One Health Report on **Antimicrobial Utilisation and Resistance, 2019**

One Health Antimicrobial Resistance Workgroup, Singapore

One Health Report on Antimicrobial Utilisation and Resistance in Singapore, 2019

A Report by the One Health Antimicrobial Resistance Workgroup

Participating ministries and agencies:

Supported by:

This Report on Antimicrobial Utilisation and Resistance in Singapore is published by the One Health Antimicrobial Resistance Workgroup, comprising representatives of the Ministry of Health (MOH), Health Promotion Board (HPB), National Environment Agency (NEA), National Parks Board (NParks), PUB, the National Water Agency, and Singapore Food Agency (SFA). This report was compiled with the assistance of the Antimicrobial Resistance Coordinating Office (AMRCO), National Centre for Infectious Diseases (NCID).

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Acknowledgments

The One Health AMR Workgroup thanks the National Antimicrobial Resistance Control Committee (NARCC) and staff of the following for their provision and analyses of surveillance data:

- Centre for Animal & Veterinary Sciences, NParks
- National Centre for Food Science, SFA
- Environmental Health Institute, NEA
- Alexandra Hospital
- Changi General Hospital
- KK Women's and Children's Hospital
- Khoo Teck Puat Hospital
- National University Hospital
- Ng Teng Fong General Hospital
- Singapore General Hospital
- Sengkang General Hospital
- Tan Tock Seng Hospital
- Agency for Care Effectiveness, MOH

List of Abbreviations

AMR	Antimicrobial Resistance
AMRCO	Antimicrobial Resistance Coordinating Office
AMRWG	Antimicrobial Resistance Workgroup
AMU	Antimicrobial utilisation
ARB	Antibiotic resistant genes
ARG	Antibiotic resistant bacteria
ASP	Antimicrobial stewardship programme(s)
AST	Antibiotic susceptibility test/testing
ATC	Anatomical Therapeutic Chemical
AVA	Agri-food & Veterinary Authority of Singapore
AVS	Animal & Veterinary Services, NParks
CAVS	Centre for Animal & Veterinary Sciences, NParks
CFU	Colony-forming unit
CIP	Ciprofloxacin
CLSI	Clinical and Laboratory Standards Institute
CP-CRE	Carbapenemase-producing carbapenem-resistant Enterobacterales
CPE	Carbapenem-producing Enterobacterales
CR	Carbapenem-resistant
CRE	Carbapenem-resistant Enterobacterales
CRO	Ceftriaxone
CTX	Cefotaxime
DDD	Defined Daily Dose
DID	DDD per 1000 inhabitants
EHI	Environment Health Institute, NEA
EPA	US Environmental Protection Agency
ESBL	Extended spectrum beta-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FIB	Faecal indicator bacteria
GI	Gastrointestinal
GLASS	Global Antimicrobial Resistance Surveillance System
GP	General practitioner
HPB	Health Promotion Board
ID	Infectious Disease
IPM	Imipenem
IQR	Interquartile range
MDR	Multi-drug resistant
MEM	Meropenem
MIC	Minimum Inhibitory Concentration
MOH	Ministry of Health
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSP	Methicillin-resistant *Staphylococcus pseudintermedius*
NAFTEC	Nanyang Technological University Food Technology Centre
NARCC	National Antimicrobial Resistance Control Committee
NCFS	National Centre for Food Science, SFA

NCID	National Centre for Infectious Diseases
NEA	National Environment Agency
NPHL	National Public Health Laboratory
NTU	National Technological University
NUS	National University of Singapore
OIE	World Organisation for Animal Health
PUB	Public Utilities Board, Singapore's National Water Agency
QMRA	Quantitative microbial risk assessment
SDG	Sustainable Development Goals
SFA	Singapore Food Agency
VRE	Vancomycin-resistant Enterococci
WHO	World Health Organization

Executive Summary

Antimicrobial resistant organisms can be found in humans, animals, and the environment. The latter includes both natural and man-made environments such as healthcare settings and agricultural land, potentially affecting animal by-products intended as food. AMR is natural phenomenon that occurs when micro-organisms develop or acquire resistance to antimicrobials, rendering them ineffective. The development of AMR is accelerated by the use of antimicrobials in humans, animals and agriculture. Surveillance of antimicrobial consumption and resistance is one of five core strategies of Singapore's National Strategic Action Plan on AMR; data from surveillance are used to guide policy decisions and measure the impact of interventions.

Since the publication of the first One Health Report on Antimicrobial Utilisation and Resistance, 2017[1], surveillance in Singapore has been expanded to include the following:

- Antimicrobial sales for human use
- GLASS (WHO Global AMR Surveillance System) pathogens
- Resistance patterns of *Salmonella* spp. and *Escherichia coli* in local dairy farms
- Resistance patterns of indicator *E. coli* in the food production chain
- Resistance patterns of environmental bacteria in beaches, man-made water features and indoor environments

With the expansion of AMR surveillance programmes, baseline data are now available for key populations and surveillance sites, which will contribute towards the formulation of science- and risk-based targets to further drive AMR control efforts. This report collates the main findings of national surveillance activities conducted up to 2019, summarised below for each sector.

ONE HEALTH

A multi-sectoral study of non-typhoidal *Salmonella* isolated from human, animal and raw food samples was conducted in 2016. *Salmonella* isolates were most frequently resistant to ampicillin and tetracycline. Ceftriaxone-resistant strains were also detected in human extra-intestinal (16.0%), human gastrointestinal (6.8%) and poultry meat (15.9%) isolates. Continued One Health surveillance is recommended to monitor the emergence and spread of antimicrobial resistant *Salmonella* strains across sectors for risk assessment and mitigation.

HUMAN

The National Antimicrobial Resistance Control Committee (NARCC) monitors antimicrobial resistance, utilisation and stewardship in public acute care hospitals to encourage hospital accountability for patient safety and care.

In public hospitals, the total utilisation of broad-spectrum penicillins (IV amoxicillin-clavulanate and

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[1] One Health Report on Antimicrobial Utilisation and Resistance in Singapore, 2017. https://www.ncid.sg/About-NCID/OurDepartments/Antimicrobial-Resistance-Coordinating-Office/Documents/One%20Health%20Report%20on%20Antimicrobial%20Utilisation%20and%20Resistance%202017.pdf

piperacillin-tazobactam) has been on the rise since 2011, increasing from 114.5 defined daily doses (DDD) per 1000 inpatient days as last reported[1], to 123.1 DDD per 1000 inpatient days in 2019. Meanwhile, utilisation of 3rd & 4th generation cephalosporins has declined overall, with utilisation relatively unchanged at 82.6 DDD per 1000 inpatient days since last reported. Oral amoxicillin-clavulanate was the most heavily used of all antibiotics monitored in 2019, at approximately 508 DDD per 1000 inpatients days. Oral ciprofloxacin was the next most utilised, at 163 DDD per 1000 inpatient days.

Antimicrobial sales in the human health sector are being reported for the first time, as an additional reference to monitor trends. Based on private sector market research, the reported nation-wide sales volumes were generally stable from 2015 to 2019, ranging from 11.4 to 12.7 DID (DDD per 1000 inhabitants). Sales of penicillins, macrolides, tetracyclines (mainly doxycycline) and fluoroquinolones (mainly ciprofloxacin) were the highest. Overall sales to private sector clinics[2] (outpatient use) were approximately twice that of sales to hospitals[3] (mostly inpatient use).

In hospital settings, the incidence densities of *Clostridioides difficile*, multidrug-resistant *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus* (MRSA) and ceftriaxone-resistant *Klebsiella pneumoniae* continue on a downward trend observed since 2012. Since the last report, *C. difficile* incidence density has declined from 5.5 per 10,000 inpatient days in 2017, to 4.3 per 10,000 inpatient days in 2019. This decline is temporally correlated with the implementation of antimicrobial stewardship programmes in public hospitals since 2011, as well as the continual enhancement of infection control measures in hospitals. However, ciprofloxacin-resistant *Escherichia coli* rates have continued to rise, and the proportion of *K. pneumoniae* isolates resistant to ciprofloxacin remains relatively high. While the incidence of carbapenem-resistant *A. baumannii* and *Pseudomonas aeruginosa* are declining, carbapenem-resistant *E. coli* and *K. pneumoniae* rates are gradually increasing, with OXA being the predominant carbapenem-producing enzyme detected. Carbapenem-resistant Enterobacterales (CPE) are a growing concern worldwide and warrants close monitoring.

At the international level, Singapore enrolled in the WHO Global AMR Surveillance System (GLASS) in 2019 to support global data collection and benchmarking. The collection of data on GLASS pathogens offers additional insights on community-associated pathogens that lie outside the scope of NARCC, such as *Salmonella spp* and *Streptococcus pneumoniae*. Global benchmarking highlighted areas for possible improvement: in 2019, the proportions of MRSA and *E. coli* resistant to 3rd-generation cephalosporins in Singapore's two sentinel acute care hospitals were higher than the median of 31 high income countries reporting to GLASS.

ANIMAL

The total antimicrobial consumption (total kg of active ingredient) for animals is relatively low due to the small animal production and aquaculture industry here. Sales of veterinary antimicrobials are used as a proxy for consumption. Sales data are solicited through voluntary reporting by local veterinary drug wholesalers. In 2019, over 90% of wholesalers reported data, compared to approximately half of them in 2015. Based on reported data, tetracyclines, fluoroquinolones and penicillins were the top

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[2] All private dispensing clinics (GPs and Specialists) including specialists dispensing clinics within Private Hospitals
[3] Restructured/public hospitals and private hospitals (excluding dispensing clinics in private Hospitals)

three antimicrobial classes used for veterinary purposes from 2015 to 2019. No antimicrobials were sold for non-therapeutic uses (e.g. growth promotion), in line with national directives. The aquaculture industry remains the main consumer of antimicrobials, accounting for about 70% to 88% of total antimicrobial sales from 2015 to 2019.

Salmonella and *E. coli* are the main targets for AMR monitoring in food-producing animals. In local poultry farms, the average prevalence of multi-drug resistant (MDR) *Salmonella* in local chicken layer farms remained low (3.3%), MDR being defined as resistance to three or more classes of antimicrobials. However, the prevalence of MDR *Salmonella* was higher in local quail layer farms (>30%); this could reflect differences in farming systems between the more advanced chicken layer farms and small-holding quail farms. Resistance profiles of indicator *E. coli* are being reported for the first time: from 2018 to 2019, the percentage of MDR *E. coli* isolated from local chicken and quail farms remained stable between 17% to 26%, while that of ruminant MDR-*E. coli* isolates increased significantly from 2018 to 2019. *E. coli* isolates from all livestock populations showed highest resistance to tetracycline, ampicillin and nalidixic acid, with full susceptibility to meropenem and trimethoprim-sulfamethoxazole.

AMR surveillance in the companion animal sector is largely passive. Among clinical isolates from sick companion animals, a large majority of methicillin-resistant *Staphylococcus* spp. were identified as *S. pseudintermedius,* which rarely infect humans but can complicate treatment options for the infected animals due to its concurrent resistance to multiple antibiotics. Only one MRSA isolate was identified from clinical specimens from 2018 to 2019.

Wild birds and rodents in urban environments were also assessed for their potential to serve as vectors in AMR transmission. A joint study by NEA, SFA, and Nanyang Technological University (NTU) found that the proportion of wild bird *E. coli* isolates resistant to at least one of the antimicrobials tested was 80.8%, while that of isolates from rodents was 40.0%. A large proportion of the isolates were resistant to ampicillin (73.1%). These findings underscore the need for continued environment management and monitoring on drug-resistant bacteria in wild animals to better understand the risk posed to other animals and humans.

FOOD

Drug-resistant microorganisms are found in food chains globally as well as in Singapore, hence surveillance is necessary. Among various types of foodborne pathogens, non-typhoidal *Salmonella* is a priority organism for control at both import and retail levels, being the leading cause of foodborne illness in Singapore. Prevalence of this organism in food products is relatively low, owing to strict food safety measures in Singapore. Nevertheless, of the *Salmonella* isolates obtained from retail food products in 2017 to 2018, most were resistant to tetracycline and ampicillin, two antibiotics commonly used in the agricultural sector worldwide. In addition, over 30% of isolates were resistant to trimethoprim-sulfamethoxazole and chloramphenicol. MDR-*Salmonella* isolates were detected in raw poultry, raw pork and cooked/ready-to-eat food, and at a lower frequency, in raw seafood and raw vegetables.

In 2017, AMR surveillance was expanded to include the monitoring of indicator *E. coli* in retail raw and cooked/ready-to-eat food. *E. coli* isolates from food products were more frequently resistant to tetracycline and ampicillin but less frequently resistant to ciprofloxacin.

Extended spectrum beta-lactamase–producing *E. coli* (ESBL-Ec) is of particular concern in public health, and has been reported worldwide in various food products, particularly in meat. A joint study by SFA, NEA, Nanyang Technological University Food Technology Centre (NAFTEC) and the National Food Institute of Technical University of Denmark found ESBL-Ec in retail raw meats in Singapore, especially in raw chicken[4]. The study examined a total of 634 raw meats sampled from 97 supermarkets and 65 wet markets. A total of 225 ESBL-Ec isolates were recovered from 184 samples. The prevalence of ESBL-Ec in raw chicken, pork and beef was determined to be 51.2% (109/213), 26.9% (58/216) and 7.3% (15/205), respectively.

Enterococcus spp. in imported poultry is monitored for vancomycin-resistance. The rate of vancomycin resistant enterococci (VRE) detection from poultry intestinal samples continues to be low (1.6% in 2019).

ENVIRONMENT

In the environmental sector, the resistance profiles of enterococci, *Pseudomonas* and staphylococci present in various natural and built environments were examined, and a risk assessment of AMR in our urban waters was conducted.

Enterococci are frequently used to assess faecal contamination in fresh and marine recreational waters. The recreational beach waters monitored in this study by NEA met WHO recommendations of <200 counts per 100 mL of water. However, 61.1%, 65.4% and 67.7% of enterococci isolates from recreational beach waters, beach sand and coastal drainage sites respectively were non-susceptible to more than one antibiotic. Enterococci isolated from these sites showed similar susceptibility profiles: a large proportion were non-susceptible to erythromycin, and approximately half were non-susceptible to quinupristin-dalfopristin. Non-susceptibility to norfloxacin, tetracyclines and ciprofloxacin were also observed. A small proportion of these isolates were identified as vancomycin non-susceptible.

Man-made water features, including multi-use spa pools and other public water features used for recreational activity, are regulated by NEA under the Environmental Public Health (Licensable Aquatic Facilities) Regulations. One of the quality parameters is the level of *P. aeruginosa*. Among *P. aeruginosa* isolates recovered from man-made water features (spa establishments and other public water features used for recreational activities), 7% were found to be multidrug-resistant. In indoor environments surveyed, the proportion of staphylococci exhibiting resistance to more than one antibiotic was generally higher in childcare centres (41.5%) than offices (6.5%). *S. aureus* was found in small numbers of childcare centres (4.6%) and offices (2.6%); however, none were MRSA. Non-aureus staphylococcal species were the most commonly detected.

Antimicrobial-resistant bacteria and genes can be found in varying degrees in urban waters. However, potential risks are mitigated by effective waste treatment strategies. Local treatment processes of

[4] Guo S., Aung KT., Leekitcharoenphon P., Tay MYF., Seow KLG., Zhong Y., Ng LC., Aarestrup FM., and Schlundt J., 2020. Prevalence and genomic analysis of ESBL-producing *Escherichia coli* in retail raw meats in Singapore. J Antimicrob Chemother doi:10.1093/jac/dkaa461

wastewater were found to be efficient in removing antimicrobial-resistant bacteria and opportunistic pathogens. Using a risk assessment approach based on the quantitative microbial risk assessment (QMRA) framework, a study led by PUB found no perceived risks to our water supply. In addition, the probability of gastrointestinal illnesses from total *E. coli* and *Enterococcus* for recreational activities in reservoirs and catchments was assessed to be low. The probability of illness due to resistant, pathogenic strains of these organisms would therefore be even lower based on their low prevalence. The probability of getting folliculitis due to infection by pathogenic or resistant strains of *P. aeruginosa* by swimming in reservoirs and catchments were all found to be below the accepted threshold.

Overall, these findings underscore the importance of monitoring antibiotic-resistant bacteria in human, animals, food and the environment, in order to address their potential spread via various routes, and to assess possible linkages and associated health risks.

Introduction

Surveillance is one of five core strategies of Singapore's National Strategic Action Plan on Antimicrobial Resistance (AMR) (see Textbox 1). Surveillance of AMR and antimicrobial utilisation (AMU) provide important data for monitoring trends, assessing risks, guiding policy decisions and measuring their impact.

The *One Health Report on Antimicrobial Utilisation and Resistance, 2017*[1], was published as a first step towards an integrated surveillance system in Singapore. This second report updates on key findings of national surveillance and monitoring programmes in the human, animal, food and environment sectors, up to 2019.

Overview of surveillance structure

National AMR and AMU surveillance and monitoring programmes in Singapore are implemented by the ministries and national agencies responsible for human health, animal health, food and environment. These sectors are in turn supported by participating hospitals, laboratories and various stakeholders providing surveillance data to the relevant authorities within the sector. Across sectors, data sharing and One Health reporting is centrally coordinated under the AMR Workgroup (Figure 1).

Human health – Surveillance of key drug-resistant organisms and utilisation of important antimicrobials is carried out by all acute care hospitals in Singapore, and overseen by the National Antimicrobial Resistance Control Committee (NARCC; Textbox 2) appointed by the Ministry of Health (MOH). Antibiotic susceptibility testing (AST) is carried out by the hospitals' microbiology laboratories, while the National Centre for Infectious Diseases' National Public Health Laboratory serves as the national reference laboratory for examining new and emerging resistance. Data analysed and compiled by NARCC are reported to MOH, and provided to individual hospitals on a yearly basis for monitoring and control. Surveillance has been instituted in public hospitals since 2011, and more recently implemented in private hospitals in 2018. At time of writing, private hospital data were in the process of being compiled and have not been included in this report. Singapore also partipates in the Global Antimicrobial Surveillance System (GLASS), which collects AMR data on the WHO priority pathogens [5] in humans. The national surveillance programmes for drug-resistant gonococcal infections, HIV and tuberculosis are currently beyond the scope of this report.

Animal Health – Monitoring of priority drug-resistant organisms in poultry farms has been in place since 2010. This was extended to all local terrestrial livestock farms in 2018. Surveillance of local farms was undertaken by the former Agri-food and Veterinary Authority (AVA) until 2019. Following a re-organisation of Singapore's statutory boards in April 2019, surveillance is now implemented by the National Parks Board (NParks) in consultation with the Singapore Food Agency (SFA). NParks' Centre for Animal & Veterinary Sciences (CAVS) conducts the AST of animal bacteria, as well as examines bacterial resistance from clinically affected aquaculture and companion animals, and other animal

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[5] *E. coli, K. pneumoniae, A. baumannii, S. aureus, Streptococcus pneumoniae, Salmonella spp, Shigella spp, Neisseria gonorrhoeae*

populations such as local wildlife. Data on antimicrobial sales for veterinary use is collected yearly by NParks and reported to the World Organisation for Animal Health (OIE).

Food – Monitoring of drug-resistant foodborne pathogens has been in place since 2010 as part of the national food safety surveillance programme, with a focus on *Salmonella* spp. Prior to 1 April 2019, surveillance of food imports and slaughterhouses was the purview of the former AVA, while retail food surveillance was conducted by the National Environment Agency (NEA). The Singapore Food Agency (SFA), formed in April 2019, now oversees all food-related surveillance, including the surveillance of AMR foodborne pathogens. AST of food-borne bacteria is conducted by SFA's National Centre for Food Science.

Environment – National surveillance programmes for drug-resistant organisms in the enviroment are jointly developed by NEA and PUB. Studies on the presence of antibiotic resistant bacteria and genes in urban waters have been conducted by PUB in collaboration with local research institutions for assessing risks of AMR in local urban waters.

National Coordination – The One Health AMR Workgroup (AMRWG, see Textbox 1) coordinates the sharing of AMR and AMU data across sectors. This work is supported by the AMR Coordinating Office (AMRCO) of the National Centre of Infectious Diseases (NCID). The longer-term goal is to build a more integrated approach for national AMR and AMU surveillance in Singapore that would better elucidate the prevalence and transmission routes of AMR pathogens across sectors.

Textbox 1

Singapore's National Strategic Action Plan on AMR

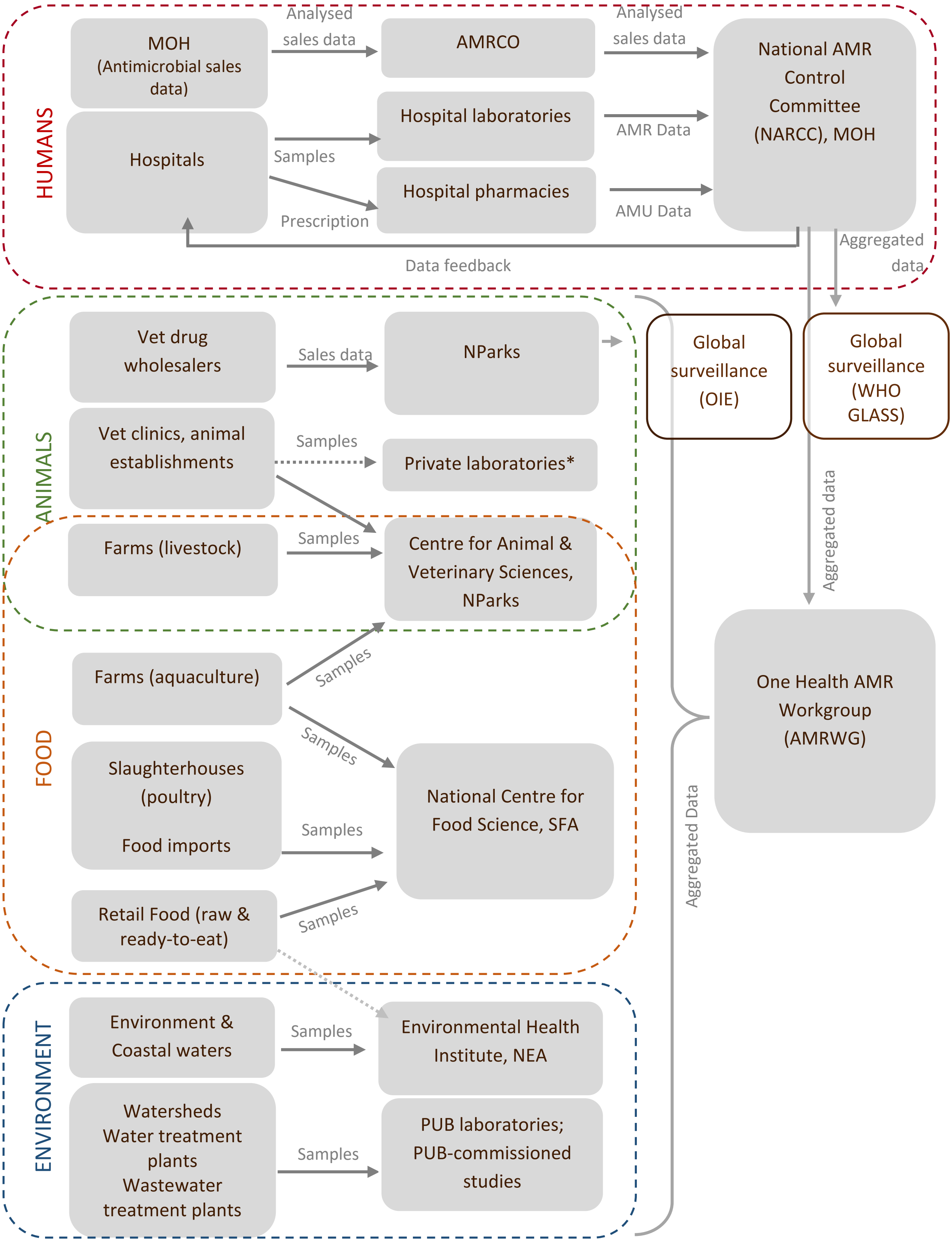
The National Strategic Action Plan (NSAP) was launched in November 2017. It aims to reduce the emergence and prevent the spread of drug-resistant organisms in Singapore through five core strategies:

- Education,
- Surveillance and Risk Assessment,
- Research,
- Prevention and Control of Infection, and
- Optimisation of Antimicrobial Use.

Implementation is overseen by the One Health AMR Workgroup (AMRWG), a multi-sectoral committee comprised of representatives from the Ministry of Health (MOH), Health Promotion Board (HPB), National Environment Agency (NEA), National Parks Board (NParks), PUB the National Water Agency and the Singapore Food Agency (SFA). The AMRWG is supported by the Antimicrobial Resistance Coordinating Office (AMRCO) of the National Centre for Infectious Diseases (NCID). Singapore's NSAP may be found at:

https://www.ncid.sg/About-NCID/OurDepartments/Antimicrobial-Resistance-Coordinating-Office/Documents/National%20Strategic%20Action%20Plan%20on%20Antimicrobial%20Resistance.pdf

Figure 1. AMR & AMU surveillance and monitoring in Singapore



*Veterinary clinics may choose to send their samples to the national laboratory (CAVS) or to private laboratories. Data from these private laboratories currently do not contribute to national surveillance.

Human and Animal Populations

Over the past 9 years, the population of Singapore has increased from approximately 5.2 million in 2011 to 5.7 million in 2019[6]. Currently, a total of 10 public acute care hospitals[7] account for 80% of hospital admissions. Total inpatient days in public hospitals have from risen from 2.5 million in 2011, to 3.3 million in 2019[8]. Another 8 private acute care hospitals[8] account for the remaining 20% of admissions, including a sizeable proportion of international patients. In Singapore, primary care is provided through 20 public polyclinics[8] and 2,304 general practitioner clinics[8] run by private sector general practitioners (GP). The private GP clinics meet about 80% of the total primary care demand[9].

Pet ownership in Singapore is also on the rise. The number of dogs licensed by the NParks has increased from 59,000 in 2011 to 70,000 in 2019, while Singapore's population of companion dogs, cats and small mammals was estimated to be nearly 300,000 in 2019[10]. There are currently 96 veterinary centres registered with NParks. The non-food producing animal population consists of an estimated 300,000 dogs, cats and small mammals, 1700 horses, and 8000 pet birds.

As a highly urbanised country with low local agricultural production, Singapore is highly dependent on imports for its food requirements. More than 90% of food is imported from over 170 countries[11]. Nevertheless, Singapore has a small, but thriving and increasingly important food fish aquaculture industry, which currently accounts for about 10% of local food fish consumption, and has been rising through the years. As Singapore aims to produce 30% of the population's nutritional needs locally by 2030, it is envisaged that the local aquaculture sector would continue to develop and expand in the long term. Three chicken layer farms producing more than 20% of local consumption of table eggs are currently the most significant livestock establishments. The population of food animals in Singapore and production outputs are presented in Table 1.

Table 1. Production of food animals, eggs and fish, Singapore 2019

Type	No. of farms	Total population	Production (% national consumption)
Chicken layers	3	≈2,524,000	≈ 500M eggs (27%)
Quail layers	2	155,000	-
Dairy cattle	3	180	-
Dairy goats	1	520	-
Farmed fish	117 (27 land-based)	Not applicable	≈4,700 tonnes (10%)

[6] www.singstat.gov.sg
[7] www.moh.gov.sg/resources-statistics/singapore-health-facts/health-facilities, 2019
[8] Ministry of Health, Singapore
[9] Primary Healthcare Services, www.moh.sg. Accessed on 21 Oct 2020
[10] Source: Euromonitor International, reported in www.businesstimes.com.sg, 11 Jan 2020. Accessed on 21 Oct 2020.
[11] SFA annual report, 2019

PART I. ANTIMICROBIAL UTILISATION

Antimicrobial Utilisation in Humans

Antimicrobial Utilisation and Stewardship in Public Hospitals

Antimicrobial Stewardship Programmes (ASP) were established in all public hospitals in 2011 with the aim of improving patient outcomes and optimising antimicrobial use through a system of audits and feedback. The rates of appropriate antibiotic prescribing and the acceptance rates of ASP interventions given are monitored by MOH through NARCC. Under this programme, ASP pharmacists and infectious disease specialists work closely to promote the appropriate use of antimicrobials to reduce the emergence of AMR in public hospitals.

NARCC (Textbox 2) monitors the utilisation of important antimicrobial groups, such as broad-spectrum penicillins, 3rd & 4th generation cephalosporins, fluoroquinolones and carbapenems, by the acute care hospitals. Hospitals report utilisation on a six-monthly basis using defined daily doses (DDD) per 1,000 inpatient days. DDD is the average daily maintenance dose for a drug's main indicated use in adults and is a standard determined by the WHO (Textbox 3).

Utilisation is calculated based on prevailing DDD values for each drug published by WHO[12]; adjustments to DDD values by WHO should therefore be taken into consideration when interpreting AMU trends presented in DDD. These limitations notwithstanding, the use of DDD is a commonly accepted and practical way to measure antimicrobial consumption.

Textbox 2

National AMR Control Committee (NARCC)

The National AMR Control Committee (NARCC) is appointed by the Ministry of Health (MOH) to oversee surveillance in the human health sector. NARCC is represented by all acute care hospitals and assists MOH in developing strategies to control the emergence and spread of AMR. NARCC is supported by two expert panels: The National Antimicrobial Resistance Expert Panel (NAREP), and the National Antimicrobial Stewardship Expert Panel (NASEP). The expert panels, comprising microbiologists, infectious disease physicians and pharmacists from public healthcare institutions, advise on issues related to surveillance of antimicrobial resistant organisms and antimicrobial utilisation. NARCC collects AMR and AMU data every 6 months from hospital laboratories and antibiotic stewardship teams. Data compiled and analysed by NARCC are provided to hospitals' management and MOH on a yearly basis. The data are used to monitor trends in hospitals and implement control measures where appropriate.

[12] https://www.whocc.no/atc_ddd_index/

In public acute care hospitals, the utilisation of broad-spectrum penicillins (IV amoxicillin-clavulanate and piperacillin-tazobactam) has been on the rise since 2011 (Figure 2), while utilisation of 3rd and 4th generation cephalosporins and oral ciprofloxacin has declined overall (Figures 3 & 4). The reported increase in oral ciprofloxacin use from 2018 was due to the inclusion of all hospital outpatient oral ciprofloxacin use; previously some hospitals had reported only their inpatient use.

In 2019, NARCC introduced the reporting of oral amoxicillin-clavulanate utilisation. Oral amoxicillin-clavulanate was the most heavily used of all antimicrobials monitored in 2019, at approximately 628.9 DDD per 1000 inpatients days. Oral ciprofloxacin was the next most utilised, at 163 DDD per 1000 inpatient days, followed by IV/oral levofloxacin (65.8 DDD per 1000 inpatient days) and IV amoxicillin-clavulanate (62.8 DDD per 1000 inpatient days). The use of carbapenems have remained generally stable, with a gradual decrease in imipenem use over the years. Meropenem remains the most widely used carbapenem in public hospitals (Figure 5).

Figure 2. Utilisation of broad-spectrum penicillins in public hospitals, 2011 – 2019, excluding oral amoxicillin-clavulanate

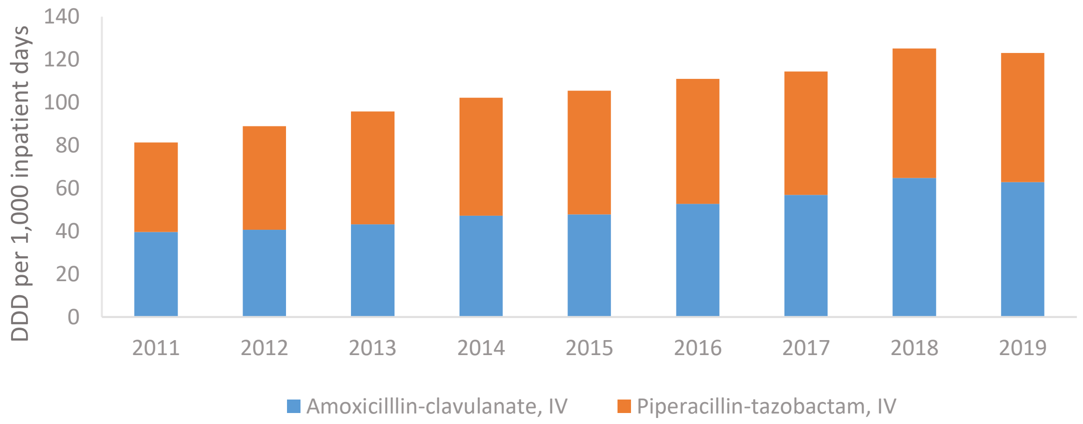
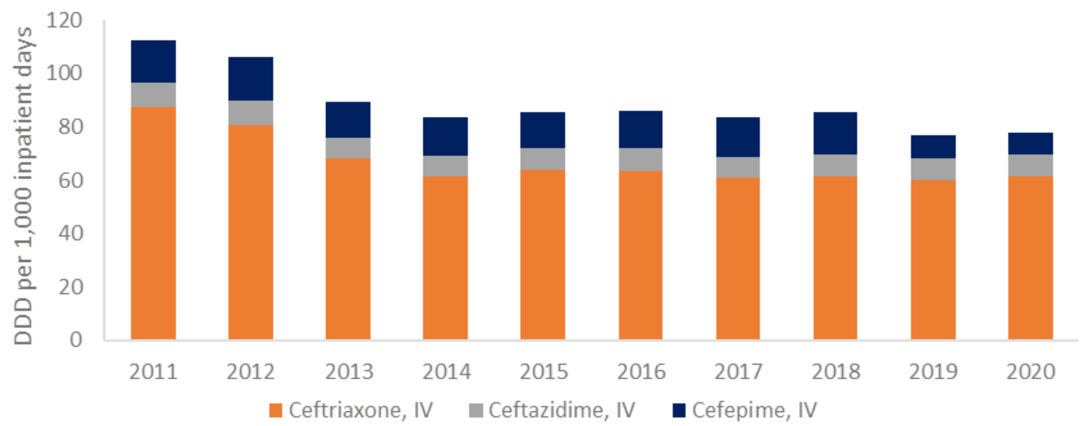
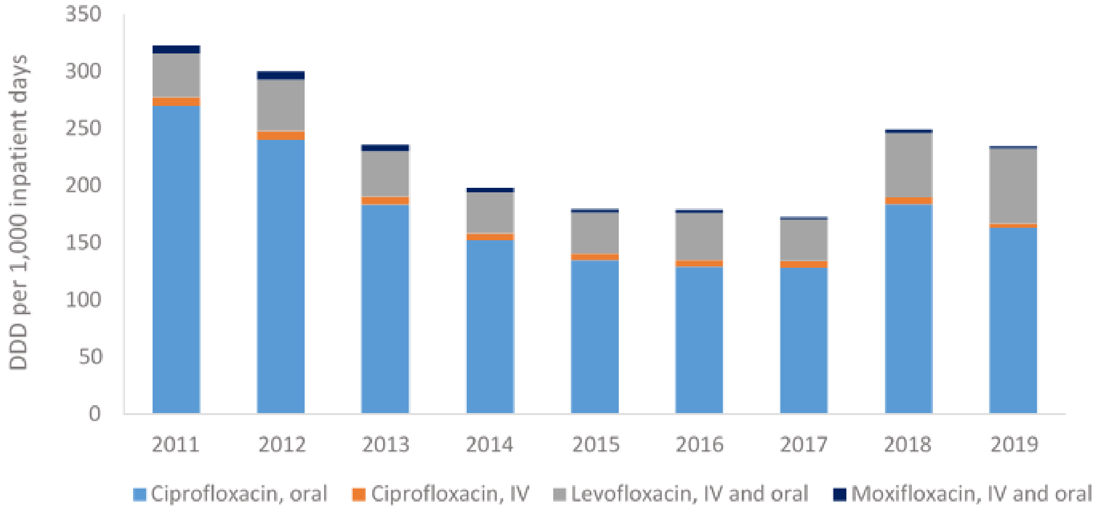


Figure 3. Utilisation of 3rd and 4th generation cephalosporins in public hospitals, 2011-2019



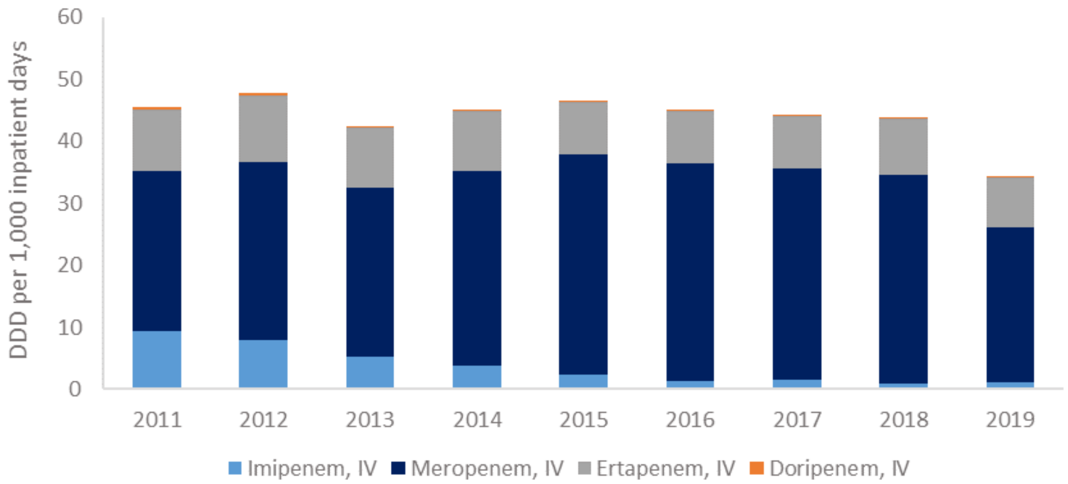
Note: Revised DDD assignment for IV cefepime from 2g to 4g in 2019 may have contributed to observed reduction in utilisation for that year.

Figure 4. Utilisation of fluoroquinolones in public hospitals, 2011-2019



Note: In 2018 and 2019, the reported increase in oral ciprofloxacin was due to the inclusion of outpatient use of oral ciprofloxacin.

Figure 5. Utilisation of carbapenems in public hospitals, 2011-2019



Antimicrobial Sales for Human use

Sales data[13] serve as an additional reference to antimicrobial trends. National antimicrobial consumption is typically reported as DDD per 1,000 inhabitants, or DID (Textbox 3). The main category of antimicrobials tracked are those classified under Anatomical Therapeutic Chemical (ATC) code J01 – Antibacterials for systemic use.

The national sales volume of J01 antibiotics in 2019 was 11.6 DID. Sales volumes remained fairly stable from 2015 to 2019, ranging from 11.4 to 12.7 DID (Figure 6). Sales of penicillins were the highest, followed by macrolides, tetracyclines (mainly doxycycline) and fluoroquinolones (mainly ciprofloxacin). Private sector clinics (outpatient use) accounted for more than half of the reported sales volume, approximately double that of sales to hospitals (mostly inpatient use) (Figure 7). Sector clinics include all private dispensing clinics (GPs and specialists) including specialists dispensing clinics within private hospitals, whereas hospitals include all restructured (public) hospitals and private hospitals.

Sales data is a more readily available form of data, and may be used as a general reference to antimicrobial consumption trends. This data should however be interpreted in context. The total DDD per 1000 inhabitants (DID) value was based on market research sales quantities, and may not be a true reflection of the national consumption. In addition, sales data may not correlate well with utilisation data, since not all antimicrobials sold may be utilised within the period of sales data reporting. Nevertheless, in the absence of national-level utilisation data, sales data enables the monitoring of trends within different healthcare settings. As we increase the comprehensiveness of local AMU data collection, we will be better able to draw associations between sales and consumption/utilisation patterns.

Textbox 3

Defined Daily Doses (DDD) and the Anatomical Therapeutic Chemical (ATC) classification system

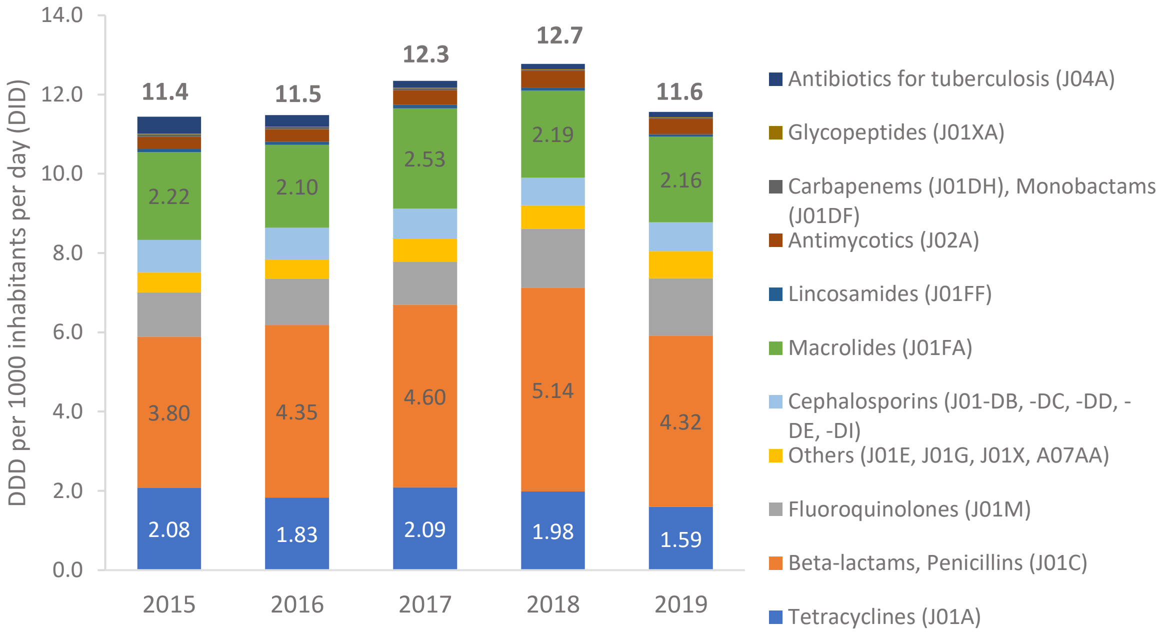
The Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a medicine used for its main indication in adults. The DDD is a technical unit of use and does not necessarily reflect the recommended or average prescribed dose. The number of DDDs is calculated as follows:

Number of DDDs = Total grams of active ingredient used / DDD value in grams

The DDD value is assigned by the WHO only for drugs that already have an Anatomical Therapeutic Chemical (ATC) code. The ATC classification system is the most commonly used method for aggregating data on medicines. Under this system, the active ingredients are classified into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

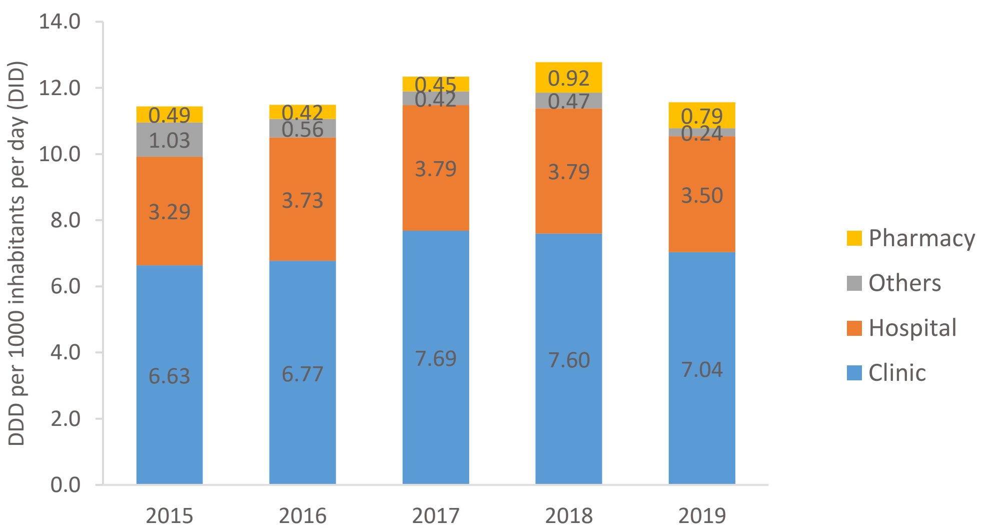
[13] Data source: MOH Singapore

Figure 6. Total Sales of antimicrobials, 2015 – 2019, by antimicrobial class (in DID)



DID of the three most commonly sold classes of antimicrobials are indicated within the columns. The total annual reported sales for the year in DID are indicated above each column. Data Source: MOH Singapore

Figure 7. Total Sales of antimicrobials by sales channel 2015 – 2019 (in DID)



Channels: **Pharmacy** - All pharmacies e.g. chained pharmacies and independent; **Others** - Polyclinics and other institutes like nursing homes, social service centres, community hospitals; **Hospital** – Restructured/public hospitals, private hospitals (excluding dispensing clinics in private hospitals); **Clinic** - All private dispensing clinics (GPs and Specialists) including specialists dispensing clinics within private hospitals. Data: IQVIA National Sales Audit. Source: MOH Singapore

Antimicrobial Utilisation in Animals

Singapore allows the use of antimicrobials for the treatment and prevention of diseases in animals, but prohibits their use for growth promotion. Additionally, the use of certain antimicrobials and substances, such as chloramphenicol, polymyxins, avoparcin, beta-agonists and nitrofurans, is prohibited for use in local food-producing animals and in animal feed owing to food safety concerns. The use of antimicrobials in local chickens throughout the laying period is also disallowed to prevent the presence of antimicrobial residues in eggs. These prohibitions are supported by a robust residue monitoring programme and post-market surveillance.

Antimicrobial Sales for Veterinary Use

Singapore has been reporting data on AMU in animals to the World Organisation for Animal Health (OIE) annually since 2015. Sales data is collected by the NParks through a voluntary survey of veterinary drug wholesalers, which serves as a proxy for antimicrobial utilisation in animals.

Overall, the total antimicrobial sales recorded from 2015 to 2019 has been increasing. This is attributed in part possibly to the growing animal populations in Singapore, and in part to the increase in wholesalers submitting data, the proportion of which increased from 52.2% in 2015 to more than 90% in 2019 (Figure 8).

Tetracyclines, fluoroquinolones and penicillins were the most commonly sold antimicrobials for veterinary use from 2015 to 2019 (accounting for about 74% to 92% of total antimicrobial sales) (Figure 9). Reported sales of tetracyclines has generally increased each year from 2015 to 2019, attributed largely to increased sales to the aquaculture sector. There has been a decreasing trend in fluoroquinolone sales, from 437 kg in 2015 to 239 kg in 2019. On the other hand, penicillin sales have generally increased from 2015 to 2019, with a significant increase in 2019 in sales to the aquaculture sector associated with an outbreak of bacterial infection in farmed food fish. No antimicrobials were sold for non-therapeutic uses (e.g. growth promotion) from 2015 to 2019.

Of the food production sectors in Singapore, the aquaculture industry consumes the most antimicrobial (by weight) each year, accounting for about 70% to 88% of total antimicrobial sales from 2015 to 2019 (Figure 8). In contrast, AMU in terrestrial livestock remains low despite the highly intensive nature of local chicken layer farms. This is reflective of the mature state of the chicken layer industry here, characterised by adherence to good animal husbandry practices, effective biosecurity measures to prevent disease introduction, routine vaccination programmes for disease prevention and good compliance to antibiotic restrictions. Whereas in the local aquaculture industry, other than a few large progressive farms, most fish farms here are small holdings. Antimicrobial usage is further compounded by the limited availability of tropical food fish vaccines worldwide, and reduced cost-effectiveness of vaccination for smaller holdings. To reduce reliance on antimicrobials, the SFA and NParks are working with the aquaculture sector to improve vaccination regimens and health management programmes.

AMU in the companion animal sector has generally remained stable over the years (Figure 8), despite a growing companion animal sector. The number of licensed dogs in Singapore has increased by almost 13% from about 62,000 in 2015 to 70,000 in 2019, and the estimated cat population is also increasing. The number of veterinarians in companion animal practice and the number of companion animal veterinary clinics have also correspondingly increased. The stable AMU in the companion animal sector reflects responsible prescribing and use of antimicrobials in this sector. Other contributing factors include good animal husbandry and management practices of animal owners and caregivers, and improved uptake and awareness of preventative care, such as vaccination, anti-parasitic treatments, and regular health checks. To further reinforce these practices, NParks, together with the Singapore Veterinary Association, developed and published a set of national vaccination guidelines for companion animals in 2020.

Figure 8. Annual reported sales (kg) of antimicrobial drugs by animal sector, 2015 – 2019

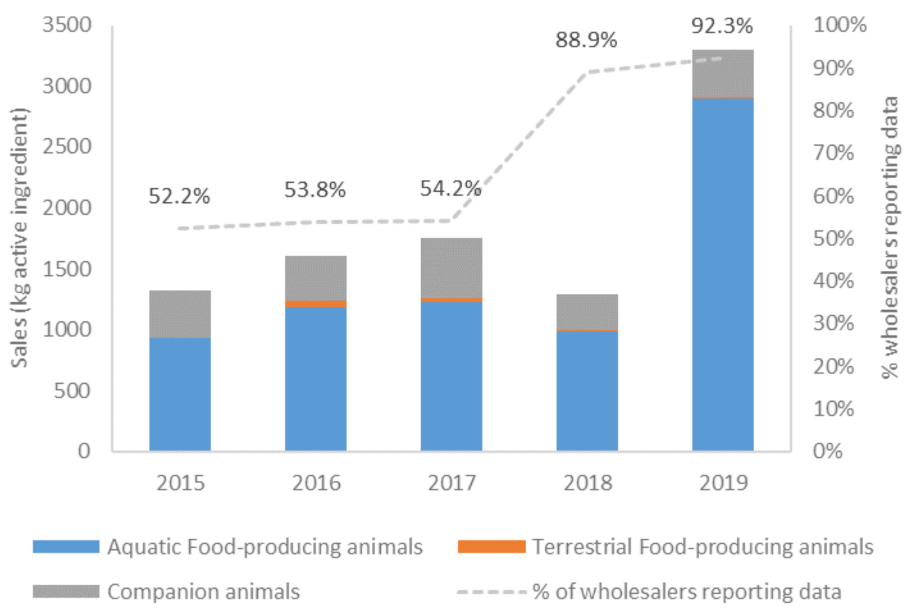
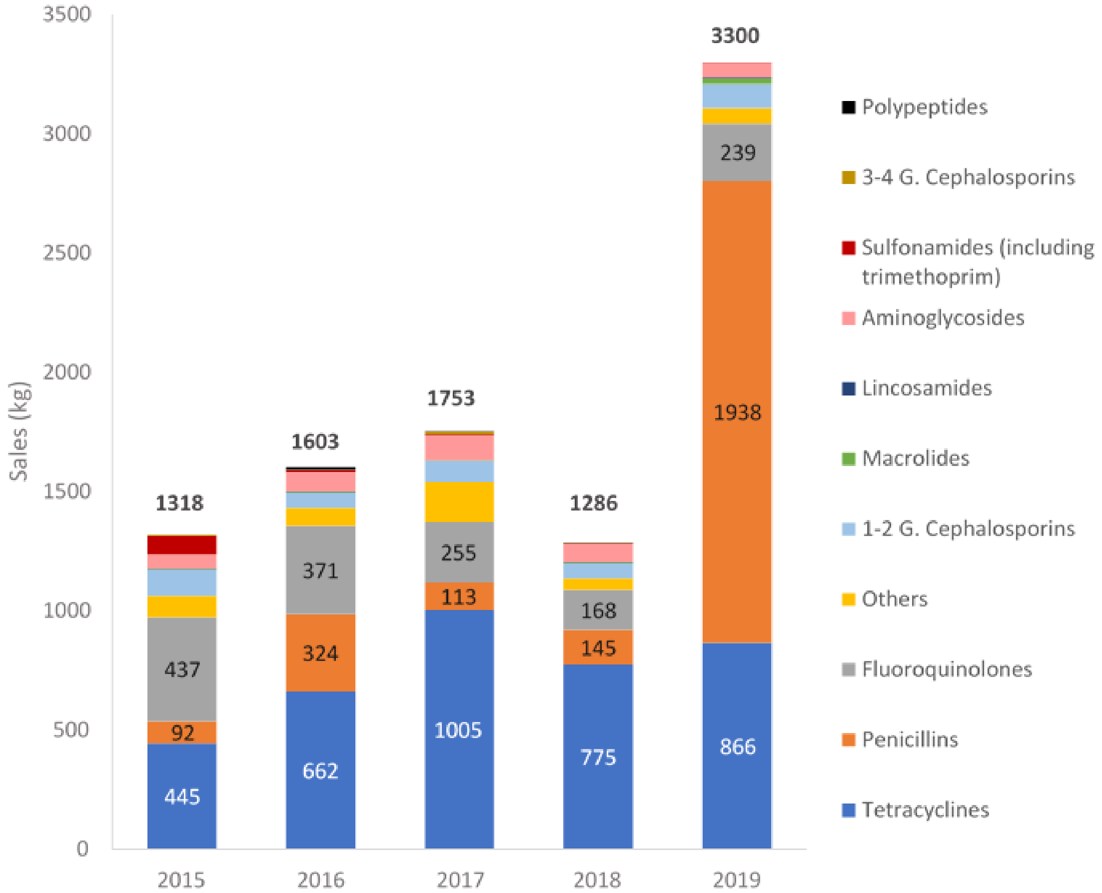


Figure 9. Annual reported sales (kg) of antimicrobial drugs in the animal sector, by antimicrobial class, 2015 to 2019



Note: Volumes (kg) of the three most commonly sold antimicrobials are indicated. Total annual reported sales in kg are indicated above each column. No sales were reported from 2015 to 2019 for arsenicals, glycopeptides, glycophospholipids, nitrofurans, orthosomycins, pleuromutilins, quinoxalines, streptogramins and quinolones other than fluoroquinolones. The volume of amphenicols sold (< 1 kg) are too small to be reflected in this chart.

Conclusions and Steps Forward

Efforts to collect data on antimicrobial consumption, particularly antibiotic consumption, have been expanding in recent years, with the aim towards obtaining reliable estimates of national consumption in the human and animal sectors.

In the absence of national-level antimicrobial utilisation data, sales volumes currently serve as the main source of national consumption estimates for the human and animal health sectors and provide some useful insights as to where antimicrobials are most used. Given the limited agriculture sector, sales for human use in Singapore well exceed that for animal use, while sales to private outpatient clinics is approximately twice that for public and private inpatient use. The aquaculture industry in Singapore continues to be the main consumer of antimicrobials in the animal sector. However, sales data are insufficient to illuminate consumption patterns and volumes at the clinic or farm level. Annual sales trends should be interpreted with caution as they do not necessarily correspond with utilisation. The collection of comprehensive utilisation data therefore remains the most valuable for monitoring consumption and guiding the development of targeted, effective strategies and interventions.

The increasing participation of veterinary drug wholesalers reporting sales data over the years is an encouraging trend that has allowed for a more accurate reflection of antimicrobial sales in the animal and veterinary sector. It signifies a growing acceptance of data reporting by the industry and a positive response to NParks' engagement efforts even as Singapore reviews the prevailing regulation of veterinary medicines. A combination of outreach and education, promoting good animal husbandry and management practices, facilitating vaccine registration and use, development of vaccination and antimicrobial prudent use guidelines, and strengthening of regulations on veterinary medicines and animal industries are part of NParks' overall strategy towards a reduction of AMU in the animal sector, especially those critically important to human health.

Work is underway in the human health sector to collect data on antimicrobial utilisation in sentinel private and community sectors, through engagement and pilot programmes to encourage data sharing at the prescriber level. Likewise, expanding AMU data collection at the farm and community levels are our next steps in the animal sector.

PART II. ANTIMICROBIAL RESISTANCE

Antimicrobial Resistance - One Health

One Health is an integrated, unifying approach that aims to achieve optimal and sustainable health outcomes for people, animals, and ecosystems. It recognises that the health of humans, domestic and wild animals, plants, and the wider environment (our ecosystems) are closely linked and inter-dependent. One Health is especially valuable when combatting zoonoses and AMR, where cross-sector collaboration is essential for effective control.

Antimicrobial resistance in non-typhoidal *Salmonella* from humans, food and animals in Singapore

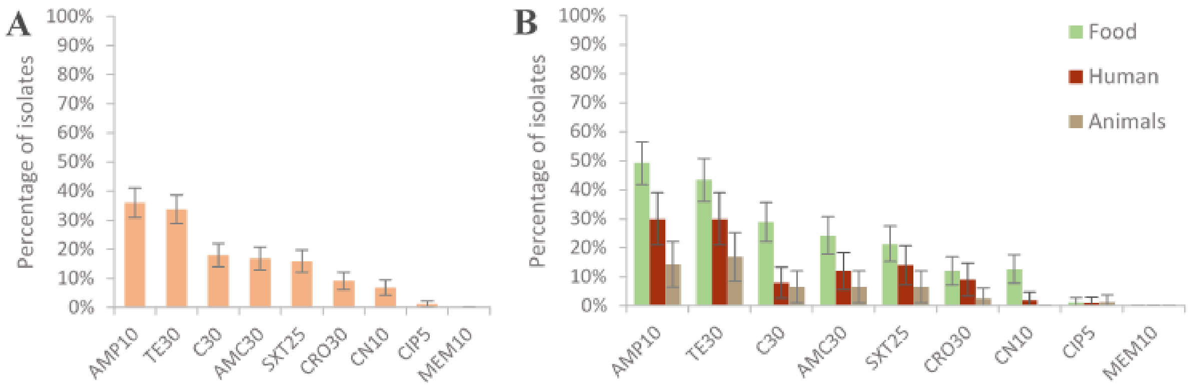
Salmonellosis is a leading cause of food poisoning in Singapore[14] and a notifiable disease since 2008. It is caused by pathogenic strains *Salmonella enterica* serovars naturally present in the digestive tracts of many animals, which can be transmitted to humans via direct contact with the animal, or indirectly through the consumption of contaminated food. Infection with drug-resistant *Salmonella* can further complicate treatment and result in poorer outcomes for patients. In 2016, a collaborative study by NEA, the former AVA and participating public hospitals was initiated to examine the resistance profiles of *Salmonella* isolated from human, animal and raw food samples in Singapore. This study involved 345 *Salmonella* isolates obtained from humans (n=99), raw food commodities (n=169) and animals (n=77; comprised of layer chickens, companion animals and wild birds). The isolates were subjected to AST using the disc diffusion method according to the Clinical and Laboratory Standards Institute (CLSI, 2013).

<u>Resistance profile of all *Salmonella* isolates</u>

Overall, the study showed that resistance against ampicillin (36.0%) and tetracycline (33.7%) were the most frequent, whereas resistance against meropenem, ciprofloxacin and gentamicin were the least (Figure 10A). This profile was generally consistent across human, food and animal isolates (Figure 10B). However, the resistance percentage among food isolates was relatively higher than that of human and animal isolates, and resistance percentage of human isolates higher than animal isolates. This, notwithstanding, should be interpreted against the relative low percentage (2% in 2016) of Salmonella detection in food samples along the food chain (Figure 11). Resistance profiles of *Salmonella* isolates within each of these three groups are summarised below in Figures 12 to 14.

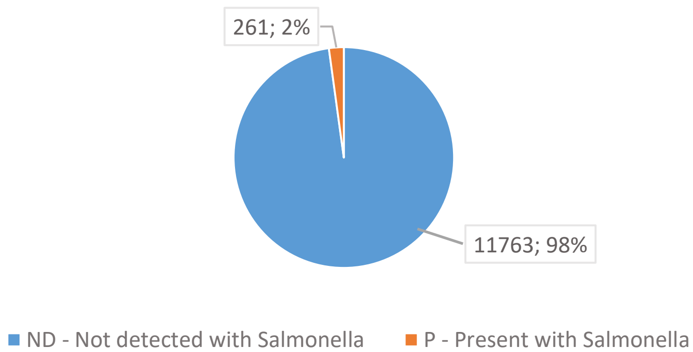
[14] Epidemiology News Bulletin 2019, 45(2), Ministry of Health, Singapore

Figure 10. Percentage resistance of *Salmonella* isolates (n=345) obtained from humans, food and animals, 2016



Note: Figure 10A presents the % resistance of all isolates in this study, Figure 10B compares the % resistance across food, human and animal isolates to antimicrobials tested. Disc diffusion was performed with 8 classes of 9 antimicrobials: AMP10 = ampicillin, TE30 = tetracycline, C30 = chloramphenicol, AMC30 = amoxicillin-clavulanic acid, SXT25 = trimethoprim-sulfamethoxazole, CRO30 = ceftriaxone, CN10 = gentamicin, CIP5 = ciprofloxacin, MEM10 = meropenem

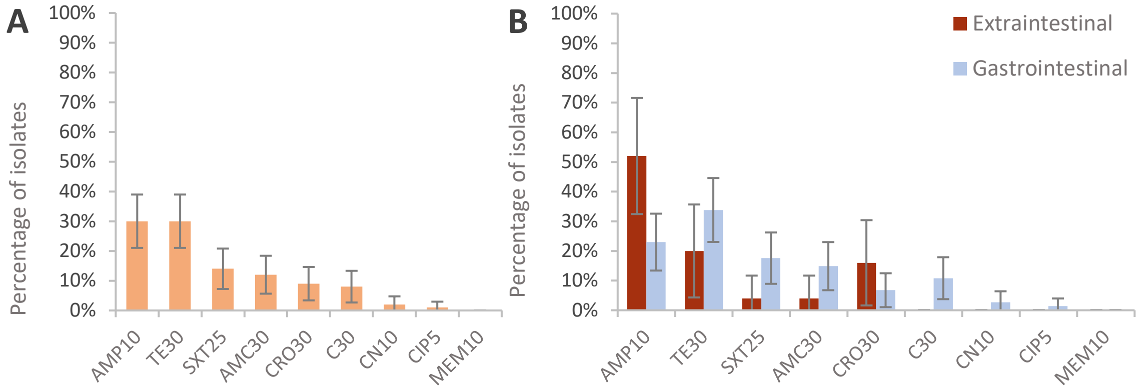
Figure 11. Percentage (%) detection of *Salmonella* from food samples along the food chain, 2016



Resistance profile of *Salmonella* isolates from human samples

Of 99 *Salmonella* isolates from human samples, resistance against ampicillin (30.0%) and tetracycline (30.0%) were the most frequent (Figure 12A). Human extra-intestinal and gastrointestinal isolates displayed somewhat different resistance profiles: amongst human extra-intestinal isolates (n=25), resistance against ampicillin (52.0%) and tetracycline (20.0%) were the most frequent, whereas resistance against tetracycline (33.8%) and ampicillin (23.0%) were the most frequent among human gastrointestinal isolates (n=74) (Figure 12B).

Figure 12. Percentage resistance of *Salmonella* isolates (n=99) obtained from human samples, 2016

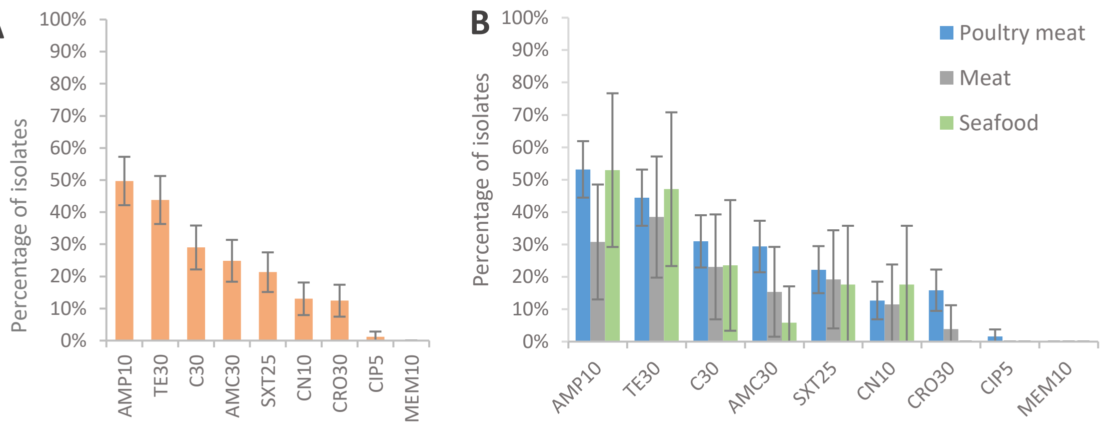


Note: Figure 12A provides the overall % resistance of the human isolates, Figure 12B compares the % resistance between human extra-intestinal and gastrointestinal isolates to antimicrobials tested. Disc diffusion was performed with 8 classes of 9 antimicrobials: AMP10 = ampicillin, TE30 = tetracycline, C30 = chloramphenicol, AMC30 = amoxicillin-clavulanic acid, SXT25 = trimethoprim-sulfamethoxazole, CRO30 = ceftriaxone, CN10 = gentamicin, CIP5 = ciprofloxacin, MEM10 = meropenem.

Resistance profile of *Salmonella* isolates from food samples

Of 169 *Salmonella* isolates from food samples, resistance against ampicillin (49.1%) and tetracycline (43.4%) were the most frequent (Figure 13A).Resistance percentages of *Salmonella* isolates from poultry meat and seafood were generally higher than that from other meats (pork, beef, others). Among *Salmonella* isolates from poultry meat (n=126), resistance against ampicillin (53.2%) and tetracycline (44.4%) were the most frequent. In other meat isolates (n=26), resistance against tetracycline (38.5%) and ampicillin (30.8%) were the most frequent. Among isolates (n=17) from

Figure 13. Percentage resistance of *Salmonella* isolates (n=169) obtained from food samples, 2016.



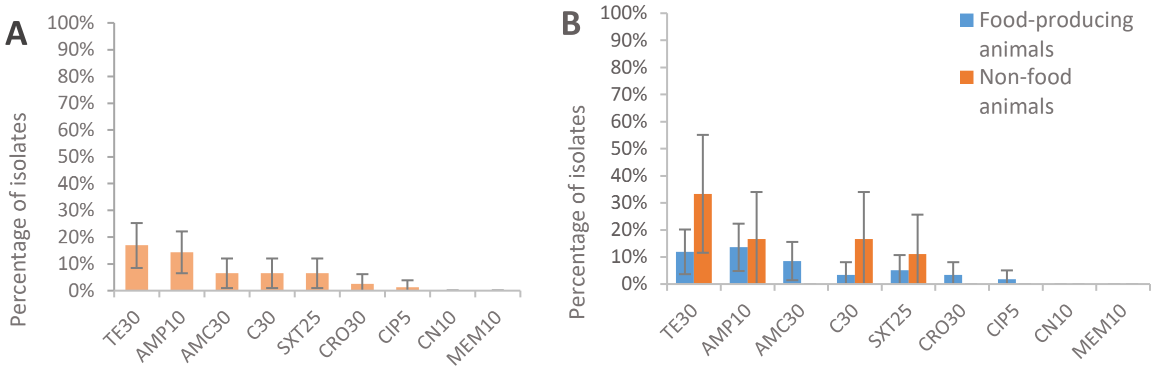
Note: Figure 13A presents the overall % resistance of food isolates; Figure 13B compares the % resistance among isolates from poultry meat, meat (pork, beef, others) and seafood samples to antibiotics tested. Disc diffusion was performed with 8 classes of 9 antimicrobials: AMP10 = ampicillin, TE30 = tetracycline, C30 = chloramphenicol, AMC30 = amoxicillin-clavulanic acid, SXT25 = trimethoprim-sulfamethoxazole, CRO30 = ceftriaxone, CN10 = gentamicin, CIP5 = ciprofloxacin, MEM10 = meropenem.

seafood samples, many were resistant to ampicillin (52.9%) and tetracycline (47.1%), but the proportion of seafood isolates resistant to amoxicillin-clavulanic acid was significantly lower than other food types (Figure 13B).

Resistance profile of *Salmonella* isolates from animal samples

Among 77 isolates from animals, resistance against tetracycline (16.9%) and ampicillin (14.3%) were the most frequent (Figure 14A). Isolates from food-producing animals (chicken layers, n=59) and non-food animals (companion animals and wild birds, n=18) had distinct resistance profiles (Figure 14B): non-food animal isolates had relatively higher proportions of resistance against tetracycline (33.3%), ampicillin (16.7%) chloramphenicol (16.7%) and trimethoprim-sulfamethoxazole (11.1%).

Figure 14. Percentage resistance of *Salmonella* isolates (n=77) obtained from animal samples, 2016.



Note: Figure 14A presents the % resistance of all animal isolates, Figure 14B compares the % resistance among isolates from food-producing animals and non-food animals to antimicrobials tested. Disc diffusion was performed with 8 classes of 9 antimicrobials: AMP10 = ampicillin, TE30 = tetracycline, C30 = chloramphenicol, AMC30 = amoxicillin-clavulanic acid, SXT25 = trimethoprim-sulfamethoxazole, CRO30 = ceftriaxone, CN10 = gentamicin, CIP5 = ciprofloxacin, MEM10 = meropenem.

Comparing across sectors, ceftriaxone-resistant strains occurred more frequently in human extra-intestinal (16.0%), human gastrointestinal (6.8%) and poultry meat (15.9%) samples than in other sample types (ranging from 0.0% - 3.9%). Ciprofloxacin resistant strains were detected in human gastrointestinal samples (1.4%), poultry meat (1.6%), and food animals (layer chickens; 1.7%). Both ciprofloxacin and ceftriaxone are classified by the WHO as highest priority critically important antimicrobials for human medicine[15] , hence resistance against these antibiotics should be closely monitored. On a positive note, all isolates were susceptible to meropenem, representative of the carbapenem class of antibiotics.

The study highlights the importance of continued surveillance on the emergence and spread of antimicrobial resistant *Salmonella* strains across One Health sectors for risk assessment.

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[15] Critically important antimicrobials for human medicine, 6th revision. Geneva: World Health Organization; 2019. https://www.who.int/foodsafety/publications/antimicrobials-sixth/en/

Antimicrobial Resistance in Human Health

AMR surveillance in public hospitals

NARCC collects data on seven important pathogens isolated from clinical samples from acute care hospitals: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphyloccocus aureus, Enterococcus faecium* and *Enterococcus faecalis*. In addition to specific pathogen-drug combinations, NARCC monitors the incidence density rates of *Clostridioides difficile*, which is associated with antimicrobial overuse.

E. coli and ***K. pneumoniae*** are monitored for resistance to three important antibiotic classes:

i. Ceftriaxone resistance (or an equivalent 3rd-generation cephalosporin) is an indicator for extended-spectrum beta-lactamase (ESBL), and cephalosporinases. These resistance mechanisms usually result in patients needing treatment with carbapenems, which are very broad-spectrum, second- or later-line antibiotics.

ii. Ciprofloxacin resistance is a marker for fluoroquinolone resistance, and can potentially be correlated with widespread fluoroquinolone use in the community as well as in hospitals.

iii. Carbapenem resistance (defined as meropenem or imipenem non-susceptibility) is an emerging concern because infections caused by carbapenem-resistant organisms typically require treatment with other last-line antibiotics. Resistance mechanisms include carbapenemase production, and a combination of ESBL or AmpC production with porin loss. Carbapenemases are beta-lactamases with the ability to hydrolyse penicillins, cephalosporins, monobactams and carbapenems.

P. aeruginosa is an opportunistic pathogen which can cause serious community-acquired and nosocomial infections, and is of particular concern in neutropaenic patients. *P. aeruginosa* is also a relatively frequent coloniser of medical devices, such as in-dwelling catheters. It has the ability to harbour multiple antibiotic resistance mechanisms.

A. baumannii is an important cause of nosocomial infections including pneumonia, urinary tract, bloodstream, catheter and wound infections. *Acinetobacter* is intrinsically resistant to a broad range of antimicrobials. Multi-drug resistant (MDR) *A. baumannii* (defined as concurrent resistance to imipenem/meropenem, ciprofloxacin, and amikacin) is therefore monitored as infections are more likely to require treatment with polymyxin or colistin, which are considered last-line antibiotics.

S. aureus is a frequent coloniser of the skin and mucosa. *S. aureus* more commonly causes skin infections, but can also spread through the bloodstream and cause a broad range of severe conditions such as pneumonia, endocarditis and osteomyelitis. Methicillin-resistant *S. aureus* (MRSA) are of particular concern due to their resistance to more effective first-line antibiotics used to treat ordinary staphylococcal infections.

Enterococci constitute a part of the normal intestinal microbiota in humans and animals. The majority of human enterococci infections are caused by *E. faecalis* and *E. faecium.* Enterococci are intrinsically resistant to many groups of antimicrobials, with severe and penicillin-resistant infections typically treated with vancomycin. Presence of vancomycin resistance further restricts treatment choice.

Table 2. Summary of pathogen-drug combinations under surveillance and corresponding specimen types

Pathogen	Specific resistance	Specimen types to report
Staphylococcus aureus	Cloxacillin (or equivalent anti-staphylococcal penicillin; MRSA), vancomycin	(i) All clinical specimens (ii) Blood (MRSA only)
Escherichia coli	Ceftriaxone, ciprofloxacin, carbapenem (meropenem or imipenem)	(i) All clinical specimens (ii) Blood
Klebsiella pneumoniae	Ceftriaxone, ciprofloxacin, carbapenem (meropenem or imipenem)	(i) All clinical specimens (ii) Blood
Pseudomonas aeruginosa	Carbapenem (meropenem or imipenem)	(i) All clinical specimens (ii) Blood
Acinetobacter baumannii	Carbapenem (meropenem or imipenem), MDR[a]	(i) All clinical specimens (ii) Blood (for carbapenem resistance)
Enterobacterales	Carbapenemase-producing (CPE)	(i) All clinical specimens (ii) Screening specimens
Enterococcus faecalis, Enterococcus faecium	Vancomycin (VRE)	(i) All clinical specimens (ii) Blood

[a] Multi-drug resistance for *Acinetobacter spp.* is defined for this purpose as concurrent resistance to ampicillin/sulbactam, imipenem/meropenem, ciprofloxacin and amikacin [1]

Clinical isolates are counted once in every six-month period per patient. Duplicate isolates from the same patient, sample type and bacterial species collected within each six-month period are excluded. While clinical isolates may include colonisation, they provide a useful indicator for the total AMR burden, which in turn impacts the consumption of hospital resources (e.g. isolation rooms, gowns, gloves and manpower). Bacteraemia rates generally represent true infection. Screening samples are excluded in most instances. Clinical isolates are tested for antimicrobial susceptibility by hospitals' clinical microbiology laboratories in accordance with the standards of Clinical & Laboratory Standards Institute (CLSI), European Committee on Antimicrobial Susceptibility Testing (EUCAST), or with the Calibrated Dichotomous Sensitivity (CDS, Australia) method, where applicable. Rates and trends are presented to MOH and individual hospitals for their monitoring and control. The data are presented as (i) incidence density per 10,000 inpatient days and where relevant, (ii) the proportion (%) of resistant clinical isolates.

Incidence density trends

Incidence density is measured as the number of clinical isolates per 10,000 inpatient days. The use of inpatient days as a denominator allows for normalisation across hospitals of different size and patient load.

Figure 15 summarises the trends in incidence density of specific pathogen-drug combinations across all public hospitals. Since 2012, we have observed a decreasing trend in the incidence density of multi-drug resistant *A. baumannii*, methicillin-resistant *Staphylococcus aureus* (MRSA) and ceftriaxone-resistant *K. pneumoniae* in public hospitals (Figure 15). The incidence density of MDR *A. baumannii* in 2019 was 0.7 per 10,000 inpatient days, down from 5.0 per 10,000 inpatient days in 2012. Likewise, MRSA incidence density had declined from 16.3 per 10,000 inpatient days in 2012 to 10.2 per 10,000 inpatient days in 2019, and ceftriaxone-resistant *K. pneumoniae* from 15.4 per 10,000 inpatient days in 2012 to 11.2 per 10,000 inpatient days in 2019. *C. difficile* incidence density has also been on a downward trend since 2014, with an incidence density of 3.5 per 10,000 inpatient days in 2019 (Figure 16).

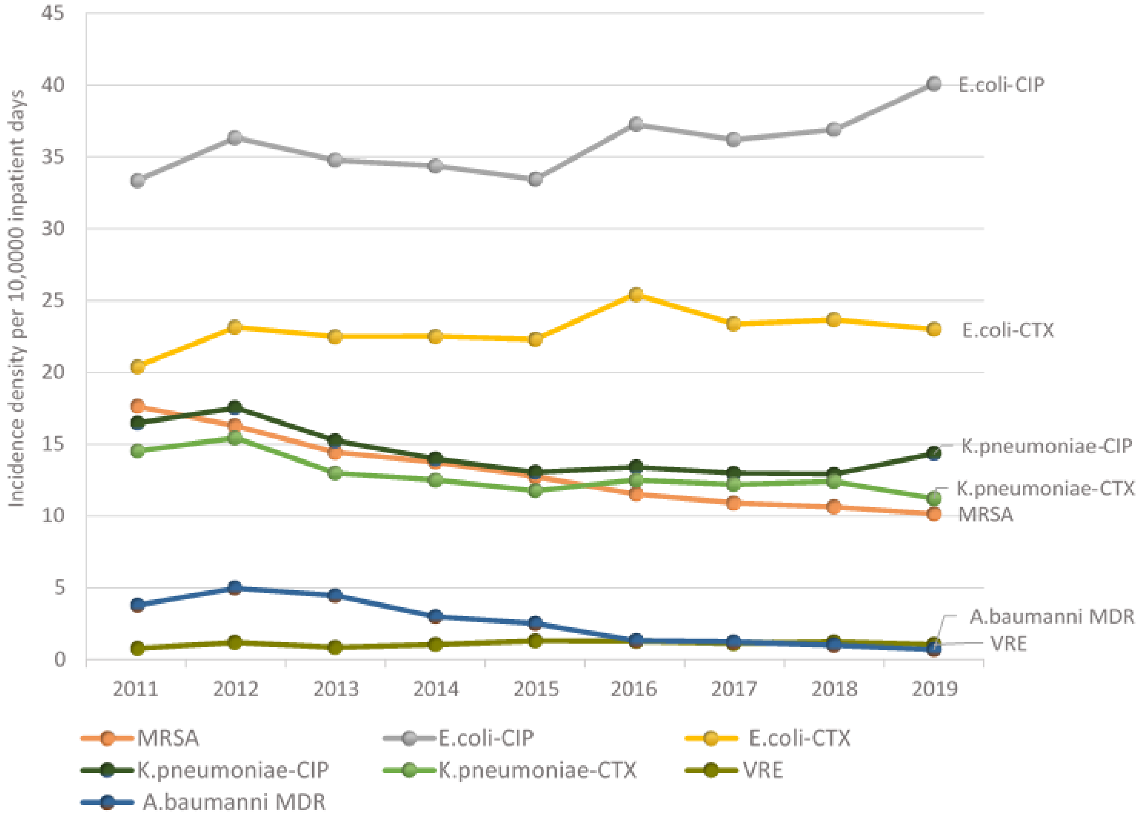
These declining rates correspond with the implementation of antimicrobial stewardship programmes in public hospitals in 2011, and are also attributed to the continual enhancement of infection control measures in hospitals. However, there has been an increasing trend of ciprofloxacin-resistant *E. coli* incidence rates since 2015, as well as an uptick in ciprofloxacin-resistant *K. pneumoniae* in 2019 (Figure 15). The incidence density of ciprofloxacin-resistant *E. coli* increased in 2019 to 40.1 per 10,000 inpatient days. This is despite a steady decline in ciprofloxacin and overall fluoroquinolone use in public hospitals in general (

Figure 4), suggesting that not all pathogens, and the environments that harbour them, are equally responsive to the same infection prevention and control measures. Fluoroquinolone use in the community, which can lead to increasing resistance in the community, may have also contributed to the rise in ciprofloxacin resistance in the hospital setting.

The incidence density of ceftriaxone-resistant *E. coli* was generally stable, with a rate of 23.0 per 10,000 inpatient days in 2019. VRE has remained low since 2011, and further declined to 1.1 per 10,000 inpatient days in 2019 (Figure 15).

Carbapenem-resistant *Enterobacterales* (CRE), particularly carbapenemase-producing CRE (CP-CRE), are of particular importance due to their resistance to a wide range of antibiotics and the challenges associated with treating patients with CP-CRE infections. This group of pathogens includes the meropenem or imipenem-resistant strains of *E. coli* and *K. pneumonia.* Since 2012, there has been a sharp decline in the incidence rates of carbapenem-resistant *A. baumannii,* and a more gradual decrease in carbapenem-resistant *P. aeruginosa* incidence (Figure 17). In contrast, though the incidence is low, a slow but gradual increase in carbapenem-resistant *E. coli* and *K. pneumoniae* has been observed since 2011, with rates being relatively stable in the last 4 years. The most frequently detected carbapenemases in Singapore were New Delhi metallo-beta-lactamase-mediated carbapenemase (NDM), *Klebsiella pneumoniae* carbapenemase (KPC) and OXA-type beta-lactamase (OXA). Since 2017, OXA has replaced NDM as the predominant carbapenemase-producing enzyme detected in public hospitals (Figure 18).

Figure 15. Incidence density of AMR organisms in public hospitals,all clinical isolates, 2011 - 2019



Notes: MRSA = methicillin-resistant *Staphylococcus aureus*; E. coli-CIP = ciprofloxacin resistant *E. coli*; E. coli-CTX = ceftriaxone-resistant *E. coli*; K. pneumoniae-CIP = ciprofloxacin-resistant *K. pneumoniae*; K. pneumoniae-CTX = ceftriaxone-resistant *K. pneumoniae*; VRE = vancomycin-resistant *Enterococcus* (*E. faecium* and *E. faecalis*); *A. baumannii* MDR = multi-drug resistant *A. baumannii*.

Figure 16. Incidence density of *C. difficile* in public hospitals, all clinical isolates, 2011 - 2019

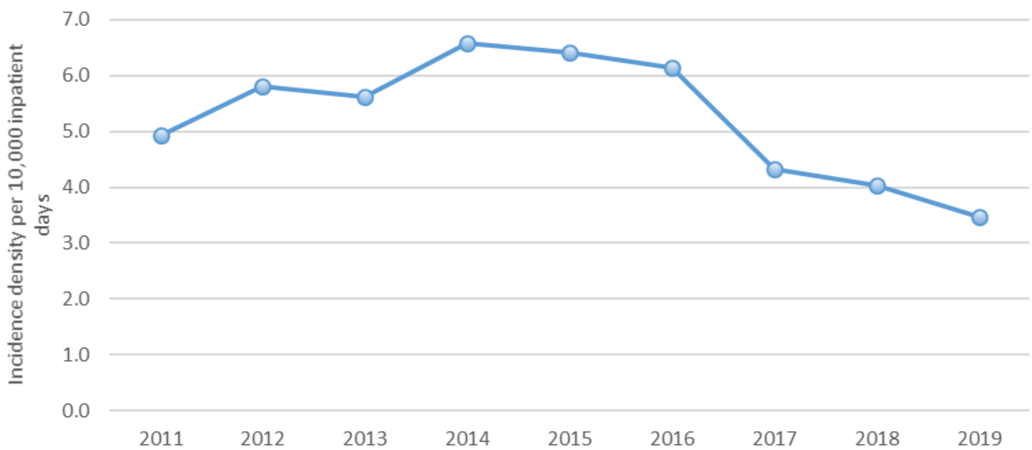


Figure 17. Trends in incidence density of carbapenem (meropenem or imipenem)-resistant organisms (CRO) in public hospitals, all clinical isolates, 2011 - 2019

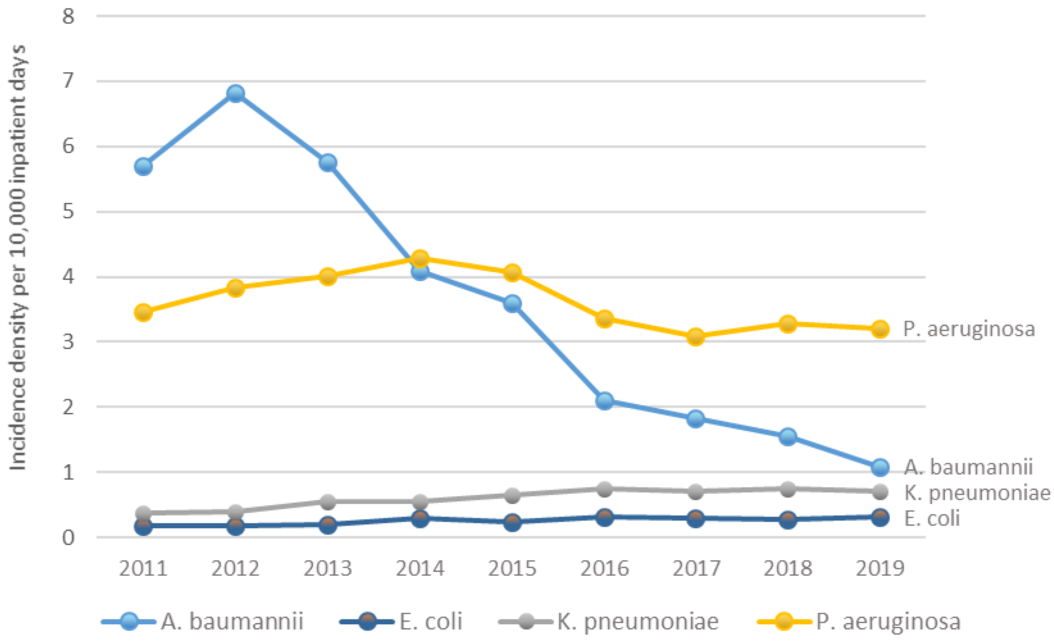
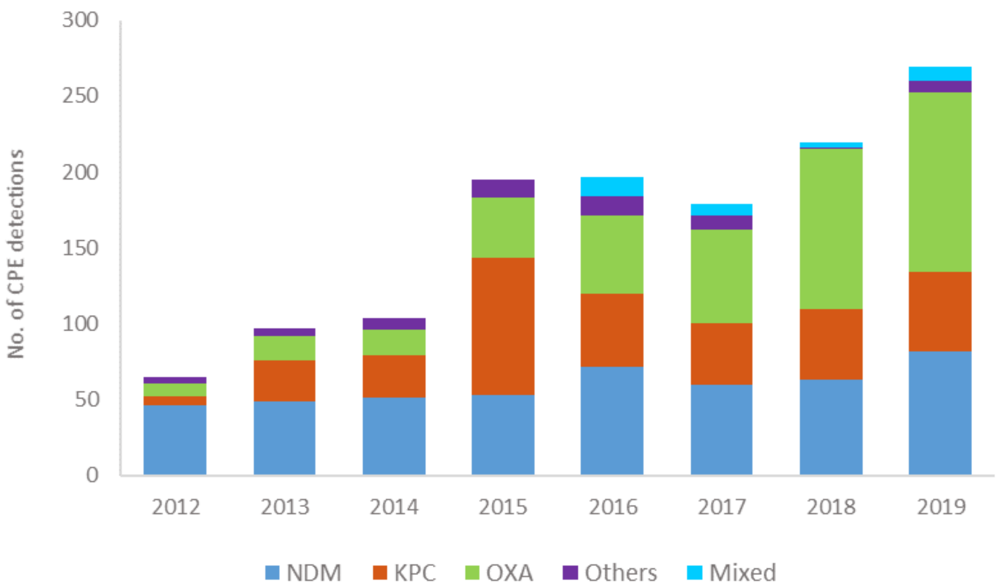


Figure 18. Carbapenemase-producing enzymes detected in clinical samples, 2012-2019



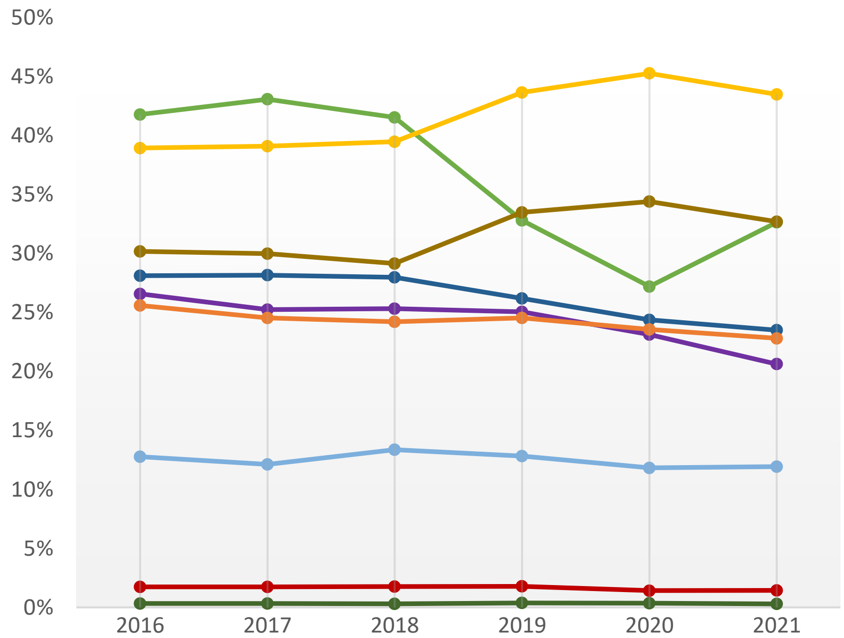
NDM = New Delhi metallo-beta-lactamase-mediated carbapenemase; **KPC** = *Klebsiella pneumoniae* carbapenemase; **OXA** = OXA-type beta-lactamases; **Others** = other carbapenemases; **Mixed** = combination of two or more carbapenemases detected

Resistance percentages

The resistance percentage reported by NARCC refers to the proportion, expressed as a percentage, of clinical isolates tested as non-susceptible (resistant and intermediate) to a specified antimicrobial. The resistance percentage is typically calculated only when the denominator contains at least 30 isolates to ensure a minimum level of precision in the calculation.

Reporting of resistance percentages started in 2016. Clinical isolates of *E. coli* and *K. pneumoniae* were frequently resistant to ciprofloxacin. The average percentage of clinical isolates resistant to specific antimicrobials have remained stable or decreased for most pathogens under surveillance, except for ciprofloxacin-resistant *E. coli* and *K. pneumoniae*, which showed an increase in 2019 (Figure 19).

Figure 19. Trends in resistance percentages (%R) of target pathogen-drug combinations, all clinical isolates from public hospitals



	2016	2017	2018	2019	2020	2021
A. baumannii, Meropenem or imipenem resistance	41.8%	43.1%	41.5%	32.8%	27.2%	32.7%
E. coli, Ceftriaxone resistance	26.6%	25.2%	25.3%	25.1%	23.1%	20.6%
E. coli, Ciprofloxacin resistance	39.0%	39.1%	39.5%	43.7%	45.3%	43.5%
E. coli, Meropenem or imipenem resistance	0.3%	0.3%	0.3%	0.4%	0.4%	0.3%
K. pneumoniae, Ceftriaxone resistance	28.1%	28.2%	28.0%	26.2%	24.4%	23.5%
K. pneumoniae, Ciprofloxacin resistance	30.2%	30.0%	29.2%	33.5%	34.4%	32.7%
K. pneumoniae, Meropenem or imipenem resistance	1.7%	1.7%	1.8%	1.8%	1.4%	1.4%
P. aeruginosa, Meropenem or imipenem resistance	12.8%	12.1%	13.4%	12.8%	11.8%	11.9%
S. aureus, Methicillin resistant	25.6%	24.6%	24.2%	24.6%	23.6%	22.8%

Note: Resistant isolates include those of intermediate susceptibility.

Participation in Global Antimicrobial Resistance Surveillance System (GLASS)

GLASS[16] was launched by WHO in 2015 as a collaborative global effort to provide a standardised approach to the collection, sharing and analysis of AMR data. GLASS collects aggregated country data on four priority specimens (blood, stool, urine and genital), and eight organisms (*E. coli, K. pneumoniae, A. baumannii, S. aureus, Streptococcus pneumoniae, Salmonella* spp., *Shigella* spp., *Neisseria gonorrhoea)*, stratified by age group, gender, and origin of infection (hospital vs community). Singapore enrolled in GLASS in September 2019, with the AMRCO and the NPHL appointed by MOH as the national coordinating centre and the AMR reference laboratory respectively.

Aggregate data from two sentinel inpatient and one outpatient sites were submitted to GLASS. The sole outpatient site provided data on genital samples for *N. gonorrhoea* surveillance, which currently lies outside the scope of this report. The two sentinel inpatient sites were both acute care hospitals, which provided data on blood, urine and stool samples. The number of bacterial isolates from blood, urine and stool samples reported are shown in Figure 20, stratified by sample type and origin of infection. *E. coli* was the most frequently isolated organism from blood and urine samples, while *Salmonella* spp. was more frequently isolated than *Shigella* from stool samples. Pathogens were more frequently isolated from samples collected less than 48 hours of admission to hospital, suggesting community-onset infection. However, this category may also include samples from re-admitted patients or patients transferred from other hospitals.

AST profiles of *E. coli, K. pneumoniae* and *Salmonella* spp. are shown in Figure 21, Figure 22 and Figure 23. *E. coli* and *K. pneumoniae* showed similar resistance profiles for the antibiotics tested. *Salmonella* spp. isolates (typhoidal and non-typhoidal) showed some resistance to fluoroquinolones but were mostly susceptible to carbapenems and cephalosporins.

Sustainable Development Goal (SDG) AMR indicators

Two new AMR indicators were recently introduced for the Sustainable Development Goal (SDG) 3, which aims to "ensure healthy lives and promote well-being for all at all ages".[17] The AMR indicators serve to measure the reduction in the percentage of bloodstream infections due to selected antimicrobial resistant organisms, specifically, the frequency of bloodstream infection among hospital patients due to (i) *E. coli* resistant[18] to 3rd-generation cephalosporin (e.g., ESBL- *E. coli*) and (ii) MRSA.

Based on data from Singapore's GLASS sentinel surveillance sites, the proportion of *E. coli* resistant to 3rd-generation cephalosporins in blood samples in 2019 was 28.7%, with a frequency of 11.3 per 1000 patients with blood samples taken**.** This proportion was higher than the median of 17.5% (IQR 11.4–25.2) of 31 high income countries reporting to GLASS. The proportion of MRSA (characterised by resistance[18] to oxacillin) in 2019 was 28.6%, with a frequency of 4.3 per 1000 patients with blood samples taken, also higher than the median of 15.0% (IQR 6.8–36.4) of 30 high income countries reporting to GLASS**.**

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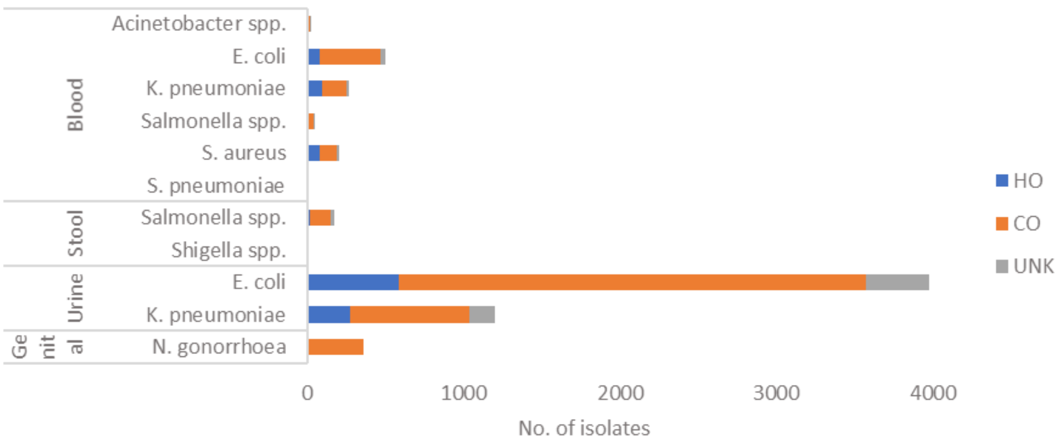
[16] www.who.int/glass/en/
[17] https://sdgs.un.org
[18] Excludes those of intermediate susceptibility

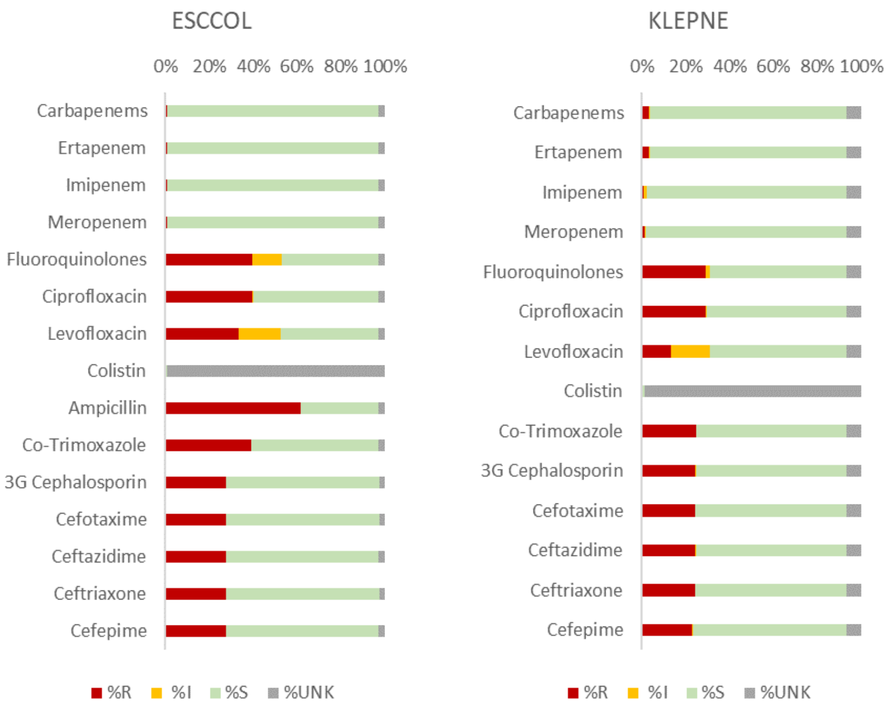
The full GLASS report is found at https://www.who.int/publications/i/item/9789240027336. Country profiles may be viewed at https://www.who.int/data/gho/data/themes/topics/global-antimicrobial-resistance-surveillance-system-glass/glass-country-profiles. The SDGs AMR Indicator dashboard is found at https://www.who.int/data/gho/data/themes/topics/global-antimicrobial-resistance-surveillance-system-glass/sustainable-development-goals-amr-indicator.

Figure 20. Number of GLASS priority pathogens reported, stratified by sample type and origin of infection, 2019



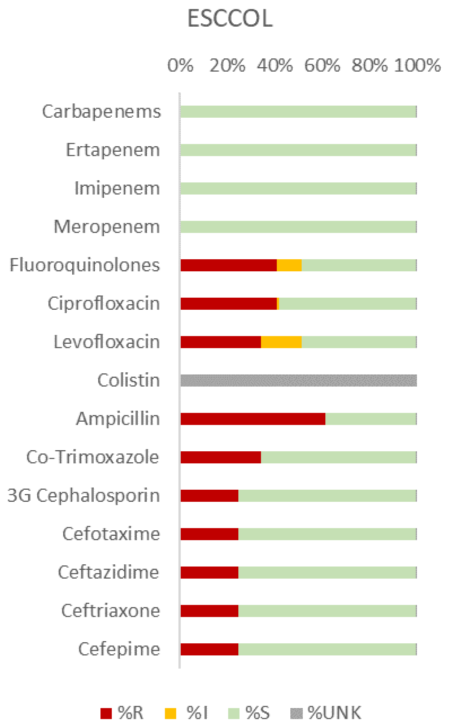
HO: Hospital-origin (sample ≥48 hours from admission); CO: Community-origin (sample <48 hours from admission); UNK: Unknown origin of infection

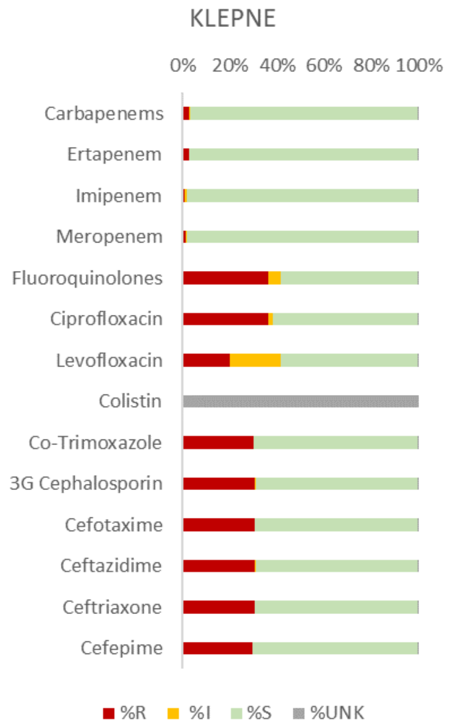
Figure 21. Resistance percentages of *E. coli* (ESCCOL) and *K. pneumoniae* (KLEPNE) isolated from blood samples



BLOOD - *E. coli* (n = 502); *K. pneumoniae* (n=269) AST results (**S**=susceptible, **I**=intermediate, **NS**=non susceptible, **R**=resistant, **UNK**= unknown no AST)

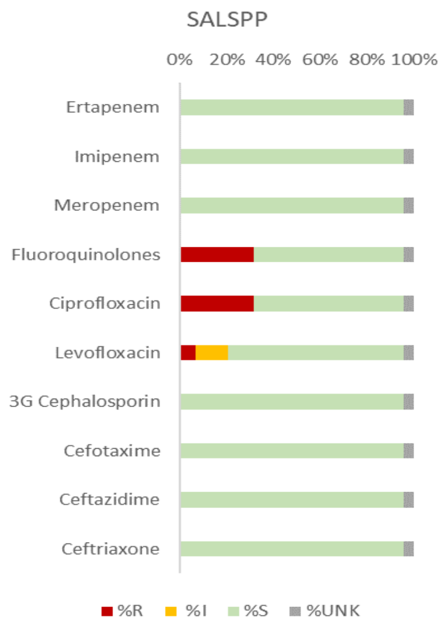
Figure 22. AST results of *E. coli* (ESCCOL) and K. pneumoniae (KLEPNE) isolated from urine samples



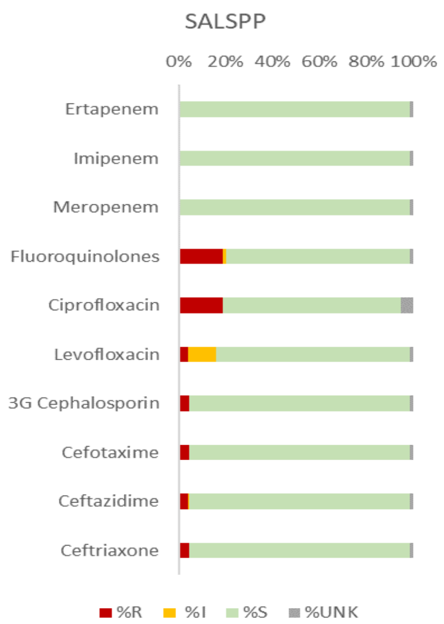


URINE - *E. coli* (n = 3976); *K. pneumoniae* (n=1204) AST results (**S**=susceptible, **I**=intermediate, **NS**=non susceptible, **R**=resistant, **UNK**= unknown no AST)

Figure 23. Proportion of AST results in *Salmonella* spp. (SALSPP) isolated from blood and stool samples



(a) Blood samples



(b) Stool samples

Antimicrobial Resistance in Bacteria in the Food Chain

National AMR surveillance along the food chain covers local food-producing animals, animals imported for slaughter, food imports and retail food products. Organisms monitored include *Salmonella* spp., *E. coli* and vancomycin-resistant Enterococci (VRE), to assess potential impacts of AMR in the food chain on consumers and food handlers. Bacteria isolated are subjected to AST against clinically and epidemiologically important antimicrobial agents.

Salmonella are a major cause of food-borne illness worldwide and in Singapore. *Salmonella enterica* serovars are naturally present in the digestive tracts of many animals, but most frequently isolated from poultry and its associated products. Of over 2000 different serovars of *Salmonella enterica*, the serovar Enteritidis is the main serovar associated with non-typhoidal Salmonellosis in Singapore. *Salmonella* spp. are monitored for specific resistance as well as multi-drug resistance (MDR), defined as resistance to three or more classes of antimicrobials.

E. coli are ubiquitous commensal bacteria found in all warm-blooded animals and may be exposed to antimicrobials from animal feed and/or water. Therefore, *E. coli* may act as reservoirs for transferable resistance determinants in the animal or human gut [19]. The bacteria also serve as an indicator for resistance in different reservoirs along the food chain. As most AMR phenotypes from animal populations are present in commensal bacteria, it is more accurate to monitor the effects of antimicrobial use and AMR trends in commensal bacteria than in food-borne pathogens[20]. With the exception of several strains relevant to human health, most strains of *E. coli* are non-pathogenic. However, these bacteria have the potential to transfer resistance determinants to pathogenic Gram-negative bacteria. *E. coli* are monitored for specific resistance as well as multi-drug resistance (MDR). Extended spectrum beta-lactamase-producing (ESBL) *E. coli* are of specific concern due to their concurrent resistance to many other antibiotics.

Enterococci are Gram-positive bacteria commonly found in intestine of humans and animals and have the ability to acquire and transfer antibiotic resistance genes from and to other bacteria. The main species of public health concern are vancomycin-resistant strains of *E. faecium* and *E. faecalis*. VRE are often implicated in hospital-acquired infections such as in the urinary tract, wounds and the heart. They are known to be intrinsically resistant to several antimicrobials and can survive in severe conditions caused by temperature and pH variations and dehydration[21]. As a result, it is harder to treat infections caused by harmful *Enterococcus* spp. that are resistant to vancomycin and other antibiotics.

Key findings from surveillance of these organisms in the food supply chain are summarised below.

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[19] Food and Agriculture Organisation of the United Nations (FAO), 2019. *Regional Antimicrobial Resistance Monitoring and Surveillance Guidelines Volume 1 (Monitoring and surveillance of antimicrobial resistance in bacteria from healthy food animals intended for consumption*.

[20] European Food Safety Authority (EFSA), 2018. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016. *EFSA Journal,* 16(2), 5182.

[21] Giraffa, G. 2002. Enterococci from foods. FEMS Microbiology Reviews 26 (2): 163–171. https://doi.org/10.1111/j.1574-6976.2002.tb00608.x

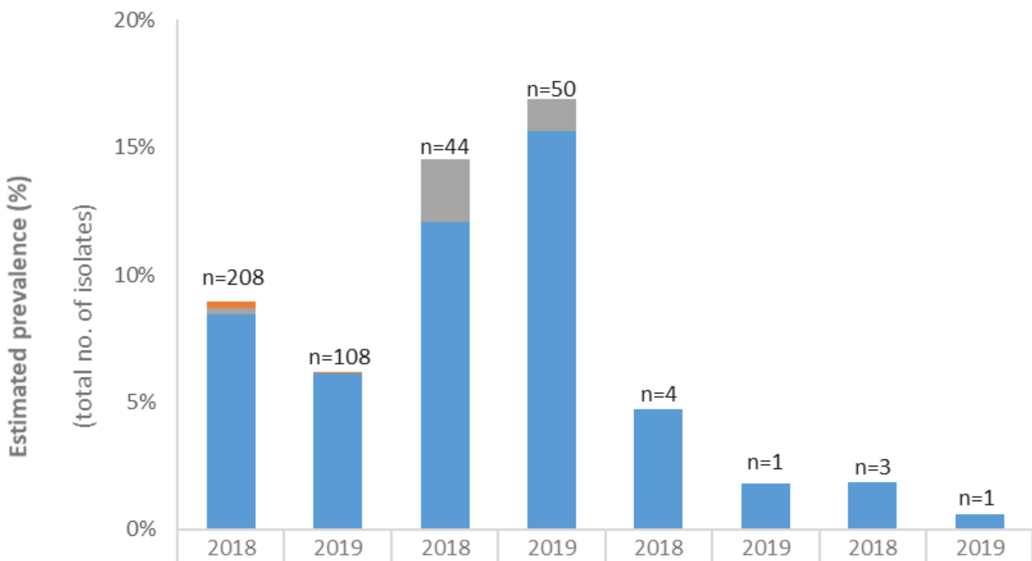
Antimicrobial resistance in *Salmonella*

In Production animals

Poultry farms, imported poultry and eggs have been monitored for the presence of *Salmonella* under the national *Salmonella* Enteritidis surveillance programme since 2008. Surveillance for drug-resistant *Salmonella* was expanded in November 2017 to include the ruminant (dairy goat and cattle) farms.

The overall prevalence of *Salmonella* Enteritidis and Typhimurium has remained relatively low, as compared to the prevalence of other *Salmonella* spp. In 2018 and 2019, 281 (9.1%) and 165 (7.2%) *Salmonella* spp. were respectively isolated from local farm samples (Figure 24). The overall prevalence of *S.* Typhimurium ranged from 0.0-2.5% in 2018 to 0.0-1.3% in 2019, while the prevalence of *S.* Enteritidis ranged from 0.0-0.2% in 2018 to 0.0-0.1% in 2019. Majority of isolates were Group C and E *Salmonella* spp., with prevalence ranging from 1.9-12.1% in 2018 and 0.6-15.6% in 2019.

Figure 24. Estimated overall prevalence of *Salmonella* spp. in local farms, 2018 – 2019 (n= number of *Salmonella* spp. isolated)



	Chicken		Quail		Cattle		Goat	
	2018	2019	2018	2019	2018	2019	2018	2019
S. Enteritidis	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
S. Typhimurium	0.3%	0.0%	2.5%	1.3%	0.0%	0.0%	0.0%	0.0%
Other Salmonella*	8.4%	6.1%	12.1%	15.6%	4.7%	1.8%	1.9%	0.6%

Livestock population

*Most of the isolates were Group C and E *Salmonella* spp.

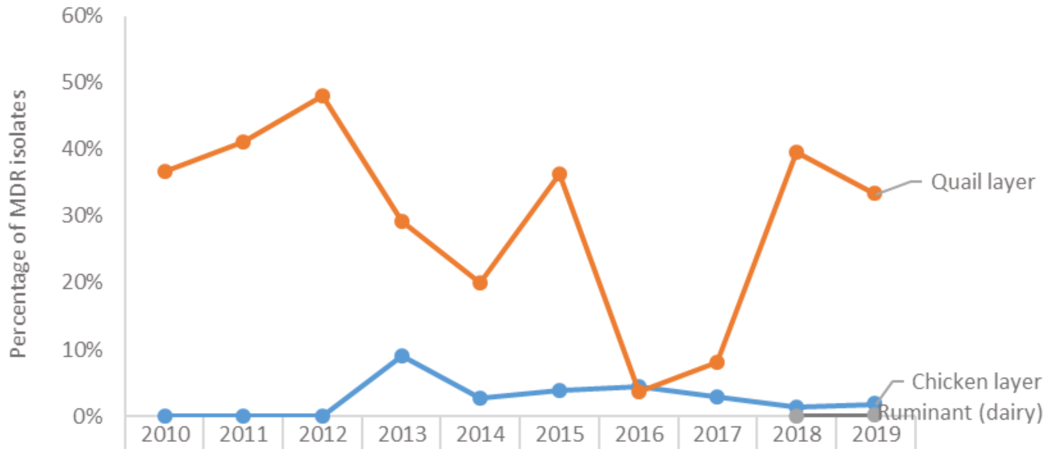
MDR Salmonella in terrestrial farm animals

MDR *Salmonella* is a worldwide challenge, particularly when occurring in serovars of public health importance. Farm isolates were tested for susceptibility to antibiotics by broth microdilution, applying CLSI M100 and/or VET01 standards and interpretative breakpoints. For 2018 and 2019, the antimicrobial panel was expanded to include medically important classes of antibiotics, such as 3rd generation cephalosporins, carbapenems and macrolides. These antimicrobials are not routinely used in agriculture; inclusion in the AST panel was to assess resistance to medically important antimicrobials in bacteria from local farms.

In chicken layer farms, the proportion of MDR *Salmonella* spp. has remained low (Figure 25). In 2018 and 2019, <2% of all *Salmonella* isolated from chicken layer farms were MDR. In ruminant farms, none of the nine isolates were MDR. The low occurrence of MDR *Salmonella* corresponds with the low prevalence of *Salmonella* in the ruminant farms.

MDR *Salmonella* was found more frequently in local quail farms than in other farms (Figure 25). From 2010 to 2019, a total of 469 *Salmonella* spp. were isolated from quail farms in Singapore. Following a decline in 2016 and 2017, the percentage of MDR *Salmonella* increased significantly by 31.6% to 39.6% in 2018 ($p<0.01$) and 25.3% to 33.3% in 2019 ($p<0.05$) compared to 2017. However, none of these were *Salmonella* Enteritidis, with a small proportion being *S.* Typhimurium (Figure 24).

Figure 25. MDR *Salmonella* in local poultry and ruminant farms



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Chicken layer	0.0%	0.0%	0.0%	9.0%	2.7%	3.8%	4.5%	2.9%	1.4%	1.8%
Quail layer	36.7%	41.2%	48.0%	29.3%	20.0%	36.4%	3.6%	8.0%	39.6%	33.3%
Ruminant (dairy)									0.0%	0.0%

Note: AMR surveillance in ruminant farms started in 2018; AST data prior to 2018 are not available for ruminant farms. AST were performed with 12 antimicrobials in 2018 and 2019, as compared to 4 antimicrobials (ampicillin, chloramphenicol, streptomycin and tetracycline) from 2010 to 2017.

Resistance profiles of Salmonella from local farms

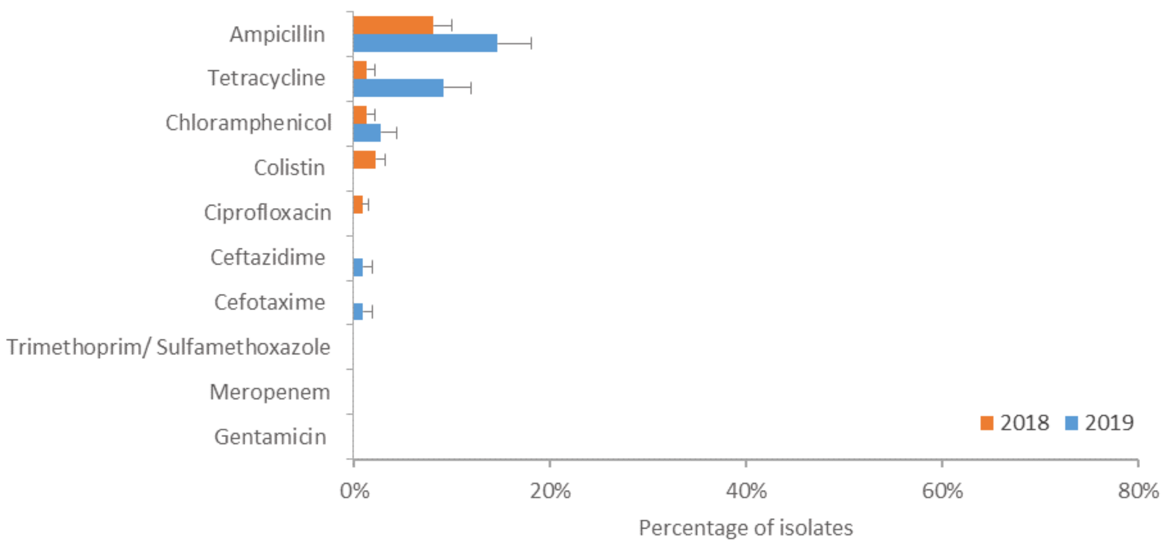
<u>Ruminant farms</u>

Ruminant farm isolates were susceptible to most antibiotics tested. Two *Salmonella* spp. (representing 28.6% of samples tested) isolated from local ruminant farms were resistant to tetracycline and chloramphenicol in 2018, while one *Salmonella* spp. isolate was resistant to tetracycline and chloramphenicol in 2019. All were susceptible to ampicillin, cefotaxime, ceftazidime, ciprofloxacin, colistin, gentamicin, meropenem and trimethoprim-sulfamethoxazole.

Chicken layer farms

In 2018, the percentage of isolates resistant to ampicillin was the highest (8.1%), while low levels of resistance to colistin (2.3%), tetracycline (1.4%), chloramphenicol (1.4%) and ciprofloxacin (0.9%) were observed (Figure 26). All *Salmonella* spp. isolated from local chicken farms in 2018 were susceptible to ceftazidime, cefotaxime, trimethoprim-sulfamethoxazole, meropenem and gentamicin. Similarly, in 2019, the percentage of isolates (n=108) resistant to ampicillin (14.7%) remained the highest. There was a significant increase ($p<0.01$) in the percentage resistance to tetracycline (by 7.8%) from 2018 levels. Percentage resistance to tetracycline was 9.2% in 2019, up from 1.4% in 2018. Low levels of resistance to chloramphenicol (2.8%), ceftazidime (0.9%) and cefotaxime (0.9 %) were observed. All *Salmonella* spp. isolated from local chicken farms in 2019 were susceptible to colistin, ciprofloxacin, trimethoprim- sulfamethoxazole, meropenem and gentamicin.

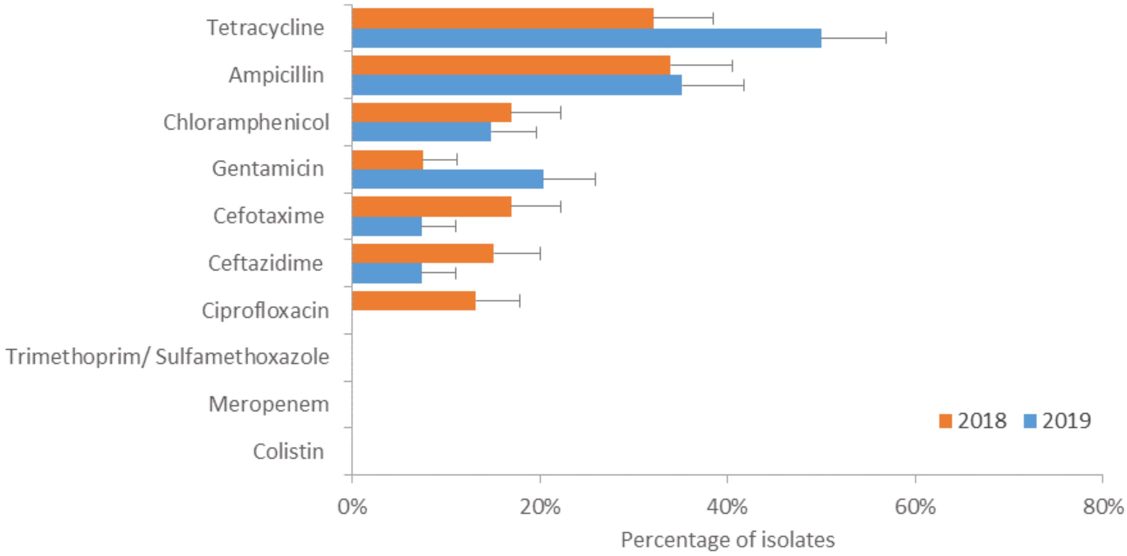
Figure 26. Percentage resistance of *Salmonella* spp. isolated from local chicken farms, 2018 -2019.



Quail layer farms

Salmonella isolated from quail farms were more frequently drug-resistant than those isolated from other farms. Among the 2018 quail isolates (n=44), percentage resistance to ampicillin was the highest (34.0%), followed by tetracycline (32.1%), chloramphenicol (17.0%), cefotaxime (17.0%), ceftazidime (15.1%), ciprofloxacin (13.2%) and gentamicin (7.5%). In 2019, the percentage resistance to tetracycline was the highest (50.0%), followed by ampicillin (35.2%), gentamicin (20.4%), chloramphenicol (14.8%), cefotaxime (7.4%) and ceftazidime (7.4%). There was a significant ($p<0.01$) increase in the percentage resistance to tetracycline, and a decrease to ciprofloxacin in *Salmonella* spp. isolated in 2019, compared to 2018. All *Salmonella* spp. isolated from local quail farms in 2018 and 2019 were susceptible to trimethoprim-sulfamethoxazole, meropenem and colistin.

Figure 27. Percentage resistance of *Salmonella* spp. isolated in local quail farms, 2018 -2019



Overall, the presence of drug-resistant *Salmonella* spp. in local farms was deemed to have little implication to public health. Across all the local farms, there were no MDR *S*. Enteritidis and few MDR *S.* Typhimurium, accounting for 0.006% of all *Salmonella* spp. isolated in 2018 and 2019. Other serovars detected were less frequently associated with human cases of Salmonellosis. MDR *Salmonella* was more frequently detected among quail farms isolates; however, quail eggs do not constitute a major food source here. Nevertheless, these findings support the need for continual monitoring of drug-resistant pathogens on local farms.

In Imported and Retail Food Products

Salmonella in Imported food

Singapore implements a risk-based food safety system. Licensing and accreditation requirements are in place for food sources, establishments and retailers to ensure the safety of food imported, produced and sold here. At-risk products are subjected to routine surveillance for the presence of important foodborne pathogens, including *Salmonella* spp.

Under the national food safety monitoring programme, 489 *Salmonella* isolates were obtained from 7296 (6.7%) imported chicken, duck and pork meat products tested in 2018 and 2019. The majority (63.5%; 311/489) of *Salmonella* isolates were obtained from chicken meat products.

All 489 isolates were subjected to AST by microbroth dilution applying CLSI breakpoints (M100, 30th Edition). Tests for Minimum Inhibitory Concentration (MIC) were performed with 10 classes of 12 antimicrobials (ampicillin, azithromycin, cefotaxime, ceftazidime, ciprofloxacin, chloramphenicol, colistin, gentamicin, meropenem, sulphamethoxazole, tetracycline and trimethoprim) using the Sensititre^{TM} Asia Surveillance Plates for *Salmonella*/*E. coli*.

Among all *Salmonella* isolates tested, over 60% were resistant to tetracycline, sulphamethoxazole and ampicillin. In addition, approximately one-third of isolates tested (35.0% to 37.8%) were resistant to cephalosporins such as cefotaxime and ceftazidime (Figure 28). Among *Salmonella* from imported chilled and frozen chicken meat products between 2018 and 2019, 67.8% to 79.5% of the isolates tested were found to be MDR (Table 3).

Figure 28. Percentage resistance of *Salmonella* isolates (n=489) from imported chicken (n=311), duck (n=61) and pork meat (n=117) products, 2018 – 2019

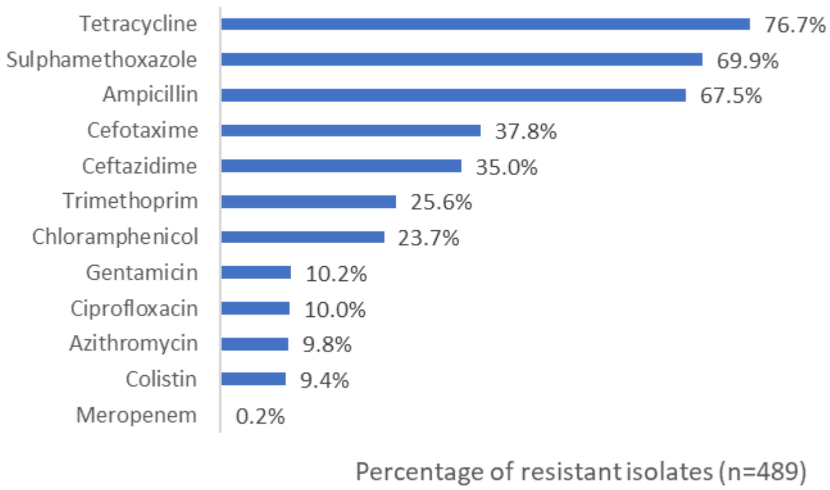


Table 3. Percentage of MDR *Salmonella* in imported chicken meat products, 2018 - 2019

Product type	2018	2019
Imported chilled chicken meat products	67.8% (40/59)	73.2% (41/56)
Imported frozen chicken meat products	74.1% (80/108)	79.5% (70/88)

Note: MIC tests using Sensititre™ Asia Surveillance Plates for *Salmonella/E. coli* were introduced in 2018. Due to changes in methodology, 2018-2019 data are not trended with MDR *Salmonella* data reported for 2011-2017[1].

Salmonella from retail food products

Retail food products monitored for foodborne pathogens include cooked/ready-to-eat food prepared and/or sold at retail food service premises (e.g. hawker centres, restaurants, coffee shops, caterers and food courts). Raw food such as poultry, meat, vegetables and seafood products from wet markets and supermarkets are also monitored.

The antibiotic resistance profiles of 204 *Salmonella* spp. isolated from 6683 retail food between 2017 and 2018 were examined. These *Salmonella* were isolated from raw poultry, pork, seafood, vegetables, and cooked/ready-to-eat food. Tests for MIC were performed for 8 classes of 9 antimicrobials (ampicillin, cefotaxime, ceftazidime, ciprofloxacin, chloramphenicol, colistin, meropenem, tetracycline and trimethoprim-sulphamethoxazole) using the Microscan NM44 panel. Of these, more than half were resistant to tetracycline and ampicillin (Figure 29), two antibiotics commonly used antimicrobials for therapeutic or sub-therapeutic purposes in animal and agricultural sectors. In addition, more than 30% of isolates were resistant to trimethoprim-sulfamethoxazole and chloramphenicol. Resistance percentages between raw and cooked/ready-to-eat foods were comparable, except for colistin resistance which was higher in cooked/ ready-to-eat food isolates.

MDR *Salmonella* isolates were relatively more frequent in raw poultry, raw pork and cooked/ready-to-eat food, but less frequently detected in raw seafood and raw vegetables (Figure 30).

Figure 29. Percentage of antimicrobial resistant *Salmonella* isolates in retail food, 2017 and 2018 (n=204)

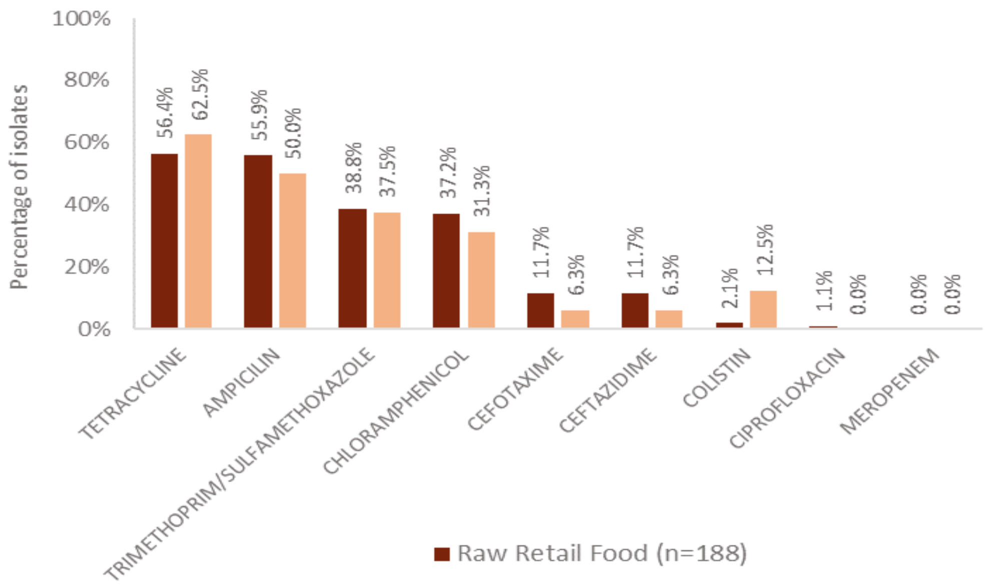
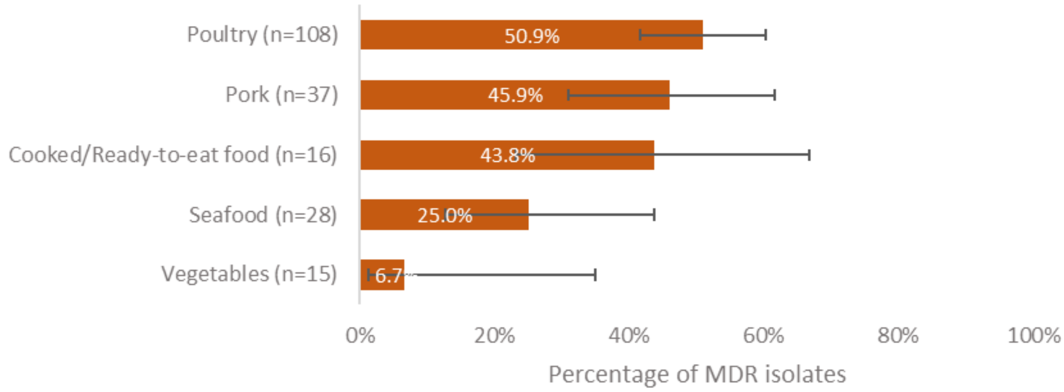


Figure 30. Percentage of MDR *Salmonella* isolates in retail food, 2017 and 2018 (n=204)

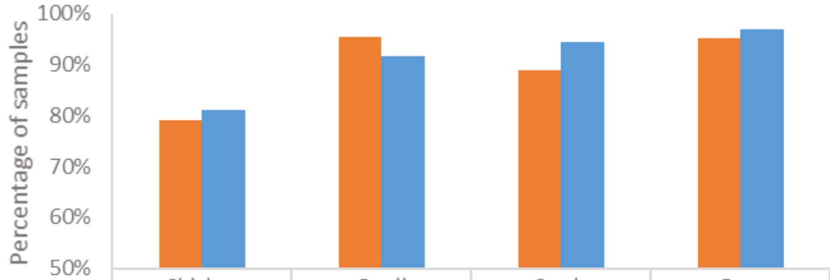


Antimicrobial resistance in *E. coli*

In Production animals

Monitoring of AMR profiles of indicator *E. coli* isolated from local poultry and ruminant farms was introduced in November 2017. In 2018 and 2019, 632 (84.2%) and 540 (88.2%) *E. coli* were isolated from healthy local farm animals, respectively. As expected of commensals, the prevalence of *E. coli* in local poultry and ruminant (cattle and goat) farms were high, ranging from 79.0 - 95.3% in 2018 to 81.1 - 97.0% in 2019 (Figure 31).

Figure 31. Estimated prevalence of *E. coli* in local livestock populations

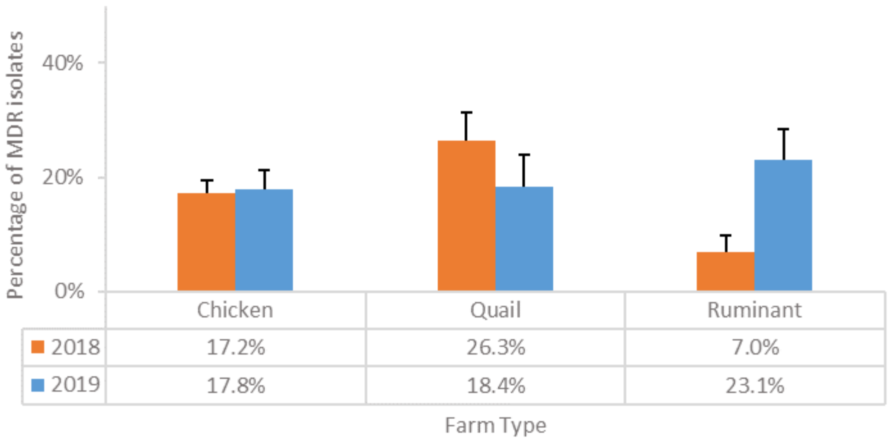


	Chicken	Quail	Cattle	Goat
2018	79.0%	95.5%	88.9%	95.3%
2019	81.1%	91.7%	94.5%	97.0%

MDR E. coli

From 2018 to 2019, the percentage of MDR *E. coli* isolated from local chicken and quail farms remained relatively stable. In contrast, there was a significant increase in the percentage of ruminant MDR *E. coli* isolates from 7.0% in 2018 to 23.1% in 2019 ($p<0.01$; Figure 32).

Figure 32. Percentage of MDR *E. coli* isolated in local farms, 2018 and 2019



Resistance profiles in Indicator E. coli

E. coli isolates from all livestock populations showed resistance to tetracycline (27.9% - 50.0%), ampicillin (10.5% - 35.6%) and nalidixic acid (4.7% - 34.7%) in 2018 and 2019 (Figures 33-35). The isolates had lower resistance to cefotaxime (2.2% - 12.3%), chloramphenicol (0.0% - 9.3%), ceftazidime (0.7% -4.7%), colistin (0.0% - 3.9%) and gentamicin (0.0% - 4.1%). All *E. coli* isolates were susceptible to meropenem and trimethoprim-sulfamethoxazole. Unlike poultry farm isolates, there were significant increases in the percentage of *E. coli* isolated from ruminant farms that were resistant to ampicillin (by 20.3%, $p<0.05$) and nalidixic acid (by 24.5%, $p<0.01$) from 2018 and 2019 (Figure 35).

Figure 33. Percentage resistance of *E. coli* isolated in local chicken farms, 2018-2019

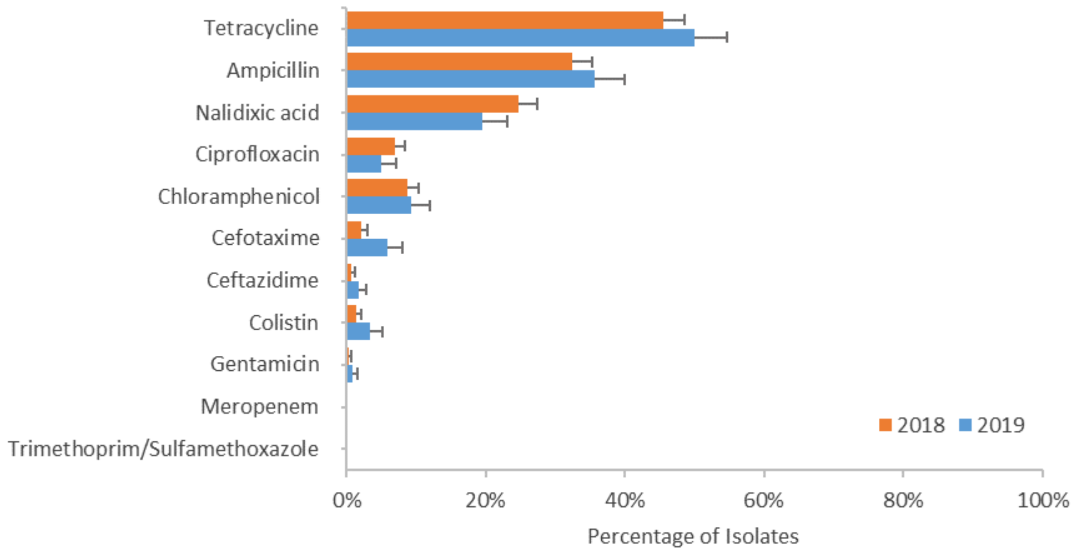


Figure 34. Percentage resistance of *E. coli* isolated in local quail farms, 2018-2019

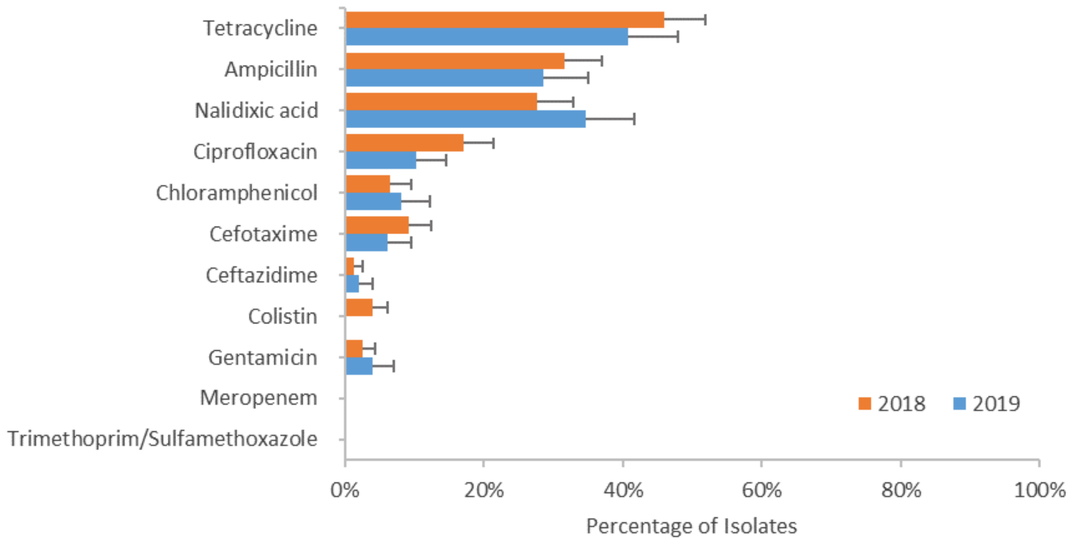
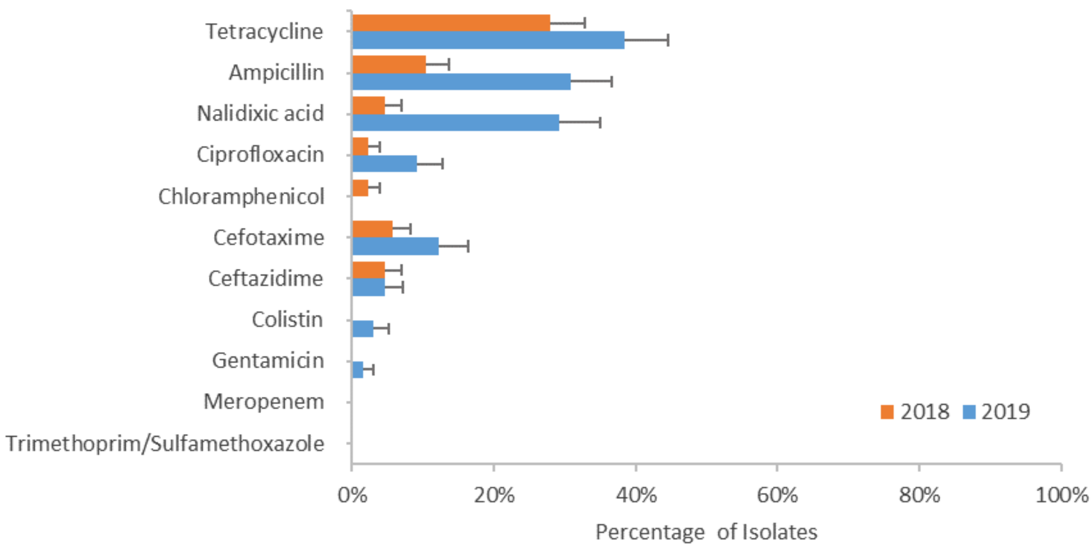


Figure 35. Percentage resistance of *E. coli* isolated in local ruminant farms, 2018-2019



In Retail Food Products

E. coli

A total of 210 *E. coli* isolates obtained from 1553 retail raw food, and 30 *E. coli* isolates from 5230 retail cooked/ready-to-eat food tested in 2017 and 2018 were subjected to AST. Tests for MIC were performed with 9 classes of 10 antimicrobials (ampicillin, cefotaxime, ceftazidime, ciprofloxacin, chloramphenicol, colistin, gentamicin, meropenem, tetracycline and trimethoprim-sulphamethoxazole) using the Microscan NM44 panel.

Of these, 69.5% were resistant to ampicillin and 50.0% were resistant to tetracycline. Raw food isolates were more frequently resistant to chloramphenicol (39.5%), ciprofloxacin (28.1%), colistin (18.1%) and gentamicin (14.3%) (Figure 36). Isolates from cooked/ready-to-eat food had lower percentage resistance than raw food isolates. In addition, resistance to 3rd generation cephalosporins was observed among raw food isolates but not in cooked/ready-to-eat isolates. Meropenem resistance was not observed in all isolates. MDR *E. coli* were found among isolates from raw poultry (48.8%), and raw pork (47.1%) (Figure 37).

Figure 36. Resistance percentages of *E. coli* isolates from retail food (2017 – 2018)

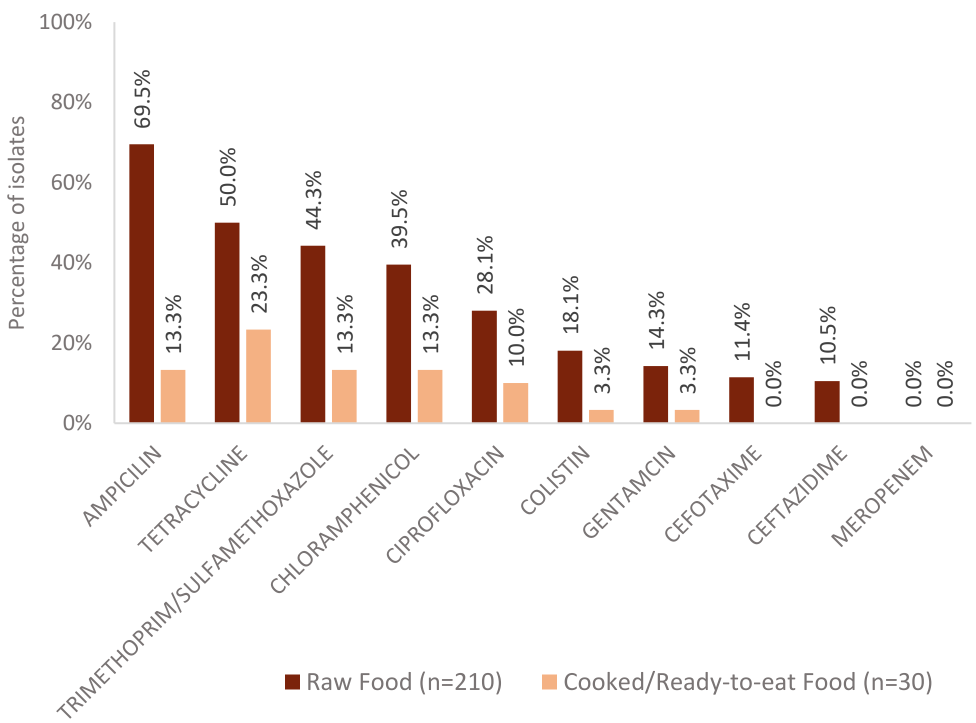
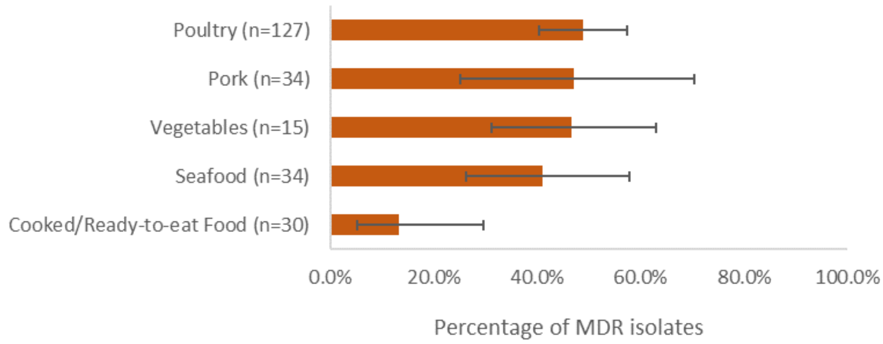


Figure 37. Percentage of MDR *E. coli* isolates from retail food, 2017 – 2018



Extended Spectrum Beta-lactamase-producing E. coli (ESBL-Ec)

ESBL-Ec are typically concurrently resistant to many other available antibiotics. Infections with ESBL-Ec are therefore more likely to result in severe morbidity and mortality in humans, with significant associated health costs and disease burdens. ESBL-Ec may also be present in food-producing animals and may be found in food products as a result of extraneous contamination arising from handling, processing or from the environment.

A joint study by SFA, NEA, Nanyang Technological University Food Technology Centre (NAFTEC) and the National Food Institute of Technical University of Denmark showed that ESBL-Ec was widely found in retail raw meats in Singapore, especially chicken[22]. The study examined a total of 634 raw meats sampled from 97 supermarkets and 65 wet markets over the period from June 2017 to October 2018. A total of 225 ESBL-Ec were isolated from 184 samples. The prevalence of ESBL-Ec in chicken, pork and beef was determined to be 51.2% (109/213), 26.9% (58/216) and 7.3% (15/205), respectively. The prevalence in frozen pork and beef samples was lower than chilled (never frozen) meats, but there was no difference between frozen and chilled chicken (Table 4).

Beta-lactam resistance genes were detected in all isolates, and aminoglycoside resistance genes in most isolates (92.4%). Other genes detected were *bla*CTX-M (76.4%), *bla*TEM (45.3%), *bla*SHV (23.1%). The most frequent ESBL genes were *bla*CTX-M-55 (25.3%) and *bla*CTX-M-65 (17.8%). Colistin resistance genes (*mcr-1, mcr-3* and *mcr-5*) were found in 15.6% of isolates. Results of this study have been published at https://academic.oup.com/jac/article-abstract/76/3/601/6040691.

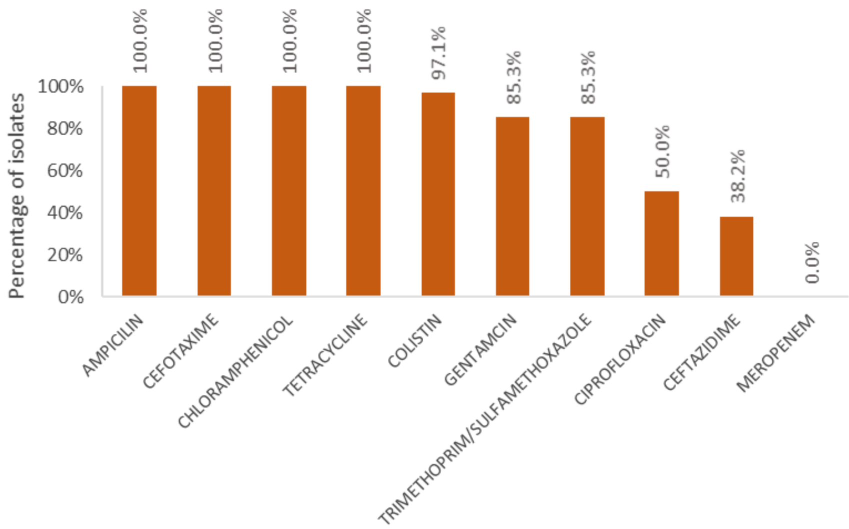
Thirty-four of these ESBL-Ec isolates with colistin resistance genes detected were further subjected to antimicrobial susceptibility testing using the Microscan NM44 panel. All 34 ESBL-Ec isolates obtained from raw poultry (n=27), raw beef (n=5) and raw pork (n=2) were MDR and were resistant to ampicillin, cefotaxime, chloramphenicol and tetracycline (Figure 38). All were susceptible to meropenem.

[22] Guo S., Aung KT., Leekitcharoenphon P., Tay MYF., Seow KLG., Zhong Y., Ng LC., Aarestrup FM., and Schlundt J., 2020. Prevalence and genomic analysis of ESBL-producing Escherichia coli in retail raw meats in Singapore. J Antimicrob Chemother. doi:10.1093/jac/dkaa461

Table 4. Prevalence of meat samples containing ESBL-Ec (adapted from Guo et al[16])

		From supermarkets		From wet markets
Meat type	*ESBL-Ec Prevalence*	*Chilled meats*	*Frozen meats*	*Chilled meats*
Chicken	51.2%	56.7%	51.5%	41.8%
Pork	26.9%	33.0%	5.0%	39.3%
Beef	7.3%	5.6%	0.0%	20.0%

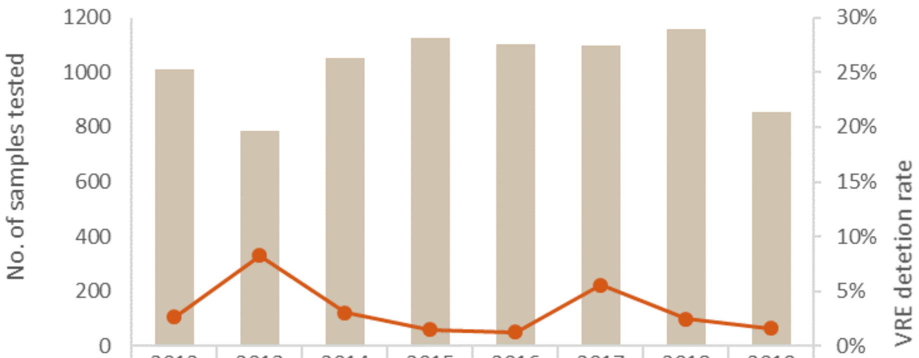
Figure 38. Resistance percentages of ESBL-producing *E. coli* isolates (n=34) from retail meats, 2017 – 2018



Vancomycin Resistant Enterococci (VRE)

As *Enterococcus* spp. are part of the normal flora in poultry, imported poultry are monitored for VRE in the interests of public health. The rate of VRE detection from poultry intestinal samples continues to be consistently low in recent years (Figure 39).

Figure 39. VRE detection in poultry intestinal samples



	2012	2013	2014	2015	2016	2017	2018	2019
No. of samples tested	1010	787	1050	1125	1104	1097	1157	855
VRE detection (%)	2.7%	8.3%	3.0%	1.5%	1.3%	5.6%	2.5%	1.6%

Antimicrobial Resistance in Bacteria from Pets and other Animals

MRSA and MRSP in sick companion animals

In dogs and cats, methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus pseudintermedius (*MRSP) are most often associated with skin, wound or surgical site infections, otitis, or urinary tract infections. MRSA in dogs and cats is generally acquired from people, in turn serving as potential reservoirs of the bacteria[23]. MRSP is more commonly isolated from animals than humans. MRSP more commonly colonise dogs, and to lesser extent, cats. It is an opportunistic pathogen and a major cause of canine pyoderma. Pet owners and veterinary staff are at risk of zoonotic transmission if the dog suffers from pyoderma. However, reports of human infections of MRSP are uncommon[24].

Surveillance of *S. aureus* in companion animals is passive and based on clinical isolates from samples submitted by veterinarians from sick animals. Clinical isolates of *Staphylococcus* spp. undergo AST according CLSI (VET01) to guide treatment options, using the disk diffusion method to a panel of antibiotics of veterinary importance. Isolates identified as *S. aureus* and *S. pseudintermedius* are tested for methicillin resistance and specific resistance genes, in particular, the *mecA* gene, which is the most common gene conferring methicillin resistance in staphylococci. Cefoxitin-resistant *S. aureus* carrying the *mecA* gene are identified as MRSA, while oxacillin-resistant *S. pseudintermedius* with the *mecA* gene are identified as MRSP.

From 2018 to 2019, MRSP was found to be the predominant methicillin-resistant *Staphylococcus* spp., consistent with our 2017 findings[1]. *Staphylococcus* spp. isolates were obtained mostly from ear swab (39.6%), followed by skin swab (15.1%), lung (13.2%), and other samples (Figure 40). Of 53 obtained, 13 (24.5%) were methicillin-resistant, of which the 12 were MRSP and only one was MRSA (Figure 41). This was isolated from a local mongrel dog in 2018.

Concurrent resistance to other antibiotics is frequently seen with MRSP and MRSA. Isolates from 2018 and 2019 were all resistant to ampicillin and ceftiofur, as well as showed high resistance rates to many of the antibiotics tested (Figure 42). However, some differences between 2018 and 2019 isolates were observed: all MRSP isolated in 2019 were found to be susceptible to trimethoprim-sulfamethoxazole, enrofloxacin and doxycycline, while retaining high resistance rates to the other antibiotics (Figure 42). Concurrent resistance to many commonly-used antimicrobials may limit treatment options for animals and increase the need for alternative, or last-line, antimicrobial therapies. As these MRSA and MRSP were isolated from sick companion animals, the prevalence of MRSA and MRSP in local companion animals in Singapore is elusive at present. Given the potential risks of transmission

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[23] Ferreira JP, Anderson KL, Correa MT, Lyman R, Ruffin F, Reller LB, Fowler VG Jr, 2011. Transmission of MRSA between companion animals and infected human patients presenting to outpatient medical care facilities. PLoS One 6(11):e26978.

[24] Reflection paper on meticillin-resistant *Staphylococcus pseudintermedius*. EMA/CVMP/SAGAM/736964/ 2009 Committee for Medicinal Products for Veterinary Use (CVMP), 20 September 2010.

between humans and companion animals[25] and increasing pet ownership in Singapore, CAVS will continue to monitor these trends in MRSA and MRSP resistance in local companion animals.

Figure 40. Isolation of *Staphylococcus* spp. from sick companion animal samples in Singapore, 2018-2019 (n=53)

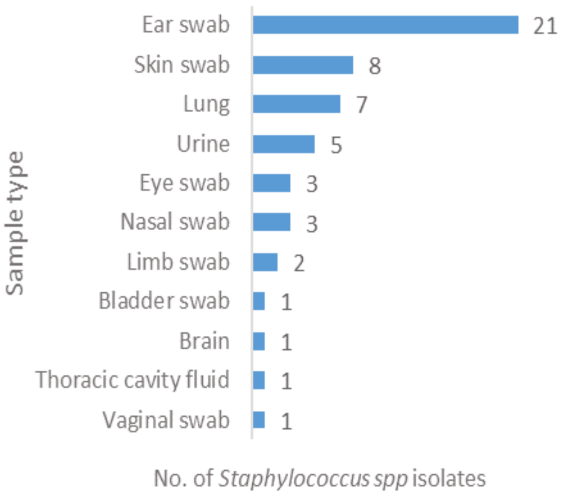
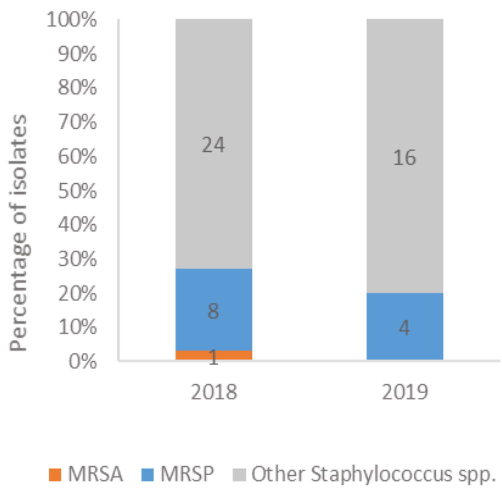
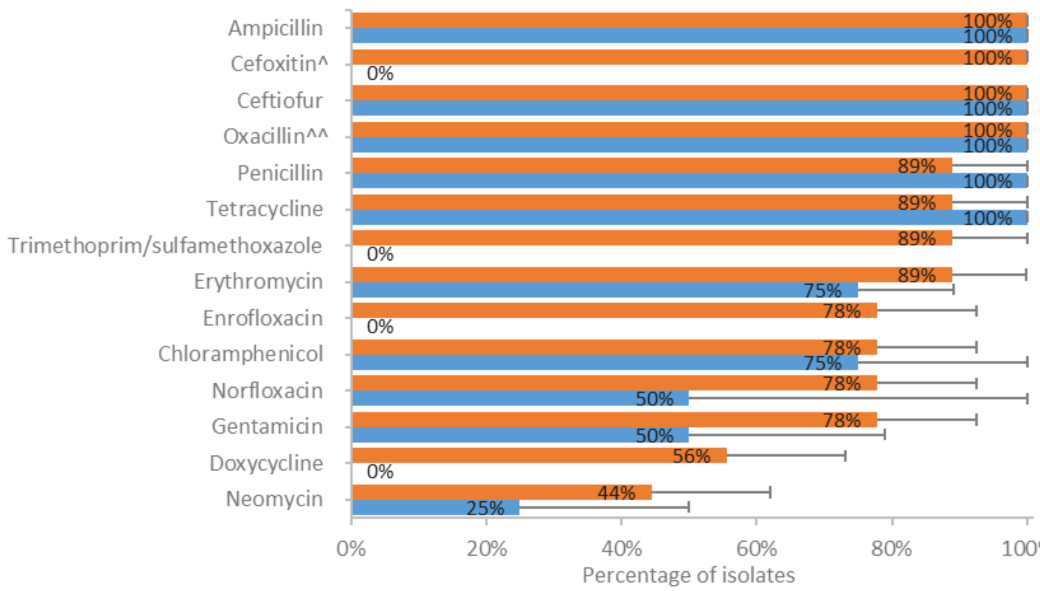


Figure 41. Proportion of MRSA and MRSP in sick companion animals in Singapore, 2018 and 2019



2018: Isolated from 24 dogs, 9 cats
2019: Isolated from 15 dogs, 4 cats and 1 rabbit

Figure 42. Percentage resistance of MRSA and MRSP isolated from sick companion animals in Singapore, 2018 and 2019 (n=13)



Note: Cefoxitin was tested on *S. aureus* only and oxacillin was tested for *S. pseudintermedius* only, in accordance with CLSI M100. "^" refers to the AST results of MRSA only and "^^" refers to the AST results of MRSP only.

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[25] Weese JS and van Duijkeren E., 2010. Methicillin-resistant *Staphylococcus aureus* and *Staphylococcus pseudintermedius* in veterinary medicine. Vet Microbiol. 140: 418-29

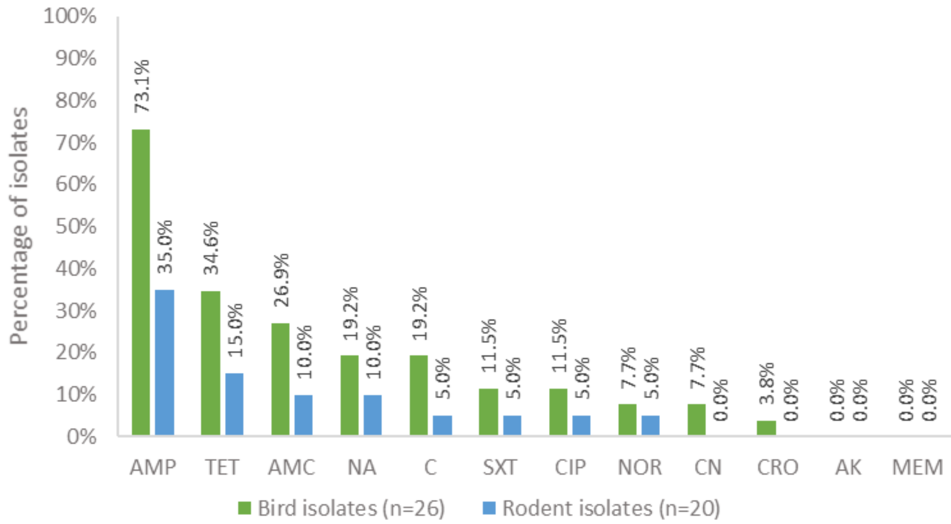
AMR in wild birds and rodents in urban environments

Findings of a joint study by NEA, SFA and NTU in 2017 have suggested that wild birds and rodents could play a potential role in disseminating antimicrobial resistant *E. coli* through pathways such as contact of faecal materials and contamination of food items[26].

To investigate the occurrence of antimicrobial-resistant *E. coli* in wild birds and rodents, 96 samples of wild bird faecal matter and 135 rodent droppings were collected and analysed. From these samples, 46 *E. coli* isolates were subjected to AST by the disk diffusion method according to the CLSI standards. The proportion of *E. coli* isolates resistant to at least one of the antimicrobials tested from wild birds (80.8%) was significantly higher than that of isolates from rodents (40.0%). A large proportion of wild bird isolates were resistant to ampicillin (73.1%), while 35% of rodent isolates were also resistant to ampicillin (Figure 43). The full study may be found at https://pubmed.ncbi.nlm.nih.gov/32756497/.

These findings underscore the need for environment management and monitoring on AMR bacteria in wild birds and rodents to prevent the potential spread of resistant organisms to other animals and humans.

Figure 43. Resistance profiles of *E. coli* isolates from wild birds and rodents (adapted from Ong et al[25])



AK= Amikacin; AMC= Amoxicillin-Clavulanic acid; AMP = Ampicillin; C = Chloramphenicol; CIP = Ciprofloxacin; CN = Gentamicin; CRO = Ceftriaxone; MEM = Meropenem; NA = Nalidixic acid; NOR = Norfloxacin; SXT = Sulfamethoxazole-Trimethoprim; TE = Tetracycline

[26] Ong KH, Khor WC, Quek JY, Low ZX, Arivalan S, Humaidi M, Chua C, Seow KLG, Guo S, Tay MYF, Schlundt J., Ng LC and Aung KT., 2020. Occurrence and Antimicrobial Resistance Traits of *Escherichia coli* from Wild Birds and Rodents in Singapore. Int. J. Environ. Res. Public Health, 17, 5606; doi:10.3390/ijerph17155606

Antimicrobial Resistant Bacteria in the Environment

Humans and animals may exchange pathogenic and non-pathogenic bacteria, with or without resistance to antimicrobials, in their shared environments. Therefore, surveillance of AMR in the environment would contribute toward a better understanding of the complex interplay between the health of humans, animals and the ecosystem.

NEA conducts surveillance of AMR in the water environment and indoor environment, specifically to monitor the prevalence of opportunistic pathogens commonly found in these environments, and to determine their antimicrobial susceptibilities. These include *Enterococcus* spp. from recreational beach environments, *Pseudomonas aeruginosa* from man-made water features and *Staphylococcus* spp. from indoor air environments.

Enterococci are abundant in human and animal faeces. It is also capable of causing gastrointestinal illness through accidental ingestion of contaminated waters from primary contact activities[27]. As their presence is often correlated with human health outcomes in water environments, *Enterococcus* spp. is regarded as an important indicator organism to determine the extent of faecal pollution in aquatic environments.

P. aeruginosa is ubiquitous in the environment and can persist at length in water. As an opportunistic pathogen, *P. aeruginosa* may be associated with a broad range of infections in humans. Management of these infections is challenging as *P. aeruginosa* is inherently non-susceptible to many antimicrobials and there have been reports on the emergence and spread of resistance leading to limited therapeutic options.

***Staphylococcus* spp.** are members of the human skin flora but they have been associated with hospital- and community-associated infections[28]. Some species can be commonly found in indoor air and sedimented dust. MRSA is of particular concern as such infections are difficult to treat. It has been found not only in hospital settings but also as airborne bacteria in homes of metropolitan cities[29].

In the water environment

Enterococci

The NEA conducts weekly monitoring of water quality by collecting *Enterococcus* spp. counts from seven recreational beaches in Singapore. This monitoring assesses the microbiological water quality and safety of the beaches for primary contact activities. All seven beaches monitored were given a grading of “Good” for the past three years (2017 – 2019), with the 95th percentile of *Enterococcus* spp.

[27] Water Quality: Recreational Beaches [cited 2020 April 9] Available from: https://www.nea.gov.sg/our-services/pollution-control/water-quality/recreational-beaches
[28] Madsen AM, Moslehi-Jenabian S, Islam MZ, Frankel M, Spilak M, Frederiksen MW, 2018. Concentrations of Staphylococcus species in indoor air as associated with other bacteria, season, relative humidity, air change rate, and S-aureus-positive occupants. Environ Res 160, 282-291
[29] Moon KW, Huh EH Jeong HC, 2014. Seasonal evaluation of bioaerosols from indoor air of residential apartments within the metropolitan area in South Korea. Environ Monit Assess 186, 2111-2120.

counts measured at concentrations below 200 counts per 100 mL of water[30].

Two beaches were selected for further surveillance. *Enterococcus* spp. were isolated from monthly recreational beach water samplings from October to December 2019. In addition, beach sand, and drainage water sites (n=6) leading out to these recreational beaches were sampled to determine the differences in antimicrobial resistance profiles of enterococci isolated. AST was conducted on the isolates by the disc diffusion method according to CLSI standards (M02-A12, 2016). Enterococci isolates that exhibited non-susceptible resistance to more than three classes of antibiotics were classified as MDR. Comparisons of the antimicrobial resistance profiles observed between the enterococci isolates from the three sample types are summarised below.

Antibiotic susceptibility profiles of enterococci in recreational beach waters, beach sand and drainage sites

Of the 113 enterococci isolated from recreational beach waters, 61.1% were resistant to more than 1 antibiotic tested, and 38.1% were MDR (Figure 44). More than half of the *Enterococcus* spp. isolated were non-susceptible to erythromycin (69.0%), followed by quinupristin-dalfopristin (43.4%), norfloxacin (27.4%), tetracyclines (21.2%) and ciprofloxacin (20.4%). These antibiotics belong to four different classes including macrolides (erythromycin), streptogramins (quinupristin-dalfopristin), tetracyclines (tetracycline) and fluoroquinolones (norfloxacin and fluoroquinolone). Excluding *E. gallinarum* and *E. casseliflavus* which have intrinsic resistance to vancomycin due to the presence of chromosomal *vanC* gene, 4.4% (n=5/113) of the isolates were non-susceptible to vancomycin. These isolates belonged to *E. faecalis. Enterococcus* spp. with resistance to vancomycin is categorised as a pathogen of high priority on the WHO list of antimicrobial-resistant pathogens.

For the *Enterococcus* spp. (n=104) isolated from beach sand, 65.4% were non-susceptible to more than 1 antibiotic tested and 39.4% of the isolates were MDR (Figure 45). The enterococci isolates displayed a similar trend of non-susceptibility to the antibiotics tested in the recreation beach waters including to erythromycin (70.2%), quinupristin-dalfopristin (51.9%), ciprofloxacin (28.8%), norfloxacin (27.9%) and tetracyclines (18.3%). As the sand samples were collected near the shoreline of the beach, it was not surprising to observe similar antibiotic susceptibility profiles as recreational beach waters. Non-susceptibility to vancomycin was detected in 3.9% of the isolates (n=4/104), three belonging to *E. faecalis* and one to *E. faecium* recovered from beach sand.

Of the total 102 *Enterococcus* spp*.* isolates from drainage sites, 67.6% were non-susceptible to more than 1 antibiotic tested and 36.3% were MDR (Figure 46). A large proportion of enterococci isolated was non-susceptible to erythromycin (60.8%), quinupristin-dalfopristin (51.0%), ciprofloxacin (34.3%), norfloxacin (34.3%) and tetracyclines (12.7%), similar to antimicrobial resistance profiles observed in recreational beach waters and sand samples. Approximately 5.9% of the isolates (n=6/102) were non-susceptible to vancomycin, of which five were *E. faecalis* while one was *E. faecium*.

[30] Sunger N, Haas CN, 2015. Quantitative Microbial Risk Assessment for Recreational Exposure to Water Bodies in Philadelphia. Water Environ Res 87, 211

Although enterococci counts were below the WHO recreational water guidelines of 200 counts per 100 mL, the detection of isolates which were non-susceptible to vancomycin in all three sample types highlights potential transmission to humans from the environment. Therefore, it would be ideal if enterococci non-susceptible to vancomycin could be monitored in water environments. Should the proportion of non-susceptibility increase over time, microbial source tracing could be conducted to determine their point sources, and to implement mitigation measures to reduce their respective levels in recreational beach waters.

Figure 44. Percentage resistance of *Enterococcus* spp. (n=113) isolated from recreational beach water.

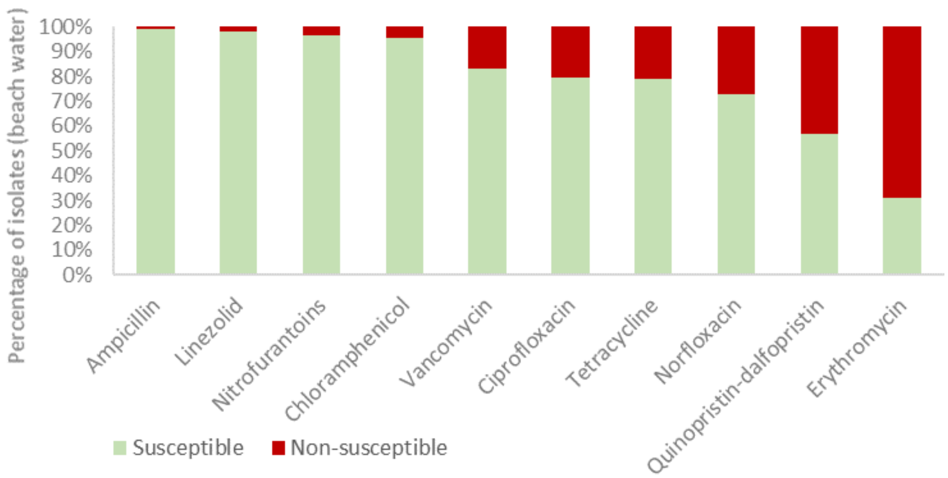


Figure 45. Percentage resistance of *Enterococcus* spp. (n=104) isolated from beach sand

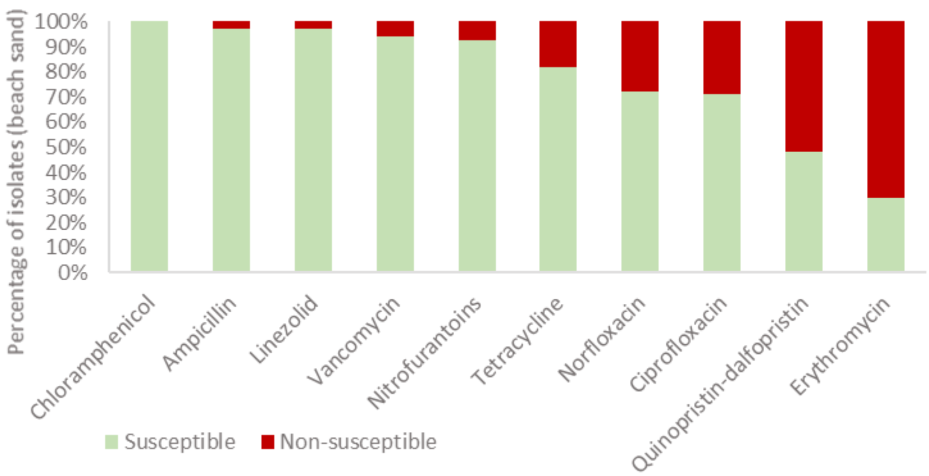
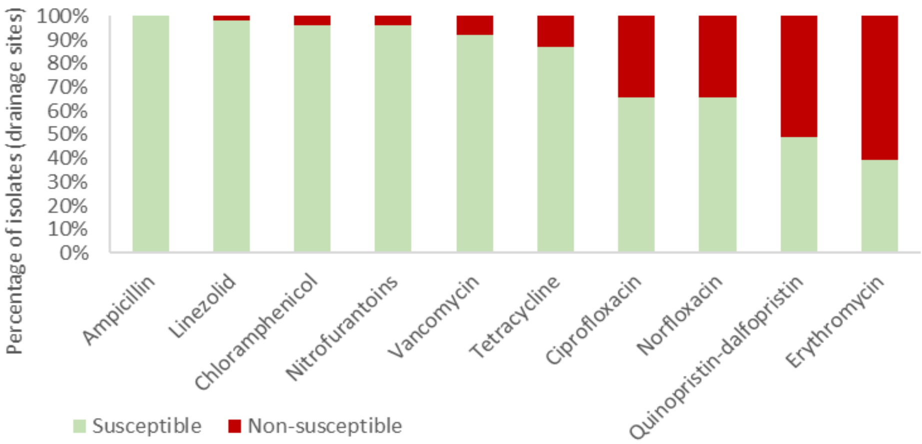


Figure 46. Percentage resistance of *Enterococcus* spp. (n=102) isolated from drainage water



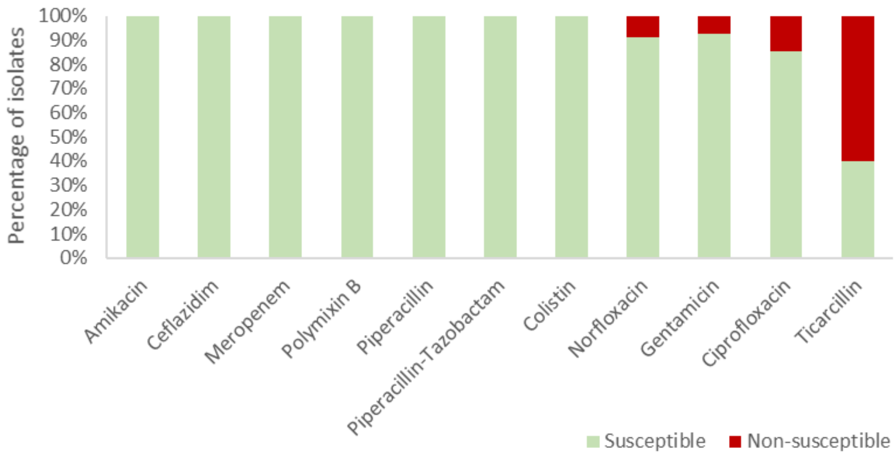
P. aeruginosa

NEA conducts surveillance programmes on the microbiological quality of water environments such as water playgrounds and multi-use spa pools in Singapore biennially. These water features are regulated by NEA under the Environmental Public Health (Licensable Aquatic Facilities) Regulations. The AST profiles of *P. aeruginosa* isolated from water playgrounds (n=22), fish (n=28) and adult recreational spas (n=5) over 2015 – 2016 are summarised below.

Antibiotic susceptibility profiles of *P. aeruginosa* in man-made water features

A total of 55 *P. aeruginosa* strains that were isolated across the man-made water features were selected for this investigation. Of the 55 isolates, 16.4% were non-susceptible to at least one of the eleven antibiotics tested in this study and approximately 7% were non-susceptible to three or more classes of antibiotics thereby classified as MDR. The *P. aeruginosa* strains isolated in this study were mainly non-susceptible to ticarcillin (60%), ciprofloxacin (14.5%), norfloxacin (9.1%), and gentamicin (7.3%), which belong to the beta-lactam (ticarcillin), fluoroquinolones (ciprofloxacin and norfloxacin), and aminoglycosides (gentamicin) antibiotic classes, respectively (Figure 47). Variable AST profiles can be seen in studies reported elsewhere.

Figure 47. Percentage resistance of *P. aeruginosa* strains (n=55) isolated from man-made water features



In the indoor environment

Staphylococcus spp.

The human population typically spends 80–90% of their lifespan in indoor urban environments and the microbiome of the built environment has a potential impact on human health[31,32]. There are numerous studies reporting the presence of antimicrobial resistance in the air of the indoor environments which may impact the air quality standards in terms of public health. NEA conducted a pilot study on the prevalence of *Staphylococcus* spp. from air samples of childcare centres (n=14) and offices (n=6) and their corresponding AST profiles in Singapore between 2018-2019.

Resistance profiles of staphylococci in childcare centres and offices

Among air isolates from childcare centres (n=65), 70.8% were non-susceptible to at least one of the seven antibiotics tested in this study and 6.2% were MDR (Figure 48). A larger proportion of staphylococci isolates were non-susceptible to azithromycin (55.4%), cefoxitin (24.6%), tetracycline (10.8%), trimethoprim-sulfamethoxazole (10.8%), and chloramphenicol (4.6%) which belonged to macrolides, 2nd -generation cephalosporin, tetracycline, folate pathway inhibitors and phenicols antibiotic classes respectively.

Among air isolates collected from an office (n=77), 50.6% of the isolates were non-susceptible to at least one of the seven antibiotics tested in this study and 2.6% were MDR (Figure 49). A larger proportion of *Staphylococcus* spp. isolates were non-susceptible to azithromycin (41.6%), tetracycline (9.1%) and cefoxitin (5.2%).

The majority of the isolates belonged to non-aureus *Staphylococcus* spp. *S. aureus* was only found in 4.6% (n=3/65) and 2.6% (n=2/77) of isolates recovered from childcare centres and offices, respectively. Additionally, none of them was likely to be MRSA as they were phenotypically sensitive to methicillin. Low prevalence of MRSA in indoor air has been reported[1] even though *Staphylococcus* spp. are commonly isolated airborne bacteria in childcare centres, offices and in other indoor spaces[33,34]. The proportion of staphylococci exhibiting resistance to more than one antibiotic was generally higher in childcare centres (41.5%; n=27/65) than offices (6.5%; n=5/77); almost all were non-aureus. The results suggest that clinically relevant MRSA was not detected in the air samples but non-aureus *Staphylococcus* spp. may be reservoirs of AMR genes and should not be overlooked.

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[31] Hoisington AJ, Brenner LA, Kinney KA, Postolache TT, Lowry CA, 2015. The microbiome of the built environment and mental health. Microbiome 3, 60

[32] Rintala H, Pitkäranta M, Toivola M, Paulin L, Nevalainen A, 2008. Diversity and seasonal dynamics of bacterial community in indoor environment. BMC Microbiol. 8, 56

[33] Hewlett A, Falk P, Hughes K and Mayhall C, 2009. Epidemiology of Methicillin-Resistant *Staphylococcus aureus* in a University Medical Center Day Care Facility. Infection Control & Hospital Epidemiology, 30(10): 985-992.

[34] Kozajda A, Jeżak K and Kapsa A, 2019. Airborne *Staphylococcus aureus* in different environments—a review. Environmental Science and Pollution Research, 26(34):34741-34753.

Figure 48. Percentage resistance of *Staphylococcus* spp. (n=65) isolated from air samples in childcare centres

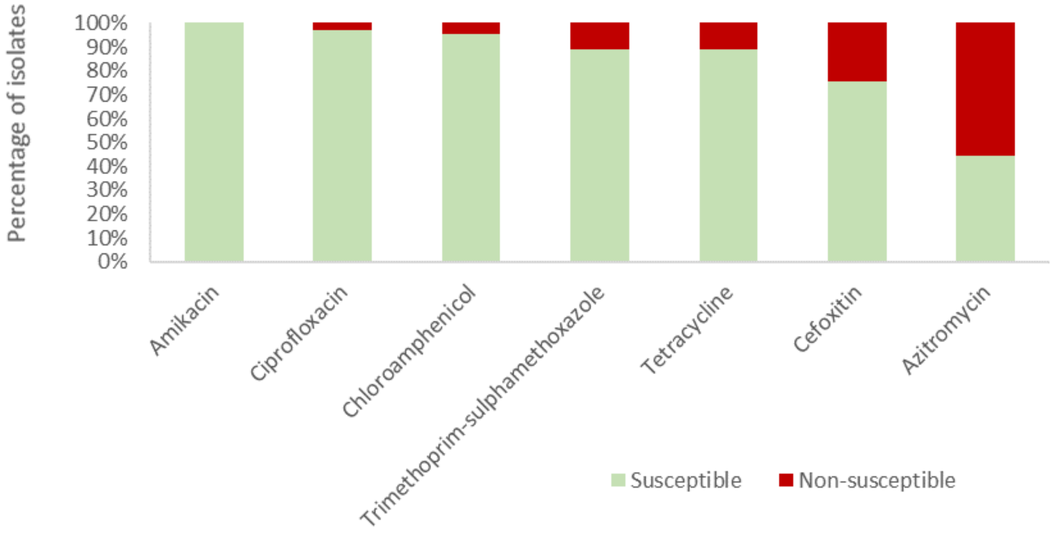
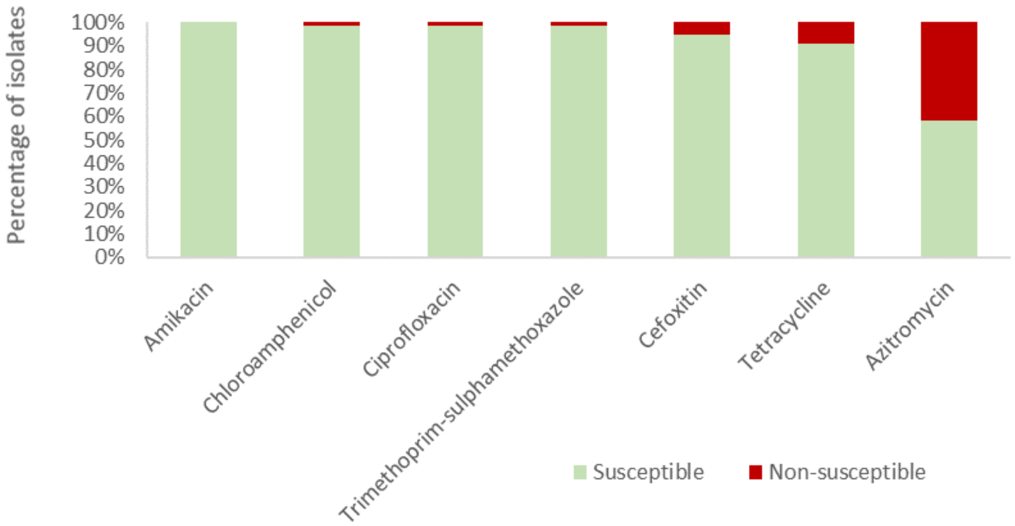


Figure 49. Percentage resistance of Staphylococcus spp. (n=77) isolated from air samples in offices



NEA's preliminary studies showed the presence of antimicrobial resistance amongst opportunistic pathogens isolated from both indoor and outdoor environments, possibly driven by human activities. The findings suggest that these opportunistic pathogens may act as reservoirs of resistance genes, which can be transferred to other pathogens. The collected data will be useful to understand their potential risk impacts to human and animal health and to establish guides for mitigation measures. Further work will be needed to establish the molecular mechanisms contributing to antibiotic resistance in these pathogens and to better define the role of environmental bacteria in the maintenance and dissemination of antimicrobial resistance to other potentially pathogenic bacteria. Overall, these findings underscore the importance of surveillance for monitoring the prevalence of antibiotic-resistant bacteria in the environment, which are crucial to address the potential spread of these AMR pathogens via environmental routes.

Risk Assessment of Antimicrobial Resistance in Urban Waters

The levels of antibiotic resistant bacteria (ARB) and associated antibiotic resistance genes (ARG) in domestic and hospital wastewater, reservoirs and water catchments were reported previously[35], whereby various approaches were used to compare the abundance of ARB and ARG in different sources of waters in Singapore.

To further define the risk of ARG and ARB in the urban water cycle, PUB continued to work with NUS Department of Civil and Environmental Engineering through a collaborative project commissioned in 2016. The study quantified the resistance profile of faecal indicators like *E. coli and Enterococcus*, and opportunistic pathogens like *P. aeruginosa* and *K. pneumoniae* in 4 reservoirs and 2 catchments, a water reclamation plant (wastewater treatment plant), a NEWater[36] plant and a water treatment plant. The study showed that the processes of the water treatment plant were efficient in removing ARBs and opportunistic pathogens (Table 5).

Table 5. Range of total and ESBL- and carbapenem-resistant (CR) bacteria detected in freshwater, water intake and product water of water treatment plants.

	E. coli	***K. pneumoniae***	***P. aeruginosa***
Freshwater	10^3 - 10^4 CFU/100mL [1% ESBL; 0.7% CR]	~10^3 CFU/100mL [<1% ESBL and CR]	10^4 - 10^5 CFU/100mL [1 - 8% ESBL and CR]
Water intake of water treatment plant	10^1 - 10^2 CFU/100mL [5.5% ESBL; 0.3% CR]	10^2 - 10^2 CFU/100mL [<1% ESBL and CR]	~10^3 CFU/100mL [22% ESBL; 20% CR]
Product water of water treatment plant	<1 CFU/100mL Complete removal	<1 CFU/100mL Complete removal	<1 CFU/100mL Complete removal

For wastewater treatment processes, samples taken from the water reclamation plant showed that 2-3 logs of bacteria are removed in the wastewater treatment processes. The treated effluent of the water reclamation plant is fed to the NEWater plant as feedwater. The data showed that the NEWater processes were efficient in removing the studied ARBs or any opportunistic pathogens (Table 6). Hence there are no perceived AMR risks to the NEWater supply as well.

[35] One Health Report on Antimicrobial Utilisation and Resistance in Singapore, 2017

[36] NEWater is high-grade reclaimed water produced from treated used water that is further purified using advanced membrane technologies and ultra-violet disinfection, rendering it clean and potable.

Table 6. Range of total and ESBL- and carbapenem- resistant (CR) bacteria detected in the influent to water reclamation plant, treated effluent of water reclamation plant (also feedwater to NEWater plant), and NEWater.

	E. coli	*K. pneumoniae*	*P. aeruginosa*
Influent to water reclamation plant	10^7 CFU/100mL [3.8% ESBL; 0.4% CR]	10^6 - 10^7 CFU/100mL [<1% ESBL and CR]	~10^5 CFU/100mL [75% -93% ESBL and CR]
Treated effluent from water reclamation plants/Feedwater to NEWater plant	10^4 - 10^5 CFU/100mL [4% ESBL; 0.4% CR]	10^4 - 10^5 CFU/100mL [<1% ESBL and CR]	10^2 - 10^3 CFU/100mL [3% ESBL; 50% CR]
NEWater	<1 CFU/100mL Complete removal	<1 CFU/100mL Complete removal	<1 CFU/100mL Complete removal

Consistent with data reported previously[31], the levels of ARBs were found to be relatively low in all freshwater reservoirs, but higher in catchments. To predict the relative risk of ARB from recreational activities in surface waters, quantitative microbial risk assessment (QMRA) calculations were done using concentrations of *Enterococcus*, *E. coli* and *P. aeruginosa,* as well as the resistant fractions of these three bacteria to a range of antibiotics covering the different generations of cephalosporins, penicillins, carbapenems, fluoroquinolones, aminoglycosides, nitrofuran and trimethoprim-sulfamethoxazole. The risk assessment approach used was based on the QMRA framework that comprises 4 essential components: (1) problem formulation; (2) exposure assessment; (3) health effects assessment; (4) risk characterisation.

For problem formulation, the assessment focused on the recreational risks posed by *Enterococcus*, *E. coli* and *P. aeruginosa* in surface waters, as well as their resistant strains, to selected antibiotics. The risks to activities included secondary contact recreational activities (including boating, canoeing, fishing, playing with water) and primary contact activities like swimming.

For exposure assessment, the magnitude and frequency of exposure to *Enterococcus, E. coli* and *P. aeruginosa* via the identified recreational water exposure pathways were quantified. The hazardous events identified were gastrointestinal (GI) infections for the exposure to *Enterococcus, E. coli* with ingestion as the primary route, and using assumptions for the volumes of water ingested for the different types of activities[37]. Water-related folliculitis was identified as the most relevant disease for the exposure to *P. aeruginosa* through the dermal route.

For the health effects assessment, the risk potential was evaluated using the 1986-U.S. EPA Ambient Water Quality Criterion that relies on *E. coli* and *Enterococcus* as indicator organisms and limits the acceptable level of GI illnesses to 36 illnesses per 1000 swimmers per day (U.S. EPA, 1986, 2004). The

[37] Sunger N., Haas C.N. 2015. Quantitative Microbial risk assessment for recreational exposure to water bodies in Philadelphia. Water Environ. Res. 87(3):211-222.

exponential[32] and beta-Poisson[38] dose-response models were used to calculate the probabilities of GI infection (Pi) resulting from the incidental/intentional ingestion of *Enterococcus* and *E. coli* in freshwater respectively. A dose-response relationship was established for *P. aeruginosa* pool folliculitis, using bacterial and lesion density estimates. The exponential model[39] was used to assess the probability of folliculitis from *P. aeruginosa.*

Finally, risk characterisation informed the likelihood of risks posed by their prevalence in our reservoirs and catchments. Results were derived using the Monte Carlo simulation (using the software Crystall Ball) outputs from *Enterococcus, E. coli* and *P. aeruginosa* dose-response models for boating, canoeing fishing, playing with water and swimming in reservoirs and catchments. The probability of GI illnesses from total *E. coli* and *Enterococcus* for all secondary and primary contact recreational activities in reservoirs and catchments, was quite low and almost all were below the accepted threshold of 36 illnesses per 1000 swimmers per day. As there are no established dose response models for pathogens resistant to antibiotics, the probability of GI illness due to resistant pathogenic strains of *E. coli* and *Enterococcus* was likely to be even lower, based on the low prevalence of these bacteria. The probabilities of getting folliculitis due to pathogenic or resistant strains of *P. aeruginosa* by swimming in reservoirs and catchments were all below the accepted threshold.

CONCLUSION

Notwithstanding that there are no perceived risks of AMR to the potable water and NEWater supply, PUB will continue to collect AMR data in water and wastewater including developing appropriate risk assessment tools to better ascertain the risk and impact, if any, of AMR in the urban water cycle. PUB will also continue to work with the relevant agencies to support the national One Health initiative on the monitoring, surveillance and risk assessments of AMR across animal, human, food and environment sectors.

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[38] DuPont HL, Formal SB, Hornick RB, Snyder MJ, Libonati JP, Sheahan DG, LaBrec EH, Kalas JP, 1971. Pathogenesis of *Escherichia coli* diarrhoea. N Engl J Med. 285(1):1-9.

[39] Roser D.J., Vn den Akker B., Boase S. Haas C.N., Ashbolts N.J., Rice S.A., 2015. Dose-response algorithms for water-borne *Pseudomonas aeruginosa* folliculitis. Epidemiol. Infect. 142:449-462.

Conclusions and Steps Forward

AMR surveillance in Singapore is being expanded in a step-wise fashion across the human, animal, food and environment sectors.

In the human health sector, Singapore enrolled in GLASS in 2019 and began collecting data on the WHO priority pathogens. This dataset enhanced our understanding of resistance in community-associated pathogens such as *Streptococcus pneumoniae, Salmonella* spp*., Shigella* spp*.,* and *N. gonorrhoea* which are not included in the national hospital surveillance programmes. Participation in GLASS has also enabled benchmarking based on a standardised methodology, with particular attention to the SDG indicators: MRSA and third-generation resistant *E. coli*. Surveillance was recently expanded to include private hospitals, and analyses of the data collected are underway. With the almost complete coverage of Singapore's secondary/tertiary healthcare facilities, the next step will be to extend surveillance to the community, beginning with sentinel sites within the primary care sector.

Surveillance in the food chain now covers all terrestrial livestock farms in Singapore. In addition, surveillance along the food chain has expanded to include indicator *E. coli*. *Salmonella* continues to be the focus of national surveillance efforts: the prevalence of drug-resistant *Salmonella* in local poultry farms has remained low, correlating with the low sales of antimicrobials to the poultry sector. MDR *Salmonella* continues to be detected in imported poultry and poultry products. *Salmonella* spp. is less frequently isolated from cooked/ready-to-eat food, and while infrequent detections tend to be associated with food containing poultry products. Food safety measures along the entire food chain have kept contamination rates relatively low, but food pathogens, including drug-resistant food pathogens, continue to be detected from time-to-time. These findings highlight the importance of reinforcing safe food practices and good personal hygiene to reduce exposure to pathogens and drug-resistant organisms in food.

One observation here is the consistently high percentage of *Salmonella* spp. that are resistant to ampicillin, and *E. coli* in the food chain that are resistant to nalidixic acid and ampicillin, even among local farm isolates. The observed resistance to nalidixic acid and ampicillin of local farm *E. coli* isolates did not correlate with sales/use: ampicillin accounted for less than 0.2% of penicillin sales for veterinary use and there was no recorded sales data of nalidixic acid in 2018 and 2019 (Figure 9). It appears that the trends of ampicillin and nalidixic acid resistance were unlikely driven by usage of these antimicrobials and warrants the need to monitor this resistance profile and examine other contributing factors.

Surveillance has also been expanded to recreational and indoor environments to assess prevalence and potential risks to the public. Singapore is completely sewered and all waste are treated before being released to the environment. Nevertheless, anthropologic activities can contribute to AMR in the environment. This is evident from MDR P. *aeruginosa* strains found in man-made water features, and MDR *Enterococcus* spp*.* at recreational beach waters, sand sample and drainage sites. However, this is mitigated by total counts of enterococci being well within WHO's recommended limits. Furthermore, a QMRA study found no perceived risks of AMR to the potable water and NEWater supply.

With the expansion of AMR surveillance programmes across sectors, baseline data is now available for key populations and surveillance sites. Efforts are now being made to extend surveillance to the community and to aquaculture farms, as well as establish an integrated surveillance programme that examines the linkages of common pathogens across all sectors. Baseline data would contribute towards the formulation of science- and risk-based targets to drive antimicrobial resistance control efforts.