mellitus, heart diseases and cancer accounted for 23.2% (2305), 18.7 % (1850) and 13.8% (1371) of the total deaths respectively. In the primary healthcare level on the other hand, diseases of the respiratory system, diseases of the musculoskeletal system and connective tissue and diseases of digestive system accounted for 24%, 11% and 8% respectively (MOHW, 2017).

## Mauritius Economy and Sanitation

Since the 1980's, Mauritius has shifted from agriculture of sugarcane to the tourism Industry (*Tourism in Republic of Mauritius*, 2020). Today, the tourism industry is one of the main incomes of the island. In 2019, there were 1.8 million arrivals and 1.8 million departures each year. Among the arrivals, 1.4 are non-Mauritian citizens with 835,946 tourists from Europe, 310,928 tourists from Africa, 189,849 tourists from Asia and the rest from other regions of the world. Among the departures, about 320,000 persons are Mauritians. United Arab Emirates, South Africa, India, Reunion Island, France, and United Kingdom form 71 % of the countries of departure (*Tourism in Republic of Mauritius*, 2020). This information is crucial as the role of travel contributes to the spread of resistant bacteria and genes from country to another as mentioned earlier.

A Housing and Population Census was done in 2011 in Mauritius. According to the report, 99.7% and 99.8% have safely managed drinking water service and sanitation respectively (MOHW, 2017; *Tourism in Republic of Mauritius*, 2020).

## Healthcare expenditure in Mauritius

The healthcare expenditure in Mauritius has increased from 2005 to 2020 from 192 US\$ to 560 US\$ as seen in table 2 ('Global Health Expenditure Database', 2023). The percentage expenditure for private healthcare was slightly higher than in the public healthcare institutions from 2005 to 2018 as seen in figure 7 (*Pharmaceutical Industry In Mauritius*, 2020; 'Global Health Expenditure Database', 2023).

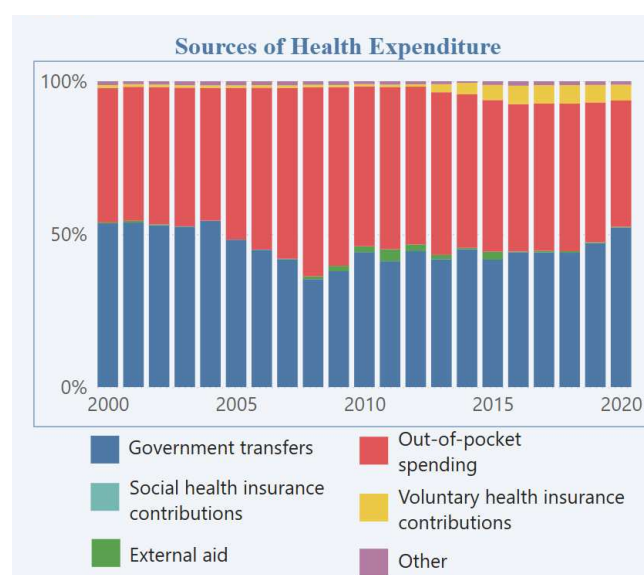
## Distribution of antibiotics in the country

The Pharmacy Board is responsible for the approval of all importations of antibiotics entering the country. Importation is the main source of supply of pharmaceutical products in Mauritius. In the private channel of distribution, pharmaceutical products are sold by registered retail pharmacies.

These pharmaceutical retail outlets are administered by registered pharmacists-in-charge on a private licensed premises. In 2019, there were 354 registered retail pharmacies in Mauritius (*Pharmaceutical Industry In Mauritius*, 2020).

**Table 2: Healthcare expenditure in Mauritius from 2005 to 2020** ('Global Health Expenditure Database', 2023)

Key Statistics				
	2005	2010	2015	2020
Health spending US\$ per capita (CHE)	192	357	515	560
Government health spending % Health spending (GGHE-D%CHE)	48.2%	44.1%	41.7%	52.2%
Out-of-pocket spending % Health spending (OOPS%CHE)	49.6%	52.3%	49.6%	41.3%
Priority to health (GGHE-D%GGE)	7.4%	8.3%	9.5%	10.2%
GDP US\$ per capita	5,386	7,795	9,042	8,415



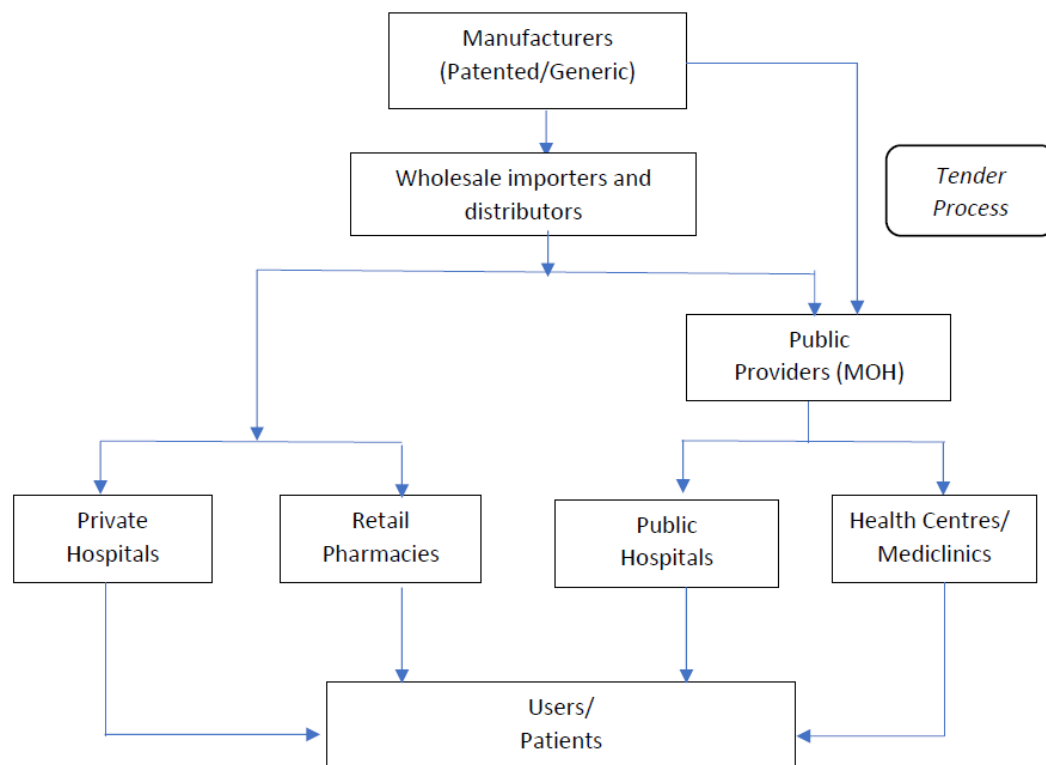
**Figure 7: Sources of Healthcare expenditure from 2000 to 2020 In Mauritius** ('Global Health Expenditure Database', 2023)

In the public health sector, the Central Supply Division (CSD) of the Pharmacy Unit is responsible for the distribution of antibiotics. The distribution of all medications including antibiotics is illustrated in figure 8.

At the CSD, the data is entered regularly in an electronic format and can be retrieved on a Microsoft excel or pdf format.

According to a report on the pharmaceutical industry in Mauritius, the public sector caters for about 73% of healthcare needs of the population (*Pharmaceutical Industry In Mauritius*, 2020).

In the private sector, patients are allowed to buy their antibiotics only when a prescription form from a recognized treating doctor is presented. This is stipulated in the Pharmacy Act 1983 (*Mauritius Pharmacy Act, 1983*). All private pharmacies are requested to keep the prescriptions of antibiotics for regular check by the authorities.



*Figure 8: Pharmaceutical Supply Chain in Mauritius (Pharmaceutical Industry In Mauritius, 2020)*

To our knowledge, no analysis and interpretation of data on antibiotic consumption has been done till date. A few studies have presented some sporadic antibiotic use data as part of their research. However, no in-depth survey had been done on antibiotic use in the country.

#### Surveillance system of Antibiotic Resistance data

The Central Health Laboratory (CHL) at Victoria Hospital and the microbiology laboratory at Dr A.G. Jeetoo hospital carry out antibiotic susceptibility testing (AST) daily on different types of samples sent by hospitals or health centers for the human sector. AST is done for all public institutions all over the island by the Kirby Bauer disk diffusion method and interpreted by the

Clinical and Laboratory Standards Institute (CLSI) breakpoints. AST is done on blood, urine, stool, endotracheal secretions, and other samples. The data is collected on a paper-based system but can be retrieved easily at CHL and Dr A.G. Jeetoo Hospital.

#### Antibiotic Resistance and Use in the island of Mauritius

No results on antibiotic consumption are available. However, two studies have provided some information on antibiotic use. The most recent one done in 2020 shows an increase in duration of antibiotic use from 11 to 24 days in the Intensive Care Unit of a hospital in Mauritius in patients infected with MDR organisms (Nuckchady and Boolaky, 2020b). Another study done in 1992 states that among the inpatients in the hospitals of Mauritius, more than one third received antibiotics as part of their treatment (Jepsen *et al.*, 1993). No in-depth survey had been done till then.

On the other hand, several studies have been done concerning Antibiotic Resistance in Mauritius. As from 2009, Klebsiella producing the enzyme NDM-1 and ESBL respectively have been detected in the hospitals of Mauritius (Laurent *et al.*, 2012; Khurshid Mungloo-Rujubali, Issack and Jaufeerally-Fakim, 2013). Other studies further demonstrate the extent of antibiotic resistance in Mauritius. From March 2005 to July 2014, the resistance of *Escherichia coli* to cefotaxime in hospitalized patients (N=84 in 2005 and N=183 in 2014) has increased from 18% to 46% while the resistance to ciprofloxacin has increased from 24% to 58% (Jepsen *et al.*, 1993). Another study shows that 68% of 214 organisms in an Intensive Care Unit of Mauritius were Multi Drug Resistant organisms. Among the MDR organisms, 78% of *Enterobacteriaceae* were ESBL-producers, 86% of *Acinetobacter baumannii* were carbapenem resistant and 30% of the *Enterobacteriaceae* were carbapenem resistant (Nuckchady and Boolaky, 2020b). A recent publication in 2022 stated that an increase in CRE was observed in the ICUs of the public general hospitals of Mauritius, with three small outbreaks of Klebsiella species resistant to carbapenems and colistin in three different NICUs (Basu *et al.*, 2022). Chloramphenicol was the only available susceptible antibiotic with variable prognosis for each NICU (Basu *et al.*, 2022).

In Reunion Island, patients arriving from SWOI islands for medical treatment were screened for Antibiotic resistant bacteria and a high prevalence of carbapenemase-producing *Enterobacteriaceae* was detected from 2010 to 2017 in those patients coming from Mauritius (Holman *et al.*, 2017; Gay *et al.*, 2020).

## National Action Plan on AMR and importance of One Health Approach to tackle AMR

A National Action Plan (NAP) was formulated in 2017 and implemented from 2017 to 2022 (*Republic of Mauritius NAP AMR 2017-2022*, 2017). Several actions have been taken such as registration to Global Antimicrobial Resistance and Use Surveillance System (GLASS) and data entry of AMR on WHONET, amongst others ('GLASS-AMR Module', 2022). However, a lot remains to be done. First, another Action Plan on AMR needs to be formulated from 2024 to 2028. Here also, the World Health Organization (WHO) and World Organization for Animal Health (OIE) plans should be followed (WHO Action Plan AMR, 2015; International Office of Epizootics., 2016). The WHO adopted in May 2015 a Global Action Plan on Antimicrobial Resistance (AMR) with five objectives aimed at reducing the development and spread of antimicrobial resistance (WHO Action Plan AMR, 2015). The OIE also published in November 2016, "The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials", with four objectives (International Office of Epizootics., 2016). In both documents, one of the objectives aims at improving our knowledge through surveillance and research. These are essential tools to understand not only the burden of antibiotic consumption, use and resistance but also the factors affecting them, so that evidence-based recommendations can be formulated in the different sectors. In each country, AMR should be approached using this One Health perspective, which recognizes the interconnectedness of humans, animals, and the environment. The intersectoral committee should include the focal points of the Ministry of Health and Wellness, the Ministry of Agro-Industry and Food Security and the Ministry of Environment, Solid Waste Management and Climate Change and they should work together to formulate and ultimately implement the plan (*Republic of Mauritius NAP AMR 2017-2022*, 2017). Mauritius has its own demographic and cultural background and these should be taken into consideration when formulating the NAP AMR plan as well as other guidelines.

Concerning the implementation of the National Action Plan AMR, the Réseau SEGA of the IOC, the WHO, IOE, FAO and other institutions should be approached to help Mauritius with their expertise and budget to put into practice the AMR activities.



## STATEMENT OF THE PROBLEM

In this thesis, the focus is mainly on antibiotic consumption, use and resistance in Mauritius. It is to be noted that ABR is increasing all over the world. AMR is one of the ten major public health burden globally. Having information on the subject of ABR in the local context will bring out the gaps in the country so that priority actions can be determined.

Mauritius, like other countries, has known a rapid evolution of resistance. Several studies have shown the high prevalence of resistance in the hospitals of Mauritius, suggesting a possible high selection pressure of antibiotics. So far, the actual status on antibiotic consumption and use is not available. Having data on antibiotic consumption and use is crucial to understand the factors contributing to this high rate of resistance in the country. This study looks also at recent resistant data to explore the trend with time.

The planning process has resulted in a number of questions that have been raised regarding a) how to obtain data on antibiotic consumption and use as a means to understand ABR, b) measuring antibiotic consumption in the human and animal sector, c) the antibiotic consumption locally as compared to other countries, d) the antibiotic consumption in the public and private human healthcare institutions, e) the antibiotic consumption by public health institutions in Mauritius, f) antibiotic use in the hospital settings of Mauritius, g) the prevalence of MDR *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* which are priority pathogens according to GLASS-WHO ('GLASS-AMR Module', 2022), h) the prevalence of carbapenem resistant bacteria in public healthcare institutions of Mauritius.

Specifically, these major concerns led us to the following three research questions set in this thesis:

- 1) What is the distribution of antibiotic consumption in the different sectors of Mauritius?  
This was achieved by comparing the consumption of antibiotics in kilograms for human and animal sectors and in Defined Daily Dose (DDD) for the human public and private sectors.
- 2) What is the pattern of antibiotic consumption and use in public healthcare institutions of Mauritius? The consumption of antibiotics by healthcare institutions was

determined as DDD per outpatient and DDD per admission. A point prevalence study was done to explore the distribution of antibiotics in the hospital settings.

- 3) What is the prevalence of Multi Drug Resistant (MDR) and Carbapenem resistant bacteria in the public healthcare institutions on Mauritius? The proportion of *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* sensitive to several antibiotics including carbapenems was determined in the hospital settings. The prevalence of MDR *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* was determined as well as their distribution by ward.

Concerning the usage of antibiotics in hospitals, the major concern is to have more information on the misuses of antibiotics. This will assist the authorities in the setting up and the implementation of an appropriate antibiotic stewardship program in the country.

Moreover, a few studies have stated Mauritius to have a high prevalence of Carbapenem resistant bacteria in hospitalized patients or patients coming from Mauritius. Having more information on the pattern of consumption and use of these last resort antibiotics is important to understand the role of selection pressure and to be able to take suitable actions to reduce the use of these lifesaving medications. Another concern is to obtain data on antibiotic consumption and use which would help in understanding the Mauritian context.

Concerning antibiotic resistance, the AST results of *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in patients with bacteremia are included in the thesis. Those bacteria included in the study, have been identified as priority pathogens by WHO ('GLASS-AMR Module', 2022),. The MDR rate of those priority pathogens will also be determined in the hospital settings to gain an understanding of the problematic of ABR.

The thesis aims at estimating the burden of antibiotic consumption, use and resistance in Mauritius. The results will in turn guide us to formulate evidence-based recommendations and develop strategies in the next National Action Plan on Antimicrobial Resistance 2024-2029 in Mauritius.

## RESULTS

## Section 1. Epidemiology of Antibiotic Consumption and Resistance in Mauritius

### Introduction

This section: **Epidemiology of Antibiotic Consumption and Resistance in Mauritius**, describes the distribution and pattern of antibiotic consumption in the human and animal sector from 2015 to 2017 as well as the AST results of *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* from 2015 to 2023 in the hospital settings of Mauritius.

Antibiotic resistance is a critical global public health problem with the main driver being antibiotic overuse (Goossens *et al.*, 2005; Laxminarayan *et al.*, 2013a; Aslam *et al.*, 2018). The huge amount of antibiotics consumed and the way antibiotics are used contribute greatly to the selection pressure exerted by those medications (Barbosa and Levy, 2000; Goossens *et al.*, 2005; Bell *et al.*, 2014; Oz *et al.*, 2014b). As a result, it is vital to understand the distribution of antibiotic consumption so that evidence-based recommendations can be taken to decrease antibiotic resistance in the country.

The interconnectedness of the human, animal and environment regarding antibiotic resistance has been well-documented in several studies (Robinson *et al.*, 2016; Hernando-Amado *et al.*, 2019; Kim and Cha, 2021; Velazquez-Meza *et al.*, 2022; Cella *et al.*, 2023). It was thus of utmost importance to explore antibiotic consumption in both human and animal sector in the Mauritian context to determine where the main burden of antibiotic lies. This study provides the figures on antibiotic consumption in both sectors.

Moreover, the healthcare system of Mauritius consists of a public and private sector. Having data on antibiotic consumption in 2015 to 2017 will enable the authorities to determine the pattern of antibiotic consumption. It is important to note that no data on antibiotic consumption is available as of date in Mauritius.

The AST pattern of the priority pathogens from 2015 to 2023 will also be explored to obtain recent data on ABR in hospital settings in Mauritius. The trend of the MDR rate of those pathogens will be illustrated during the same time period.

Exploring and comparing data on antibiotic consumption and resistance is a must to tackle antibiotic resistance in Mauritius.

Article: Epidemiology of Antibiotic Consumption and Resistance in Mauritius

The manuscript below was submitted for peer-review in the Frontiers journal. We are awaiting response from the editorial team.

#### Title

Epidemiology of Antibiotic Consumption and Resistance in Mauritius

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#### Abstract

**Introduction:** This study aims at determining the pattern of antibiotic consumption and antibiotic resistance in Mauritius, a tropical island in the Indian Ocean.

**Methodology:** The national antibiotic consumption data from 2015 to 2017 in the human and animal sector was collected from the Pharmacy Board. Antibiotic consumption was measured in kilograms of purchased antibiotics and also in Defined Daily Dose (DDD) in the different health institutions. Data on antibiotic resistance was collected at the Central Health Laboratory (CHL) at Victoria Hospital and at Jeetoo Hospital Laboratory, where Antibiotic Sensitivity Testing is done for all public health institutions. For this study, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolates from

blood samples of patients were included from 2015 to 2023. The proportion of isolates sensitive to antibiotics with (95% Confidence Interval) and prevalence of Multi Drug Resistant (MDR) organisms was calculated.

**Results:** The amount of antibiotics in kilograms distributed to the human sector was between 11000 to 13000 kg as compared to 700 to 1500 kg in the animal sector. The DDD per 1000 inhabitants per day was 20.9, 22.1 and 21.7 in 2015, 2016 and 2017 respectively, with a greater consumption of WATCH and RESERVE group antibiotics in the private sector. The health centers with the highest DDD per 1000 outpatients per day for beta-lactams penicillins and quinolones were in the north of Mauritius. Concerning antibiotic resistance, the prevalence of MDR *E. coli* and *Pseudomonas aeruginosa* isolates ranged from 27% to 41% of total while that of *Klebsiella pneumoniae* and *Acinetobacter baumannii* was between 46% and 62% in the public health institutions of Mauritius. From 2015 to 2023, a decrease in the proportion of above isolates sensitive to third generation cephalosporins and carbapenems was observed in hospitals of Mauritius.

**Conclusion:** This study offers important insights that need to be incorporated into the National Action Plan on Antimicrobial Resistance (AMR) in Mauritius. It illustrates the priority actions concerning antibiotic consumption, use and resistance in the local context and the importance of the One Health perspective in AMR. This information will guide policymakers in taking appropriate actions to tackle the problematic of AMR in Mauritius.

## Keywords

Antibiotic consumption, Human and animal sector, Antibiotic resistance, Multi-drug resistant organisms, Mauritius, tropical island, Epidemiology, Defined Daily Dose

## 1.0 Introduction

The discovery of antibiotics stands as one of the most critical advances in medical history. It has saved countless lives and revolutionized the treatment of infections (1). However, their efficacy is now being threatened due to the misuse and overuse of antibiotics in humans, animals, and plants. Between 2000 and 2015, antibiotic consumption rates worldwide increased by 39%, from 11.3 to 15.7 defined daily doses per 1000 inhabitants per day (DID)

(2). This trend is expected to continue, and the consumption of antibiotics could double by 2030 (2). The same report shows an increase in the consumption of last resort antibiotics such as carbapenems and polymyxins across the world (2). We cannot ignore the implications of this massive selection pressure on bacterial resistance mechanisms. Research reveals that this is causing an acceleration in said mechanisms, rendering antibiotics ineffective (2,3). A few examples of such multi-resistance mechanisms include *Extended Spectrum Beta Lactamase Enterobacteriaceae* (ESBL), *Carbapenem Resistant Enterobacteriaceae* (CRE), and the *mcr-1* gene, all of which is rising at an alarming pace globally (2,4,5,6). This poses a serious challenge to the treatment of infected individuals, as multi-resistant strains require newer and more expensive antibiotics that are often unaffordable in low- and middle-income countries (1). This underscores the urgent need for effective strategies in combating the spread of these resistant mechanisms.

In 2015, the World Health Organization (WHO) developed a global action plan on Antimicrobial Resistance with one of the objectives being to strengthen knowledge through surveillance and research. (7). Surveillance remains an essential component to understand the burden of antibiotic consumption and resistance so that evidence-based recommendations, specific to the country and local context can be formulated. Globally, research should be continued to understand the causes and mechanisms of antibiotic resistance. This will provide further information on consumption of antibiotics and resistance of bacteria and shed light on the complex relationship between them (8,9,10,11,12,13).

The healthcare system in Mauritius is composed of both a public and a private sector. The public sector is divided into primary, secondary, and tertiary healthcare levels, with a total of 141 health centers, two district hospitals, five regional hospitals, and eight specialized hospitals spread throughout the island (14). The five regional hospitals offer both outpatient and inpatient care. The public healthcare system provides free treatment, including medications and laboratory tests (14). The Pharmacy Board oversees the importation of antibiotics entering the country, for both human and animal use while the Central Supply Division, being a sub-branch of the Pharmacy Board, is responsible for the distribution of antibiotics in the public sector only (15). Mauritius has a Pharmacy Act which states that all antibiotics should be given only when a prescription from a registered treating doctor or

veterinarian is presented. (16) So far, there has been no comprehensive analysis of antibiotic consumption and use in Mauritius.

According to the Ministry of Agro-Industry, in 2017, the number of poultry, pigs, small ruminants, cattle and domestic dogs was estimated at 8 million, 20 000, 20 000, 6 000 and 200 000 respectively. The human population was estimated at 1.22 million in 2017 (14).

The Central Health Laboratory at Victoria Hospital and the microbiology laboratory at Jeetoo hospital carry out antibiotic susceptibility testing (AST) on a daily basis on different types of samples sent by hospitals or health centers for the human sector. *Klebsiella* producing ESBL and NDM-1 enzymes have been detected in isolates from Mauritius as well (17,18). Other studies further highlight the growing issue of antibiotic resistance in Mauritius. For instance, between March 2005 to July 2014, the resistance of *Escherichia coli* to cefotaxime in hospitalized patients (N=84 in 2005 and N=183 in 2014) has increased from 18% to 46% while the resistance to ciprofloxacin has increased from 24% to 58% (19, 20). Another study shows that 68% of 214 organisms in an Intensive Care Unit of Mauritius were Multi Drug Resistant organisms, out of which 78% were *ESBL-producing Enterobacteriaceae* (21). Moreover, a study done in Reunion Island revealed high prevalence of CRE in patients coming from Mauritius (22). This study shows that as in different parts of the world, Mauritius also has not been spared the threat of antibiotic resistance.

Mauritius is a tropical island in the middle of the Indian Ocean (23). It is one of the five member countries of the Indian Ocean Commission (IOC) (24). The Communicable Disease Control Unit (CDCU) of the Ministry of Health and Wellness of Mauritius collaborates with the SEGA network, “Surveillance Epidemiologique et Gestion des Alertes” i.e, Epidemiologic Surveillance and Response Unit of the IOC and the French Agricultural Research Centre for International Development (CIRAD) in Reunion towards a One Health approach to antibiotic resistance (24,25). This study aims to determine for the first time in Mauritius, the pattern of antibiotic consumption in different sectors and the prevalence of antibiotic resistance by ward type in the regional hospitals of Mauritius. The findings of this study will help to inform policy decisions and guide the development of effective strategies to combat AMR on the island.



## *2.0 Materials and Methods*

This study is a retrospective descriptive analysis of the consumption patterns of purchased antibiotics in both human and animal sectors of Mauritius, covering the period from January 2015 to December 2017. Additionally, the study also examines the prevalence of antibiotic resistance in the public human sector in 2015, 2016, 2017, 2021 and 2023.

Antibiotic consumption data was obtained from the Pharmacy Board and the Ministry of Agro-Industry. The antibiotics distributed to the health centres and hospitals were provided by the CSD while the antibiotics distributed to the private pharmacies and private farms were obtained via private companies. The Ministry of Agro-Industry provided the data on antibiotics used by them. The data was then collected and analyzed on Microsoft Excel. The total antibiotics distributed to the institutions of the country were calculated in kilograms in both sectors irrespective of route of administration.

Further analysis on antibiotic consumption was done for the human sector. The antibiotics were coded according to the ATC (Anatomical Therapeutic and Chemical) classification on the WHO Collaborating Centre for Drugs Statistics Methodology website (26). The Defined Daily Dose (DDD) indicator was used to measure systemic antibiotics for human consumption (26). Only oral and parenteral antibiotics were included and all topical and drops were excluded in the calculation of the DDD. The DID was determined for antibiotic consumption in both private and public sector of the population. The antibiotics were classified according to the AWARE classification and the proportion of antibiotics used in the ACCESS, WATCH and RESERVE groups was calculated (27).

Moreover, in the public sector, additional indicators were calculated such as the DDD per 1000 outpatients per day and DDD per 1000 admissions per day. The number of outpatients and admissions per institution were obtained from the Mauritius Health Records department (14,28,29). The DDD per 1000 outpatients per day and DDD per 1000 admissions per day were calculated for the health centers, regional hospitals, specialized hospitals and district hospitals. A Point Prevalence Survey on antibiotic use was carried out in three regional hospitals in 2018-2019 and it was found that more than 80% of the admitted patients were given parenteral antibiotics compared to oral (30). Hence, oral antibiotics used at the regional hospitals were allocated to the outpatient department while antibiotics administered via parenteral route were allocated to the inpatients.

Data on antibiotic resistance was collected at the Central Health Laboratory (CHL) at Victoria Hospital and at Dr A.G. Jeetoo Hospital, where AST is done for all public institutions all over the island by the Kirby Bauer disk diffusion method and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints (31). For this study, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolates from blood samples of patients admitted in regional hospitals were included. Data from CHL and Dr A.G. Jeetoo hospital laboratory was collected from 2015, 2016, 2017, 2021 from January to December, which includes data from all five regional hospitals of Mauritius. The data on antibiotic resistance for 2023 was collected from CHL and Dr A.G Jeetoo hospital from January to May 2023, which includes data from 5 regional hospitals of Mauritius. The blood samples were sent by the treating doctors and often formed part of the standard patient care. The data was collected from the record books and analyzed on Epi Info and Microsoft Excel. All duplicates were removed prior to analysis of data.

The proportion of isolates sensitive to antibiotics tested was determined with a confidence interval (CI) of 95%.

If  $p$  = the estimated proportion of sensitivity,

$n$  = the size of the sample

critical value = 1.96 (95% CI)

The confidence interval for a population proportion becomes:

$$\hat{p} \pm (\text{critical value}) \sqrt{\frac{\hat{p}(1 - \hat{p})}{n}}$$

Multi drug resistant (MDR) organisms were those that developed acquired resistance to three or more classes of antibiotics. The Ethics Committee of the Ministry of Health and Wellness of Mauritius gave approval for this study (Ref MHC/CT/NETH/VMLP).

### 3.0 Results

#### 3.1 Antibiotic consumption

##### Total antibiotic consumption in human and animal sector

The total antibiotic consumption ranged from 12000 to 14000 kg from 2015 to 2017, as illustrated in table 1. In the human sector, about 11000 to 13000 kg of antibiotics were used to treat the population of Mauritius which is about 1.22 million inhabitants (14). For the animal

sector, 700 to 1500 kg of antibiotics were used to treat the different animal species which was estimated by the Ministry of Agro-Industry to be about 8 million poultry, 20 000 pigs, 20 000 small ruminants, 6 000 cattle and 200 000 domestic dogs in 2017. In 2017, 7607 kg of penicillins, 1180 kg of quinolones and 765 kg of sulphonamides were consumed in all sectors. In the same year, 339 kg and 80 kg of tetracyclines and 142 kg and 623 kg of sulfonamides were used in the animal and human sector respectively.

As illustrated in table 2, the DID was 20.9, 22.1 and 21.7 in 2015, 2016 and 2017 respectively. In the public sector, the consumption of beta-lactam antibacterial penicillins and the quinolones fell from 2015 to 2017 while that of tetracyclines, sulfonamides, cephalosporins had a general increase. In the private sector, the DID of macrolides, sulfonamides and cephalosporins increased from 2015 to 2017. The DID of tetracyclines, macrolides, lincosamides and streptogramins group and cephalosporins in the private sector was greater than in the public sector.

*Table 1 shows the antibiotic consumption in kg in the human and animal sector of Mauritius from 2015 to 2017*

	Human			Animal			Total		
By Year	2015	2016	2017	2015	2016	2017	2015	2016	2017
Class of antibiotics									
Penicillins	8177	8543	7474	91	102	133	8268	8645	7607
Quinolones	1255	1469	1136	40	37	44	1295	1506	1180
Sulfonamides	581	629	623	211	126	142	792	755	765
Nitroimidazoles	743	910	755	1	1	2	744	911	757
Macrolides	607	741	687	31	21	9	638	762	696
Cephalosporins	660	644	698	4	4	4	664	648	702
Carbapenems	36	40	32	0	0	0	36	40	32
Tetracyclines	86	74	80	1110	469	339	1196	543	419
Aminoglycosides	66	26	18	38	59	27	104	85	45
Glycopeptides	8	13	9	0	0	0	8	13	9
Lincosamides	27	36	32	0	0	0	27	36	32
Amphenicol	9	5	5	0	0	0	9	5	5
Steroid	5	2	2	0	0	0	5	2	2
antibacterial									
Streptogramins	0	1	0	0	0	0	0	1	0
Polymyxin	0	0	0	1	1	0	1	1	0
Total in kg	12234	13098	11517	1527	831	700	13761	13929	12217

# Antibiotic consumption in the human sector

Defined Daily Dose per 1000 inhabitants, outpatients and admissions per day

Table 2 shows the DID by ATC Classification of antibiotics in Mauritius from 2015 to 2017

ATC Classification of antibiotics	Public			private			total		
	2015	2016	2017	2015	2016	2017	2015	2016	2017
J01C Beta-lactam antibacterials, penicillins	9.50	9.42	8.17	2.48	2.46	3.81	11.98	11.88	11.98
<i>J01CA Penicillins with extended spectrum</i>	7.20	6.95	5.63	1.05	1.05	1.24	8.25	8.00	6.87
<i>J01CR Combinations of penicillins</i>	1.14	1.37	1.32	1.37	1.24	2.54	2.51	2.61	3.86
<i>J01CF Beta-lactamase resistant penicillins</i>	1.16	1.10	1.22	0.06	0.17	0.03	1.22	1.27	1.25
J01M Quinolone antibacterials	2.19	1.85	1.77	0.87	1.81	1.02	3.06	3.66	2.79
<i>(J01 MA Fluoroquinolones)</i>									
J01F Macrolides, lincosamides and streptogramins	1.11	1.31	1.21	1.23	1.83	1.91	2.34	3.14	3.12
J01A Tetracyclines	0.28	0.30	0.36	1.04	0.94	1.07	1.32	1.24	1.43
J01E Sulfonamides and trimethoprim	0.29	0.30	0.31	0.01	0.01	0.04	0.30	0.31	0.35
J01D Other beta-lactam antibacterials	0.30	0.29	0.31	1.02	1.10	1.46	1.32	1.39	1.77
<i>J01DB/C/D Other beta-lactam antibacterials-cephalosporins*</i>	0.28	0.27	0.30	1.01	1.09	1.45	1.29	1.36	1.75
<i>J01DH Other beta-lactam antibacterials-carbapenems</i>	0.02	0.02	0.01	0.01	0.01	0.01	0.03	0.03	0.02
J01G Aminoglycosides	0.04	0.04	0.05	0.15	0.03	0.06	0.14	0.07	0.11
J01X Other antibacterials	0.10	0.20	0.10	0.24	0.20	0.03	0.30	0.40	0.10
Total DID	13.81	13.71	12.28	7.04	8.38	9.40	20.85	22.09	21.68

\*Only first, second and third generation cephalosporins

Figure 1 shows the proportion of antibiotics classified by the AWARE category in the public and private sector from 2015 to 2017 in Mauritius

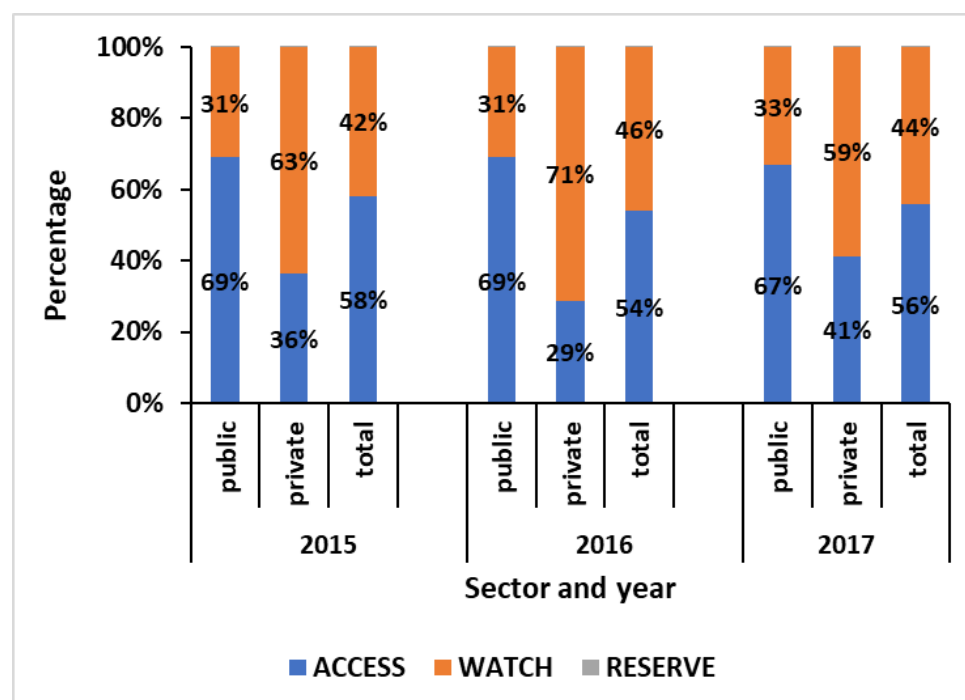


Figure 2 shows the average DDD per 1000 outpatients per day by class of antibiotics administered via oral route in primary health centers, regional hospitals, specialized Hospitals and district hospitals in Mauritius from 2015 to 2017

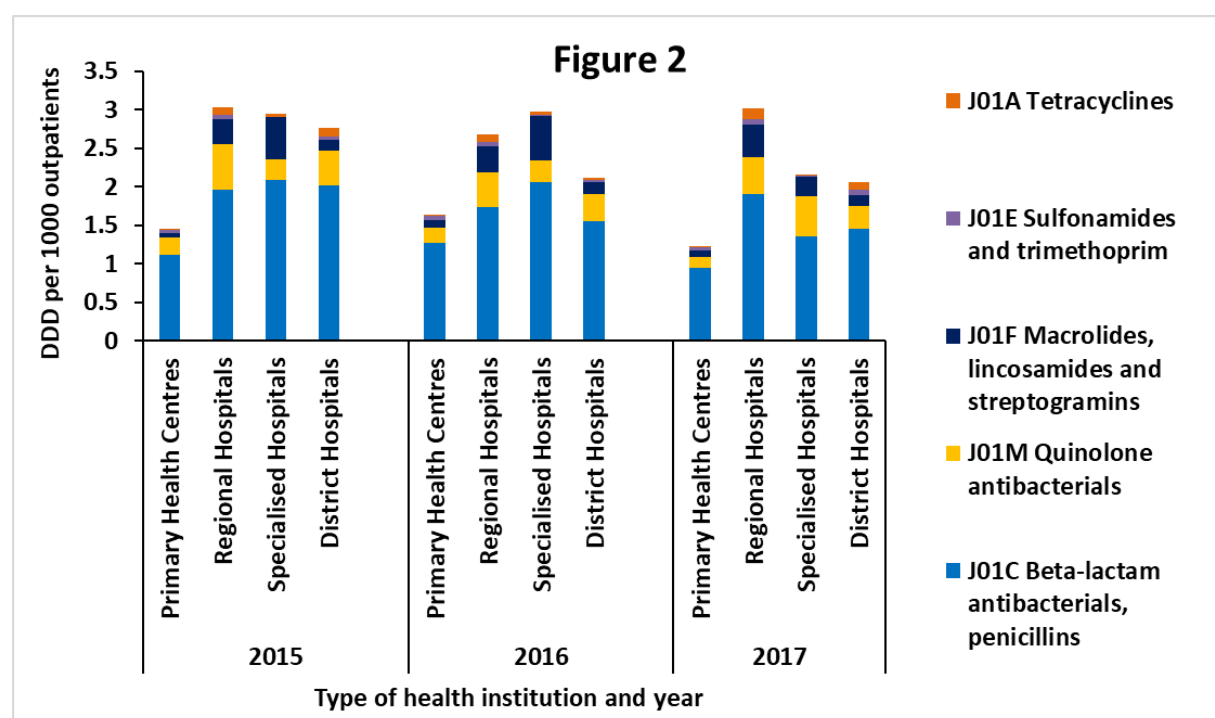


Figure 3 shows the average DDD per 1000 admissions per day for antibiotics administered via parenteral route in regional hospitals, specialized hospitals and district hospitals in Mauritius from 2015 to 2017

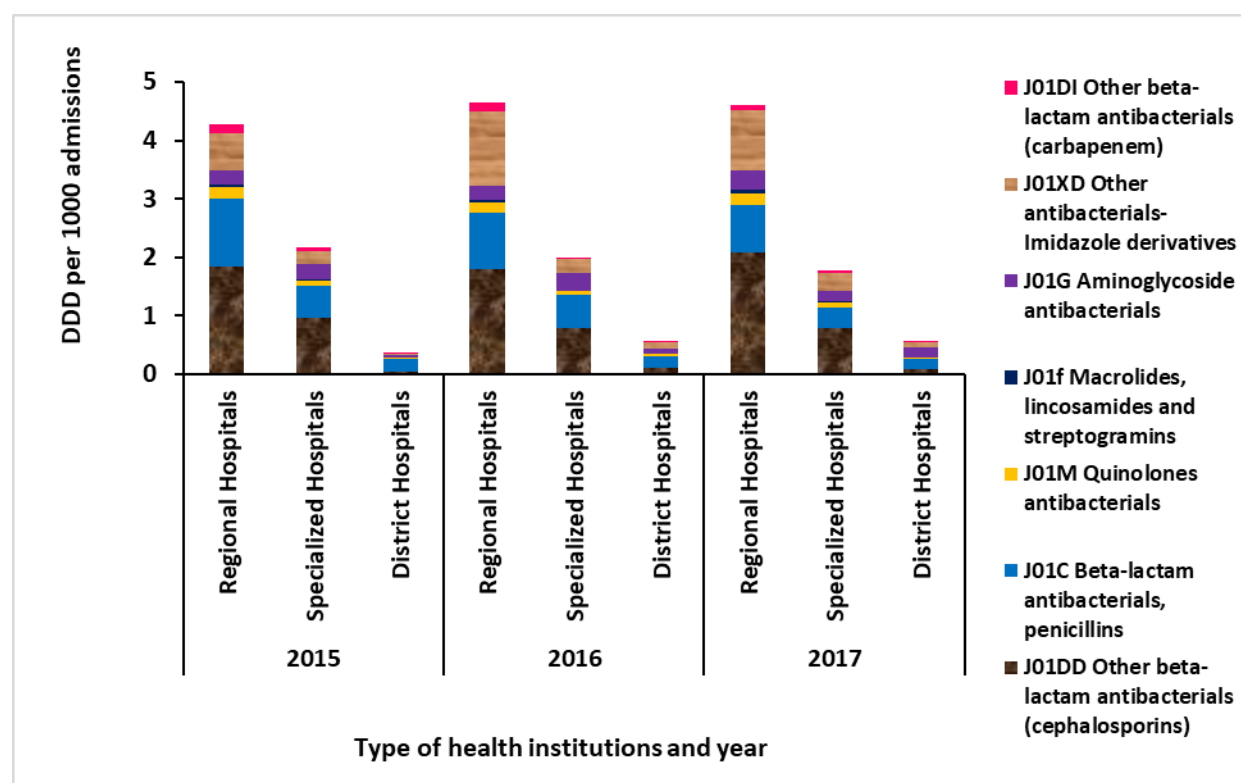


Figure 1 shows the proportion of antibiotics classified according to the AWARE group of antibiotics. It shows that in the public health sector, the proportion of ACCESS and WATCH antibiotics used were 67-69% and 31-33% respectively. On the other hand, in the private health sector, a higher range of 59-71% of WATCH antibiotics were used.

Among the outpatients, penicillins were the most commonly used antibiotic in all institutions, followed by quinolones and macrolides, lincosamides and streptogramins group, as shown in figure 2.

Among the inpatients in figure 3, the other beta-lactam antibacterials cephalosporins were the most frequently used antibiotic followed by penicillins and imidazole derivatives. The DDD per 1000 admissions per day of the carbapenem group was less than 0.01 in all institutions in figure 3 and no parenteral antibiotics are given in primary health care centers.

Among the 25 primary health centers with the highest DDD per 1000 outpatients per day for penicillins in 2017, 15 health centers were found in the north and northwest regions of the island, 5 health centers in south west region of Mauritius and 5 health centers were distributed in the east

and south east of the island. Among the 25 primary health centers with the highest DDD per 1000 outpatients per day for fluoroquinolones in 2017, a total of 16 centers were found in the north and north west regions of the country, 4 health centers in the south west region of Mauritius and 5 health centers in the east and south east of the island. The primary health centers in the north and north west regions had the highest DDD per 1000 outpatients per day for beta-lactams penicillins and quinolones.



### 3.2 Antibiotic Resistance in the hospitals of Mauritius

Table 3 shows the proportion with 95% Confidence Interval of *E. coli*, *Klebsiella* species, *Acinetobacter* and *Pseudomonas* specimens sensitive to the listed antibiotics isolated in blood cultures collected from the regional hospitals from 2015 to 2023 in Mauritius

	Year (number of samples)	Proportion of isolates sensitive (with 95% Confidence Interval)							
		Cotrimoxazole	Coamoxiclav	Ciprofloxacin	Gentamycin	Piperacillin/ tazobactam	Meropenem	Ceftriaxone	Colistin
<i>Escherichia coli</i>	2015 (n=248)	48% (41-54)	42% (36-48)	40% (34-46)	68% (62-74)	88% (84-92)	98% (96-100)	55% (49-61)	100% (99-100)
	2016 (n=277)	52% (46-57)	40% (34-46)	41% (36-47)	61% (55-67)	85% (81-89)	96% (94-99)	48% (43-54)	100% (100-100)
	2017 (n=347)	49% (43-54)	40% (34-45)	48% (42-53)	64% (59-69)	82% (78-86)	96% (94-98)	46% (41-52)	100% (100-100)
	2021 (n=317) &	48% (43-53)	-	49% (43-55)	-	-	97% (95-99)	45% (40-50)	98% (96-100)
	2023(n=153) *&	56% (48-64)	28% (21-35)	33% (26-40)	74% (67-81)	-	94% (90-98)	39% (31-47)	99% (97-101)
<i>Klebsiella pneumoniae</i>	2015 (n=271)	44% (38-50)	35% (29-40)	42% (36-48)	48% (42-54)	68% (63-74)	83% (78-87)	37% (31-42)	100% (99-100)
	2016 (n=207)	38% (31-44)	23% (17-28)	32% (26-38)	42% (35-49)	59% (52-66)	82% (77-88)	26% (20-32)	99% (97- 100)
	2017 (n=243)	47% (41-53)	38% (32-44)	50% (44-56)	59% (53-65)	72% (67-78)	87% (83-91)	38% (32-44)	100% (100-100)
	2021 (n=245) &	35% (29-41)	-	42% (36-48)	-	-	65% (59-71)	27% (21-33)	93% (90-96)
	2023(n=103) *&	32% (23-41)	23% (15-31)	30% (21-39)	45% (35-55)	-	53% (43-63)	22% (14-30)	100% (100-100)
<i>Acinetobacter baumannii</i>	2015 (n=154)	46% (38-54)	-	32% (25-40)	36% (29-44)	35% (28-43)	45% (37-53)	-	99% (98-101)
	2016 (n=194)	46% (39-53)	-	35% (29-42)	39% (33-46)	35% (29-42)	47% (40-54)	-	99% (98-100)
	2017 (n=190)	43% (36-51)	-	38% (31-45)	41% (34-48)	41% (34-48)	47% (40-54)	-	100% (100-100)
	2021 (n=258) &	--	-	--	28% (23-33)	-	25% (20-30)	-	97% (95-99)
	2023 (n=99) *&	34% (25-43)	-	23% (15-31)	29% (20-38)	-	28% (19-37)	-	98% (95-100)
<i>Pseudomonas aeruginosa</i>	2015 (n=63)	-	-	66% (54-77)	56% (44-69)	78% (68-88)	63% (51-74)	-	100% (100-100)
	2016) n=89)	-	-	52% (41-62)	52% (41-62)	67% (58-77)	52% (41-62)	-	99% (97-101)
	2017 (n=82) &	-	-	64% (53-74)	67% (57-78)	72% (63-82)	67% (57-78)	-	99% (96-101)
	2023 (n=55) *&	-	-	51% (38-64)	51% (38-64)	55% (42-68)	47% (34-60)	-	96% (91-101)

\*= Data for 2023 are from January to May 2023 compared to data collected from 2015, 2016, 2017 and 2021 years, where data are from January to December in five regional hospitals.

&= According to CLSI 2017, AST findings for colistin should be reported as resistant or intermediate. However, in this study, for comparison purposes, the intermediate isolates for colistin were labelled as sensitive

Table 3 shows that the proportion of *E. coli*, *Klebsiella pneumoniae* and *Acinetobacter baumannii* sensitive for cotrimoxazole, co-amoxiclav, ciprofloxacin and ceftriaxone were on average below 56%. Moreover, the proportion of above isolates susceptible to meropenem, ceftriaxone and ciprofloxacin was seen to decrease from 2015 to 2023. The proportion of *E.coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* sensitive to meropenem decreased from 2015 to 2023, from 98% to 94%, 83% to 53%, 45% to 28% and 63% to 47% respectively. From 2015 to 2023, the proportion of *E.coli* and *K.pneumoniae* sensitive to ceftriaxone decreased from 55% to 39% and from 37% to 22% respectively.

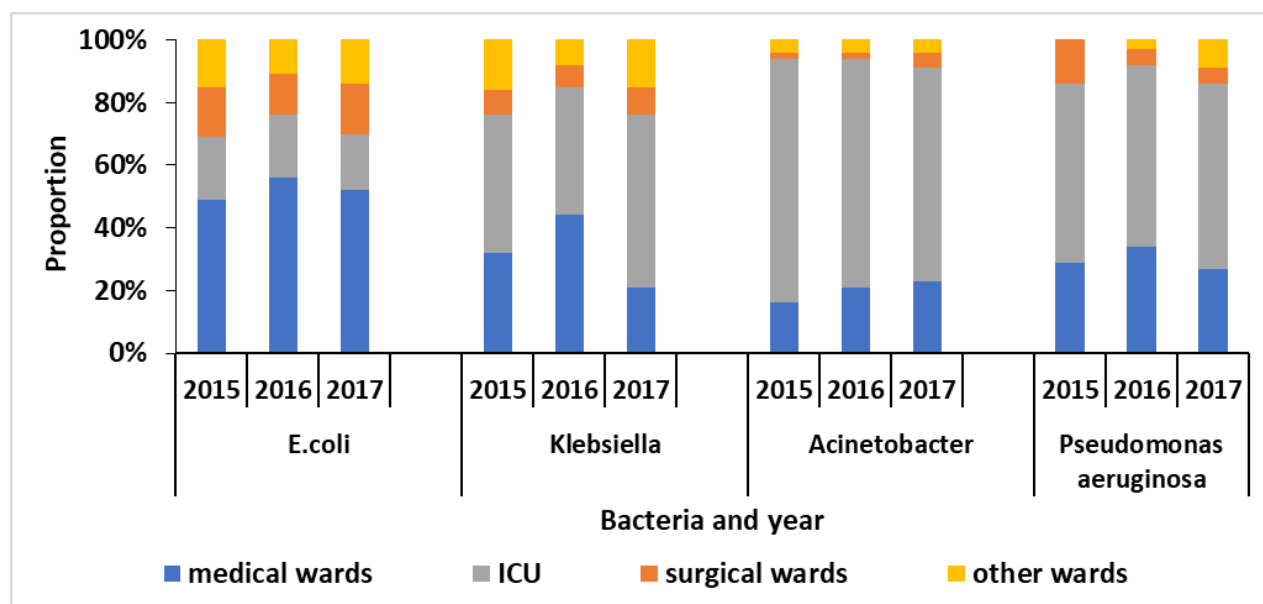
No seasonal trend was observed in the trend of ABR in Mauritius from January to December.

Additionally, it was found that more than 50% of the meropenem resistant species were isolated in the Intensive Care Units of the regional hospitals.

The MDR *E. coli* represented 35%, 40%, 41% and 41% of the total *E. coli* isolates in 2015, 2016, 2017 and 2023 respectively. The MDR *Klebsiella pneumoniae* represented 47%, 56%, 46 % and 60% of the total *Klebsiella* isolates in 2015, 2016, 2017 and 2023 respectively. The MDR *Acinetobacter baumannii* represented 58%, 53%, 56% and 74% of the total *Acinetobacter baumannii* isolates in 2015, 2016, 2017 and 2023 respectively. The MDR *Pseudomonas aeruginosa* represented 33%, 27%, 27% and 45% of the total *Pseudomonas aeruginosa* isolates in 2015, 2016, 2017 and 2023 respectively. It is to be observed that 60% of MDR *Klebsiella pneumoniae* and 62 % of the MDR *Acinetobacter baumannii* were found in the hospital situated in the northwest of the island.

About 40-50% of the MDR *Klebsiella pneumoniae*, 60-80% of MDR *Acinetobacter baumannii* and 50-60% of *Pseudomonas aeruginosa* were identified in ICU of the regional hospitals of Mauritius as illustrated in figure 4.

Figure 4 shows the proportion of multidrug resistant *E.coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolated in the ward type from 2015 to 2017 in the hospitals of Mauritius.



#### 4.0 Discussion

This study provides vital data on the consumption of antibiotics in the human and animal health sector along with antibiotic resistance in the public health institutions of Mauritius from 2015 to 2017. While studies on antibiotic use have been done before in the country, antibiotic consumption is being explored for the first time in Mauritius.

The results provide insights into the Mauritian context, where most of the antibiotic selection pressure is concentrated in human healthcare institutions. The data indicates that between 2015 to 2017, approximately 11,000 to 13,000 kg of antibiotics were used in the human sector, which serves a population of 1.22 million. In contrast, a smaller amount of 700 to 1500 kg of antibiotics was used in the animal sector, which consists of a population estimate of 8 million poultry, 20 000 pigs, 20 000 small ruminants, 6 000 cattle and 200 000 domestic dogs. This higher consumption of antibiotics in the human sector in Mauritius differs from several countries where antimicrobials in the animal health sector largely exceeds that used in human medicine (32, 33). In France, 760 tonnes of antibiotics were used in the human sector while 1320 tonnes were used in animals in 2005 (33). While the Population Correction Unit and the DDD are important indicators for monitoring antibiotic consumption in the human and animal health respectively, illustrating the data in kilograms or tonnes allows comparison of antibiotic consumption in the two sectors (34).

The findings underline the importance of implementing a One Health national surveillance system to gain a comprehensive understanding of the local context. Establishing an antibiotic stewardship program for human medicine, would therefore be expected to be an effective means of reducing antibiotic consumption and resistance in the country.

The data on antibiotic consumption in the animal sector also shows a decrease from 1527 kg to 700 kg from 2015 to 2017. These figures suggest that during the writing of the NAP on AMR in 2016, measures had already been taken to decrease antibiotic consumption by the Ministry of Agro-Industry of Mauritius. Moreover, it is important to note that colistin, an antibiotic in the RESERVE category is sparingly used in the animal sector.

The consumption of antibiotics in terms of DID in Mauritius for both public and private sector was 20.9 in 2015, 22.1 in 2016 and 21.7 in 2017. The results suggest that while there is room for improvement, the DID in Mauritius is not excessively high. Among the countries in the European region, the DID in Mauritius is comparable to the United Kingdom (DID 20.1) but lower than several countries such as Greece (DID 36.1) France (DID 29.9), and Italy (DID 27.5) (35). In the African region, the DID in Mauritius is lower than the United Republic of Tanzania (DID 27.3) but higher than Burkina Faso (DID 13.8) (36). In Asia, the DID in India (DID 16) in 2012 and China (DID 17.4) in 2015 was surprisingly lower compared to that of Mauritius (37,38). However, it is important to interpret the data with caution as the DID reflects the national average and the population of Mauritius has a greater access to free healthcare compared to India and China. Data from subsequent years must be collected to identify a clear trend of DID in Mauritius.

Another important point is the higher DID of other beta lactams (cephalosporins, carbapenems and monobactams) in India (DID 2.6) in 2012 and Europe (DID 2.0) in 2017 compared to Mauritius (DID 1.8) in 2017 (35,37). Monitoring the consumption of the WATCH and RESERVE group of antibiotics is crucial to be able to preserve them (27). In Mauritius, the higher consumption of the WATCH antibiotics in the private sector compared to that of the public sector is of concern (27). The greater DID of antibiotics in the WATCH category, such as macrolides, lincosamides and streptogramins group, tetracyclines and cephalosporins was higher in the private sector than in the public. These findings are important, especially as the public sector caters for about 73% of healthcare needs of the population, according to a report on the pharmaceutical industry in Mauritius (15). Hence, the greater proportion of WATCH and RESERVE category of antibiotics are being used to treat only 27

% of patients in the private (27). An explanation for this might be the prescribing pattern of the private doctor who wants to meet their patients' expectations (40). Also, though a Pharmacy Act prohibiting the sale of antibiotics without prescription exists, its implementation in the country should be properly monitored to avoid over-the-counter sales in private pharmacies (16). Till date, in Mauritius, most efforts in tackling AMR have been concentrated in the public hospitals. The results show that the private sector should be considered as well during the awareness programs on AMR and an antibiotic use survey should be carried out regularly to obtain more information on the prescribing practices. This shift to the WATCH and RESERVE category of antibiotics has been observed in other countries as well and might be due to an increasing number of pathogens being resistant to the ACCESS group of antibiotics (2).

The health centers having the highest DDD per 1000 outpatients per day for penicillins and quinolones, the most used antibiotics, are in the north and northwest regions of the country. Concerning antibiotic resistance data, 60% of MDR *Klebsiella pneumoniae* and 62 % of the MDR *Acinetobacter baumannii* were found in the hospital situated in the northwest of the island. Possible reasons include the prescribing pattern of the doctors, the patients requesting more antibiotics or a higher number of infections in these regions. Additional studies need to be done to determine the actual cause of this higher antibiotic consumption and resistance in those regions. Mauritius, like all countries, has a limited budget and limited skilled human resources. Therefore, using this approach to identify the regions with the highest DDD and resistance is important for national monitoring. Consequently, appropriate measures such as awareness campaigns can be initiated in the identified regions for both doctors and patients, to reduce overuse and misuse of antibiotics. It is therefore a key strategy in the country to monitor and evaluate the progress of antibiotic consumption and resistance on the island (14,28,29).

In all institutions of the public sector, the DDD per 1000 outpatients per day showed a very high DDD for penicillins, followed by quinolones and macrolides, lincosamides and streptogramins group of antibiotics. Patients with severe symptoms, diseases and complications have a higher tendency to go to the outpatient departments of regional and specialized hospitals, accounting for the higher DDD per 1000 outpatients and proportion of macrolides and tetracyclines consumed in hospitals compared to primary healthcare level.

Concerning the DDD per 1000 admissions per day, the other beta-lactam antibacterials, cephalosporins had the highest DDD followed by penicillins and imidazole derivatives. Similar data have been observed in the different WHO regions (36).

In Mauritius, the DDD per 1000 admissions in the regional hospitals was higher than in the specialized hospitals of Mauritius. The reason may be due to the inclusion of Brown Sequard Mental Hospital which has a low antibiotic consumption and Subramanian Eye Hospital which uses mostly antibiotics in eye drops form, among the specialized hospitals.

According to the ECDC report on antimicrobial consumption, in 2017 the average consumption of carbapenems in the hospitals of Europe was 0.06 DID and ranged from 0.02 to 0.17 (35). Compared to the European countries, the DID of carbapenem in Mauritius (0.02-0.03) are lower. However, looking at the AST data in Mauritius, the proportion of patients infected with *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* species that were sensitive to meropenem were between 60-90%, 25-47% and 50-67% respectively. In Europe, the average resistance of *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, to carbapenem was 8.1%, 37.6% and 18.9% respectively (40). It is important to note while interpreting the data that in Europe, all isolates detected in blood and cerebrospinal fluids were included in the data above while for this study in Mauritius, only data of bacteria from blood samples was collected and analyzed.

Another alarming finding is the proportion of isolates susceptible to meropenem, ceftriaxone and ciprofloxacin was seen to decrease from 2015 to 2023. The proportion of *E.coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* sensitive to meropenem decreased from 2015 to 2023, from 98% to 94%, 83% to 53%, 45% to 28% and 63% to 47% respectively. From 2015 to 2023, the proportion of *E.coli* and *K.pneumoniae* sensitive to ceftriaxone decreased from 55% to 39% and from 37% to 22% respectively. This increase in resistance of *E.coli* and *K.pneumoniae* to carbapenems has been observed on average in the countries of Europe as well according to the ECDC report 2021. This increase in resistance to the last resort antibiotics is alarming as this decreases the treatment options available for sick patients, who may go into multi organ failure, develop complications, and die. The situation is hence critical, and it is urgent for the authorities to take urgent actions to address this issue.

Moreover, the results showed that more than 50% of the meropenem resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii* were isolated in the Intensive Care Units of the regional hospitals of Mauritius. Another study done in 2020 in the ICU of one hospital showed a similarly high prevalence (21). It was observed that those carbapenem resistant organisms led to an increase in antibiotic use and prolonged hospital stay (21). However, although more than 50% of the carbapenem-resistant strains were identified in the ICU, the other 50% were detected in the remaining wards of the hospital, it is hence important to take appropriate measures as the reinforcement of Infection and Prevention Control measures to prevent the spread.

A study done in Reunion Island shows a high CRE carriage rate in patients coming from Mauritius for medical treatment. (22). The high CRE incidence detected can be due to the severity of the patients' illness requiring carbapenems while they were treated in Mauritius. Mauritius having a free healthcare system and access to carbapenems can provide the necessary medications to the patients. Another reason is the high flux of tourists coming to Mauritius for holidays and patients going abroad for medical treatment each year (41, 42). In 2019, there were 1.8 million arrivals among whom 1.4 were non-Mauritian citizens (43). These persons might be asymptomatic carriers of CRE, and they can in turn spread the resistant bacteria in Mauritius (44, 45,46). Since the consumption and use of carbapenems is found to be low in the country, it is vital to carry out surveys and studies to determine the cause of this high CRE rate in the hospitals of Mauritius. As for example, studies should be carried out on the effect of travel on the microbiome in persons coming from abroad.

The proportion of MDR strains in Mauritius was compared with that of the European Centre for Disease Prevention and Control report 2017 (ECDC) as well as that of India (2014) and Malawi (2016) (41, 47,48). The proportion of MDR *Klebsiella pneumoniae* was found to be 50-60% of the isolated bacteria in Mauritius against 15.5% in Europe, 44% in India and 92% in Malawi. The proportion of MDR *Acinetobacter* species was found to be 50-60% of the isolated bacteria in Mauritius against 43.2% in Europe and 89% in India. Also, the proportion of MDR *E. coli* was 25-41% in Mauritius, 7.3% in Europe, 9% in India and 69% in Malawi. Concerning MDR *Pseudomonas aeruginosa* isolates, the proportion was 25-41% in Mauritius, 4% in Europe and 30% in Malawi (41). The MDR rates in Mauritius are comparable to that of India and Malawi but high compared to Europe. The choice of samples in Europe might explain the above data as the samples collected in the ECDC report included cerebrospinal fluid along with blood while for this study in Mauritius,

only blood samples were included (41). Additional studies should be done to follow the trend of MDR bacteria and determine the mortality rate due to AMR in the hospitals of Mauritius.

However, it is vital to note that from 2015 to 2023, the proportion of MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa* has further increased from 58% to 74% and from 33% to 45% respectively. Some reasons explaining this increasing MDR and high prevalence of resistance can be poor infection prevention control in the hospitals, the misuse of antibiotics, non-adherence to the dose of antibiotics as prescribed by the treating doctor, importation of animals with resistant bacteria, the high flux of tourists in the country or the choice of patients in whom blood culture was done.

The first limitation of the study is that the amount of antibiotics expired, thrown away and not used by the patients or healthcare staff is not known. While the pharmacists and dispensers are of the opinion that the amount expired or thrown away by them is negligible, we have no data on the total amount of purchased antibiotics by patients. Some interviews with patients revealed that the antibiotics were taken only for a few days till the recovery of patients. The whole course was not taken. This information is vital when interpreting the data on antibiotic consumption.

Another limitation is that resistance data for only four pathogens isolated in blood culture in the public hospitals were collected in this study because data on resistance had to be retrieved manually from the register. It would have been interesting to have more details on the resistance pattern of other microorganisms, from various samples including the private sector. In 2023, data on ABR only included January to May 2023, while data in 2015, 2016, 2017 and 2021 was from January to December. However, no seasonal trend in ABR was observed during the years 2015 to 2021.

A last limitation is the lack of data in the animal sector on antibiotic consumption by species and live weight so that the PCU can be calculated as well as data on antibiotic resistance in farms (48).

Several studies have acknowledged the link between antibiotic consumption and resistance, while others are still investigating the different factors causing the emergence and spread of antibiotic resistance across the world (3,8,9,10,11,12,13, 21, 44, 45,46).

Just as with the COVID-19 outbreak, no one is safe until everyone is safe. Indeed, drug-resistant organisms do not respect national borders; they can affect people of any race, gender or color, as



well as animals. Addressing this issue requires global cooperation and each country should make antimicrobial resistance a top priority in their agenda. In order to understand the burden of antibiotic consumption and resistance, an electronic surveillance is essential. Additionally, implementing antibiotic stewardship programs in the human and animal sector is crucial for responsible antibiotic use and prescription. In the animal sector, a study on farm animals has been undertaken to assess the presence of MDR bacteria in Mauritius (49). Moreover, a One Health committee has been established, bringing together the Ministry of Health and Wellness, the Ministry of Agro-Industry and partners including the SEGA network of the Indian Ocean Commission to address AMR in the country. This committee facilitates information sharing and guides the policy makers make informed decisions to tackle antibiotic resistance across all relevant sectors.

### Conclusion

This study provides valuable insights that should be taken into consideration when implementing the National Action Plan on AMR in Mauritius. The findings suggest that the consumption of antibiotics in human medicine is considerably higher than in animals, there is a higher consumption of antibiotics belonging to the WATCH and RESERVE categories in the private healthcare sector, and more urgently, a decrease in susceptibility of *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* to the several WATCH and RESERVE antibiotics from 2015 to 2023. Moreover, the study highlights a high prevalence of carbapenem-resistant bacteria across various hospital wards, and not just in ICU. It is imperative to establish a national surveillance system for monitoring antibiotic consumption and resistance using a One Health approach. This comprehensive approach is key to understand the burden of AMR in Mauritius, enabling policymakers to implement effective strategies to address this threat.

## Abbreviations

AMC	Antibiotic Consumption
AMR	Antibiotic Resistance
AST	Antibiotic Susceptibility Testing
ATC	Anatomical Therapeutic and Chemical
CDCU	Communicable Disease Control Unit
CHL	Central Health Laboratory
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
DDD	Defined Daily Dose
DID	Defined Daily Dose per 1000 inhabitants per day
ECDC	European Centre for Disease Prevention and Control
ICU	Intensive Care Units
IOC	Indian Ocean Commission
MDR	Multi Drug Resistant
PCU	Population Correction Unit
SEGA	« Surveillance Epidemiologique et Gestion des Alertes” (french)

## Figure Captions

Figure 1: The Proportion of antibiotics classified by the AWARE category in the public and private sector from 2015 to 2017 in Mauritius

Figure 2: The average DDD per 1000 outpatients per day by class of antibiotics administered via oral route in primary health centers, regional hospitals, specialized hospitals and district hospitals in Mauritius from 2015 to 2017

Figure 3: The average DDD per 1000 admissions per day for antibiotics administered via parenteral route in regional hospitals, specialized hospitals and district hospitals in Mauritius from 2015 to 2017

Figure 4: The proportion of multidrug resistant *E.coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in the different ward types from 2015 to 2017 in the hospitals of Mauritius

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#### Conflict of interest

The study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Conclusion

This study illustrates for the first time the distribution of antibiotic consumption in human and animal sector. It is noted with great interest that contrary to the global distribution, the consumption of antibiotics in the human sector in Mauritius contribute 10 times more to the selection pressure and to the emergence of resistance compared to the animal sector. Moreover, the DID of antibiotics, including that of the last resort antibiotics was not high compared to other countries in Africa and Europe. Another interesting finding was the high consumption of WATCH antibiotics in the human private sector.

Concerning antibiotic resistance, a decrease in proportion of *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* susceptible to the WATCH and RESERVE antibiotics from 2015 to 2023 was observed. Additionally, an increasing prevalence of MDR *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* were observed in the hospitals of Mauritius from 2015 to 2023. This trend is alarming as it limits the treatment options of patients with septicemia. A large proportion of MDR *Escherichia coli*, *Klebsiella pneumoniae* was detected in other wards, apart from the ICU. Although 50 % of carbapenem- resistant bacteria were isolated in the ICU, the rest were detected in non-ICU wards.

This study offers valuable insights that need to be incorporated into the National Action Plan on AMR in Mauritius. It illustrates important information and gaps that need to be addressed. Moreover, it enables the authorities to determine the priority actions as ensuring the development and implementation of antibiotic stewardship programme in public hospitals as well as the private sector and ensuring the implementation of the Pharmacy Act in the retail pharmacies which prevent over-the-counter sales of antibiotics. Moreover, there is a need for establishing a national surveillance system for antibiotic consumption and resistance using a One Health approach in the country, which is key to understand the burden of AMR in Mauritius.

## Section 2: Point Prevalence Study on antibiotic use in the hospitals of Mauritius

### Introduction

It is with great interest, that we note in the previous article, the greater burden of antibiotic consumption in the human sector and that the DID in Mauritius is not considerably high compared to other countries. In view of the alarming decreasing pattern of susceptibility of those priority pathogens and the high prevalence of MDR strains in the hospitals of Mauritius, it is important to identify the drivers of antibiotic resistance in Mauritius. It is largely recognized that the factors contributing to resistance is the overuse and misuse of antibiotics and the way antibiotics are used (Barbosa and Levy, 2000; Julian and Dorothy, 2010; Oz *et al.*, 2014b) Since the greatest burden is in the human sector, we decided to explore antibiotic use in the hospital settings, where a higher proportion of WATCH and RESERVE antibiotics are consumed as compared to the health centers .

Consequently, a point prevalence study on antibiotic use was done in three regional/ secondary hospitals of Mauritius. This survey aimed at determining:

- 1) the antibiotic prescribing pattern in the hospitals of Mauritius, including the category and class of antibiotics used, the misuses of antibiotics, amongst others,
- 2) the diseases and indications for which antibiotics were prescribed,
- 3) the importance of several factors as the comparison of antibiotic use between different regions, administration route of antibiotics, presence of invasive devices as well as whether AST was done before treatment with antibiotics, to explore any link with an increase in antibiotic use.

The answer to these queries were the subject of section 2: **Point Prevalence Study on antibiotic use in the hospitals of Mauritius.**

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# Point prevalence survey on antibiotic use in the hospitals of Mauritius

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**Background:** This study aims at determining the antibiotic prescribing pattern  
in admitted patients in the regional public hospitals of Mauritius.

**Methods:** A Point Prevalence Survey (PPS) on antibiotic use according to the World  
Health Organization Methodology for PPS on antibiotic use in hospitals, was carried  
out in 3 secondary public hospitals. Data was collected in February 2018 for Hospital  
1 and in April-May 2019 for Hospital 2 and Hospital 3. Eligible inpatients were those  
who were hospitalized in the ward at 8.00 a.m. on the day of the survey.

**Results:** Among 915 inpatients, 482 (53%) were treated with 753 therapies or  
prescriptions of antibiotics, averaging 1.6 therapies or prescriptions per patient.  
Among those treated with antibiotics, an average of 88 patients (55%), 58  
patients (36%) and 15 patients (9%) were given 1, 2 and 3 or more antibiotics  
respectively. The highest proportion of inpatients treated with antibiotics was  
among those with community acquired infections (n=243, 50%) followed by  
surgical prophylaxis (n=191, 40%). In the three hospitals, it was observed that  
third generation cephalosporins (ceftriaxone, cefotaxime), amoxicillin,  
metronidazole (parenteral) and ciprofloxacin accounted for more than 75%  
of total prescriptions and sixteen per cent (16%) of patients had an Antibiotic  
Susceptibility Testing report before prescription of antibiotics.

**Conclusion:** This study provides valuable information on antibiotic use in the  
country. Several misuses have been identified such as the excessive use of  
antibiotics for surgical prophylaxis, the high use of third generation  
cephalosporins and of the WATCH category of antibiotics. It also  
demonstrates a low percentage of Antibiotic Susceptibility Testing prior to  
prescription of antibiotics. This investigation shows that there is now a pressing  
need to repeat the Point Prevalence Survey on antibiotic use in hospitals in  
future whilst extending the survey to the private healthcare system to get a  
complete picture concerning antibiotic use in Mauritius.

## KEYWORDS

point prevalence survey, antibiotic use, hospitals, epidemiology, Mauritius



## 1 Introduction

Antimicrobial resistance (AMR) has today become a matter of global concern. It has been proclaimed by the World Health Organization (WHO), as one of the top 10 global public health threats (World Health Organisation Antimicrobial Resistance, 2021). In May 2015, during the Sixty-Eighth World Health Assembly, the global action plan on antimicrobial resistance was adopted (World Health Organisation, 2015a). One of the five objectives of the plan is to optimize the use of antimicrobial medicines (World Health Organisation, 2015b).

One of the main drivers of AMR is the misuse of antimicrobials. Inappropriate use of antibiotics is indeed, accelerating the development of new resistance mechanisms throughout the globe, threatening our ability to treat common infectious diseases and hence, resulting in expensive and prolonged healthcare and sometimes disability or even death (World Health Organisation Antimicrobial Resistance, 2021). The link between antibiotic resistance and use has been documented in several studies in different countries (Ballow and Schentag, 1992; Melo Cristino, 1999; Kaye et al., 2000; Goossens et al., 2005). Tracking antibiotic use patterns in one's country is therefore essential to optimize antibiotic prescribing and eventually reduce antibiotic resistance in the country.

The tropical island of Mauritius is a multi-ethnic society with a population of 1.22 million (Ministry of Health and Wellness, 2018a). The Mauritius healthcare system consists of a public and a private sector. The public sector in Mauritius comprises a primary healthcare level which consists of 141 health centers, a secondary healthcare level which consists of five regional hospitals, and a tertiary healthcare level which consists of eight specialized hospitals. The public health sector of Mauritius is completely free of charge.

Concerning the distribution of antibiotics in the public sector, medications are distributed to the different hospitals and health centers of Mauritius and given freely to patients when they present themselves at the government pharmacy with a prescription from the treating doctor. Antibiotic resistance data from the Central Health Laboratory shows that resistance in hospitalized patients of *E. coli* to cefotaxime had drastically increased from 18% to 46% and resistance to ciprofloxacin from 24% to 58% from 2005 to 2014 (Issack et al., 2007). Another study carried out in the Intensive Care Unit of a hospital shows a higher antibiotic use in patients infected with Multi-Drug Resistance organisms (Nuckchady and Boolaky, 2020). This study therefore aims at determining the antibiotic prescribing pattern in admitted patients in three different hospitals in Mauritius. These valuable information on the use of antibiotics in Mauritius will enable the formulation of appropriate and contextualized protocols and

stewardship plans for the country. This in turn will help in the prevention of further resistance of bacteria to antibiotics.

## 2 Materials and methods

A point prevalence survey (PPS) of antibiotic use was carried out in three secondary public hospitals in Mauritius. The WHO methodology for PPS on antibiotic use in hospitals was used for the survey (World health organisation methodology for point prevalence survey on antibiotic use in hospitals, technical document, 2019). A training of trainer's workshop on PPS survey was initially organized by WHO and the Ministry of Health and Wellness of Mauritius. This was then followed by a 2-day workshop led by the Ministry of Health to train the team at each hospital prior to the data collection. In Hospital 1, the survey was carried out in February 2018 while in Hospital 2 and Hospital 3, the surveys were carried out in April-May 2019. Hospital 1 has a bed capacity of 618 beds and a catchment area population of 314,796, hospital 2 has a bed capacity of 443 beds and a catchment area population of 180,482 while hospital 3 has a bed capacity of 495 beds and a catchment area population of 226,377 (Ministry of Health and Wellness, 2018a; Ministry of Health and Wellness, 2018b). The study in Hospital 1, being a pilot study, 1 in 2 eligible patients were selected for the survey. In the other 2 hospitals, all eligible inpatients were selected for the study. The director of the hospital was notified one week prior to the PPS survey.

Eligible inpatients were those who were hospitalized in the ward at 8.00 a.m. on the day of the survey (excluding those admitted to the ward after 8.00 a.m.). All inpatients meeting the criteria mentioned above were included in the survey whether they were on antibiotics or not. All day care patients were excluded.

Antibiotics were captured from patient notes in the original form and were classified according to the International Non-proprietary Names (INN), the Anatomical Therapeutic Chemical classification (ATC) system and the WHO AWARE category; ACCESS, WATCH and RESERVE groups (World Health Organisation Antibiotics Portal, 2017). Only the systemic antibiotics that the patients were currently taking, were included in the survey.

Topical and ophthalmologic antibiotics were excluded. Data was collected by reviewing the patients' medical records and data was entered in five different questionnaires namely, ward data, patient data, antibiotic data, antibiotic susceptibility test/microorganisms and indication data. The data was entered on EPI Info questionnaire and Microsoft Excel was used for data analysis. The Ethics Committee of the Ministry of Health and Wellness gave approval for carrying out this study.

## 3 Results

### 3.1 Distribution of inpatients by age and comorbidities

The number of patients included in the survey in the 3 regional hospitals was 915; 276 patients in Hospital 1, 316 in

**Abbreviations:** AMR, Antimicrobial Resistance; AST, Antibiotic Susceptibility Testing; ATC, Anatomical Therapeutic Chemical Classification; HAI, Hospital-Acquired Infections; INN, International Non-proprietary Names; IPC, Infection Prevention and Control; PPS, Point Prevalence Survey; PVC, Peripheral Vascular Catheter; SSI, Surgical Site Infections; WHO, World Health Organisation.



Hospital 2 and 323 in Hospital 3. The average proportion of female patients was 52% while that of admitted male patients was 48%. In all 3 regional hospitals, the proportion of admitted cases per inhabitants was found to be greater in those less than 1 year (9-13 per 10000 population) followed by those above 60 years (5-6 per 10000 population).

Concerning the prevalence of comorbidities in the admitted patients, an average of 38% of the patients had hypertension, 36% had diabetes mellitus, 16% had ischemic heart disease, 9% had other diseases such as renal impairment, bronchial asthma and cancer. The records showed only 1% of the admitted patients were infected with the Human Immunodeficiency Virus (HIV).

### 3.2 Distribution of inpatients by administration route and invasive devices

Regarding the invasive devices used, the overall trend was quite similar among all three hospitals. An average of 84% had a peripheral vascular catheter, 15% had a urinary catheter, 4% had a central vascular catheter while 3% were intubated. The administration route of the antibiotics with the highest proportion (81-89%) in all 3 hospitals was the parenteral route, followed by the oral route (11-19%). Inhalation and rectal route accounted for less than 1%.

### 3.3 Proportion of patients administered with antibiotics:

In all 3 hospitals, among 915 inpatients, 482 (53%) were treated with 753 therapies or prescriptions of antibiotics, averaging 1.6 therapies or prescriptions per patient (Table 1). Among those treated with antibiotics, an average of 88 patients (55%), 58 patients (36%) and 15 patients (9%) were given 1, 2 and 3 or more antibiotics respectively.

Results also showed 52% of used antimicrobials to be in the WATCH category and 46% in the ACCESS category. RESERVE group accounted for only 2% among the 753 total therapies and prescriptions.

### 3.4 Use by classes of antibiotics

The antibiotics were classified according to Anatomical Therapeutic Chemical 3 (ATC 3), except for other beta lactams which had been subdivided into cephalosporins and carbapenems. The overall trend of choice of antibiotics at ATC3 level was quite consistent across the facilities. Cephalosporins in the other beta lactams category were the most commonly used antibiotics (35%), followed by beta lactams, penicillins (24%),

sulphonamides and trimethoprim (17%) and quinolones (12%) (Figure 1).

### 3.5 Indications for antibiotic use

The highest proportion of inpatients treated with antibiotics was those with community acquired infections (n=243, 50%) followed by surgical prophylaxis (n=191, 40%) (Figure 2). Ceftriaxone/cefotaxime, amoxicillin, metronidazole (parenteral) and ciprofloxacin were the most commonly used antibiotics in surgical prophylaxis and community acquired infection in all 3 hospitals (Figure 3).

The number of doses of antibiotics administered to those categorized as surgical prophylaxis was determined. Above 70% of the inpatients were given multiple doses of antibiotics on more than one day, about 20% were given multiple doses in one day and 5% had only one dose. The same trend was observed in all 3 hospitals.

### 3.6 Most common diagnosis for antibiotic use

On average, the most common diagnosis for antibiotic use was cellulitis, wound, deep soft tissue injury not involving bone and not related to surgery (20%). Acute bronchitis categories came second 14% followed by clinical sepsis and upper Urinary Tract Infection at 12 and 11% respectively. (Figure 4).

### 3.7 Most common antibiotics used overall (at the ATC5 level)

Overall, third generation cephalosporins (ceftriaxone, cefotaxime), amoxicillin, metronidazole (parenteral) and ciprofloxacin accounted for more than 75% of total prescriptions. While Hospital 2 and 3 had the same trend in the ATC5 level antibiotics, Hospital 1 showed very high cefotaxime use (28%) instead of ceftriaxone (7%). (Figure 5).

In Hospital 1, 2 and 3, 19 patients (13%, 19/151), 35 patients (24%, 35/146) and 25 patients (13.5%, 25/185) respectively had an Antibiotic Susceptibility Testing (AST) report before prescription of antibiotics. On average, 16% of patients had an AST done before prescription of antibiotics in the 3 hospitals.

## 4 Discussion

The aim of this survey was to determine the antibiotic prescribing pattern in 3 regional hospitals of Mauritius. No similar survey has been done before in the country. The findings

TABLE 1 Prevalence of antimicrobial use by ward type in hospital 1, 2 and 3.

	Ward Type	Total number of patients, n	Number of patients treated with antibiotics, n	Proportion of patients on anti-microbials (%)	Total number of prescriptions/therapies	Average number of prescription/therapies per patient on antibiotics
Hospital 1	Paediatric Medical Ward	18	9	50%	13	1.4
	Adult Medical Ward	103	54	52%	77	1.4
	Adult Surgical Ward	124	72	58%	114	1.6
	Adult High-Dependency Ward	5	3	60%	3	1.0
	Adult ICU	26	13	50%	16	1.2
	All Wards	276	151	55%	223	1.5
Hospital 2	Paediatric Medical Ward	27	20	74%	42	2.1
	Adult Medical Ward	163	42	26%	57	1.4
	Adult Surgical Ward	120	80	67%	134	1.7
	Adult ICU	6	4	67%	5	1.3
	All Wards	316	146	46%	238	1.6
Hospital 3	Paediatric Medical Ward	16	10	63%	13	1.3
	Adult Medical Ward	204	98	48%	149	1.5
	Adult Surgical Ward	93	68	73%	115	1.7
	Adult ICU	10	9	90%	15	1.7
	All Wards	323	185	57%	292	1.6
All facilities	Paediatric Medical Ward	61	39	64%	68	1.7
	Adult Medical Ward	470	194	41%	283	1.5
	Adult Surgical Ward	337	220	65%	363	1.7

(Continued)

TABLE 1 Continued

	Ward Type	Total number of patients, n	Number of patients treated with antibiotics, n	Proportion of patients on anti-microbials (%)	Total number of prescriptions/therapies	Average number of prescription/therapies per patient on antibiotics
	Adult high-dependency and ICU	47	29	62%	39	1.3
	All Wards	915	482	53%	753	1.6

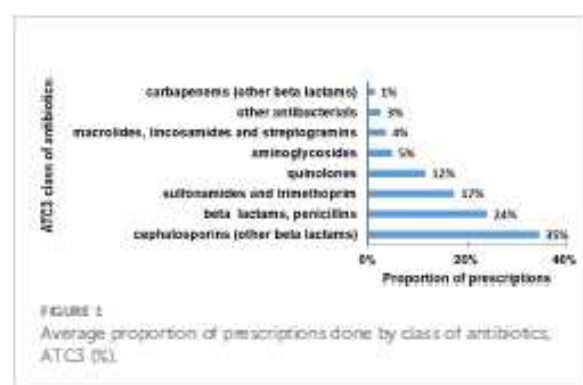


FIGURE 1  
Average proportion of prescriptions done by class of antibiotics, ATC3 (%).

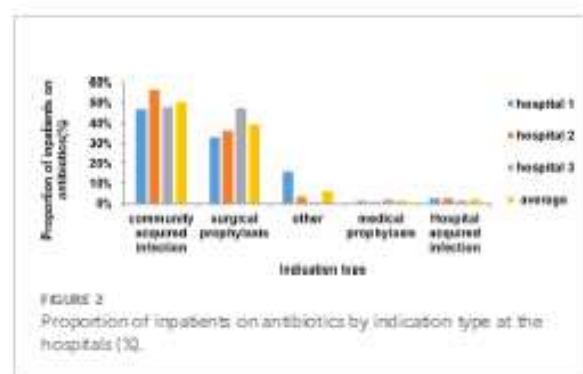


FIGURE 2  
Proportion of inpatients on antibiotics by indication type at the hospitals (%).

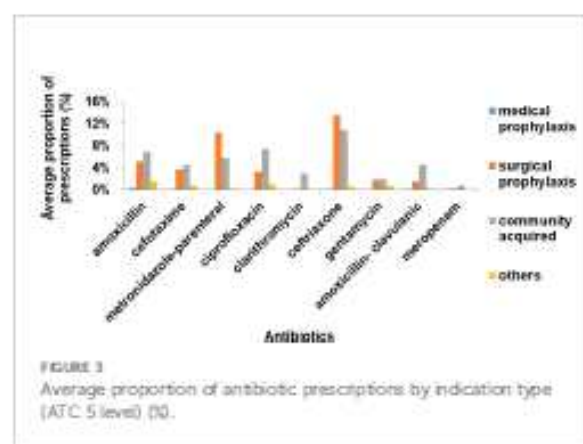


FIGURE 3  
Average proportion of antibiotic prescriptions by indication type (ATC 5 level) (%).



FIGURE 4  
Proportion of the most common diagnosis among the inpatients on antibiotics (%).

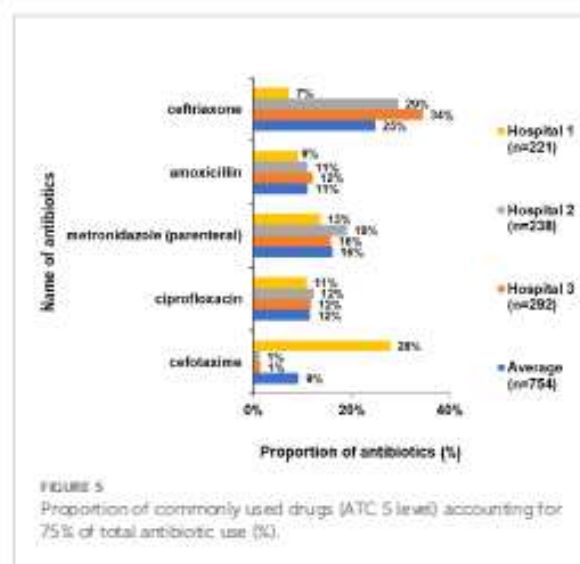


FIGURE 5  
Proportion of commonly used drugs (ATC 5 level) accounting for 75% of total antibiotic use (%).

show a more or less similar trend in all the 3 hospitals regarding the gender and age of admitted patients, the use of invasive devices, the administration route of antibiotics and the prevalence of comorbidities. Mauritius being a small country, the socioeconomic status, the climate, comorbidities and demographic pattern of the population residing in each region



or catchment area of hospitals 1, 2 and 3 are more or less similar. The prevalence of comorbidities calculated in the study were comparable with the prevalence of non-communicable diseases in the country (Ministry of Health and Wellness, 2018a). The population of Mauritius has a high prevalence of diabetes mellitus and hypertension. It is not surprising therefore that the most common diagnosis for the use of antibiotics was in patients with cellulitis (20%). Several studies have shown the high tendency of patients with diabetes mellitus to develop cellulitis (Bristow and Spruce, 2009; Zacay et al., 2021). Patients at age extremes are more vulnerable to diseases and infections and might explain the higher admission in those age groups.

Hospital 3 and 1 had both a greater proportion of admitted patients administered with antibiotics as well as a higher annual number of admissions compared to Hospital 2 (Ministry of Health and Wellness, 2018a). The higher percentage might also be due to the different prescribing habits of the doctors in the 3 hospitals.

In Hospital 1, the adult surgical ward had the highest average number of prescriptions/therapies per patient on antibiotics while in Hospital 2, the pediatric ward had the highest proportion and in Hospital 3, the highest proportion was in adult ICU and adult surgical ward. The pediatric ward of Hospital 2 was a mixed ward where both surgical patients and medical patients were admitted. A higher number of prescriptions in surgical pediatric patients than in medical children may explain the high proportion in Hospital 2. Hence, on average, the proportion of antibiotic prescriptions was higher in the surgical wards. Furthermore, proportion of patients on antibiotic due to surgical prophylaxis was found to be high (33–48%) and more than 60% of them were given multiple doses of antibiotics on more than one day. A similar high use of antibiotics in surgical prophylaxis has also been observed in Europe, Saudi Arabia, Turkey, Ghana, Egypt, India and China (Usauer et al., 2005; European Centre for Disease Prevention and Control, 2011–2012; Talaat et al., 2014; Xie et al., 2015; Matar et al., 2016; Labi et al., 2018; Singh et al., 2019). The WHO and several studies recommend the use of one dose of antibiotic just before the surgical procedure with appropriate choice of antibiotic and clean aseptic conditions during the operation (Nichols, 2004; Hawn et al., 2013; World Health Organisation, 2018). The reason for this excessive use of antibiotics after surgery in Mauritius might be the high rate of Surgical Site Infections (SSI) and poor Infection Prevention Control (IPC) measures. In this study, the proportion of SSI was found to be 5% while in 1993 and 2021, two studies done in a regional hospital of Mauritius found a higher incidence of 8.2% and 17% respectively (Jepien et al., 1993; Nuckchady, 2021). A follow up of patients after surgery is important to get more accurate data and might explain the low proportion of SSI obtained in this point prevalence study. The high SSI incidence might explain the behavior of the doctors in using several doses of antibiotics for surgical prophylaxis after surgery. A surveillance of SSI and IPC is therefore important to measure the

burden in Mauritius. This will help in formulating and implementing National IPC guidelines and antibiotic stewardship protocols in all hospitals.

The proportion of patients on antibiotics due to medical prophylaxis on the other hand was found to be surprisingly very low in this study (<2%) compared to Europe (11%), Egypt (23%) and India (17%) (European Centre for Disease Prevention and Control, 2011–2012; Talaat et al., 2014; Singh et al., 2019). Given the high rates of admitted patients with non-communicable diseases as diabetes, hypertension, ischemic heart disease in these cohorts as well as high incidence of nosocomial infections in one hospital of Mauritius, it is surprising that antibiotics given for medical prophylaxis is low (Nuckchady, 2021). A reason explaining this discrepancy in data might be due to the fact that in Europe and India, data was collected in acute care settings and tertiary hospitals respectively while data was collected in secondary hospitals in Mauritius. Another reason for this difference of data with other countries might be due to improper documentation in patients' files as the reason for administration of antibiotics is often not specified.

A PPS on antimicrobial use in Europe, China, Turkey (Matar et al., 2016; Labi et al., 2018; Singh et al., 2019) showed adult ICU to have higher antibiotic therapies than Mauritius. Here also, the higher rate of antibiotic therapies might be due to the different hospital settings of Europe and Turkey where the PPS surveys were carried out in acute care hospitals and tertiary hospitals respectively. The data should therefore be compared with caution. In Mauritius, this greater rate was observed in Hospital 3 only. The lower use of antibiotics in the ICUs of Hospital 1 and 2 may be due to bacterial culture and susceptibility testing being done regularly for every patient in the ICUs. Hence, only those antibiotics which were sensitive to the pathogen isolated were administered to the patients.

The use of meropenem was very low at less than 2% in the hospitals. An antibiotic susceptibility test is usually recommended by the hospital pharmacists before dispensing meropenem and might explain its low proportion used in the study.

A high proportion (84%) of patients with peripheral vascular catheter (PVC) was seen in the 3 hospitals. The data is comparable to the PPS on antibiotic use done in several countries of Europe, Saudi Arabia, Ghana, Democratic Republic of Congo, Botswana and China (European Centre for Disease Prevention and Control, 2011–2012; Matar et al., 2016; Wanshale et al., 2016; Labi et al., 2018; Paramadhas et al., 2019; Singh et al., 2019). Though it can be argued that PVC helps in providing urgent care in case of deterioration of the patient, clear guidelines should be elaborated on the use of PVC along with the administration of oral v/s parenteral treatment. The proportion of antibiotics given via parenteral route was 85%. This data is comparable to proportion reported in Europe (71.9%), Saudi Arabia (80.6%) and China (98%) and (European Centre for Disease Prevention and Control, 2011–2012; Xie et al., 2015; Matar et al., 2016). The increased use of catheter and unnecessary use of vascular access



can lead to the development of HAI and as a result, oral antibiotics should be preferred if patient is stable and tolerating orally. More information on these variables is needed to assess the patients in the study.

The proportion of inpatients with HAI indication was found to be surprisingly very low at 2–3% in these cohorts. Two studies done in 1993 and 2021 showed the prevalence of HAI to have increased from 4.9% to 18% in one hospital of Mauritius (Jepsen et al., 1993; Nuckchady, 2021). However, the results have to be compared with caution as the collection of data may not have been uniform in the different studies. Mauritius is seen to have a lower proportion of HAI compared to Europe (6%), India and several countries of Africa (European Centre for Disease Prevention and Control, 2011–2012; Talaat et al., 2014; Labi et al., 2018; Paramadhas et al., 2019; Singh et al., 2019). It is important to keep in mind that the survey in Europe, India and some countries of the African region were carried out in different healthcare settings as acute care and tertiary hospitals which might explain this difference in data. Moreover, this lower HAI proportion in Mauritius could also be due to underestimation and lack of documentation in the patient files. The PPS survey only collects data at one point in time so that there is no follow up of patients from admission to discharge. HAI in the inpatients could be happening at a later stage and therefore be missed. Proper reporting of HAI in the files and follow up of the patient till discharge will help in getting accurate data on HAI and in assessing IPC measures in the hospitals.

As for the AWARE categorization (World Health Organisation Antibiotics Portal, 2017), around half of total use were in the ACCESS or WATCH category while only 1–4% was in the RESERVE group. Since the data was collected from inpatient records at regional hospitals where more severe conditions are usually treated, the proportion of ACCESS and WATCH antibiotics seems acceptable. However, since the country has not elaborated its own therapeutic guidelines of antibiotic use, their adoption in both public and private facilities could optimize the use of antibiotics.

A third-generation cephalosporin (ceftriaxone or cefotaxime), amoxicillin, metronidazole and ciprofloxacin accounted for 75% of the total antibiotic prescriptions. This data is comparable to PPS studies done in Europe, Africa and China (European Centre for Disease Prevention and Control, 2011–2012; Xie et al., 2015; Wambale et al., 2016; Labi et al., 2018; Paramadhas et al., 2019). Cefotaxime was most commonly used in Hospital 1 while ceftriaxone was highest in Hospital 2 and 3. The doctor prescribing habits or the temporary non-availability of ceftriaxone at one hospital might be an explanation for the choice of antibiotic in the hospitals.

It is important to note that an AST was done for only a small percentage (16%) of inpatients prior to prescription of antibiotics. Appropriate guidelines should be elaborated so that although antibiotics can be started in critically ill patients, an AST should be sent prior to the administration of antibiotics belonging to the WATCH and RESERVE category.

Though the study provides important data, it is important to keep in mind the limitations of the study when interpreting the results. The data collection in Hospital 1 was carried out in February 2018 while the data collection in Hospital 2 and 3 was carried out in April–May 2019. The difference in season, month and year of data collection might explain differences in the data. According to the Mauritius Meteorological Services, February is identified as the warmest and wettest months of the year while May is known as the transition months (Mauritius Meteorological Services). Furthermore, categorization of the different wards was not always accurate. When the wards were full, a patient from one ward were transferred to another ward category so that the wards are often mixed wards. Also, according to the protocol, only antibiotics that the patient was currently taking on the day of the data collection, were included, underestimating the antibiotic prescriptions obtained by the patient in all. Although this PPS survey which is a standard protocol, is crucial for comparison of results with time and across countries, it is important to highlight that following a cohort of patients from admission till discharge in the hospitals would have provided more accurate data on HAI, SSI and more details on duration and different classes of antibiotics administered to the patient. This can be incorporated in the future PPS surveys on antibiotic use so that not only results can be compared to see the progress but also, a cohort of patients in the surgical wards and medical wards can be followed till discharge or death.

Also, the healthcare staff at the hospitals were aware of the survey on antibiotic use prior to the data collection and this might have influenced the documentation in the patients' files and led the doctors to prescribe antibiotics more carefully. Regular surveys on antibiotic use without prior notification to the healthcare staff will enable us to have more accurate data.

This study provides valuable information on antibiotic prescribing pattern in the country which will help in formulating contextualized antibiotic stewardship program. Afterwards, it would be imperative to continue the PPS survey on antibiotic use in at least one regional hospital each year for monitoring and evaluation of the implementation of the stewardship protocols and to disseminate the results in the hospitals to improve awareness of the healthcare workers. The study can be used in the future with the results of culture and antibiogram of the samples obtained in these hospitals for antibiotic stewardship program. The surveys on antibiotic use could then be extended to the private healthcare system of the country to get a complete picture concerning antibiotic use. Addressing the issues on antibiotic use is essential for each country to be able to fight antibiotic resistance.

## 5 Conclusion

The PPS on antibiotic use provides important information that can be used to formulate an appropriate antibiotic



stewardship program in Mauritius as well as a standard way of collecting data so that it can be compared across countries. No similar survey on antibiotic use has been done before in Mauritius. Several misuses of antibiotics have been identified in the 3 regional hospitals such as the excessive use of antibiotics for surgical prophylaxis, the high use of third generation cephalosporins and of the WATCH category of antibiotics. The survey also demonstrates an extremely low percentage of AST done prior to prescription of antibiotics. The survey should be continued each year after the implementation of an antibiotic stewardship program to constantly review its effectiveness so that we are able to tackle antibiotic resistance in Mauritius.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Author contributions

LV-M collected, analyzed, and interpreted the data. LV-M conceived the original paper and provided a rough draft. EC, MI and HR-A interpreted the data, checked the paper for consistency, corrected the language and checked the references for consistency and accuracy. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Conclusion

This study shows interesting information concerning antibiotic use in the hospitals of Mauritius.

First, a similar trend in antibiotic prescribing pattern was observed in the three regional hospitals. The few differences observed were the proportion of admitted patients administered with antibiotics and the type of wards having the highest number of prescriptions/therapies. Another important point is the high proportion (33-48%) of patients on antibiotics due to surgical prophylaxis and more than 60 % of them were given multiple doses of antibiotics on more than one day. Moreover, the third-generation cephalosporin (ceftriaxone or cefotaxime), amoxicillin, metronidazole and ciprofloxacin accounted for 75 % of the total antibiotic prescriptions. A high proportion (84%) of patients with peripheral vascular catheter (PVC) was seen in the 3 hospitals and the proportion of antibiotics given via parenteral route was 85%.

A major drawback is the low (16%) percentage of AST done prior to prescription of antibiotics.

This study confirms the presence of antibiotic misuse in the hospital settings. It provides valuable information on antibiotic prescribing pattern in the country which will help in formulating antibiotic stewardship program. It is crucial to not only develop but also ensure the implementation of the antibiotic stewardship program in the healthcare institutions of Mauritius. The misuses identified should be given priority as excessive use of antibiotics for surgical prophylaxis, the high use of third generation cephalosporins and of the WATCH category of antibiotics and the extremely low percentage of AST done prior to prescription of antibiotics.

The survey should then be continued each year after the implementation of an antibiotic stewardship program to constantly review its effectiveness to be able to reduce antibiotic use in Mauritius.

## OVERALL DISCUSSION

In section 1, antibiotic consumption in the human and animal health was discussed as well as antibiotic resistance in the hospital settings. In section 2, antibiotic use in the hospital settings was explored and several antibiotic misuses were identified.

In this chapter, we discuss the limitations of the study as well as the main findings of the two articles. We end the overall discussion with some recommendations and perspectives of ABR in Mauritius.

### Limitations of the research

#### Lack of data on usage of antibiotics in private human settings and animal farms

This study shows an increased consumption of the WATCH ('WHO AWARE Classification', 2019) category of antibiotics in the private human health sector. However, no information is available on the detailed usage of antibiotics in the private sector in Mauritius such as the diagnosis of patient, duration of antibiotic, whether the patient took the whole course of the prescribed antibiotics or whether AST was done prior to prescription, among others. Similarly, in the animal sector, though the study shows the overall consumption of antibiotics to be less compared to the human sector, there is no detailed information concerning their use in animal farms or use as growth promoters. This information is crucial to understand the factors associated with the prescription of antibiotics in the private and animal sectors. Having more information will enable the country to build a strong antibiotic stewardship program to decrease the use of WATCH antibiotics in private clinics and pharmacies as well as animal farms.

#### No resistance data from the private clinics, animal farms and the environment

The study portrays antibiotic resistance in the hospital setting. Till date, no resistance data in the private human settings, animal farms and environment sector are available. The interconnectedness of the human, animal and environment has been recognized (Walsh, 2018; Hernando-Amado *et al.*, 2019; Kim and Cha, 2021; Velazquez-Meza *et al.*, 2022). As a result, comparing the pattern of resistance rate using a One Health approach is crucial to understand the interplay and mechanism of resistance in the country.

#### No real time electronic surveillance for antibiotic resistance, consumption, and use

The data collected for this study was collected from the National Pharmacy Unit and the Central Health Laboratory (CHL). At the CHL, data is available in a paper-based format and hence, data collection for this study was tedious and time consuming. As a result, the study has only data on



blood cultures done at hospital settings from 2015 to 2017 for *E. Coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. At present, some data on antibiotic resistance is collected on the GLASS WHONET platform ('GLASS-AMR Module', 2022) but no details as age, ward and name of hospital are collected.

At the Pharmacy Unit, data on antibiotics distributed throughout the country was available with various formats. Data on antibiotics distributed to healthcare institutions was obtained on Microsoft Excel while data on antibiotics distributed to private institutions were obtained in a pdf format. Collecting all data in same format, cleaning and calculating the Defined Daily Dose (DDD) was time consuming and involved a lot of work.

Having real time electronic surveillance would enable the trend of antibiotic consumption and resistance to be determined more easily and quickly and in real time. Real time data would enable the better understanding of the trend in consumption, use and resistance and would orient the actions to be taken quickly.

#### No information on antibiotics expired or not used

Another limitation is that no information is available on the amount of antibiotics that have been thrown away due to past expiry dates. Although discussion with the pharmacists revealed that this amount is negligible, this information should be taken in consideration. Moreover, another aspect is antibiotics that have not been used or taken by the patients, especially in the public healthcare institutions. The public healthcare system provides free medications to patients. Discussion with several patients reveal that they often do not take the antibiotics given or do not take the full course. Indeed, the DDD can be overestimated due to this limitation in this study. The figures on antibiotics thrown away by the pharmacist can be estimated by gathering data at healthcare institutions.

#### Limitations in calculating the Animal Level of Exposure to Antimicrobials (ALEA) and Population Correction Unit (PCU) Indicator for antibiotic consumption in animal health

In this study, the ALEA or PCU could not be calculated due to lack of data on the live weight of animals by species in Mauritius. Though the total antibiotic consumption in animal sector and an estimate of the number of different animal species are known, the information on antibiotics allocated to the different animal species are not available. This denominator as well as an

estimated live weight of animals should hence be collected by the Ministry of Agro-Industry in order to calculate the ALEA or PCU in Mauritius.

#### Limitations of the Defined Daily Dose Indicator for antibiotic consumption in human health

The DDD is an important standard tool for monitoring and comparing the trend of antibiotic consumption with time and across countries. However, the DDD also has several drawbacks, and these should be kept in mind while interpreting the data (Monnet, 2007; WHO DDD, 2023). The calculation of the DDD excludes creams, ointments and drops. This can cause the DDD to be underestimated although in this study, the amount of topical creams and ointments used are very small.

Moreover, the DDD methodology is not applicable for children but for adults. Children are given a smaller dose of antibiotics, depending on their weight. The Prescribed Daily Dose is recommended for measuring antibiotic use in children (WHO DDD, 2023).

Also, the ATC codes and DDD values is a dynamic system in which alterations are made each year (Monnet, 2007; WHO DDD, 2023). It is hence important to keep this in mind when interpreting data.

#### No information on regular screening tests for antibiotics

The presence of substandard antibiotics plays a major role in the emergence of ABR (Johnston and Holt, 2014; Theodoros and E, 2015; Zabala *et al.*, 2022). When a dose of antibiotic is substandard, it may contain an insufficient amount of active ingredients to effectively eliminate bacterial infections. This inadequate dosage can contribute to the development of ABR, as the bacteria may not be completely eradicated, allowing them to adapt and become resistant to the antibiotic. In Mauritius, no information is available on the regular and routine screening of antibiotics to rule out substandard or falsified drugs. This information is crucial to understand the factors that can contribute to emergence of ABR in Mauritius. It is crucial to address the issue of substandard antibiotics to combat the growing problem of ABR (Zabala *et al.*, 2022)



## Consumption and use of antibiotics

### Data presented for the first time

This study presents, for the first time, data on antibiotic consumption in human and animal health in Mauritius. It provides valuable insights into the classes of antibiotics used in different sectors, including public and private health institutions. Additionally, the use of antibiotics is presented in the hospital settings for the first time. Antibiotics is the main driver of antibiotic resistance (Lin *et al.*, 2015; Chokshi *et al.*, 2019; Hutchings, Truman and Wilkinson, 2019). In order to reduce antibiotics therefore, it is vital to understand their distribution and pattern in Mauritius so that appropriate measures can be taken.

To facilitate comparison between the two sectors, antibiotic consumption in human and animal health is initially presented in kilograms. The data reveals that the major selective pressure lies in human health sector. Another essential point observed is no colistin were used in the animal sector. Although indicators such as DDD (defined daily doses), ALEA (animal-level exposure to antimicrobials), and PCU (population correction unit) are important for comparing antibiotic consumption by population and the live weight of animals, presenting the information in kg is essential for comparison.

### Antibiotic consumption in the private sector

A greater proportion of WATCH antibiotics was observed in the private human health sector compared to the public healthcare institutions. A report on the pharmaceutical industry in Mauritius states that the public sector caters for about 73% of healthcare needs of the population (*Pharmaceutical Industry In Mauritius*, 2020). The same report shows the health expenditure in the private to be higher than in the public sector (*Pharmaceutical Industry In Mauritius*, 2020). These findings suggest that the rate of antibiotic prescription, especially of WATCH antibiotics and the expenditure in the private is higher than in the public sector. Till date, most actions taken by the Ministry of Health and Wellness were in the public healthcare institutions. These figures show the urgency of taking appropriate measures in the private sector as well. The same trend in prescription habits was seen in several other countries as well. In Malaysia, the antibiotic prescribing rate was lower in public clinics (6.8 %) compared with private clinics (30.8 %) (Ab Rahman, Teng and Sivasampu, 2016). Another study done in Sweden showed that private physicians were 6% more likely to prescribe antibiotics and 9% more likely to choose broad-spectrum antibiotics (Granlund

and Zykova, 2021). In 6 countries of Africa, namely Tanzania, Ghana, Nigeria, Zimbabwe, Gambia and Ethiopia, the antibiotic use rate given by injection at private facilities was 38% (IQR 19.1–42.7) while that of the public was 32.3% (IQR 20.6–57.6), the rate of oral antibiotic prescribing at public centers was 49.7% (IQR 51.1–75.7) and that of private facilities 57.6% (IQR 39.0–69.5) (Ofori-Asenso and Agyeman, 2015). The reasons for this increased prescribed rate in the private can be due to the physicians' willingness to please the patient and meet the patients' expectations, diagnostic uncertainty, financial considerations, influence from medical representatives or inadequate knowledge (Kotwani *et al.*, 2010; Sirota *et al.*, 2017). It would be interesting to carry out an anonymous survey in the private sector in Mauritius to determine the factors that drives the private practitioners to prescribe antibiotics.

Mauritius has a Pharmacy Act which prohibits over the counter sales of antibiotics in private retail pharmacies (*Mauritius Pharmacy Act*, 1983). Pharmacists generally demand a prescription before giving antibiotics to the patient but there is no regular routine screening to verify the enforcement of the Pharmacy Act in Mauritius in both human and animal health.

The enforcement of the antibiotic stewardship program in the private sector is an important step to reduce the consumption of WATCH and RESERVE antibiotics. The Ministry of Health and Wellness together with the Medical Council should work together to promote awareness on AMR and enforce the antibiotic stewardship program in private clinics as well as by private doctors.

#### Antibiotic consumption in health centres and hospitals

The consumption of antibiotics in terms of DID in Mauritius was 20.9 in 2015, 22.1 in 2016 and 21.7 in 2017. The DID in Mauritius is not excessively high compared to other countries (*WHO Report on Surveillance of Antibiotic Consumption*, 2016; ESAC report Donguy, 2018). Still, there is room for improvement and measures should be taken to reduce consumption and use in healthcare institutions.

Several studies have shown that the antibiotic consumption and use tends to increase in public healthcare institutions whenever there is a greater volume of patients, lack of time to assess and consult each patient as well as laxity in the regulation for prescribing and dispensing antibiotics (Hutchinson and Foley, 1999; Walle-Hansen and Høye, 2018)

According to the Health Statistics report 2017 of Mauritius, the number of attendances for the treatment of common diseases and injuries at the community hospitals, mediclinics, area health centres and community centres was 4,803,243, which means that on average a Mauritian goes to health centres at least 4 times per year and the doctors in each health centre consults about 700 patients per week or about 100 patients per day (MOHW, 2017). The same report shows that 1.3 million people went to the emergency department in 2017; hence, on average, a Mauritian goes to the emergency department of the hospitals at least once per year. Moreover, about one-sixth of the population were admitted on average once per year in 2017 (MOHW, 2017). In 2022, the figures remained more or less the same as in 2017 (MOHW, 2022). Mauritius having a free healthcare system may account for this high consultation rate. This high volume of patients in the health centres and hospitals may cause the doctors to prescribe more antibiotics than needed (Kotwani *et al.*, 2010; Ab Rahman, Teng and Sivasampu, 2016; Sirota *et al.*, 2017; Walle-Hansen and Høye, 2018).

Concerning the laxity in regulation for prescribing and dispensing of antibiotics, there is currently no antibiotic stewardship program for guiding the doctors regarding the prescription of antibiotics. Although a few guidelines have been formulated in a few departments, there is no dissemination and enforcement of those guidelines among doctors at hospital level.

Responsible prescribing should therefore be encouraged in Mauritius which will entail healthcare professionals to judiciously prescribe antibiotics, considering factors such as the type and severity of the infection, the appropriateness of antibiotic choice, and the duration of treatment. This approach will help to minimize unnecessary antibiotic exposure and reduce the selection pressure for resistant strains.

#### Increase in WATCH and RESERVE antibiotics

This study shows a slight increase in WATCH and RESERVE antibiotics from 2015 to 2017. This increase is more pronounced in the private sector. Prospective studies are crucial to understand the trend and factors influencing the prescription of those antibiotics in Mauritius. One explanation, however, could be due to the increasing resistance of pathogens to the first and second line of antibiotics, which fall in the ACCESS group of antibiotics (Issack *et al.*, 2012; Khurshid Mungloo-Rujubali, Issack and Jaufeerally-Fakim, 2013; *Republic of Mauritius NAP AMR 2017-2022*, 2017; Nuckchady and Boolaky, 2020a).

A second reason could be due to doctors' habit in the public and especially in the private healthcare institutions as they expect the pathogens to be resistant to the first line drugs and prefer to be sure of the recovery of patient. In the private sector, it promotes the trust of the patient in the doctor and the financial benefits of the doctor (Hutchinson and Foley, 1999; Ab Rahman, Teng and Sivasampu, 2016).

## Antibiotic use in Mauritius and barriers to implement antibiotic stewardship program

### *Animal health*

Concerning the use of antibiotics in animal health, no information is available in the country concerning their use as growth promoters or their illegal importation in Mauritius. As it is not easy to obtain honest answers from the farmers, antibiotic residue surveys should be carried out regularly and routinely in terrestrial and aquatic animals. Additionally, in the private animal farms of Mauritius, it is important to carry out awareness campaigns on ABR. One such survey done in Ireland led to an increased awareness of farmers on AMR as their role in the contribution of AMR in the country was explained (Regan, Burrell, *et al.*, 2023; Regan, Sweeney, *et al.*, 2023). It showed the importance of not promoting interventions as an authoritarian or exclusionary approach, but rather involving the farmers in the decision-making process (Regan, Burrell, *et al.*, 2023). In Mauritius, such procedures could be adopted to increase the farmers' knowledge and willingness to adopt a responsible use of antibiotics.

In Mauritius, the Ministry of Agro-Industry is promoting the production of biofood by providing incentives to the local farmers, as giving them a "Bio Farming Development Certificate" including an 8-year tax holiday and exemption from various taxes and duties on importation of bio food inputs (MOA Strategic plan 2016-2020, 2015; Defimedia, 2016). A Biofarming Support Scheme was introduced in 2016 to encourage the local farmers in the production of bio food (MOA Strategic plan 2016-2020, 2015; Defimedia, 2016). This illustrates the growing concern among the Mauritian population on access to bio food or food with no antibiotics, chemicals, and pesticides. Several surveys across the world show an increased consumer concern for food safety and for issues related to antimicrobial-resistant bacteria in food products and the willingness to pay a higher price for antibiotic free animal products (Abrams, Meyers and Irani, 2010; Barrett *et al.*, 2021; Bradford *et al.*, 2022; Regan, Sweeney, *et al.*, 2023). While we recognize the danger of using antibiotics as growth promoters and the contribution of antibiotics in the development of ABR, it is important to consider that eliminating antibiotics completely is harmful for both animal production and welfare.

Sick animals cannot be denied antibiotic treatment to comply with the production methods behind the marketing label of antibiotic free product (Goddard, Hartmann and Klink-Lehmann, 2017; Tang *et al.*, 2017; Steede *et al.*, 2020). As a result, in Mauritius, it is crucial to sensitise consumers on those aspects so that they can make well-informed decisions when purchasing food in the country.

### *Human health*

#### *Public health institutions*

The Point Prevalence Survey on antibiotic use has identified several misuses of antibiotics in the hospital settings. One of them is the high proportion (33-48%) of patients taking antibiotics after surgery; and more than 60 % of them were given multiple doses of antibiotics on more than one day. Another point is the low proportion (average of 16%) of patients with an Antibiotic Susceptibility Testing (AST) done before a prescription of antibiotics. The survey should be repeated to get more recent data in the hospital and the misuses identified in the hospital settings will help in formulating an antibiotic stewardship program. It is also vital to find means of ensuring the implementation of the program. One way of achieving this is through the fulltime infection control nurses in the hospital setting and in giving them appropriate training on AMR. Those Infection control nurses should have the authority to go through the patients' files and submit a report regularly on the adherence to the antibiotic stewardship program.

## Antibiotic Resistance

### Factors leading to Antibiotic Resistance in Mauritius

This study demonstrates that the prevalence of resistance of *E.coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were shown to be quite high in Mauritius. An important decrease in susceptibility of *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* to meropenem was observed from 2015 to 2023, from 98% to 94%, 83% to 53%, 45% to 28% and 63% to 47% respectively. This data is important as carbapenems are among the last resort antibiotics that need to be preserved for critical cases. This high carbapenem resistance was observed in previous studies as stated earlier (Holman *et al.*, 2017; Gay *et al.*, 2020; Nuckchady and Boolaky, 2020a). It is however interesting to note that the consumption of antibiotics, including that of carbapenems in Mauritius is not very high compared to other countries (*WHO Report on Surveillance of Antibiotic Consumption*, 2016; ESAC report Donguy, 2018; Klein *et al.*, 2021). Indeed, the DDD per 1000 admissions of the carbapenem group of antibiotics was less than 0.01 in all public health institutions while the total DDD per 1000 inhabitants per day ranged from 0.02 to 0.03 in Mauritius. Additionally, the Point Prevalence survey showed that the use of meropenem was less than 2% in the hospitals on average. It is therefore vital to investigate the factors contributing to this high carbapenem resistance in Mauritius. Still, last resort antibiotics such as carbapenems should be used sparingly and it is important to ensure that the prescription of carbapenems are kept for critically ill patients or when the AST shows resistance to the other classes of antibiotics.

From 2015 to 2023, the proportion of *E.coli* and *K.pneumoniae* sensitive to ceftriaxone decreased from 55% to 39% and from 37% to 22% respectively. This finding correlates with the observed high use of third generation cephalosporins in the hospital settings in the point prevalence survey. An antibiotic stewardship program should therefore be formulated and implemented to ensure the proper use of those critically important antibiotics.

The proportion of multi-drug resistant (MDR) strains in Mauritius was compared to data from the European Centre for Disease Prevention and Control report 2017 (ECDC), as well as data from India (2014) and Malawi (2016)(ECDC, 2017; Musicha, Jennifer E. Cornick, *et al.*, 2017; Nagvekar, Sawant and Amey, 2020). The study found that the proportion of MDR *Klebsiella pneumoniae* in Mauritius was 50-60% of the isolated bacteria, compared to 15.5% in Europe, 44% in India, and 92% in

Malawi. For MDR *Acinetobacter species*, the proportion in Mauritius was 50-60%, compared to 43.2% in Europe and 89% in India. The proportion of MDR *E. coli* was 25-41% in Mauritius, 7.3% in Europe, 9% in India, and 69% in Malawi. Additionally, the proportion of MDR *Pseudomonas aeruginosa isolates* was 25-41% in Mauritius, 4% in Europe, and 30% in Malawi (ECDC, 2017; Musicha, Jennifer E. Cornick, *et al.*, 2017; Nagvekar, Sawant and Amey, 2020).

The MDR rates in Mauritius were found to be comparable to those in India and Malawi, but higher compared to Europe (ECDC AMR, 2017, 2020) . The differences in data could be attributed to the sampling methods, as the ECDC report included cerebrospinal fluid samples in addition to blood samples, while the study in Mauritius only focused on blood samples. However, it is vital to note that from 2015 to 2023, the proportion of MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa* has further increased from 58% to 74% and from 33% to 45%.

These findings are similar to previous studies which have also shown a high MDR bacteria prevalence in Mauritius (Issack, Yee Kin Tet and Morlat, 2007; Issack *et al.*, 2012; Khurshid Mungloo-Rujubali, Issack and Jaufeerally-Fakim, 2013; Nuckchady and Boolaky, 2020a).

Additional research is needed to track the trend of MDR bacteria in Mauritius, to determine the mortality rate associated with antimicrobial resistance in hospitals and to investigate the causes leading to this high MDR prevalence in the hospitals of Mauritius, especially when the DDD is not very high as compared to other countries (*WHO Report on Surveillance of Antibiotic Consumption*, 2016; Klein *et al.*, 2018, 2021). Some reasons explaining this increasing MDR and high prevalence of resistance can be the poor infection prevention control in the hospitals, the misuse of antibiotics, non-adherence to the dose of antibiotics as prescribed by the treating doctor, importation of animals with resistant bacteria, the high flux of tourists in the country or the choice of patients in whom blood culture was done. Another hypothesis is that the low proportion (16%) of samples sent for AST as seen in the PPS on antibiotic use, might suggest that samples are sent for AST only when there is failure of effective treatment with the first and second line of antibiotics. This difference of doctor's behavior might lead to greater proportion of isolates being MDR in Mauritius.

Geographically, 60% of MDR *Klebsiella pneumoniae* and 62 % of the MDR *Acinetobacter baumannii* were found in the hospital situated in the northwest of the island. Similarly, the health centers of the north and northwest regions of Mauritius had a higher consumption of antibiotics compared

to other regions. This information can be used to prioritize the control measures taken in the country.

MDR bacteria have limited treatment options and septicemia with MDR bacteria is a life-threatening condition (Bates, Pruess and Lee, 1995; Bearman and Wenzel, 2005; Gandra *et al.*, 2016; Manyahi *et al.*, 2020). The prospect of tackling this crisis through the development of new antibiotics is overshadowed by two factors. Firstly, the rate of discovering novel antibiotics is disappointingly low. Secondly, there is a high likelihood that pathogens will eventually develop resistance to these new antibiotics, similar to what has happened with existing ones. As a result, the long-term threat lies not only in the pathogens themselves but also in the ongoing process of evolution (Levy, 2002; Baquero, Alvarez-Ortega and Martinez, 2009; Clardy, Fischbach and Currie, 2009; Aminov, 2010; Hutchings, Truman and Wilkinson, 2019; MacLean and San Millan, 2019; Uddin *et al.*, 2021; Rahman, Kesselheim and Hollis, 2023). This threat and evolution in resistance is real.

While it is important to work on encompassing responsible prescribing practices at the individual level and the implementation of effective public policies at the national level, future work in Mauritius should also address these above issues to explain and understand the drivers of antibiotic resistance.

#### [Reversing antibiotic resistance in Mauritius](#)

Several countries have witnessed some decrease in resistant strains after a reduction in antibiotic consumption (Goossens *et al.*, 2005; Butler *et al.*, 2007; Andersson and Hughes, 2010; Bell *et al.*, 2014). Many articles have shown that the widespread and extensive use of antibiotics is undeniably the primary driver behind the alarming rise in resistant bacteria globally (Goossens *et al.*, 2005; Julian and Dorothy, 2010; Bell *et al.*, 2014).

Other articles on the other hand, consider that bacteria possess a remarkable ability to persist and propagate even in the absence of these antibiotics (Barbosa and Levy, 2000; Arason *et al.*, 2002; Finley *et al.*, 2013). While ABR increases with a rise in antibiotic consumption and use, the reverse is not necessarily true, where decreasing antibiotic consumption alone automatically lead to a drastic reduction on ABR (Andersson and Hughes, 2010; Rahman, Kesselheim and Hollis, 2023).

It was discussed that apart from antibiotic use, other factors, including social, ecological, and genetic elements, have a crucial role to play in the emergence and spread of bacterial resistance



(Barbosa and Levy, 2000; Berg, Tom-Petersen and Nybroe, 2005; Aminov, 2009; Gould, 2009; Wales and Davies, 2015; McCann *et al.*, 2019; Reverter *et al.*, 2020; Wang *et al.*, 2021) .

In Mauritius, for example, a high number of tourists come into the country, increasing the risk of importing resistant strains and genes (Ruppé *et al.*, 2014; Frost *et al.*, 2019; Leo *et al.*, 2019; *Tourism in Republic of Mauritius*, 2020) . The latter are present as dormant microbiomes in the individuals. They consequently spread in the environment via stools and contribute to the existing ABR in the country.

Understanding the behavior of bacterial populations and predicting the reversal of resistance, as well as estimating the time it takes for resistance to decay, is a highly intricate task. This complexity arises from the dynamic nature of bacterial populations and the intricate interplay between hosts and pathogens (Levy, 2002; Levy and Marshall, 2004; Aminov, 2009; Gould, 2009; Andersson and Hughes, 2010; Rahman, Kesselheim and Hollis, 2023). Hence, in Mauritius, continued research efforts are necessary to unravel the intricacies of bacterial population dynamics and host-pathogen interactions. By better understanding these processes, the country can develop more effective strategies to combat antibiotic resistance and mitigate its impact on public health (Levy, 2002; Gould, 2009).

### Importance of data and research in the local context

Antibiotic resistance poses a multifaceted and intricate challenge, jeopardizing the well-being of both humans and animals, impacting the national economy, and posing threats to national, regional, and global security. Mauritius has a local context that involves a free health care system, tropical climate, and a high flux of tourists. Although several studies have been done concerning AMR globally, data and information in Mauritius show the gaps in the health system concerning AMR and allows the stakeholders understand the gravity of the situation locally.

The importance of the local context can be appreciated in these two studies done in Reunion Island and Madagascar, where the phylogenetic analysis of ESBL-*Ec* isolates between the different sectors differ (Miltgen *et al.*, 2022b; Gay *et al.*, 2023a). In Reunion Island, the phylogenetic tree showed that the transmission of ESBL-*Ec* between sectors was not evident while in rural Madagascar, there were regular and recent transfer of ESBL-*Ec* between human, animal, and environment sectors (Miltgen *et al.*, 2022b; Gay *et al.*, 2023b). It would be interesting to carry out similar studies in Mauritius to produce the phylogenetic tree of ESBL-*Ec* in Mauritius and determine the distribution between the different sectors. We suppose that Mauritius, being a densely populated country with few animal farming, may have a low transmission between the animal to human sector.

A quote from Rebecca Brown can be applied to this AMR context as well. It illustrates the importance of having data in the local context and of a timely surveillance on antibiotic consumption, use and resistance in Mauritius:

*“You cannot fight a battle you do not see or know exists.*

*You cannot defeat an enemy when you do not even know he is attacking you.”*

### Surveillance of Antibiotic consumption

This thesis provides important information that can be used in the formulation of the National Action Plan on AMR.

Having a robust surveillance system at the level of the Ministry of Health and Wellness is primordial to understand the burden the antibiotic consumption and resistance before ultimately finding the right measures to be taken to tackle this issue in Mauritius.

Concerning the surveillance of antibiotic consumption, the Pharmacy Board gives approval for the entry of all antibiotics in the country, whether human and animal. The collection of data can be started at this level itself. The information that can be obtained at this level, are the total tonnes of antibiotics imported into the country.

The data on antibiotics can be obtained through the Central Supply Division of the Ministry of Health and Wellness for the public human health institutions. On the other hand, the Ministry of Agro-Industry and the wholesale importers of antibiotics can provide data on antibiotic consumption for the animal and private human sector.

The Central Supply Division already has an electronic database where the antibiotics distributed to health institutions can be retrieved and exported via Microsoft Excel or pdf. Pharmacist, statistician or dedicated personnel of the Ministry of Health and Wellness can be trained to calculate the DID as calculated in the study above. The denominator which is the attendances of each health center and hospital can be obtained via the Health Records Department. Having the denominator allows comparison to be made between the different health centers and hospitals to identify the institution with the higher antibiotic consumption.

The pharmaceutical companies distribute antibiotics to the different private pharmacies, clinics, veterinary pharmacies and even the Ministry of Agro-Industry and Ministry of Health and Wellness. They all have an electronic system containing these data and they can submit the data on a regular basis to the Pharmacy Board of the Ministry of Health and Wellness. Having a trained data collector at the Pharmacy Board who will compile those data will enable the Ministry to have a proper record of all antibiotics entering the country. Consequently, the antibiotic consumption can be calculated for the private sector. The clinics have a record of patients' attendances and that can be shared with the Ministry and be used as denominator. The private pharmacies however, have no clear records of patients coming to buy antibiotics or medications. For them, the consumption can be calculated in kilograms and DDD by class of antibiotics. This will allow the trend of sales of antibiotics in the private pharmacies to be determined and surveys can be carried out to determine the use.

Consequently, the antibiotic consumption can be monitored by the Ministry of Health and Wellness itself with little effort, budget or human resource involved. The data collector can be trained in

monitoring of both antibiotic consumption and psychotropic medications which are both priorities for the country. This will facilitate the surveillance of antibiotic consumption that would be easily done on a yearly basis, hence monitoring the consumption of each health institution, whether public and private. Training a group of healthcare personnel on the calculation of the indicators will enable the Ministry of Health to be independent and effective in the calculation of DDD at all levels. A cascade of training can be done so that each region is able to monitor the antibiotic consumption and take appropriate actions. This will enable both the surveillance and response at the region level to be effective and quick. At the regional level, surveys on antibiotic use can be undertaken to assess the implementation of antibiotic stewardship program. Particular attention should be given to identify misuse as for example wrong and lengthy duration of antibiotics given during surgical prophylaxis as well as inadequate AST done before prescription of WATCH and RESERVE antibiotics.

Full time Infection Prevention nurses should monitor not only IPC but also antibiotic use in the public and private institutions. At least two IPC nurses should be employed in each regional hospital, two per region for health centers and specialized hospitals and one in the private sector.

Surprise and regular antibiotic surveys should be done to ensure reliable and correct data to be obtained and hence, promote adherence to the guidelines. The antibiotic use surveys should be also extended to the private sector starting with the clinics and ultimately the private pharmacies. This will prevent the over prescription and over-the-counter sales of antibiotics in the private sector. Though the Pharmacy Act is present and states that antibiotics should be given against a prescription only, its implementation should be enforced through regular trials and surprised visits at the private pharmacies.

The total antibiotic consumption for the human health per year can therefore be obtained and communicated to the different stakeholders.

Another part of the surveillance is collection of data on antibiotic consumption for the animal sector. All data used for the animal sector should be sent from the Pharmacy Board to the Ministry of Agro-Industry. The Ministry of Agro Industry should also have a health personnel to work on antibiotic consumption. The variables as number and species of animals, place of farm, disease, estimate live weight of animals and prescription by veterinary should be included in the line list.

The PCU and ALEA the standard indicator measuring the consumption of antibiotic in the animal sector will then be obtained.

This system of collection and analysis of data will benefit the country and fulfill one major requirement of the National Action Plan on AMR. It will enable the stakeholders to monitor antibiotic consumption in Mauritius allowing them to take appropriate actions to meet the countries requirements.

#### Surveillance of antibiotic resistance

For the monitoring of antibiotic resistance at the Central Health laboratory, this study shows the importance of using an electronic surveillance system which will allow the trend and pattern of resistance to be seen in real time. The data is currently collected in a paper-based system. Having a dedicated person for the electronic collection of data will be greatly beneficial for the country. The priority pathogens as defined by WHO can be collected on a trial basis first. The variables to be collected at the beginning should be as in the study above; the date, serial number, name of patient, sample, pathogen detected, hospital, ward, age of patient and AST results. Once this has been established, the list of deaths in the hospitals can be shared by the records officer to determine the mortality of patient due to AMR.

Some indicators as MDR and carbapenem resistant organisms should be monitored regularly and suitable measures taken in case of any outbreaks of resistant organisms.

Furthermore, AST should be done more regularly, especially before using antibiotics of the WATCH and RESERVE category. Pharmacists should ensure that all antibiotics of the RESERVE category are administered only after the infected specimen has been sent to the laboratory for AST.

### The need for a one health approach

The One Health approach is a comprehensive and globally recognized strategy that calls for collaboration and cooperation across various disciplines to address health challenges that arise at the intricate intersection of humans, animals, and the environment (Walsh, 2018; Hernando-Amado *et al.*, 2019; Badau, 2021; Kim and Cha, 2021). Among the critical issues that necessitate the implementation of the One Health approach, antibiotic resistance stands out (Collignon, 2013; Hernando-Amado *et al.*, 2019; White and Hughes, 2019; Kim and Cha, 2021).

This study illustrates antibiotic consumption in the human and animal sector in Mauritius. Although it is now largely recognized that selection pressure exerted by bacteria is influenced by the overall antibiotic exposure, rather than just the consumption in a single sector, comprehending the pattern of consumption in the country allow the different Ministries to take appropriate steps to reduce antibiotic consumption and use.

It is now crucial to explore antibiotic resistance in animals and environment in Mauritius. Till date, no studies have been done in the country and no information is available concerning the antibiotic resistance and resistomes in the animal and environment.

Doing an investigation on resistant bacteria and resistance genes in premises of hospitals, animal farms, aquaculture settings and communities in Mauritius is a priority. Resistant bacteria originating in a specific geographic location can disseminate through cross-reservoir transmission, whether through direct contact, the food chain, or environmental pathways (Collignon, 2013; Van Puyvelde, Deborggraeve and Jacobs, 2018; Durso and Cook, 2019; Hernando-Amado *et al.*, 2019; Badau, 2021; Kim and Cha, 2021; Wang *et al.*, 2021; Kasanga *et al.*, 2023). The usage of antibiotics, persistence of antibiotic residues, and presence of resistant bacteria in the human-animal-environment niches are associated with the One Health triad due to the interdependence of these pillars in the food chain and environment (Walsh, 2018; White and Hughes, 2019; Badau, 2021; Kim and Cha, 2021; Velazquez-Meza *et al.*, 2022). Having more information on resistance will enable the country to understand the interplay between the various sectors.

To effectively combat antibiotic resistance in Mauritius, it is of the utmost importance to work on and strengthen the collaboration and coordination among healthcare professionals, veterinarians, environmental scientists, policymakers, and other stakeholders (Walsh, 2018; White and Hughes,

2019; Velazquez-Meza *et al.*, 2022). Although the One Health concept is recognized globally, each country needs to adopt this One Health strategy as well.

Since 2023, the One Health and the AMR committee has been set up in Mauritius with the different Ministries; namely Ministry of Health and Wellness, Ministry of Agro-Industry, and the Ministry of Environment. At present, the One Health and AMR Committee is already in place with the Ministries, Réseau SEGA of the IOC and WHO. Other organisations working on same topic in the region should be included as the CIRAD, OMSA, FAO, among others. It is crucial to establish coordinated and collaborative governance structures that bring together stakeholders from human health, animal health, and environmental sectors to develop and implement comprehensive strategies.

Through the One Health and AMR committee and platform, the stakeholders of the various Ministries will be able to present their data, share their concerns and difficulties in their field as well as show their progress in their work concerning AMR, instead of working in silos. By integrating insights from diverse fields such as human and veterinary medicine, environment, laboratory/microbiology, among others, each sector of the One Health committee will gain a comprehensive understanding of the development, dissemination, and potential solutions for antibiotic resistance in the country. This committee should be continued and data sharing across various sectors should be promoted.

Human and veterinary medicine provide insights into the clinical and therapeutic aspects, including the use and misuse of antibiotics in treating infections in humans and animals. By studying the interactions between bacteria, their hosts, and the surrounding ecosystems, the country can identify the pathways through which resistant strains are transmitted and the environmental factors that facilitate their survival and dissemination.

In addition, research can be done to understand the societal and economic implications of antibiotic resistance (Gronvall *et al.*, 2014; Robinson *et al.*, 2016; Durso and Cook, 2019; Hernando-Amado *et al.*, 2019; White and Hughes, 2019; Cella *et al.*, 2023). By examining the behaviors, attitudes, and practices of individuals, healthcare providers, and policymakers, Mauritius can identify barriers to implementing effective resistance management strategies and develop interventions that promote responsible antibiotic use. Additionally, economic evidence should guide decision-making to ensure the most effective and sustainable use of resources. This

multidisciplinary approach will allow the stakeholders to paint a more complete picture of this pressing issue in Mauritius. It will enable the Ministries to explore its complexities and identify the various factors contributing to the emergence and proliferation of AMR. Ultimately, by working together across disciplines, the country can address the global challenge of antibiotic resistance and safeguard the effectiveness of these life-saving drugs for future generations. Having One Health information concerning AMR in the local context is an important step to address this AMR challenge.

In the environment, AMR is of immense importance. Resistance can originate from humans, animals, or the environment itself, leading to a complex interplay that enables the transfer of resistance and the development of new clinically-relevant resistant strains. Wastewater and fecal waste, especially in cases of inadequate sanitation and open defecation, are common sources of diverse bacteria and microbes, including those that are resistant to antimicrobials (Finley *et al.*, 2013; Akiba *et al.*, 2015; Fletcher, 2015; Marathe *et al.*, 2016; Subramanya *et al.*, 2021). Therefore, it is crucial to prioritize the improvement of water and sanitation infrastructure to break the transmission chain between humans and the environment. This not only helps limit the spread of resistance but also reduces the risk of new forms of resistance emerging. While veterinary medicine, agriculture, human medicine, and the environment often operate independently, the interconnected nature of resistance calls for a comprehensive strategy aligned with the One Health approach (Stepanauskas *et al.*, 2006; Baquero, Alvarez-Ortega and Martinez, 2009; Allegranzi *et al.*, 2017; Lübbert *et al.*, 2017; Manning *et al.*, 2018; Fleming, 2019; Schmidt *et al.*, 2020; Kasanga *et al.*, 2023). No studies have been done till date on AMR genes in the environment and waste water in Mauritius.



### Political Commitment

In addition to its significant impact on human and animal health, AMR is also affecting the global economy and development. Policy makers worldwide have acknowledged the urgent need for a coordinated and proactive response to this challenge. AMR is now recognized as a pressing issue that requires the collective efforts of the global community to address effectively (Bhatia, Katoch and Inoue, 2019; Inoue, 2019; Tejpar *et al.*, 2022; Van Katwyk *et al.*, 2022).

During the last 10 years, several documents have been written and shared by WHO, OMSA, FAO, including the National Action Plan on AMR in Mauritius 2017 to 2022 (*The FAO-OIE-WHO Collaboration animal-human-ecosystems*, 2010; *Republic of Mauritius NAP AMR 2017-2022*, 2017; WHO Action Plan AMR, 2015). Nevertheless, although AMR-related commitments were made by several countries and the danger of antibiotic resistance recognised nationally and globally, measures to reduce antibiotic consumption and decrease resistance followed at a much slower pace.

AMR is a complex, multi-sectoral problem that requires a strong political commitment that enables local evidence-based solutions in Mauritius. The power of political will in the face of danger was seen during the pandemic of SARS-CoV2 worldwide. Indeed, within a short space of time, most countries across the whole world temporarily stopped air and sea travel and took important steps to prevent and control the spread of COVID 19.

Consequently, the consequences of AMR must be communicated to the political leaders of Mauritius, so that it is a high priority on national development agendas. Solid and concrete actions should be taken in the country to reduce antibiotic use and influence the factors leading to ABR. Policies that regulate antibiotic use in human, agriculture and veterinary medicine should be enforced so that the overall burden of antibiotic resistance in Mauritius is reduced.

### Role of travel on AMR

The recent Corona pandemic has shown the world to be a global village as pathogenic viruses and highly resistant bacteria can rapidly spread across the world through international travel. It has underscored the importance of close collaboration among authorities and scientists in managing health risks effectively. Consequently, AMR is not just a concern for individual countries, but a global issue that affects the entire world. The interconnectedness of the global food system, along with the increasing movement of livestock, agricultural products, and human travel, allows for the rapid spread and mixing of AMR genes that emerge.

In Mauritius, NDM-1, *Klebsiella pneumoniae* ESBL producers and colistin resistant *Klebsiella* were already present (Laurent et al., 2012; Khurshid Mungloo-Rujubali, Issack and Jaufeerally-Fakim, 2013; Basu et al., 2022)(Laurent et al., 2012; Khurshid Mungloo-Rujubali, Issack and Jaufeerally-Fakim, 2013; Basu et al., 2022). Moreover, a high prevalence of resistance of various pathogens and MDR organisms are present in the public health institutions of Mauritius (Issack et al., 2012; Gay et al., 2020; Nuckchady and Boolaky, 2020a)(Issack et al., 2012; Gay et al., 2020; Nuckchady and Boolaky, 2020a).

One explanation for this high prevalence of resistance could be due to the high number of tourists coming to Mauritius and Mauritians going to other tropical countries. According to the Tourism Statistics report, Mauritius has about 1.8 million tourists entering the country each year (Tourism in Republic of Mauritius, 2020)(Tourism in Republic of Mauritius, 2020). These tourists and Mauritians are important reservoirs of antibiotic resistance genes that are spread throughout the island (Ruppé et al., 2014; Hassing et al., 2015; Leo et al., 2019)(Ruppé et al., 2014; Hassing et al., 2015; Leo et al., 2019). These persons might be asymptomatic carriers of CRE or other resistant strains and they can in turn spread the resistant bacteria in the country.

Furthermore, India has emerged as a prominent destination for medical tourism, attracting a considerable number of individuals from Mauritius seeking specialized medical care. The advanced healthcare facilities, skilled healthcare professionals, and cost-effective treatment options available in India make it an appealing choice for Mauritians in need of medical interventions. However, it is essential to be aware of the potential risks associated with medical tourism, such as the transmission of antibiotic resistance genes especially from patients returning from India which is considered as an epicenter of the global antimicrobial resistance crisis as seen earlier (Kaur et al., 2017; Taneja and Sharma, 2019; Broom and Doron, 2020; 'India Emerging as a Medical Tourism

Hub \_ IBEF', 2023)). The emergence and spread of antibiotic-resistant bacteria, including *Klebsiella pneumoniae* ESBL producers, pose a concern in healthcare settings. Therefore, it is crucial for both patients and healthcare providers in Mauritius to prioritize infection control measures, appropriate antibiotic use, and surveillance strategies to mitigate the risk of antibiotic resistance transmission in patients returning from treatment abroad (Ruppé *et al.*, 2014; Hassing *et al.*, 2015; Leo *et al.*, 2019; 'India fast emerging as medical tourism hub\_ President Ram Nath Kovind', 2022; 'India Emerging as a Medical Tourism Hub \_ IBEF', 2023).

#### Role of multi drug evolutionary strategies to reverse ABR

Recent breakthroughs have shown that it is possible to reverse the evolution of antibiotic resistance by manipulating the selective advantage of resistant bacteria. While using a single drug typically promotes resistance, specific combinations of drugs can hinder bacterial growth while discouraging resistance to each individual component (Lázár *et al.*, 2013; Baym, Stone and Kishony, 2016a). Scientists have developed techniques that exploit the physiological and evolutionary interactions between drugs, directly disadvantaging resistant mutants. One approach involves a drug that partially suppresses the effect of another; resistance to the first drug removes its protection against the second, creating a disadvantage for resistant mutants. Another strategy is to counteract mutations that confer resistance by inducing synergy between the drug and another compound. Additionally, trade-offs between resistances to different compounds can occur, where resistance to one antibiotic leads to collateral sensitivity to another or to a compound whose toxicity is mediated by the resistance mechanism (Palmer and Kishony, 2013a; Andersson *et al.*, 2020; Merker *et al.*, 2020; Bottery, Pitchford and Friman, 2021). These innovative approaches can shift the selective advantage of resistant bacteria competing with their susceptible counterparts, potentially slowing down the rate of resistance evolution or even restoring drug sensitivity in resistant bacterial populations (Lázár *et al.*, 2013; Palmer and Kishony, 2013b, 2013a; Baym, Stone and Kishony, 2016b, 2016a; Gillings, Paulsen and Tetu, 2017; Andersson *et al.*, 2020; Merker *et al.*, 2020; Bottery, Pitchford and Friman, 2021; Sanz-García *et al.*, 2023).

This information should be considered during the development of the antibiotic stewardship program. Further studies are required to understand the mechanism of resistance and the factors affecting it.

## Promote alternatives (vaccines, phages, other) and biosecurity

### Vaccines as a tool to fight Antibiotic Resistance

Vaccines are administered as a preventive measure, reducing the occurrence of infectious diseases, and consequently lowering the need for antibiotic treatment. When a population achieves sufficient vaccine coverage, it not only provides direct protection to individuals but also contributes to the concept of herd immunity. This indirect protection helps to mitigate the emergence and spread of resistant strains within the population (Bloom *et al.*, 2018; Jansen and Anderson, 2018; Sevilla *et al.*, 2018; Buchy *et al.*, 2020; Alghamdi, 2021; Micoli *et al.*, 2021; Costanzo and Roviello, 2023).

In Mauritius, several vaccines are provided free of cost by the Ministry of Health and Wellness: the BCG vaccine, 2 doses of Measles Mumps Rubella, 3 doses of Hexavalent (Diphtheria, Pertussis, Tetanus, Haemophilus Influenza Type B, Polio- Inactivated, Hepatitis B) with booster dose, 2 doses of rotavirus, 3 doses of pneumococcal (quadrivalent), human papillomavirus, amongst others. The coverage of those vaccines is quite high, about 80 % among children as shown in table 3.

Other vaccines, Influenza, Covid and tetanus toxoid vaccines are also provided by the Ministry to the vulnerable population. The high vaccine coverage in Mauritius might be the reason for the moderate DDD compared to other countries (WHO Report on Surveillance of Antibiotic Consumption, 2016; ECDC AMR, 2020) (W Decreasing the incidence of viral infections with the help of vaccines also leads to a decrease in secondary infections and a decrease in prescription of antibiotics by doctors. Vaccine coverage, especially anti-bacterial vaccines however can be further improved to protect the population. The prevalence of diabetes mellitus in Mauritius is about 20%, making those people more prone to infections and antibiotic treatment (*Ministry of Health and Wellness The Trends in Diabetes and Cardiovascular Disease Risk in Mauritius*, 2021).

**Table 3: Immunisation coverage rates and performance indicators of vaccines given by the Expanded Programme on Immunisation at hospitals in Mauritius from 2005 to 2022 (MOHW, 2022)**

VACCINE  YEAR	BABIES ( 0-1 year )											
	BCG			DPT (3 <sup>rd</sup> dose)			POLIO (3 <sup>rd</sup> dose)			MMR (2 <sup>nd</sup> dose) <sup>®</sup>		
	Mauritius	Rodrigues	Republic of Mauritius	Mauritius	Rodrigues	Republic of Mauritius	Mauritius	Rodrigues	Republic of Mauritius	Mauritius	Rodrigues	Republic of Mauritius
2005	90.1	99.6	90.5	87.4	98.2	87.9	87.9	82.9	87.6	87.9	100.0	88.6
2006	89.3	100.0	89.8	88.2	94.3	88.5	89.8	95.3	90.0	92.2	97.8	92.4
2007	90.6	96.3	90.9	88.7	98.1	89.2	88.7	98.1	89.2	91.4	91.1	91.4
2008	90.6	100.0	91.4	97.0	100.0	97.8	97.2	100.0	97.8	90.0	100.0	90.9
2009	88.9	100.0	89.4	92.7	100.0	93.4	93.4	100.0	93.4	92.3	100.0	93
2010	88.4	100.0	89	88.4	100.0	89.1	89.1	100.0	89.8	88.5	92.7	88.7
2011	88	95.7	88.4	86.1	90.7	86.3	86.8	90.7	87	88.9	90.8	89.0
2012	87.2	100.0	87.9	86.6	100.0	87.3	87.7	100.0	88.3	88.5	93.5	88.7
2013	86.1	98.0	86.7	88.1	93.8	88.4	89.6	93.8	89.8	89.7	93.5	89.9
2014	86.5	94.7	86.9	85.8	99.0	86.5	87.5	99.0	88.1	88.2	91.4	88.4
2015	85.3	97.3	85.9	86.5	98.4	87.2	87.8	98.4	88.1	89.2	93.0	89.4
2016	86.3	98.6	87.0	84.3	98.4	85.1	95.8	98.4	95.9	81.6	86.2	81.8
2017	86.1	98.9	86.8	82.8	91.4	83.3	83.6	91.7	84.0	80.7	85.6	81.0
2018	85.7	90.4	86.0	86	89.5	86.2	86.7	89.5	86.9	93.1	97.1	93.4
2019	85.6	94.6	86.2	86.5	91.5	86.8	86.5	91.5	86.8	93.8	92.8	93.8
2020	82.5	95.9	83.4	82.9	99.6	84.1	82.9	99.6	84.1	82.0	88.0	82.4
2021	81.7	84.2	81.8	82.8	85.3	83.0	83.6	85.3	83.8	76.5	97.1	77.9
2022	82.1	78.9	81.9	78.9	89.7	79.7	79.6	89.7	80.4	89.1	73.0	88.0

### Role of IPC in resistance

The relationship between water, sanitation, and hygiene (WASH) and antimicrobial resistance (AMR) is intricate and multifaceted. Previous editions of AMR Control have emphasized the critical role of WASH in addressing AMR in both healthcare settings, in animal production and the environment (Allegranzi *et al.*, 2017; Manning *et al.*, 2018; Fleming, 2019; Ackers *et al.*, 2020; Lacotte *et al.*, 2020; Deryabina *et al.*, 2021). Hence, implementing infection prevention and control (IPC) measures plays a crucial role in reducing the need for antimicrobial usage and preventing the acquisition of AMR as inadequate IPC practices can contribute to the increased spread of drug-resistant infections (WHO Action Plan AMR, 2015; Fleming, 2019).

IPC has been a prominent focus on the global health agenda for several years, particularly in relation to infections acquired within healthcare facilities. There has been huge emphasis on addressing these healthcare-associated infections to ensure the safety of patients and healthcare workers. Effective leadership is essential in ensuring the success of IPC initiatives with nurses and medical doctors playing a central role in promoting IPC and leading efforts to ensure compliance with IPC guidelines (Allegranzi *et al.*, 2017; Manning *et al.*, 2018; Fleming, 2019; Deryabina *et al.*, 2021; Hansen *et al.*, 2023). Mauritius has no published information on IPC in healthcare settings till date. A National guideline is present on IPC in the healthcare settings and as from this year, 2023, IPC nurses have been allocated in the regional hospitals to ensure its implementation.

## Recommendations

This study provides useful information for a thorough understanding of ABR. The findings and results lead to the following recommendations:

- **One Health Governance:** It is crucial to establish coordinated and collaborative governance structures that bring together stakeholders from human health, animal health, and environmental sectors to develop and implement comprehensive strategies.
- **Comprehensive electronic surveillance Systems:** Implementing robust and timely surveillance systems to monitor the prevalence and patterns of antibiotic resistance, consumption and use in humans, animals, and the environment. This would enable early detection and response to emerging threats.
- **Stewardship Programs and Education:** Promoting responsible and judicious use of antibiotics through stewardship programs in healthcare settings, veterinary practices, and agriculture. Special attention should be given to the private sector, especially regarding the use of WATCH antibiotics. Infection control nurses should do periodic surveys to verify the implementation of the antibiotic stewardship program. Additionally, educating healthcare professionals, veterinarians, farmers, and the public about the importance of appropriate antibiotic use.
- **Preventive Measures:** Implementing preventive measures such as improved sanitation, infection prevention and control practices, vaccination programs, and biosecurity measures in livestock and aquaculture, ensure the proper disposal of waste by hospitals, laboratories, hotels, households, and others.
- **Studying the transmission dynamics of antibiotic resistance in the local context to prevent its spread.** Studies regarding the change in microbiome on travellers can be explored.
- **Public Education and Awareness:** Raising public awareness about antibiotic resistance, its consequences, and the individual and collective actions needed to mitigate its impact. Empowering individuals to make informed decisions regarding antibiotic use and promoting behavior change.
- **Enforcing laws and guidelines:** The Pharmacy Act should be enforced to prevent over-the-counter sales of antibiotics. Similarly, other guidelines such as IPC, antibiotic stewardship and others should be implemented. The National Focal Point should ensure the

implementation of these protocols and of the NAP AMR to be able to move forward with the plan to tackle AMR in Mauritius.

By addressing these key areas, considerable progress can be made in combating antibiotic resistance and safeguarding the effectiveness of antibiotics for current and future generations.

### Perspectives and Conclusion

This study provides important information that needs to be incorporated in the NAP AMR 2024-2028. The main objective of this thesis is to understand the incumbrance of antibiotic consumption, use and resistance in Mauritius. The investigations conducted as part of this thesis have shed light on the epidemiology of antibiotic resistance (ABR) as well as the pattern of antibiotic consumption and usage. These findings have provided valuable insights into the strengths as well as the gaps and weaknesses of the ABR situation in Mauritius. It also reveals that still more needs to be done to tackle this problematic of ABR in Mauritius. This thesis brings us to probe further into these following research questions: What is the role of animal and environment sector in the emergence and spread of ABR? Is there transmission of resistance genes between the different sectors? What are the other factors affecting ABR in Mauritius? Will antibiotic resistance decrease if antibiotic consumption and use is reduced in Mauritius? What is the role of Infection Prevention and Control in the hospital settings? What is the role of travel in the spread of ABR in Mauritius? These need to be further explored.

The importance of the One Health approach in ABR has been extensively discussed earlier in this thesis. It is essential therefore to adopt a One Health approach to understand the interplay of ABR in human, animals, and environment. Further research should be done to determine the epidemiology of ABR, antibiotic consumption and use in animals, plants and the environment. Moreover, to determine the interplay between human, animal, and the environment sector, it would be interesting to produce a phylogenetic tree of *ESBL-Ec* in the different sectors of Mauritius.

Considering the high prevalence of MDR pathogens in the country, the selection pressure was assumed to be high too. However, an intriguing finding of the study is that the antibiotic consumption expressed in terms of Defined Daily Dose per 1000 inhabitants per day was not high as compared to other countries. The data on antibiotic consumption suggest that further studies are needed to understand this high ABR in Mauritius. A decrease was observed in the proportion of selected pathogens sensitive to selected antibiotics, in the Mauritian hospitals from 2015 to



2023. It is hence urgent to explore the factors contributing to the high MDR bacteria and carbapenem resistant bacteria in the country.

The global movement of individuals, animals, and commodities facilitates the cross-border transmission of antibiotic-resistant bacteria. As a result, it would be interesting to do further research on the microbiota of medical patients or travelers returning to Mauritius from countries with high resistance rates as India, Thailand, among others.

In addition, we observed that the private sector has a higher consumption of critically important antibiotics including cephalosporins, tetracyclines, macrolides and aminoglycosides. Further information is needed on the use of antibiotics in the private sector. In the public hospitals as well, it is vital to develop and implement an antibiotic stewardship program. It is particularly important to address this issue as the implementation of an antibiotic stewardship program by the doctors in both the public and private sector will demand important changes. A brainstorming session at the Ministry of Health and Wellness and the Pharmacy Board is essential to find solutions for this issue.

Finally, it is a must for ABR to be high in the agenda of stakeholders at the Ministry level. Political commitment is crucial if the country wants to tackle ABR. A dedicated team at the different Ministries should work on this issue to ensure the implementation of the NAP AMR 2024-2028.

After working on these issues, Mauritius can develop effective strategies to combat antibiotic resistance and mitigate its impact on public health. By combining responsible prescribing practices with robust public policies, we can begin to address the complex issue of bacterial resistance. This comprehensive strategy aims to curb the selection and spread of resistant bacteria, preserve the effectiveness of antibiotics, and protect human and animal health. It is only through collective efforts and a multifaceted approach that we can hope to mitigate the threat posed by antibiotic resistance and ensure a sustainable future for our healthcare systems.

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## Annexes

### Lettre d'engagement de non-plagiat



POLE RECHERCHE  
Ecoles Doctorales

#### LETTRE D'ENGAGEMENT DE NON-PLAGIAT

Je, soussigné(e) VEERAPA-MANGROO Iovena P.  
en ma qualité de doctorant(e) de l'Université de La Réunion, déclare être conscient(e) que le plagiat est un acte délictueux passible de sanctions disciplinaires. Aussi, dans le respect de la propriété intellectuelle et du droit d'auteur, je m'engage à systématiquement citer mes sources, quelle qu'en soit la forme (textes, images, audiovisuel, internet), dans le cadre de la rédaction de ma thèse et de toute autre production scientifique, sachant que l'établissement est susceptible de soumettre le texte de ma thèse à un logiciel anti-plagiat.

Fait à Maurice, le (date) 06/10/2023

Signature :

Extrait du Règlement intérieur de l'Université de La Réunion  
(validé par le Conseil d'Administration en date du 14 décembre 2014)

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Les délits de contrefaçon, de plagiat et d'usage de faux peuvent donner lieu à une sanction disciplinaire indépendante de la mise en œuvre de poursuites pénales.



Ministry of Health and Quality of Life  
Mauritius

MHC/CT/NETH/VMLP

03 July 2017

Dr Lovena Preeyadarshini Veerapa-Mangroo  
Louis de Rochecouste Street,  
Forest side

Dear Madam,

Request for Ethical Clearance

Please refer to your letter dated 28 April 2017 regarding the above mentioned subject and be informed that your application for Ethical Clearance in respect of the project entitled "Antibiotic use and resistance in Mauritius." has been examined at the level of the Ministry.

2. This is to inform you that the Ethics Sub-Committee has given Ethical Clearance for the above project, subject to list of conditions annexed.

Dr (Mrs) M. Timol  
for Senior Chief Executive

## Questionnaires used for data collection in Epi Info for Point Prevalence Study on Antibiotic Use

### WHO pilot study: Point Prevalence Survey on Antibiotic Use in Hospitals

Count of antibiotic and related indication

Antibiotics	Related indicators

Name of antibiotic in notes

INN Name of antibiotic

Start date of current antibiotic

Unit dose

Doses of each active substance in combination product

Measurement unit

Daily frequency of administration of unit dose

Route of administration

Documented review

## WHO pilot study: Point Prevalence Survey on Antibiotic Use in Hospitals

Counter of Indication

Indications
1
2

Indication type

Duration of surgical prophylaxis

### Diagnosis

List of diagnosis 1

- ☐ Infections of the central nervous system
- ☐ Endophthalmitis
- ☐ Infections of the ear nose throat larynx and mouth
- ☐ Acute bronchitis or exacerbations of chronic bronchitis
- ☐ Pneumonia
- ☐ Cystic fibrosis
- ☐ Cardiovascular Infections: endocarditis vascular graft
- ☐ Gastrointestinal infections
- ☐ Intra-abdominal sepsis including hepatobiliary
- ☐ Surgical site infection involving skin or soft tissue but not bone
- ☐ Cellulitis wound deep soft tissue not involving bone not related to surgery
- ☐ Septic arthritis osteomyelitis of surgical site
- ☐ Septic arthritis osteomyelitis not related to surgery
- ☐ Symptomatic lower urinary tract infection
- ☐ Symptomatic upper urinary tract infection
- ☐ Asymptomatic bacteriuria
- ☐ Obstetric or gynaecological infections
- ☐ Prostatitis epididymo-orchitis
- ☐ Sexually transmitted disease
- ☐ Laboratory-confirmed bacteraemia
- ☐ Clinical sepsis
- ☐ Febrile neutropenia or other form of manifestation of infection in immunocompromised host
- ☐ Systemic inflammatory response with no clear anatomical site
- ☐ Completely undefined; site with no systemic inflammation
- ☐ Not applicable for antibiotic use other than treatment
- ☐ Viral infections

If other, please specify

The start date of treatment

Reason for antibiotics written in patient's notes

Sample taken for microbiology diagnostic



## WHO pilot study: Point Prevalence Survey on Antibiotic Use in Hospitals

Patient Unit Number

Patient Code

Gender

Age (years) if  $\geq 2$

Age (month) if  $< 2$  years

Newborns: Type of Preterm Birth

Weight of neonates in kg

Weight of child  $<$  age 13 in kg

Date of admission of patient

Surgery since admission

Presence of central vascular catheter

Presence of peripheral vascular catheter

Presence of urinary catheter

Presence of intubation device

## WHO pilot study: Point Prevalence Survey on Antibiotic Use in Hospitals

Ward ID

Ward Investigator

Ward Survey date

Ward Type

Total number of patients in ward

Eligible patients

Included patients

## WHO pilot study: Point Prevalence Survey on Antibiotic Use in Hospitals

Hospital ID	Hospital code	
<input type="text"/>	<input type="text"/>	
Survey Start Date	Survey End Date	
<input type="text" value="DD/MM/YYYY"/>	<input type="text" value="DD/MM/YYYY"/>	
Hospital Group		
<input type="text"/>		
Hospital Type	Type Speciality of Hospital	Hospital Ownership
<input type="text"/>	<input type="text"/>	<input type="text"/>
Hospital Total Beds	Hospital acute beds	Hospital ICU beds
<input type="text"/>	<input type="text"/>	<input type="text"/>
Hospital High risk beds		
<input type="text"/>		
Hospital Annual Admissions	Hospital Annual Patient days	Hospital Included Beds
<input type="text"/>	<input type="text"/>	<input type="text"/>
Hospital Eligible Patients	Hospital Included Patients	
<input type="text"/>	<input type="text"/>	