Department of health - Research Institute for Tropical Medicine
Antimicrobial Resistance Surveillance Reference Laboratory

Annual REPORT

2022

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Antimicrobial Resistance Surveillance Program

2022 Annual Report

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Preface

The Antimicrobial Resistance Surveillance Program (ARSP), running on in its 35th year, has steadfastly provided information on the national estimates and trends of antimicrobial resistance rates of aerobic bacteria in the Philippines. Implemented by capable team of medical staff, laboratorians, data management and support staff with years of experience, the surveillance upholds the collection of quality microbiology data by supporting the implementation of standard laboratory and data management methods in its sentinel sites as well as in the Antimicrobial Resistance Surveillance Reference Laboratory (ARSRL).

The ARSP 2022 Annual Report provides an overview of the surveillance, the AMR data for bacterial pathogens, recommendations based on the 2022 ARSP data, and the program future directions. AMR rates for year 2022 are described for the following bacteria: *Streptococcus pneumoniae, Haemophilus influenzae*, *Salmonella* Typhi, non typhoidal *Salmonella*, *Shigella sp, Vibrio cholerae*, *Neisseria gonorrhoeae*, *Staphylococcus aureus, Enterococcus sp* and the multidrug resistant gram negative bacilli *Escherichia coli*, *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*. For each bacteria, the resistance rates are presented for all specimen types as well as for subsets of isolates stratified as to specimen type (i.e. blood, urine or stool) and resistance characteristics (i.e. MRSA, MSSA, carbapenem resistance and colistin resistance). Demographic information, such as age, gender, hospital wards and geographic location were also presented to provide a comprehensive understanding of antibiotic resistance patterns in different populations. Resistance trends for the past 10 years are also presented for specific bacteria-antibiotic combinations.

The identification of resistance phenotypes which have not been previously reported or have been only rarely reported to date is also described in this Annual Report. This is done to document the emergence of such resistant phenotypes locally and to create awareness among relevant sectors of such occurrence. For 2022, genomic characterization of select isolates observed to be resistant to reserve antibiotics was done and is described in this report. The genomic characterization of these isolates is meant to allow for the understanding of resistance mechanisms of these isolates to last resort antibiotics as well as their potential for spread in an effort to inform control and prevention measures.

Executive Summary

Resistance data for **88,049** bacterial isolates coming from 23 hospital based bacteriology laboratories and 1 gonorrhoeae surveillance site were analysed for 2022.

Streptococcus pneumoniae

Cumulative resistance rate of *S. pneumoniae* isolates against penicillin using non-meningitis breakpoint at 1.7% (n=232) remained low making this an antibiotic viable option for non-meningitis infections. A decrease in resistance to erythromycin was noted in 2022 at 10.2% from the previous year at 11.3% in 2021. *S. pneumoniae* isolates remained susceptible to ceftriaxone meningitis and non-meningitis breakpoints at 2.3% and 1.1% respectively.

Haemophilus influenzae

Resistance rate of *H. influenzae* for 2022 to ampicillin was at 9.8% remaining within the range of 7.8% (2016) and 17.2% (2013) in the past ten years. These isolates remained mostly susceptible to ceftriaxone with non-susceptibility rate for 2022 being at 2.5%. Azithromycin resistance was at 0.4% while no resistance to levofloxacin was reported for 2022.

Salmonella enterica serotype Typhi

Salmonella Typhi isolates remained susceptible to chloramphenicol, ceftriaxone, cefotaxime and co-trimoxazole with no resistance detected against these antibiotics for 2022. Resistance to ciprofloxacin remained below 5% for the past ten years.

Nontyphoidal *Salmonella*

As in the past years, resistance of nontyphoidal *Salmonella* to ampicillin/ amoxicillin, co-trimozazole and chloramphenicol are higher compared to that of *Salmonella* Typhi with noted decrease in resistance rates to these antibiotics for 2022 compared to the rates in 2021. Resistance to ciprofloxacin remained within 10-12% range in the past seven years with 2022 resistance at 11.4%.

Shigella species

Resistance to ceftriaxone and ciprofloxacin for 2022 among *Shigella sp* were at 12.9% and 9.1% respectively. Ceftriaxone resistance has been in the 10-13% range in the past four years. No azithromycin resistance was reported for 2022.

Vibrio cholerae

Vibrio cholerae isolates remain susceptible to antibiotics with resistance to co-trimoxazole, ampicillin, azithromycin and chloramphenicol at less than 4%. No resistance reported to tetracycline. One *V. cholerae* (biotype El Tor) isolate from a stool specimen of a 67-year old male from VSM was confirmed to be azithromycin resistant. The isolate was resistant to ampicillin, chloramphenicol, and co-trimoxazole but was susceptible to tetracycline.

Neisseria gonorrhoeae

There is no confirmed resistance to ceftriaxone, cefixime and azithromycin for 2022. Resistance to tetracycline and ciprofloxacin continues to be very high for 2022 at 71.8% (n=39) and 76.3% (n=38) respectively.

Staphylocccus aureus

There is a continued decrease of oxacillin resistance among *Staphylococcus aureus* to its present rate of 42.2% (n=5,168) in 2022. Erythromycin resistance was at 12.0% (n=5,408) and clindamycin 10.6% (n=5, 299) with both rates appearing to be stable for the past years. Vancomycin resistance was noted to be at 1.5% (n=5,172) for 2022 and the increase in the resistance to vancomycin in the past decade was noted to be statistically significant. All isolates tested against daptomycin were susceptible to this antibiotic.

Enterococcus species

Resistance of *Enterococcus faecalis* to penicillin and ampicillin were at 15.8% and 8.5% respectively, with resistance to penicillin continuously increasing over the past ten years. Vancomycin resistance decreased in 2022 at 2.8%. There were 2 *E. faecalis* isolates confirmed to be linezolid resistant. The isolates were noted to be susceptible to penicillin, ampicillin, vancomycin, gentamicin (HL), and streptomycin (HL).

Enterococcus faecium continue to show higher antibiotic resistance with rates for vancomycin and nitrofurantoin being 28.1% and 38.3% respectively for 2022. The decrease in percent resistance for linezolid (1.9%) in 2022 from the previous year was noted to be statistically significant.

Escherichia coli

Carbapenem resistance among *E. coli* remained above 8% for meropenem and imipenem and above 7% for ertapenem for year 2022 with increase in rates over the past decade noted to be statistically significant. One *E. coli* isolate was confirmed to be colistin- resistant; this isolate was noted to be susceptible to the carbapenem as well as to amikacin, cefoxitin and co-trimozaxole. Overall ESBL positivity rate among *E. coli* tested for ESBL production was 43.8%.

Klebsiella pneumoniae

Carbapenem resistance among *K. pneumoniae* isolates continued to increase in 2022 with resistance rates for meropenem at 16.2% (n= 11,853), imipenem at 15.7% (n=11, 838) and ertapenem at 13.9% (n=10,882). When the subset of *K. pneumoniae* isolates from blood specimens were analysed, even higher carbapenem resistance rates were noted with meropenem resistance rate at 22.2% (n=1,173). There were 20 confirmed colistin *K. pneumoniae* isolates for 2022. Most of the isolates were susceptible to amikacin and cefoxitin and resistant to ampicillin, amoxicillin/ clavulanic acid and ciprofloxacin. The overall ESBL positivity rate among *K. pneumoniae* tested for ESBL production was 47.7%.

Pseudomonas aeruginosa

For 2022, resistance to *Pseudomonas aeruginosa* isolates to ceftazidime and piperacillin/tazobactam was 15% while resistance to gentamicin decreased at 7.7%. For 2022, carbapenem resistance was reported at 15.4% for imipenem and 12.8% for meropenem. Colistin resistance was at 5.8% (n=258). There were 15 confirmed colistin resistant *P. aeruginosa* isolates for 2022. Most of the isolates were susceptible to amikacin, aztreonam, cefepime, ceftazidime, gentamicin and tobramycin. MDR and possible XDR rates for *P. aeruginosa* were at 23% and 14% respectively for 2022.

Acinetobacter baumannii

For 2022, resistance to most antibiotics remained above 50%. There were significant decrease in rates for ceftazidime, meropenem, imipenem, co-trimoxazole, ceftriaxone and amikacin. There were 4 confirmed colistin resistant *A. baumannii* isolates for 2022. Three out of the 4 isolates were resistant against all antibiotics tested (presumptive XDR) while one of the 4 isolates was resistant to most of the antibiotics tested except for the aminoglycosides gentamicin and tobramycin. All 4 isolates were not tested for doxycycline, minocycline and cefiderocol. MDR and possible XDR for *A. baumannii* isolates for 2022 were at 60% and 50% respectively.

Introduction

Antimicrobial Resistance (AMR) is the change that occurs over time among bacteria, viruses, fungi and parasites where these organisms no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death[1]. *AMR is a serious public health threat* because of its far reaching and serious implications in health care as well as economies. AMR hampers the control of infectious diseases because patients remain infectious for a longer time increasing the risk of spreading resistant microorganisms to others. AMR increases the cost of health care as more expensive therapies must be used when infections become resistant to first-line medicines. Infections due to resistant microorganisms increases economic burden to families and societies as it often results in longer duration of illness and treatment.

With the loss of antimicrobials to resistance, the achievements of modern medicine such as organ transplant, cancer chemotherapy and major surgery would be compromised as these would not be possible without effective antimicrobials for prevention and treatment of infections. Losing antimicrobials to resistance can result in many infectious diseases becoming untreatable and uncontrollable. This can bring us back to the pre-antibiotic era.

The Philippine Committee on Antimicrobial Resistance Surveillance Program was created in 1988 through the Department of Health's Department Order 339-J. The program aims to provide critical inputs to the Department of Health's effort to promote rational drug use by determining the status and developing trends of antimicrobial resistance of selected bacteria to specific antimicrobials.

AMR surveillance remains an essential component in the control of AMR in the country. Surveillance data enable correct decisions to be made about treatment options and guide policy recommendations. The Philippine National Action Plan on Antimicrobial Resistance 2019-2023 [2] reiterates the importance of surveillance as it identifies the strengthening of surveillance and laboratory capacity as among its key strategy.

For 2022, the number of data received by ARSP has increased by more than 24% compared with the reports submitted in 2021 and is noted to be comparable with the number of data received in the years prior to the COVID-19 pandemic. This is perceived to be due to the shift of the sentinel site hospitals back to their regular operations. Interpretation in any change in AMR resistance trends for 2022 compared with the previous 3 years have to be interpreted in the context of the changes that the COVID-19 pandemic has brought to the health care scenario in the country.

SURVEILLANCE, TESTING METHODS, DATA ANALYSIS & LIMITATIONS

The Surveillance

The DOH-ARSP is a sentinel laboratory-based antimicrobial resistance surveillance on aerobic bacteria from clinical specimens.

Currently participating in the program are 24 sentinel sites, and 2 gonococcal surveillance sites, representing 16 out of the 17 regions of the country (Figure 1 & Table 1).

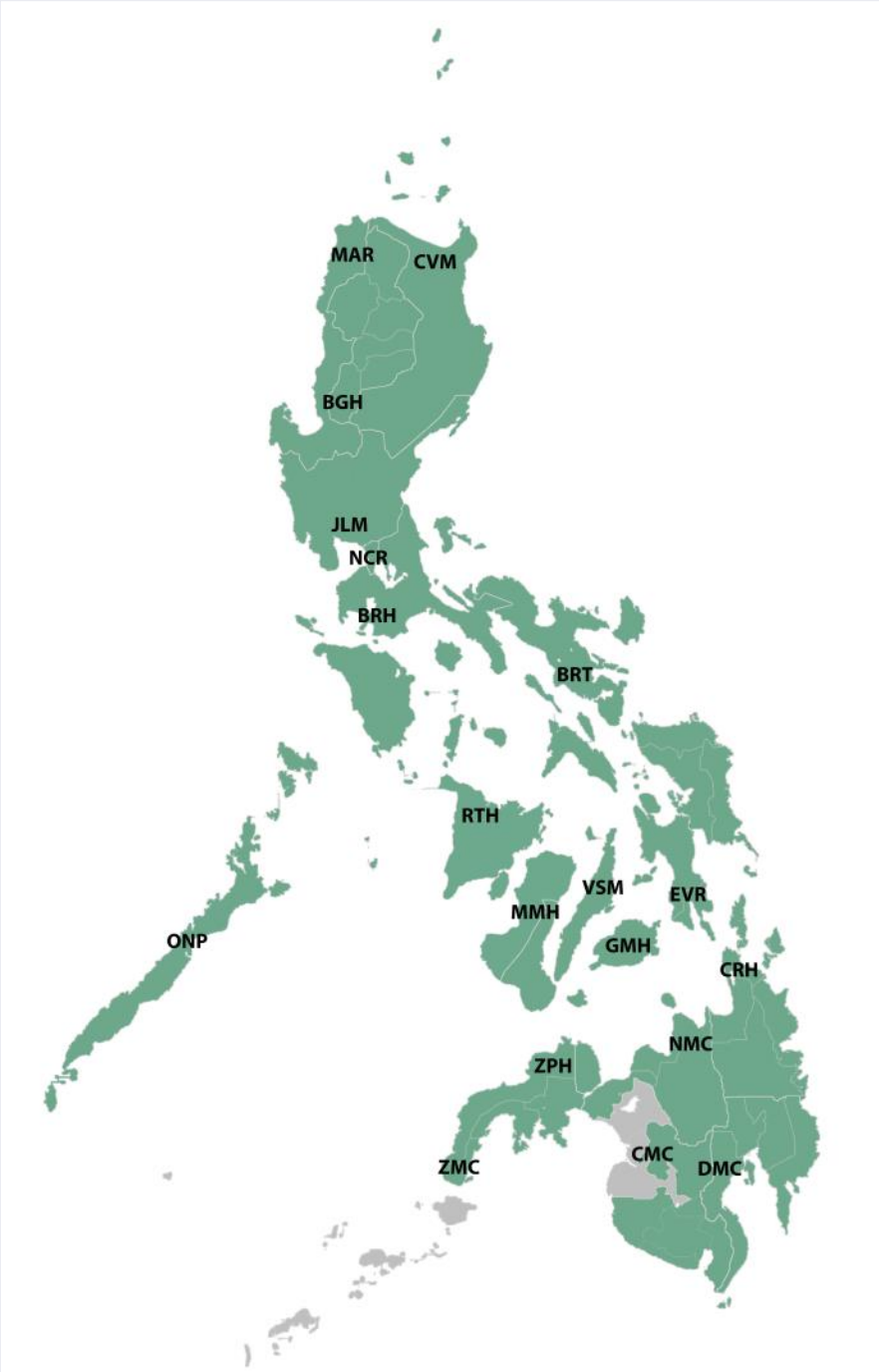


Figure 1. Regional representation in the ARSP 2022

Table 1. ARSP 2022 sentinel sites by region

Region	Sentinel Site
National Capital Region (NCR)	Lung Center of the Philippines
	National Kidney and Transplant Institute
	Rizal Medical Center
	San Lazaro Hospital
	Philippine General Hospital
	Research Institute for Tropical Medicine
	University of Santo Tomas Hospital
	Far Eastern University Nicanor Reyes Medical Foundation Medical Center
Cordillera Administrative Region (CAR)	Baguio General Hospital and Medical Center
Region 1—Ilocos Region	Mariano Marcos Memorial Hospital and Medical Center
Region 2—Cagayan Valley	Cagayan Valley Medical Center
Region 3—Central Luzon	Jose B. Lingad Memorial Regional Hospital
Region 4-A—CALABARZON	Batangas Medical Center
Region 4-B—MIMAROPA	Ospital ng Palawan
Region 5—Bicol Region	Bicol Regional Training and Teaching Hospital
Region 6—Western Visayas	Corazon Locsin Montelibano Memorial Regional Hospital
	Dr. Rafael S. Tumbokon Memorial Hospital
Region 7—Central Visayas	Celestino Gallares Memorial Hospital
	Vicente Sotto Memorial Medical Center
Region 8—Eastern Visayas	Eastern Visayas Regional Medical Center
Region 9—Zamboanga Peninsula	Zamboanga City Medical Center
	Zamboanga del Norte Medical Center
Region 10—Northern Mindanao	Northern Mindanao Medical Center
Region 11—Davao Region	Southern Philippines Medical Center
Region 12—SOCCSKSARGEN	Cotabato Regional Hospital and Medical Center
Region 13—CARAGA Region	Caraga Regional Hospital

Legend: CALABARZON: Cavite, Laguna, Batangas, Rizal, Quezon; MIMAROPA: Mindoro, Marinduque, Romblon, Palawan; SOCCSKSARGEN: South Cotabato, Cotabato, Sultan Kudarat, Sarangani, General Santos City.

The surveillance collects data on culture and antimicrobial susceptibility from its *24 sentinel sites and 2* gonococcal surveillance sites. Case finding is based on priority specimens sent routinely to sentinel sites laboratories for clinical purposes.

TESTING METHODS

All sentinel sites implement standard methods for culture and susceptibility testing based on the WHO Manual for the Laboratory Identification and Antimicrobial Susceptibility Testing of Bacterial Pathogens of Public Health Importance in the Developing World [3] and the updated Clinical Laboratory Standards Institute (CLSI) references for antibiotic susceptibility testing and quality control [4].

Panel of antibiotics for testing are based on the latest CLSI recommendations. In the analysis of antimicrobial susceptibility testing, an isolate is considered resistant to an antimicrobial agent when tested and interpreted as resistant (R) in accordance with the clinical breakpoint criteria based on the most recent Clinical Laboratory Standards Institute (CLSI) references for antibiotic susceptibility testing.

The culture and antimicrobial susceptibility test results are encoded using a database software called *WHONET*. WHONET is Windows-based database software developed by the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance based at the Brigham and Women's Hospital in Boston for the management and analysis of microbiology laboratory data with a special focus on the analysis of antimicrobial susceptibility test results.

Using a standard format, routine culture and antimicrobial susceptibility test results are sent by the sentinel sites to the coordinating laboratory of the program – the *Antimicrobial Resistance Surveillance Reference Laboratory (ARSRL) at the Research Institute for Tropical Medicine*. Beginning January 2018, sentinel sites transmit data daily to the reference laboratory. The automated data transfer facilitates prompt identification of resistant isolates of public health importance as well the identification of clustering of cases and potential outbreaks among sentinel sites. The ARSRL's Data Management Unit manages the cleaning, analysis, storage and security of the program's surveillance data.

Sentinel sites likewise send isolates with unusual antimicrobial susceptibility patterns to ARSRL for phenotypic and genotypic confirmatory testing.

At the reference laboratory, all isolates with unusual susceptibility patterns received for confirmatory testing are re-identified using both automated (Vitek) and conventional methods. Both minimum inhibitory concentration (MIC) - via automated method (Vitek) and gradient E-test, and disk diffusion are employed in antimicrobial susceptibility testing. AST indicated, additional testing are done for specific antibiotics which are not included in AST card in use in the reference laboratory and for susceptibility testing for specific bacteria such as *N. gonorrhoeae* which requires manual AST methods. Serotyping for *S. pneumoniae, H. influenzae*, *Salmonellae*, *Shigellae* and *Vibrio cholera* were done for 2022.

Further, for 2022, select isolates with resistance phenotype which have not been previously reported or have been only rarely reported to date underwent whole genome sequencing (WGS) at the Antimicrobial Surveillance Reference Laboratory (ARSRL). The genomic characterization of these isolates is meant to allow for the understanding of resistance mechanisms of these isolates as well as their potential for spread in order to inform control and prevention measures. The isolates were grown on tryptic soy broth overnight at 35°C. DNA was extracted from single colonies. The DNA extracts were sequenced through Illumina Miseq platform (Illumina, San Diego, CA, USA) with 100-bp paired- end reads. The program sentinel sites participate in an external quality assessment scheme (EQAS) conducted by the reference laboratory to ensure quality of laboratory results. Conditions permitting, periodic monitoring visits to sentinel sites are likewise done.

DATA ANALYSIS

Analysis is restricted to the first isolate received (per genus under surveillance) per patient in the calendar year. Data are expressed as a cumulative resistance percentage, i.e. the percentage of resistant isolates out of all isolates with antimicrobial susceptibility testing (AST) information on that specific organism –antimicrobial agent combination. A 95% confidence interval is determined for the resistance percentage. Cumulative percentages of resistance are compared as proportions using the either Chi square of Fischer's test, using a p value of <0.05 as statistically significant. Only species with testing data for 30 or more isolates are included in the analysis.

WHOLE GENOME SEQUENCING DATA ANALYSIS

Sequence data and metadata of select resistant isolates were uploaded to the Terra web application (app.terra.bio) and analyzed using TheiaProk_Illumina_PE(v1.2.0), a specialized tool for Illumina paired-end reads. This tool provided an automated pipeline for quality control assessment, de novo assembly and sample characterization. Raw sequences were quality trimmed and adapter removed using Trimmomatic (0.39) and bbduk_docker (38.76). Fastq-scan(0.4.4) was used for raw read and cleaned read quality assessment, while de novo assembly quality was assessed using Quast(5.0.2) and BUSCO(5.3.2). The resulting assemblies were obtained using Shovill(1.1.0) pipeline.

Molecular characterization tools were used to identify genes involved in antimicrobial resistance (AMR), virulence and stress genes, and to perform taxon assignment. Multi-locus sequence typing (MLST) was performed using MLST (2.23.0) to identify the sequence type of the assembled genome, while AMRFinderPlus(3.10.42 db 2022-10-11.2) was used to detect AMR, virulence, and stress genes. Gambit(0.5.0) was used for taxon assignment, and Prokka was used for gene annotation. PlasmidFinder(2.1.6) was used to detect plasmid replicon genes, and MUMmer(4.0.0rc1) was used for average nucleotide identity (ANI) analysis.

Species-specific characterization tools were also employed. For *Salmonella* serotype prediction, SISTR(1.1.1) and Seqsero(1.2.1) were utilized, while for *E. coli* serotype prediction, Ectyper(1.0.0) and SerotypeFinder were used. For *Klebsiella* spp., Kleborate(2.2.0) was employed for MLST, serotype prediction, AMR, and virulence profiling. Finally, kSNP3(1.2.0) workflow was utilized to produce a phylogenetic tree and SNP distance matrices for the strains to infer evolutionary relationships of the analyzed samples under study.

Finally, an annual report with a summary of the surveillance data focusing on aerobic bacterial pathogens of public health importance causing common infectious diseases with significant morbidity and mortality locally are disseminated to the program's stakeholders.

LIMITATIONS

Interpretation of data in this annual report should be undertaken with caution taking into consideration that there may be several factors that could influence and introduce bias to the data resulting in over- or underestimation of resistance percentages. Potential sources of bias include population coverage, sampling, and laboratory capacity.

1) Most of the resistance data in the program come from regional hospitals which typically cater to patients from towns and cities within the vicinity of the hospital. Resistance variations in local areas not covered by regional hospitals are not represented in the program data.
2) Data for the National Capital Region come from 8 sentinel sites while data for other regions come from 1 or 2 sentinel sites.
3) Given that the program data are from routine clinical samples, differences in factors indicating need for microbiological cultures may introduce variations in the resistance data.
4) Performance of culture and susceptibility tests in the sentinel sites is dependent on the diagnostic habits of the clinicians as well as the financial capability of patients for such test. Differential sampling can occur if cultures are typically only performed after empirical treatment shows no adequate therapeutic response. Predictably, this will lead to a serious overestimation of the percentage resistance by not including susceptible isolates in the denominator.
5) Lastly, the ability of the laboratory to identify the microorganism and its associated antimicrobial susceptibility pattern may differ.

The 2022 ARSP Data

Resistance data for **88,049** isolates were reported and analyzed for 2022. A **24.1%** increase was noted when compared with the reported **70,951** isolates in 2021. **Table 2** shows that 21 of 24 sentinel sites had an increase in data submission for 2022 while 2 sites had decreased contribution and 1 site with no submission for the analysis year.

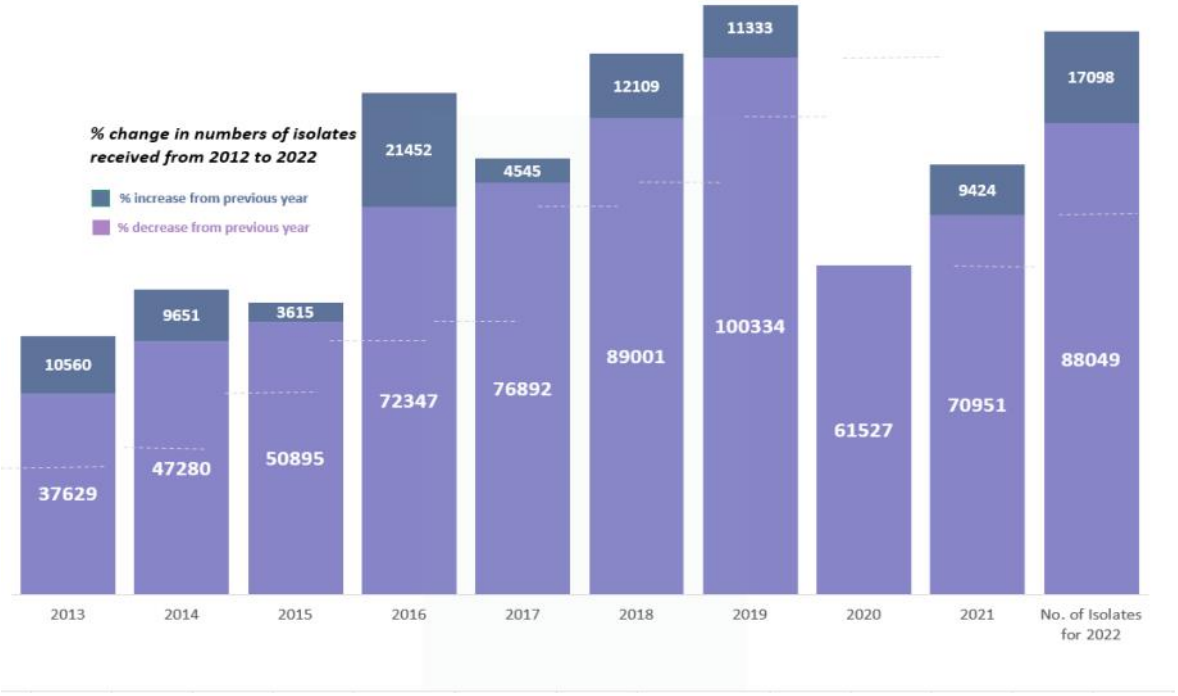


Figure 2. Number and percentage difference of isolates received from 2013-2022

Table 2. Sentinel sites isolate contribution, DOH-ARSP, 2013-2022

SENTINEL SITES	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Change %
PGH	7093	12471	11710	12860	14572	12808	13895	6818	9557	12343	22.6
RMC	1207	320	1054	3252	3160	3241	2375	2027	1968	2298	14.4
NKI	2179	2918	1455	5894	627	2959	4358		5571	5911	5.8
LCP	2253	2921	2905	3115	1367	3098	4433	2713	3205	-	-
RTM	303	303	336	410	513	598	507	255	423	528	19.9
SLH	1132	575	824	1410	2460	2044	2371	1019	1157	1060	-9.2
GMH	1307	1351	1807	1669	3153	3258	3957	2624	2818	4254	33.8
ZMC	822	819	841	1142	1222	1346	1644	1192	1341	1276	-5.1
FEU	1050	956	712	810	1201	1173	548		322	413	22.0
STU	2050	2002	1923	2275	2088	2184	2722	1419	1250	854	-46.4
EVR	697	823	1514	1731	3303	3879	3874	4056	4584	5388	14.9
MMH	1413	2289	2940	2886	3133	3026	2539	1425	1140	1575	27.6
DMC	3456	4062	5109	8058	8680	10762	12177	7412	8189	9135	10.4
VSM	3171	3951	3834	4803	6838	8714	10286	6886	6971	7596	8.2
BGH	2583	2625	3214	4628	4842	5775	5234	2968	3191	5459	41.5
CMC	796	833	1300	1599	1704	2642	3181	2076	2021	3257	37.9
BRT	611	1047	1251	1584	1640	1842	2521	1176	1903	3055	37.7
*RTH	-	-	-	25	69	159	352	289	0	4	100.0
*ZPH	-	9	8	4	7	3	69	129	1	-	-
MAR	1773	1706	1849	2759	3565	4293	4462	3581	3302	4492	26.5
BRH	-	1022	1294	2075	2472	3133	3633	1569	1472	2570	42.7
CVM	1100	1223	1512	3473	4141	4276	5668	3782	2687	4207	36.1
JLM	502	638	1266	2768	3261	3880	4824	3248	3753	5229	28.2
NMC	2131	2416	2237	3105	2245	2961	3409	3735	2780	4868	42.9
ONP	-	-	-	2	5	68	90	13	31	202	84.7
CRH	-	-	-	10	624	879	1205	1115	1314	2075	36.7
TOTAL	37629	47280	50895	72347	76892	89001	100334	61527	70951	88049	

** RTH and ZPH are the 2 gonococcal surveillance sites*

The 2022 ARSP data were collected from 23 sentinel sites and 1 *N. gonorrhoeae* surveillance site of the program which represents 16 of 17 regions in the Philippines. Majority (55.2%) of the isolates were from Luzon, 23.4% from Mindanao and 21.4% from Visayas (Figure 3). The eight sentinel sites from NCR contributed 26.6% of the total 2022 data. Majority (51.9%) of the isolates were from male patients and from 20-64 age group (58.5%) (Figure 4). The most common specimen types were blood (25.8%), respiratory (25.0%) and urine (20.0%) (Figure 4). Table 3 shows the most common isolates by specimen type.

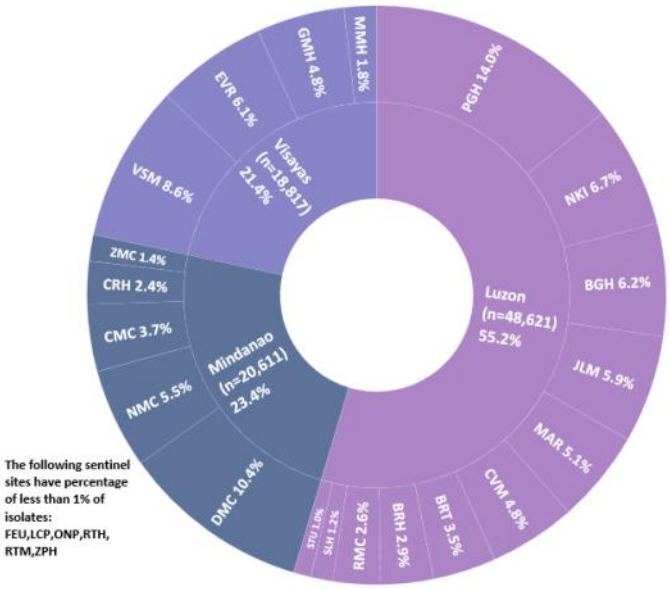
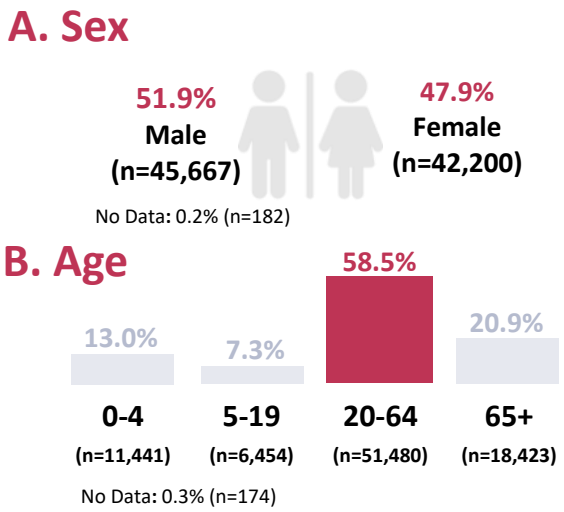


Figure 3. Sentinel sites isolate contribution, DOH-ARSP



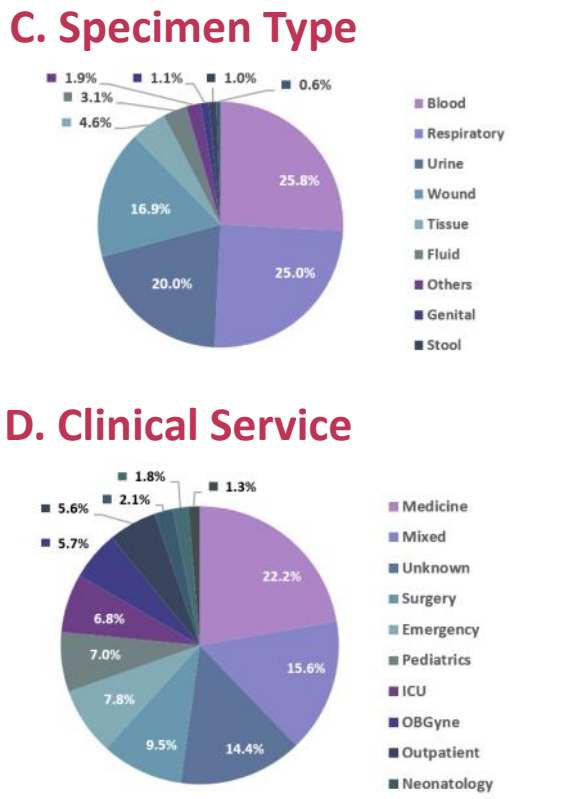


Figure 4. Patient characteristics of the 2022 ARSP isolates, DOH-ARSP, 2022 (n=88,049)

Table 3. Most common isolates by specimen type, DOH-ARSP, 2022 (n=88,049)

Respiratory Specimens		**Blood**	
1	*Klebsiella pneumoniae ss. pneumoniae*	1	*Staphylococcus epidermidis*
2	*Pseudomonas aeruginosa*	2	*Staphylococcus aureus ss. aureus*
3	*Acinetobacter baumannii*	3	*Klebsiella pneumoniae ss. pneumoniae*
Cutaneous or Wound		**Stool**	
1	*Staphylococcus aureus ss. aureus*	1	*Vibrio cholerae*
2	*Klebsiella pneumoniae ss. pneumoniae*	2	*Salmonella* species
3	*Pseudomonas aeruginosa*	3	*Shigella* species
Cerebrospinal Fluid		**Urine**	
1	*Staphylococcus epidermidis*	1	*Escherichia coli*
2	*Acinetobacter baumannii*	2	*Klebsiella pneumoniae ss. pneumoniae*
3	*Klebsiella pneumoniae ss. pneumoniae*	3	*Enterococcus faecalis*

Streptococcus pneumoniae

A total of **280** *Streptococcus pneumoniae* isolates were reported for 2022. Sentinel sites located in Luzon contributed most of the *S. pneumoniae* isolates (56.4%) with 28.6% coming from NCR; 23.6% coming from Mindanao and 20% coming from Visayas (Figure 5).

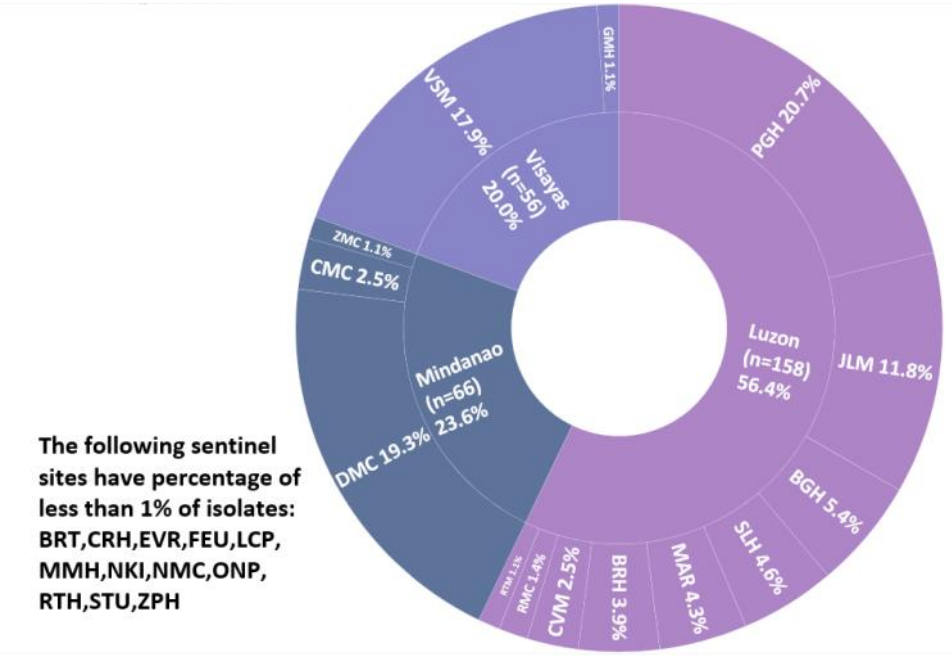


Figure 5. Isolate distribution *of S. pneumoniae*, DOH-ARSP, 2022 (n=280)

Most (62.1%) isolates came from male patients and most (55%) from aged 20-64 years old. Most (70.7%) of the isolates were detected from respiratory specimens and 22.9% from blood. (Figure 6)

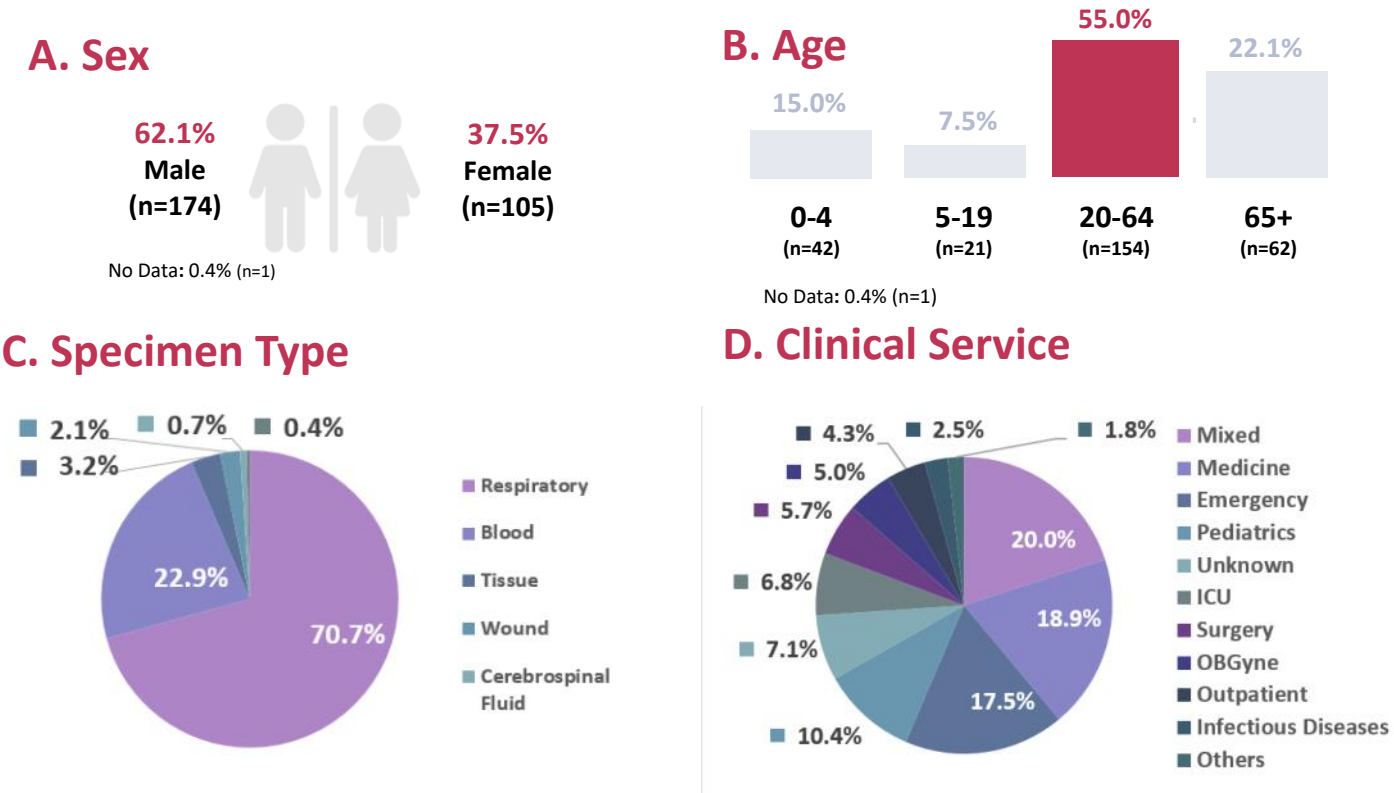


Figure 6. Patient characteristics of *S. pneumoniae* isolates, DOH-ARSP, 2022 (n=280)

For 2022, penicillin resistance in *S. pneumoniae* isolates is at 15.9% (n=232) using meningitis breakpoint, 1.7% (n=232) for non-meningitis breakpoint and 4.3% (n=232) using oral breakpoints (Figure 7). Compared with 2021, the overall resistance rates for *S. pneumoniae* decreased in 2022 for most antibiotics tested except for penicillin (NM), rifampin and meropenem (Figure 8); however the noted changes in percent resistance were not statistically significant.

There was a confirmed meropenem resistant isolate reported for 2022. This isolate was from respiratory sample of a 44-year old male from Region XII, which was identified as serotype 9N. It was noted to be susceptible to all antibiotics, intermediate to imipenem and resistant to tetracycline.

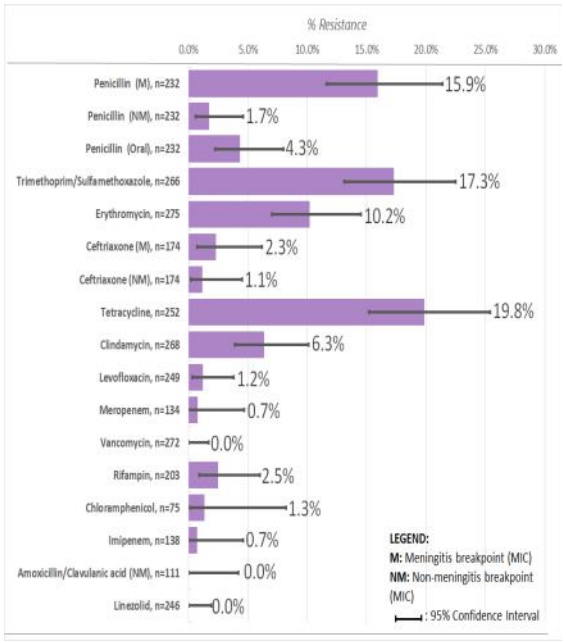


Figure 7. Resistance rates of *S. pneumoniae* isolates for all specimens, DOH-ARSP, 2022

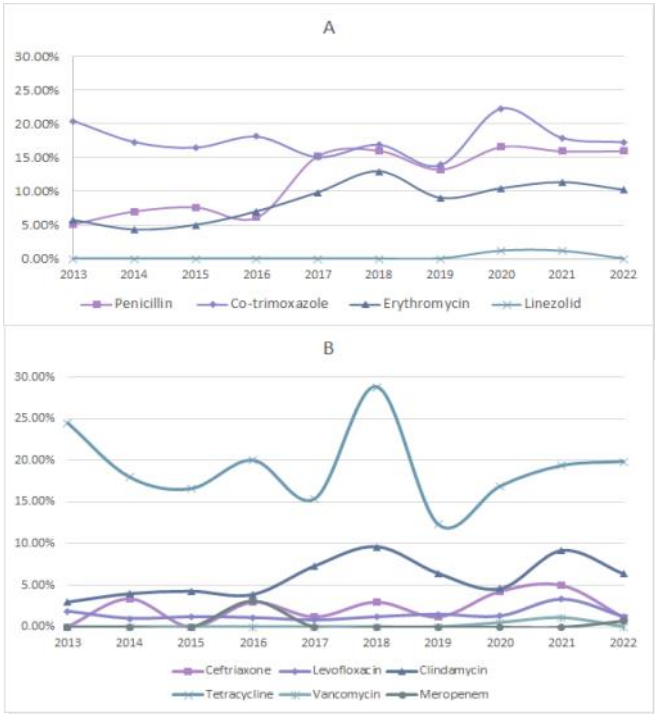


Figure 8. Yearly resistance rates of *S. pneumoniae*, DOH-ARSP, 2013-2022

Multiple year analysis results showed that changes in the resistance rates over the past decade were statistically significant for penicillin (p=0.0000) and meropenem (p=0.0003). However, changes in resistance rates for ceftriaxone was not statistically significant (p=0.0614). (Figure 8)

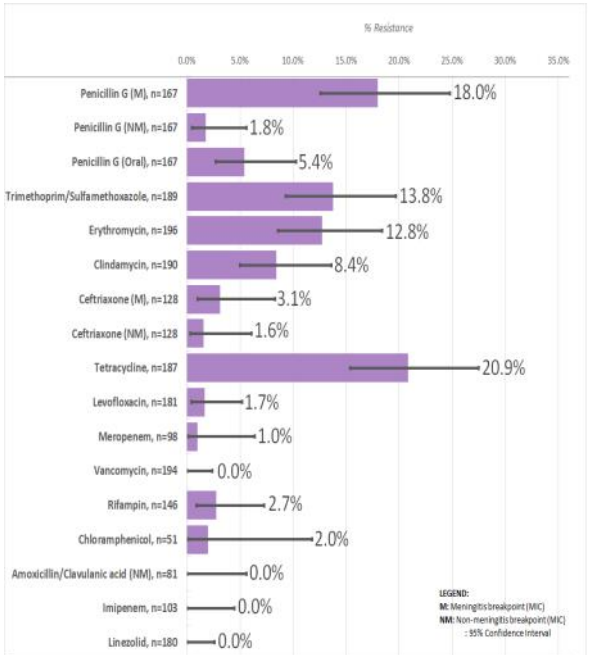


Figure 9. Percent resistance of *S. pneumoniae* respiratory isolates, DOH-ARSP, 2022

Figure 9 shows the percent resistance of *S. pneumoniae* isolates from respiratory samples. Penicillin (M) resistance was 18%, penicillin (NM) resistance was 1.8% and oral penicillin resistance was 5.4%. Tetracycline resistance was at 20.9%, co-trimoxazole resistance was at 13.8% and ceftriaxone resistance (M and NM) were at 3.1% and 1.6% respectively. No respiratory isolate of *S. pneumoniae* was found to be resistant to amoxicillin-clavulanic acid, imipenem and linezolid. Compared with overall resistance of *S. pneumoniae* from all samples, resistance to most of the antibiotics are higher for the respiratory isolates except for lower resistance to co-trimoxazole and similar resistance to amoxicillin/clavulanic and linezolid.

Among *S. pneumoniae* blood isolates (Figure 10), penicillin (M) resistance was 9.6%, and penicillin (NM) resistance was 1.9%. Resistance to co-trimoxazole was highest at 20% followed by tetracycline at 10%. No *S. pneumoniae* blood isolate was found resistant against ceftriaxone (M and NM) while resistance rate for erythromycin was at 3.2%. Compared with overall resistance of *S. pneumoniae* from all samples, resistance to most of the antibiotics were noted to be lower for the blood isolates except for higher resistance to penicillin NM, co-trimoxazole and imipenem and similar resistance for linezolid. There were few *S. pneumoniae* isolates from blood thus it can be noted that the confidence interval for the resistance rates were very wide.

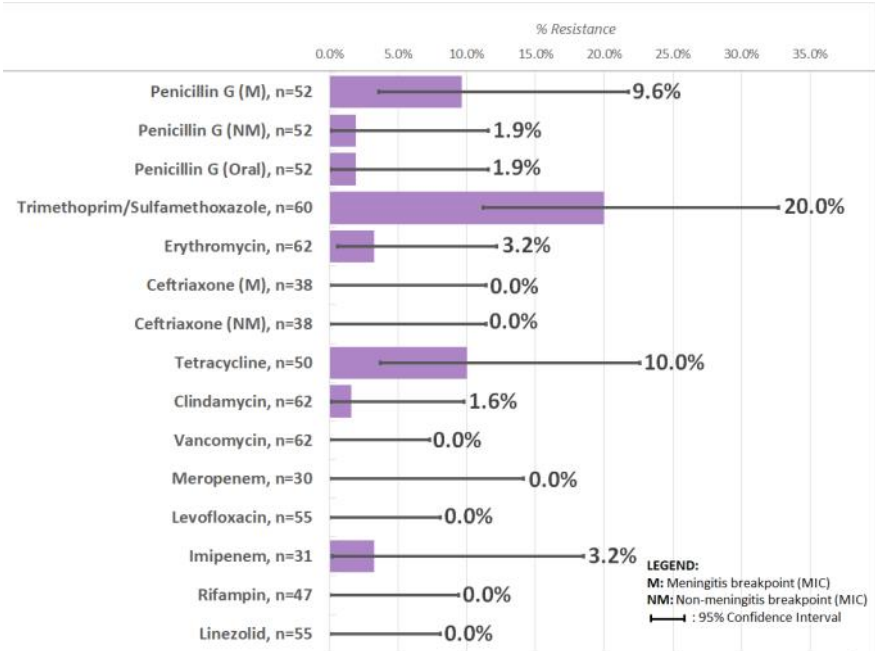


Figure 10. Percent resistance of *S. pneumoniae* blood isolates, DOH-ARSP, 2022

A look at the distribution of penicillin resistance (all specimens) of *S. pneumoniae* showed resistance of isolates from DMC and VSM were within 1-5% range, while no resistance was detected from other sentinel sites (Figure 11).

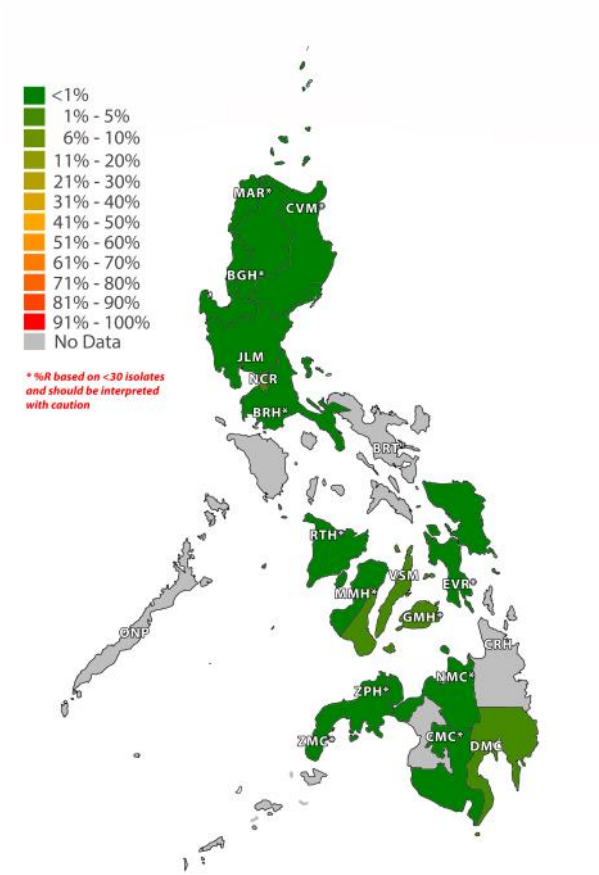
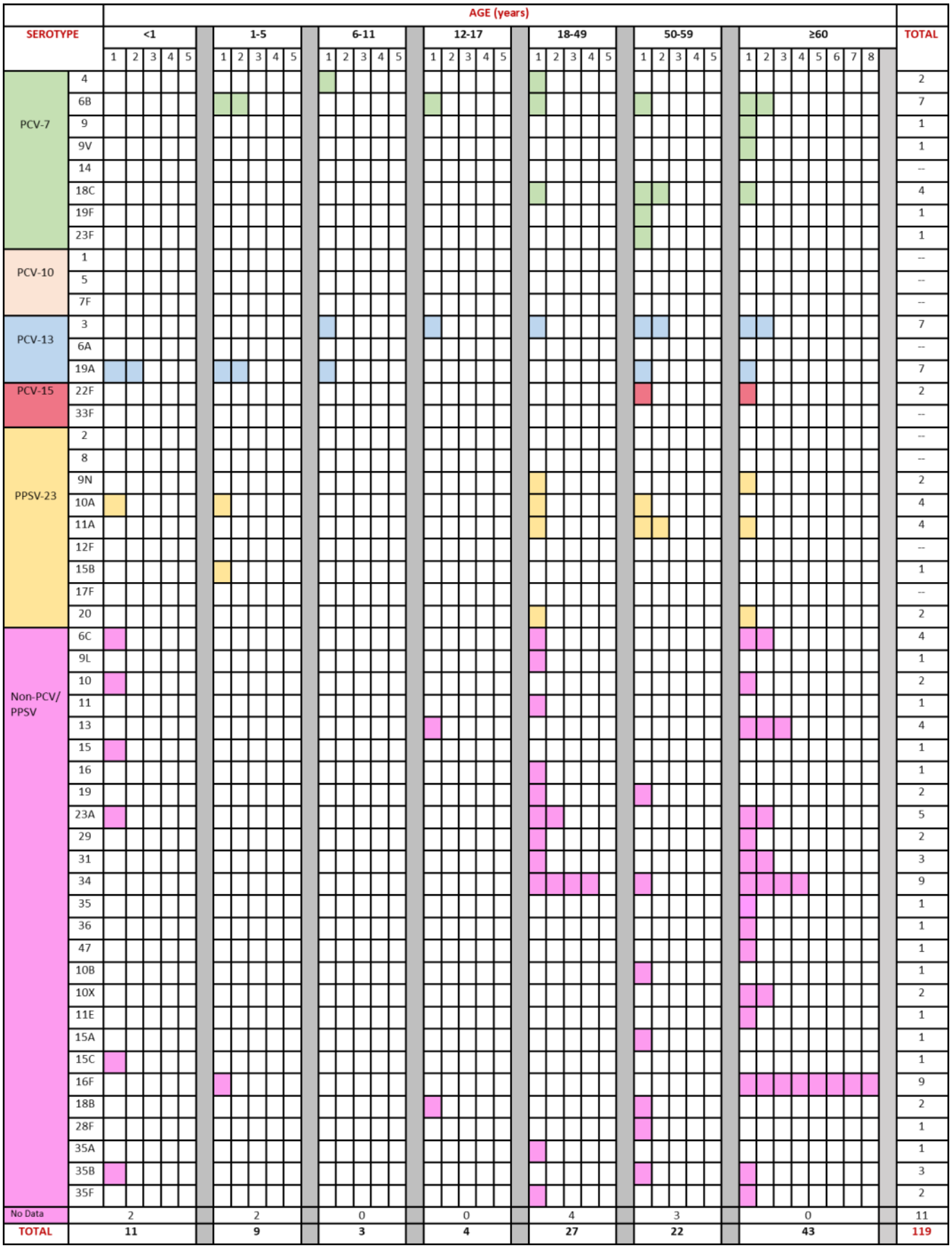


Figure 11. Geographic distribution of penicillin-resistant *S. pneumoniae* in the Philippines, DOH-ARSP, 2022

Table 4. *S. pneumoniae* serotypes and PCV serotypes per age group, DOH-ARSP, 2022



*__PCV__ – Pneumococcal Conjugate Vaccine, __PPSV__ – Pneumococcal Polysaccharide Vaccine

A total of 119 *S. pneumoniae* isolates (from all samples) were referred to ARSRL in 2022 with 49 *S. pneumoniae* serogroups/serotypes identified. Many (n=43, 36.1%) of the isolates were from the ≥ 60 years old, 18-49 years old (n=26, 21.8%) and 50-59 years old (n= 23, 19.3%). Among patients less than one up to five years old, serotype 19A (PCV7-13) was prevalent: 2 isolates out of 11 (18%) among <1 year olds and 2 out 9 isolates (22%) among patients ages 1-5 years. On the other hand, PCV serotypes 1, 6B, 3, & 19A and non-vaccine types 13 and 18B were seen among 6-11 and 12-17 age groups. It was observed that the non-vaccine serotypes 34 (n= 3/26, 11.5%) and 23A (n= 2/26, 7.7%) were prevalent among 18-49 years old. PCV serotypes 18C and 3, and PPSV serotype 11A were commonly seen among 50-59 years old. One serotype 22F isolate, which is included in the newly locally available PCV 15 was also seen in this age group. On the other hand, among the geriatric population (≥ 60 years old), non-PCV/PPSV serotype 16F (n=8, 18.6%) was the most prevalent serotype seen and also with the highest number of isolates across all age groups. This was followed by non-vaccine serotypes 34 (n=4/43, 9.3%) and 13 (n=3/43, 7.0%) and PCV serotypes 3 and 6B with two isolates each. In addition, another serotype 22F isolate (PCV15) was observed among the ≥ 60 years old patients.

One serotype 23F *S. pneumoniae* (PCV, PPSV) blood isolate was found to be penicillin (M) resistant. The most common PCV serotypes resistant to co-trimoxazole include 6B (n=4), 18C (n=1) and 19A(n=1) while PPSV23 serotypes resistant to this antibiotic include 11A (n= 1) and 10A (n= 0). Erythromycin resistance was observed among serotypes 18C (n= 1; PCV) and the non-vaccine types 23A (n= 1), 6C (n= 1) and 35A (n= 1) while rifampicin resistance was noted among non-vaccine serotypes 16F (n= 1) and 13 (n= 1). On the other hand, tetracycline resistance was noted among PCV serotypes 6B (n= 2), 19A (n= 1), 18C (n= 1), PPSV serotype 9N (n= 1), and non-vaccine serotypes 6C (n= 1) and 35A (n= 1). Carbapenem (meropenem and imipenem) resistance was noted among PPSV serotype 9N (n= 1) and non-vaccine serotypes 23A (n= 1).

Percent PCV and PPSV coverage (overall and per age group) of *S. pneumoniae* isolates sent to ARSRL for confirmation were determined by dividing the number of isolates with serotypes included in PCV or PPSV over the total number of isolates (overall and per age group). The overall (n=119) PCV7 and PCV10 coverage of 2022 *S. pneumoniae* isolates were both 14.3%; 26.1% for PCV 13 and 27.7% for PCV15. The percent coverage of referred *S. pneumoniae* isolates (n=91) in 2021 (n=91) decreased for all PCV and PPSV23, however, the decrease was statistically significant only for PCV 10 (p=0.0459). The overall PPSV23 coverage was 38.7%. For age specific vaccine coverage among less than 5 years old (n=20), the vaccine coverage for PCV7 and PCV10 was 10%, and 30% for both PCV13 and PCV15. Among the geriatric population, vaccine coverage for both PCV7 and PCV10 was 11.6%, 18.6% for PCV13, 20.9% for PCV15, and 27.9% for PPSV23. On the other hand, the overall non-vaccine percent coverage is 48.7%. The non-vaccine percent coverage among <1 year olds is 10.3%, 1.7% among 1-5, 0% among 6-11, 3.5% among 12-17, 22.4% among 18-49, 10.3% among 50-59 and 51.7% among ≥ 60 years old. The overall non-vaccine percentage coverage for 2021 was 53.8%, however the observed decrease in overall non-vaccine coverage for 2022 was not statistically significant (p=0.0745).

Haemophilus influenzae

A total of 345 *H. influenzae* isolates were reported for 2022, a 109.1% increase from 165 isolates in 2021. The highest contributor is PGH at 23.5%, VSM at 21.5% and DMC at 20.0%. (Figure 12) Based on island group distribution, 57.1% were from Luzon with 22.6% and 20.3% from Visayas and Mindanao, respectively.

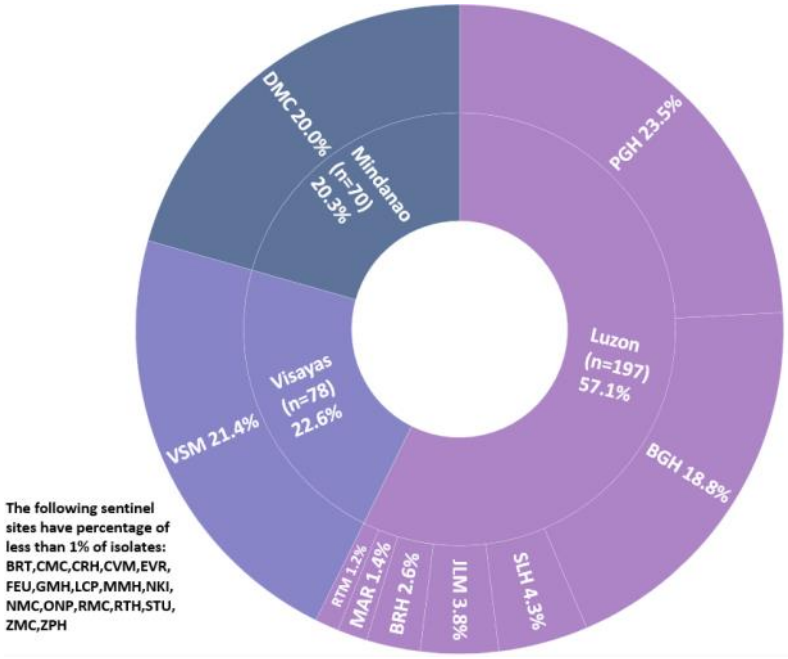


Figure 12. Isolate distribution of *H. influenzae,* DOH-ARSP, 2022 (n=345)

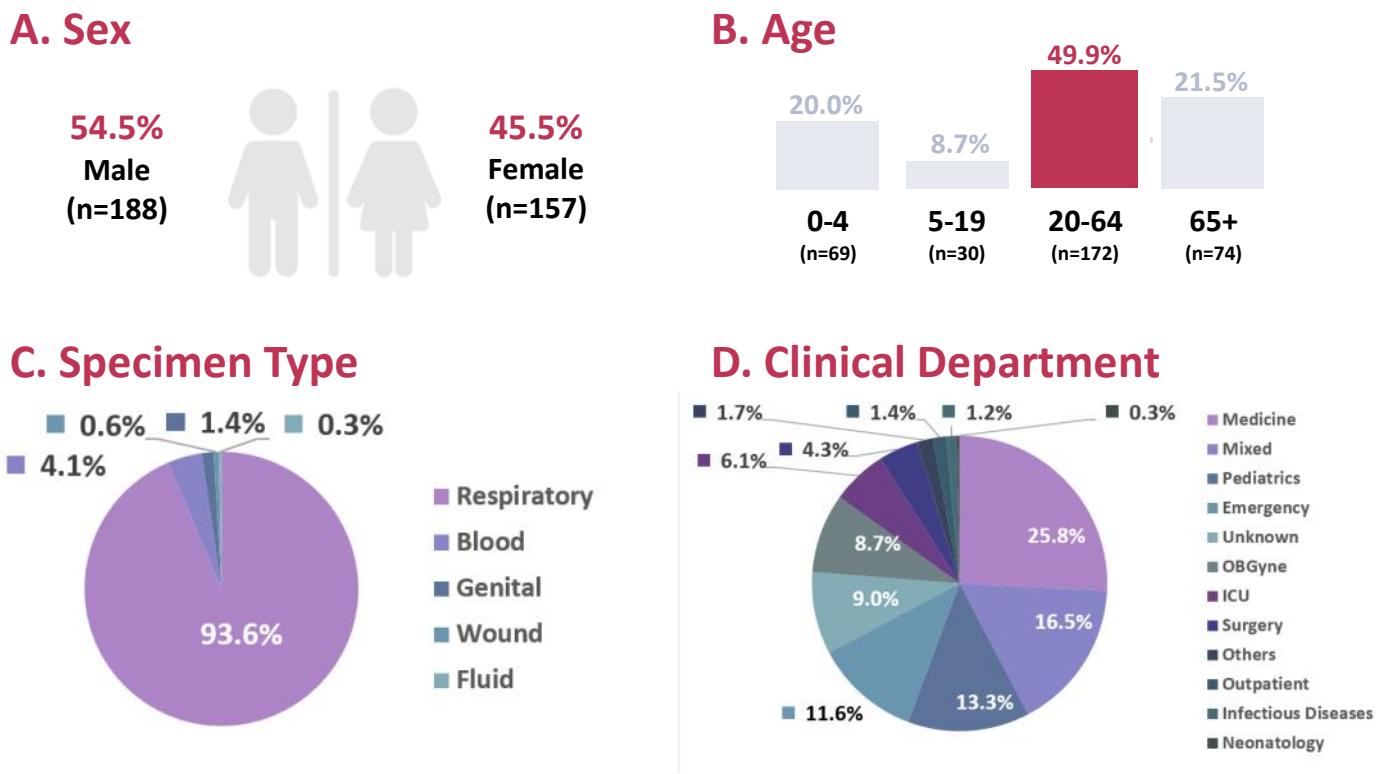


Figure 13. Patient characteristics of *H. influenzae* isolates, DOH-ARSP, 2022 (n=345)

Most *H. influenzae* were isolated from male patients at 54.5%, patients ages 20-64 years old at 49.9%, and most frequently (25.8%) from patients in the medicine department. (Figure 13) Respiratory specimens remain to be the most common source of *H. influenzae* at 93.6%.

Cumulative resistance rates of *H. influenzae* isolates from all specimens (Figure 14) show resistance to ampicillin at 9.8% (n=336) and to ampicillin/sulbactam at 6.4% (n=314). Non-susceptible rates to ceftriaxone was 2.5% (n=326), to meropenem 1.2% (n=251), to ciprofloxacin 0.8% (n=257), 0.4% to azithromycin and zero for levofloxacin. All aforementioned rates were lower compared with rates from the previous year. The highest resistance was against co-trimoxazole at 48.4% (n=312) followed by tetracycline at 15.9% (n=302). One *H. influenzae* isolate was reported to be non-susceptible against azithromycin out of 228 tested isolates.

There were 8 confirmed beta-lactamase negative ampicillin resistant (BLNAR) *H. influenzae* isolate in 2022. The isolates were from Luzon (50%, n=4) and Visayas (50%, n=4) and most (62.5%, n=5) were from male patients. Most (87.5%, n=7) of the isolates were from respiratory specimens and one isolate was from a blood sample of a 0-d old male patient. The BLNAR *H. influenzae* isolates were susceptible to ciprofloxacin, levofloxacin, azithromycin and meropenem.

One amoxicillin-clavulanic acid resistant *H. influenzae* isolate was confirmed in 2022. The isolate was reported from a respiratory specimen of a 63-male patient from JLM. The isolate was also resistant to ampicillin/sulbactam but susceptible to azithromycin, cefotaxime, ceftriaxone, chloramphenicol, co-trimoxazole, levofloxacin and tetracycline.

There were 3 confirmed ciprofloxacin non-susceptible (NS) isolates in 2022. All isolates were from respiratory samples of adult patients from BGH. The isolates were also non-susceptible to levofloxacin but susceptible to ampicillin, amoxicillin/sulbactam, amoxicillin clavulanic, ampicillin, azithromycin, ceftriaxone, chloramphenicol, meropenem and tetracycline.

This is the second year when report of these emerging resistant phenotype - amoxicillin-clavulanate acid and ciprofloxacin non-susceptible (NS) isolates of *H. influenzae* were noted, thus continued surveillance of this phenotype is warranted.

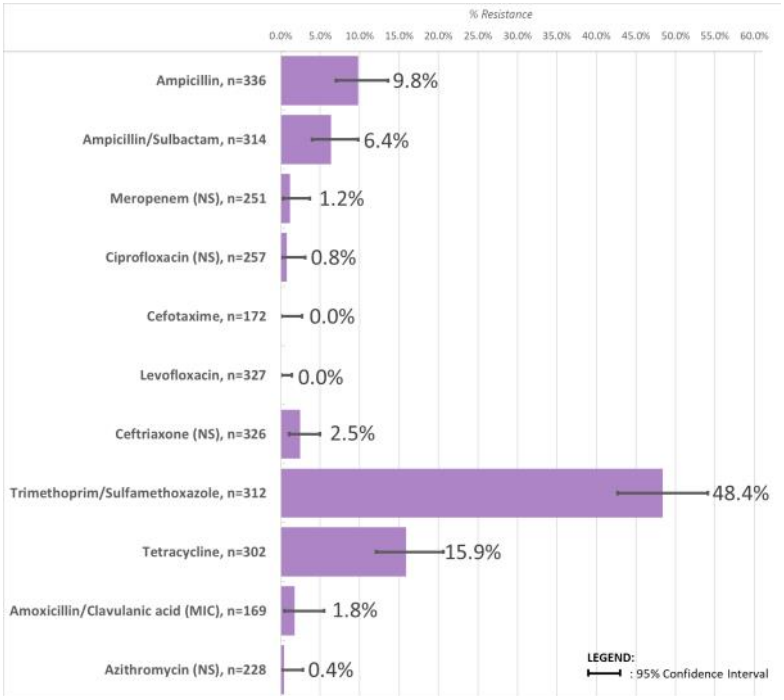


Figure 14. Resistance rates of *H. influenzae* isolates for all specimens, DOH-ARSP, 2022

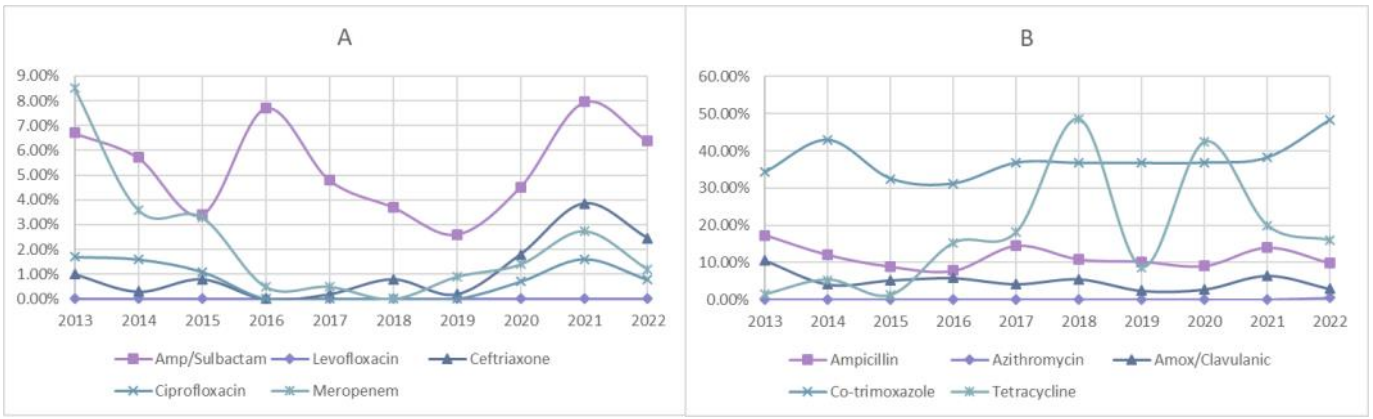


Figure 15. Yearly resistance rates of *H. infuenzae,* DOH-ARSP, 2013-2022

Most of the resistance rates decreased in 2022 (Figure 15). Highest increase was observed for co-trimoxazole which was statistically significant (p=0.0367).

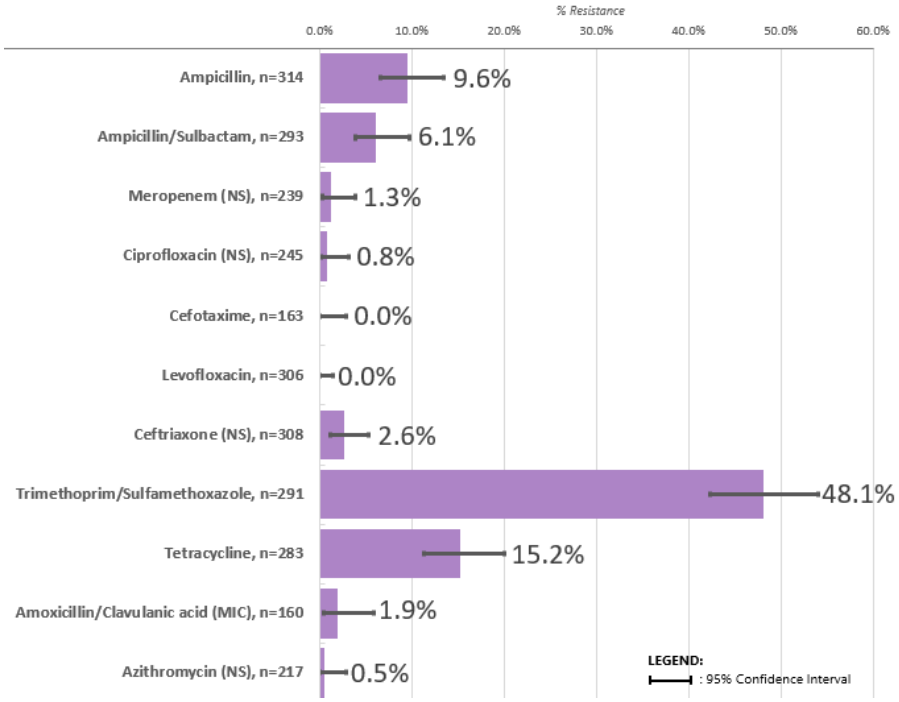


Figure 16. Percent resistance of *H. influenzae* from respiratory specimen, DOH-ARSP, 2022

Analysis of resistance rates among respiratory specimens of *H. influenzae* are shown in Figure 16. Highest resistance rate was observed for co-trimoxazole at 48.1% (n=291), followed by tetracycline at 15.2% (n=283), ampicillin at 9.6% (n= 314), and ampicillin/sulbactam at 6.1% (n=293). Percent non susceptible to ceftriaxone, meropenem, ciprofloxacin, and azithromycin were reported to be less than 3.0%. (n=217), ampicillin at 9.6% (n=314), and ampicillin/sulbactam at 6.1% (n=293). Percent non susceptible to ceftriaxone, meropenem, ciprofloxacin, and azithromycin were reported to be less than 3.0%. Compared with overall resistance of *H. influenzae* from all specimens, resistance to most of the antibiotics are lower for the respiratory isolates except for the higher resistance to ceftriaxone, meropenem & azithromycin and similar resistance to ciprofloxacin, cefotaxime, and levofloxacin.

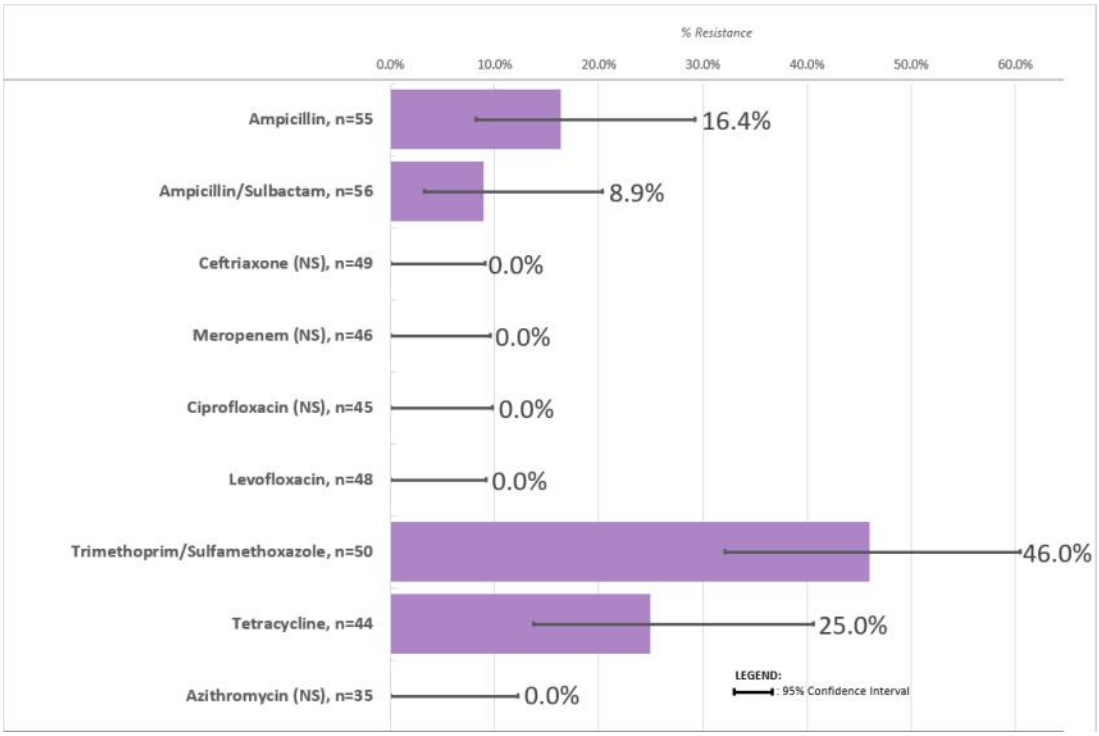


Figure 17. Resistance rates of *H. influenzae* isolates from blood and CSF specimens from 2019 – 2022.

Cumulative percentage resistance for *H. influenzae* from blood and CSF samples from 2019-2022 are shown in Figure 17. Data from the past four (4) years were presented in order obtain reasonable statistical estimates of resistance rates. Resistance rate against co-trimoxazole was still highest at 46.0% (n=50), followed by tetracycline at 25.0% (n=44), ampicillin at 16.4% (n=56), and ampicillin/sulbactam at 8.9% (n=56). Compared with overall resistance of *H. influenzae* from all specimens, resistance to most of the antibiotics were noted to be lower for the blood and CSF isolates except for higher resistance to ampicillin, ampicillin/sulbactam & tetracycline and similar resistance for levofloxacin and ampicillin/clavulanic acid. There were fewer reported *H. influenzae* isolates from blood and CSF thus it can be noted that the confidence interval for the resistance rates were very wide.

Salmonella enterica serovar Typhi

A total of **83** *S.* Typhi isolates were reported for 2022, a 98.0% increase from 42 isolates in 2021. The highest contributors were CMC, ZMC, and CVM contributing 19.3% each, VSM at 12.0% and BRT at 7.2%. (Figure 18) Based on island group distribution, 43.4% was from Mindanao, 39.8% from Luzon, and 16.9% from Visayas.

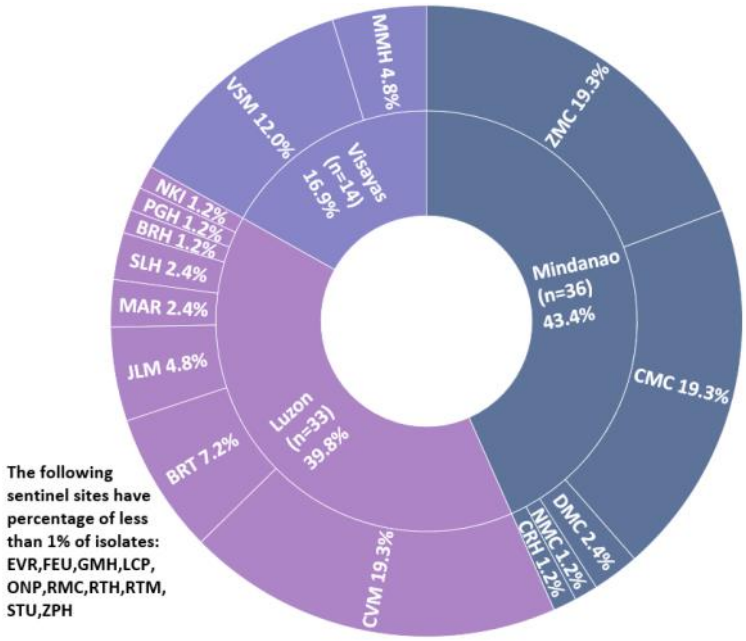


Figure 18. Isolate distribution of *S.* Typhi, DOH-ARSP, 2022 (n=83)

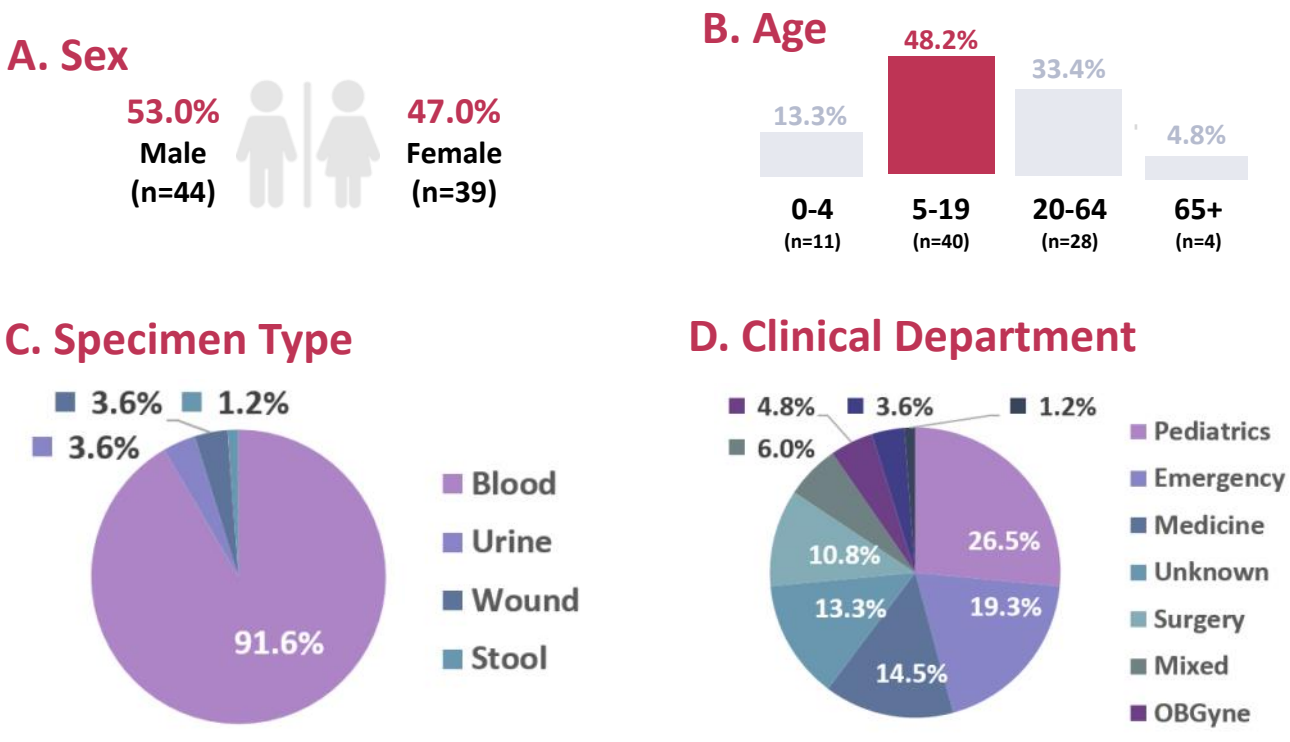


Figure 19. Patient characteristics of *S.* Typhi isolates, DOH-ARSP, 2022 (n=83)

Most (53.0%) of *S.* Typhi isolates were from male patients. Many were from patients aged 5-19 years old at 48.2%, and from patients at the pediatrics (26.5%). (Figure 19) Most of the isolates reported were from blood specimens at 91.6%.

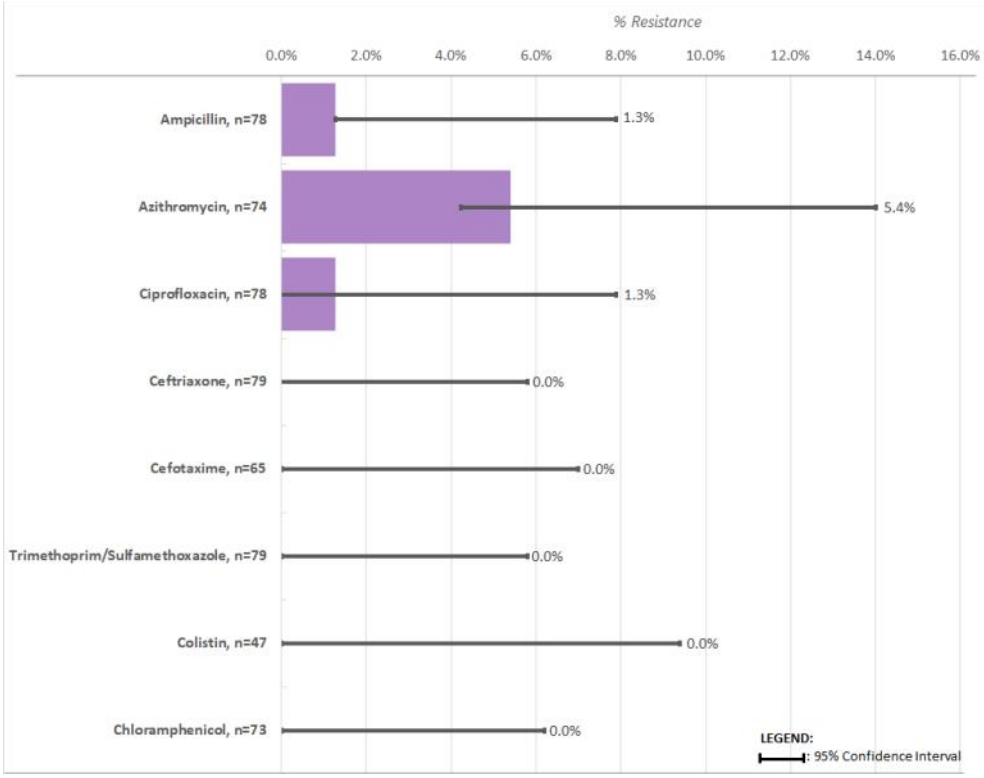


Figure 20. Resistance rates of *S.* Typhi isolates from all specimens, DOH-ARSP, 2022

Resistance rates of *S.* Typhi isolates for 2022 are shown in Figure 20, all of which are below 6.0%. Resistance to ampicillin and ciprofloxacin were both at 1.3% (n=78) while resistance to azithromycin was at 5.4% (n=74). No resistance to ceftriaxone, cefotaxime, co-trimoxazole, colistin, and chloramphenicol were noted.

One ciprofloxacin resistant *S.* Typhi isolate was reported from the blood specimen of a 3-year old female from CVM, however the isolate was not confirmed. The isolate was susceptible to co-trimoxazole, chloramphenicol, ceftriaxone, azithromycin cefoxitin and amoxicillin/clavulanic acid.

There were 4 azithromycin resistant *S.* Typhi isolates reported but these were likewise not sent to the reference laboratory for confirmation.

Similar resistance rates were noted for *S.* Typhi isolates from blood samples as shown in Figure 21. A slightly higher rate however was noted for azithromycin at 5.9%.

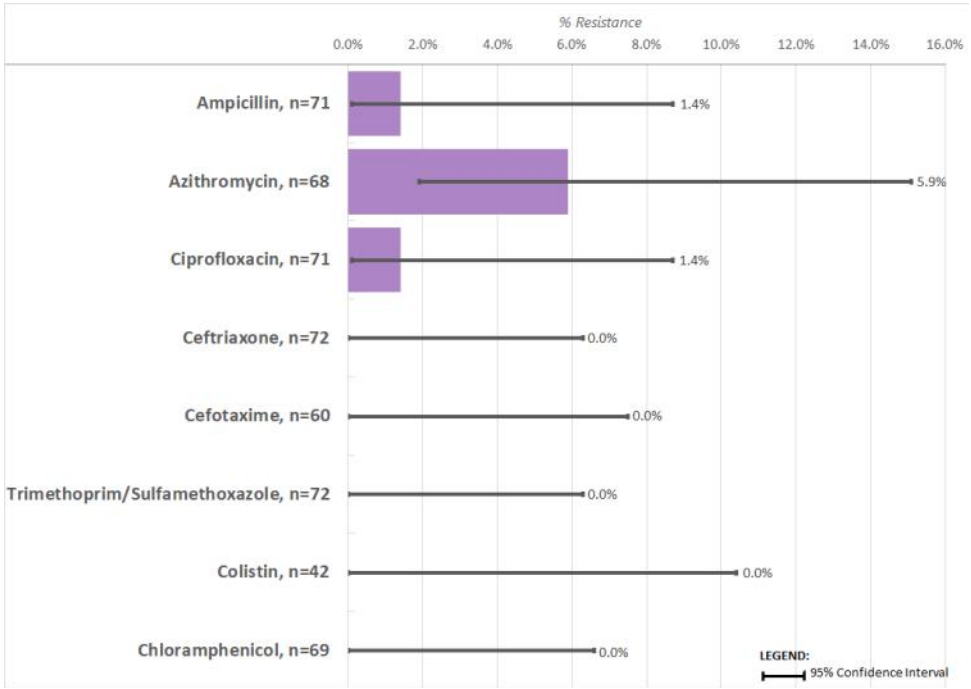


Figure 21. Resistance rates of *S. Typhi* isolates from blood specimens, DOH-ARSP, 2022.

Yearly resistance rates of *S*. Typhi remained low in the past ten years for all antibiotics used to treat infections against them with no reports of resistance against co-trimoxazole, ceftriaxone, chloramphenicol, and cefotaxime in the past 3 years (Figure 22). The increase in resistance to azithromycin in 2022 was not statistically significant. Compared with overall resistance of *S*. Typhi from all samples, resistance to ampicillin, azithromycin and ciprofloxacin were slightly higher for *S*. Typhi isolates from blood.

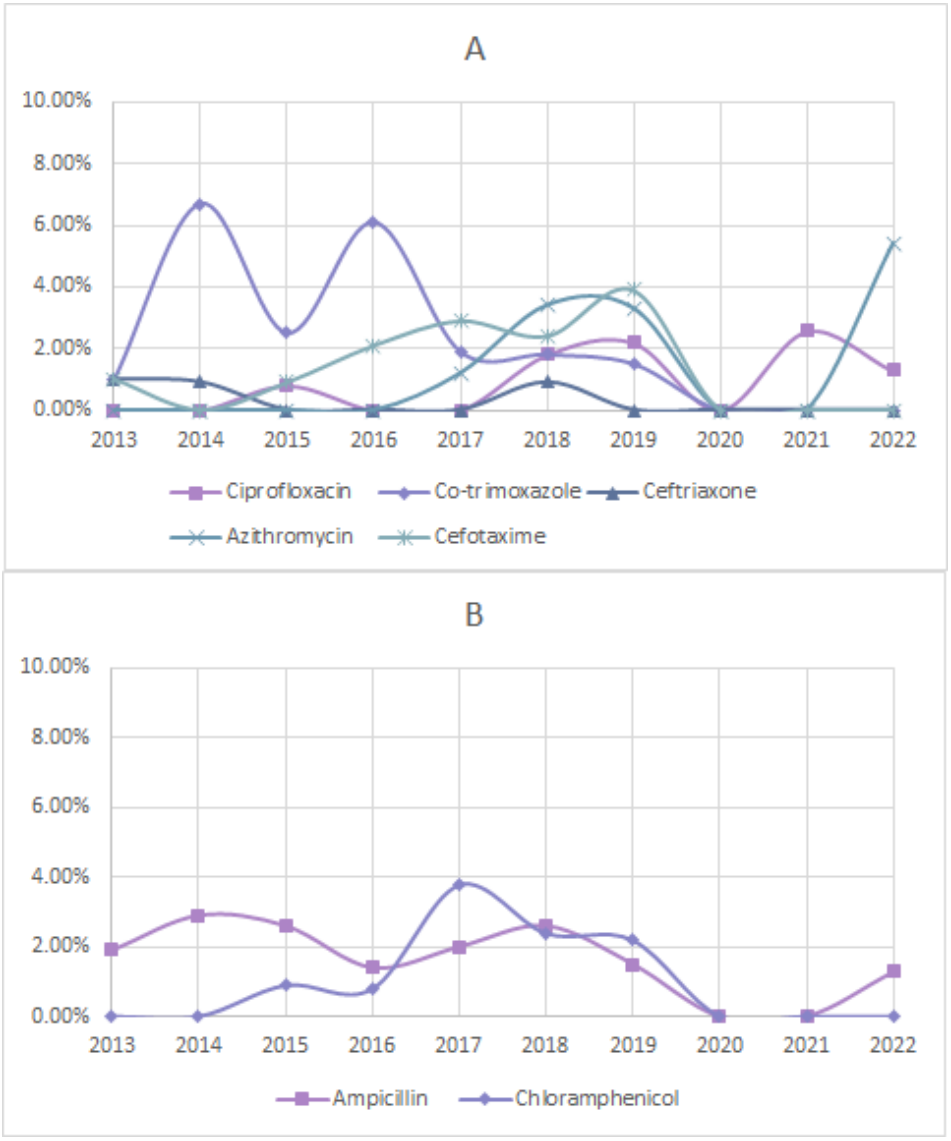


Figure 22. Yearly resistance rates of *S.* Typhi, DOH-ARSP, 2013-2022

Non-typhoidal *Salmonella*

A total of **286** non-typhoidal *Salmonella* (NTS) isolates were reported for 2022. This was 54.6% higher than the 185 isolates reported in 2021. The highest contributing sites were PGH at 14.3%, DMC at 9.8%, and VSM at 9.4%. Isolates mostly were reported from Luzon at 62.2% (n=178), Visayas at 24.8% (n=71), and the Mindanao at 12.9% (n=37).

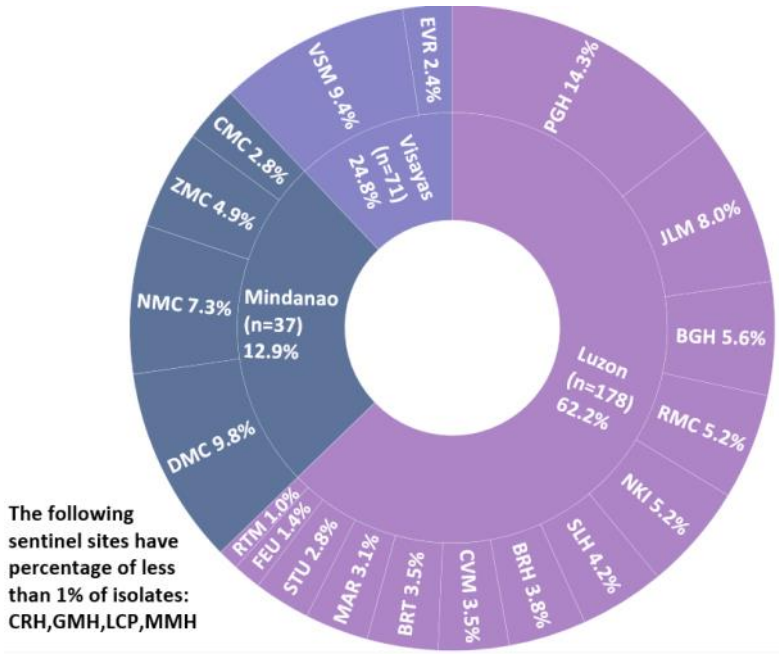


Figure 23. Isolate distribution of Non-typhoidal *Salmonella*, DOH-ARSP, 2022 (n=286)

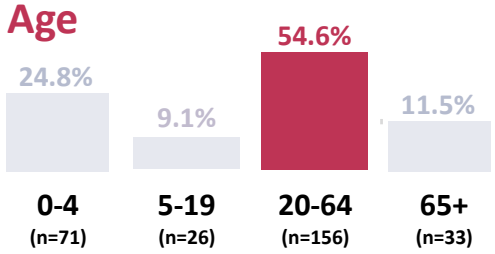
A. Sex

46.9% **Male (n=134)**

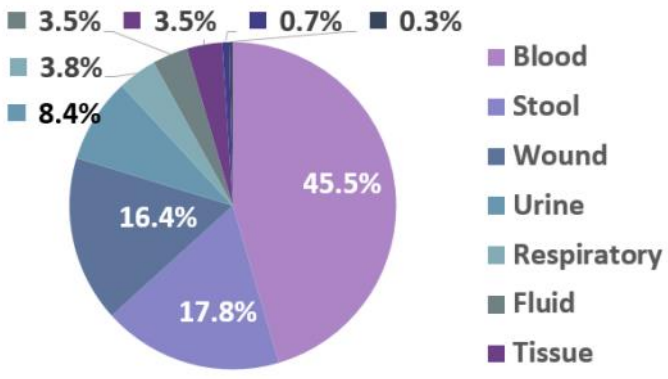
52.8% **Female (n=151)**

Unknown: 0.4% (n=1)

B. Age



C. Specimen Type



D. Clinical Service

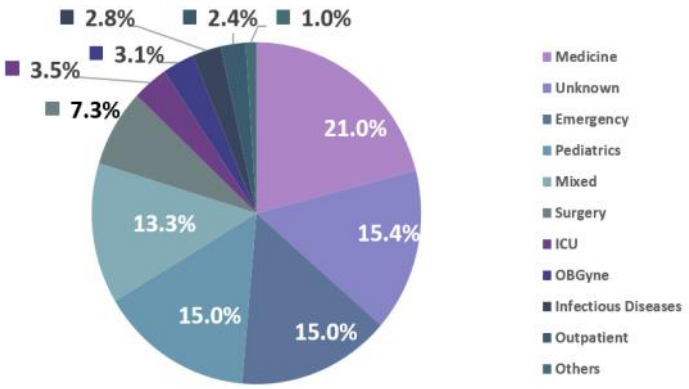


Figure 24. Patient characteristics of Non-typhoidal *Salmonella* isolates, DOH-ARSP, 2022 (n=286)

Majority (52.8%) of NTS isolates were from female patients and 54.6% were from 20-64 age group. (Figure 23) Most isolates reported were from blood specimens at 45.5%.

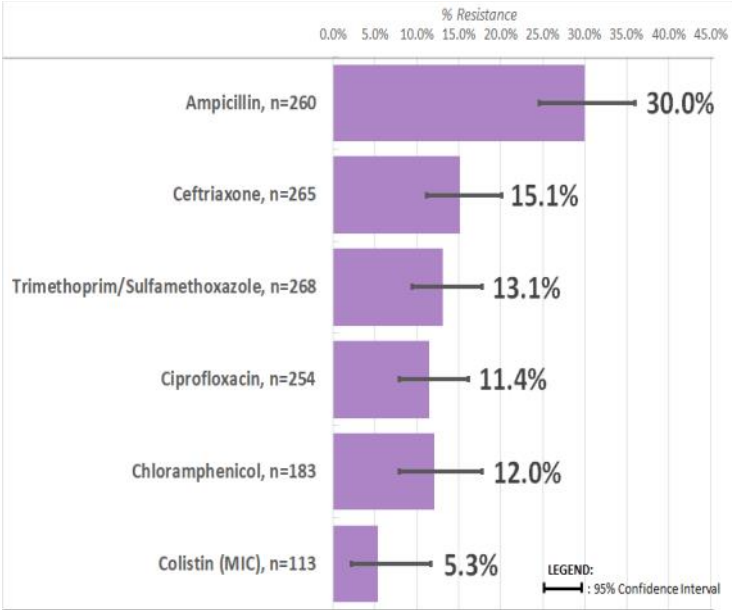


Figure 25. Resistance rates of Non-typhoidal *Salmonella* for all specimens, DOH-ARSP, 2022

Resistance rates for NTS isolates for 2022 are shown in Figure 25. The highest resistance rate was for ampicillin at 30% followed by ceftriaxone at 15.1%, co-trimoxazole at 13.1%, chloramphenicol at 12.0%, and ciprofloxacin at 11.4%. Resistance against colistin was also noted to be 5.3%.

Among NTS isolates from blood, resistance rates were at 12.4% for ampicillin, 8.5% for ciprofloxacin, 3.2% for co-trimoxazole, 2.7% for chloramphenicol, and 2.4% for ceftriaxone. Resistance rate for colistin was noted at 2.0%. Compared with overall resistance of NTS isolates from all samples, resistance to all antibiotics were lower for NTS isolates from blood.

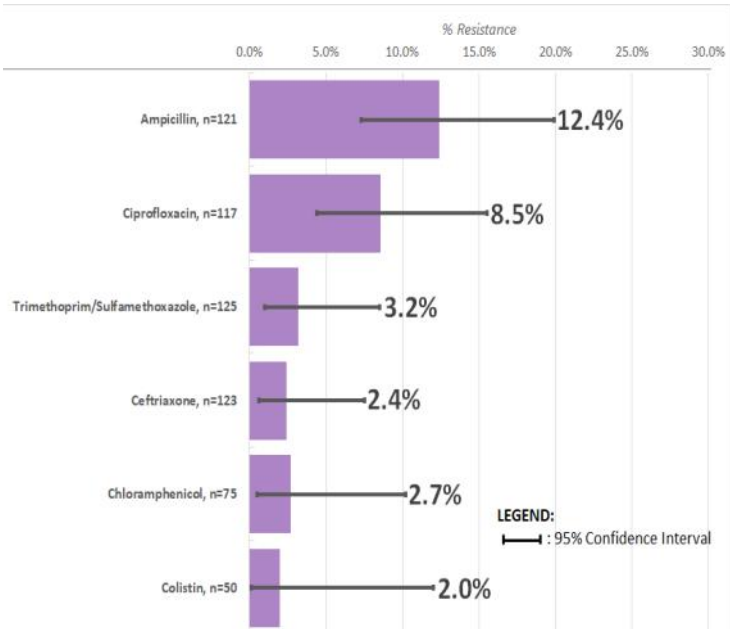


Figure 26. Resistance rates of Non-typhoidal *Salmonella* for blood specimens, DOH-ARSP, 2022

Yearly resistance rates are shown in Figure 27. For 2022, a continuous increase in resistance rates were observed for ciprofloxacin and ceftriaxone (p= 0.0034) since 2019. The overall resistance changes for ampicillin, co-trimoxazole, and chloramphenicol were not statistically significant.

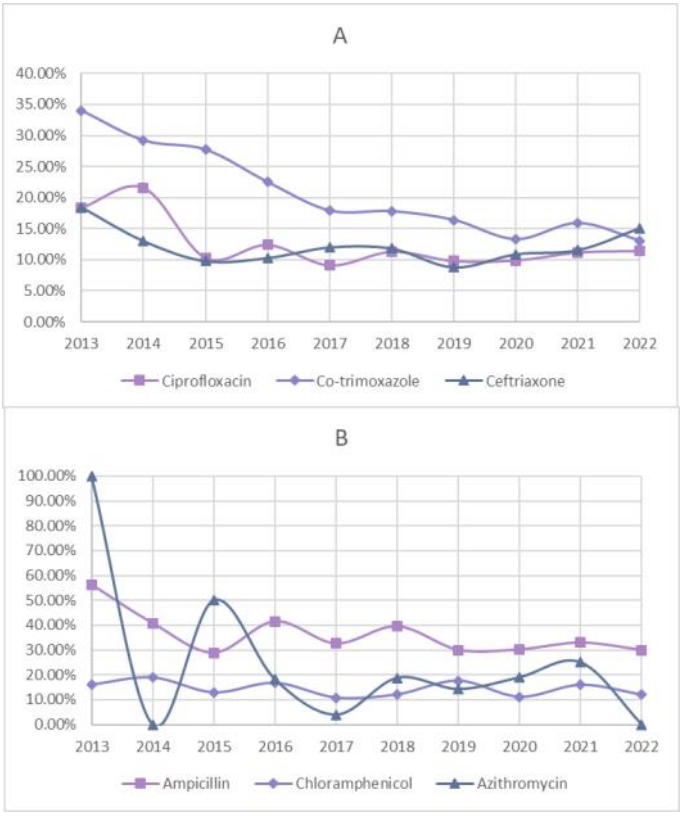
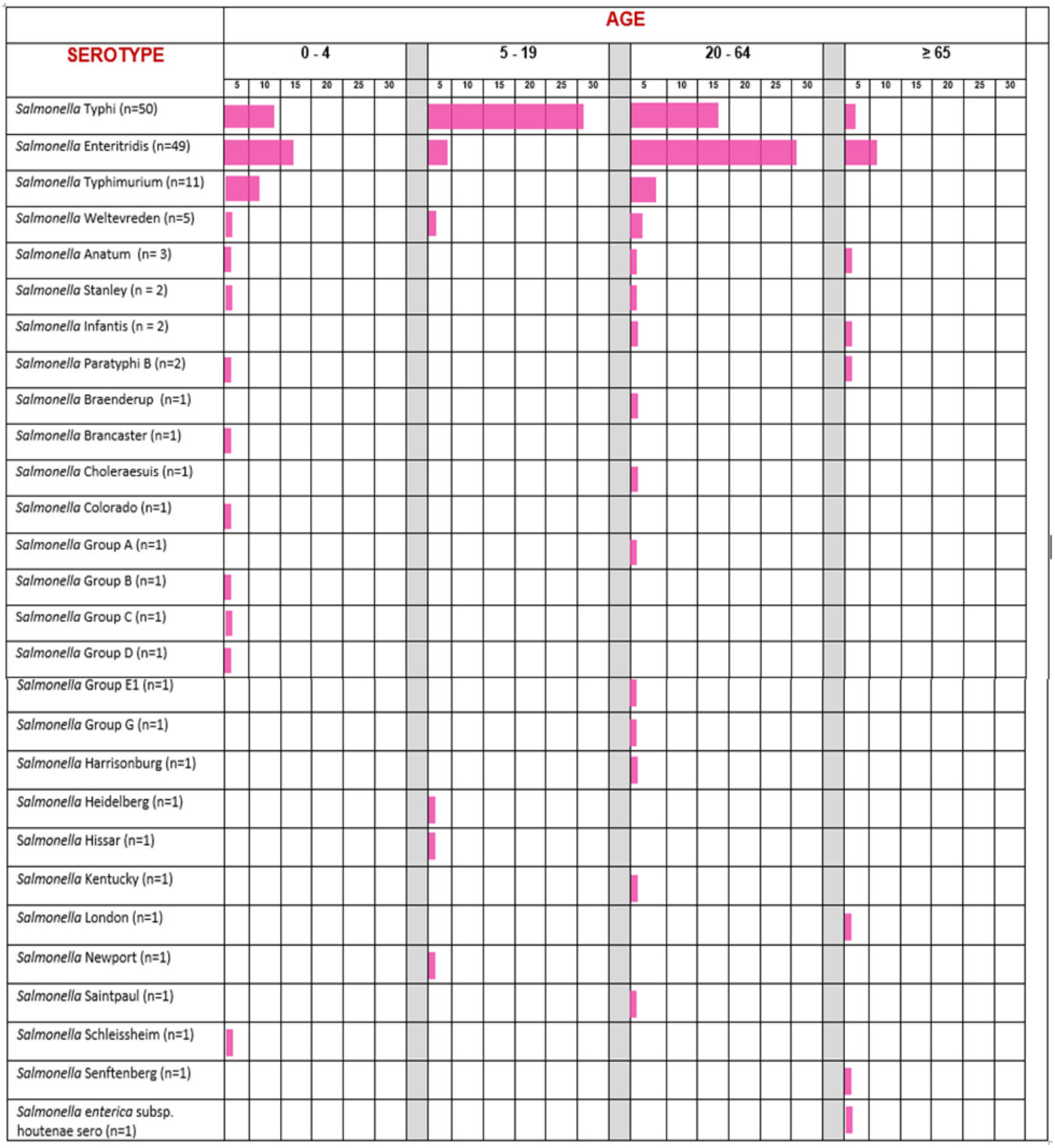


Figure 27. Yearly resistance rates of NTS isolates from 2013-2022, DOH ARSP

Table 5. *Salmonella* serotypes per age group, DOH-ARSP, 2022



There were 144 *Salmonellae* referred to the reference laboratory for serotyping. Many of the isolates were *Salmonella enterica* serovar Typhi (34.7%) and *Salmonella enterica* serovar Enteritidis (34.0%) (Table 5). Among the 94 confirmed non-typhoidal *Salmonella,* most common serotypes were *Salmonella enterica* serovar Enteritidis (n= 49) and *Salmonella enterica* serovar Typhimurium (n= 11). These two serotypes had been the most common serotypes reported for the past three years. Antimicrobial resistance among NTS reflects variations in serotypes, its distribution or both.

Shigella species

There were **24** *Shigella sp* isolates reported in 2022. Many isolates were from DMC at 20.8%, VSM and NMC both at 16.7%, and BRH at 12.5% (Figure 28). Based on island group distribution, many were from Mindanao at 45.8%, Luzon at 29.2%, and the Visayas at 25.0%. Many of the isolates (45.8%) were from patients aged 20-64 with 58.3% from stool samples (Figure 29).

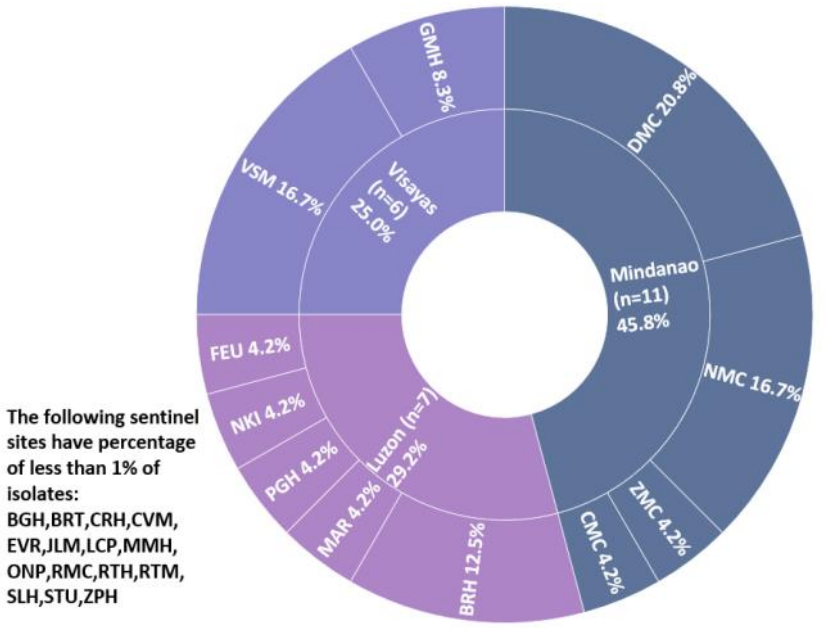


Figure 28. Isolate distribution of *Shigella* species, DOH-ARSP, 2022 (n=24)

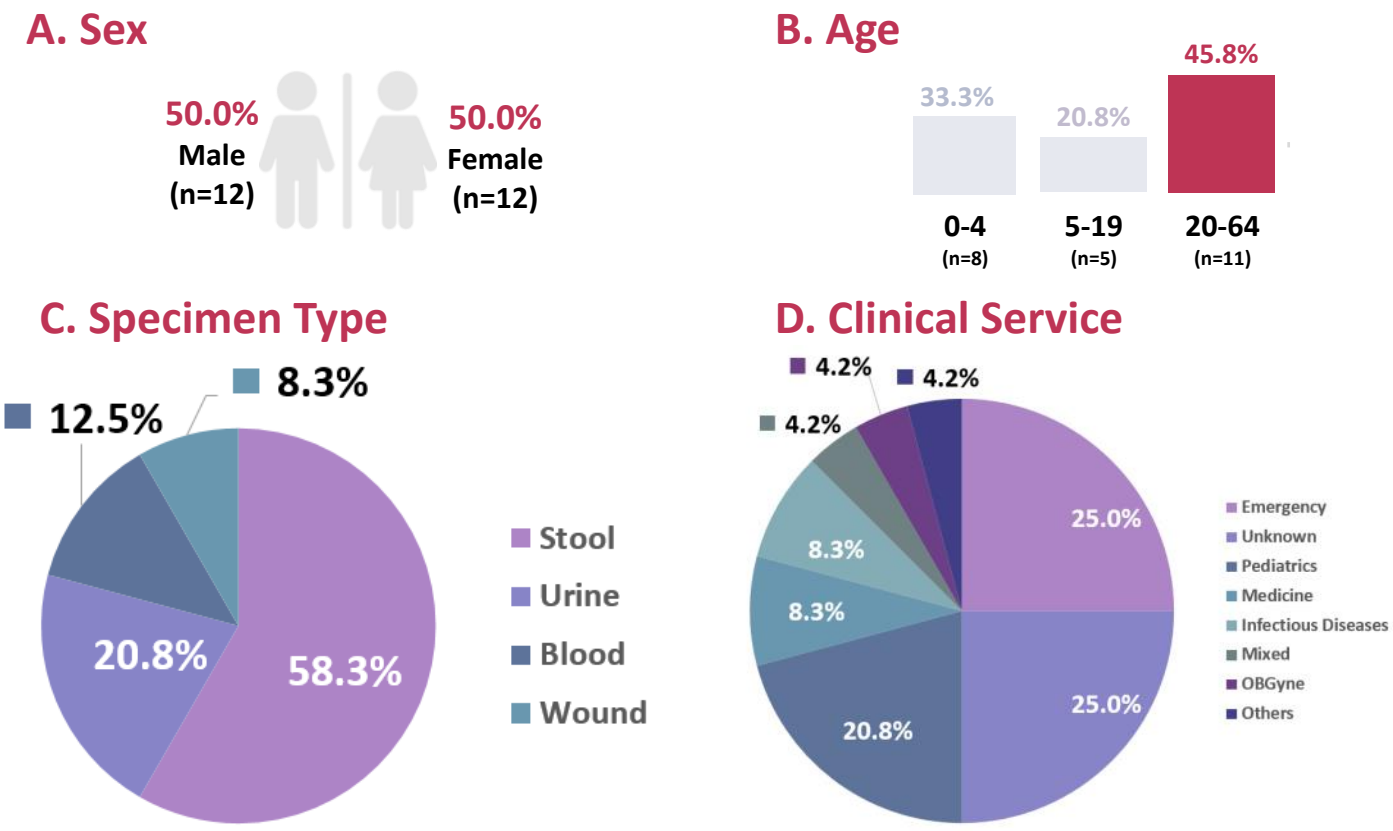


Figure 29. Patient characteristics of *Shigella* species isolates, DOH-ARSP, 2022 (n=24)

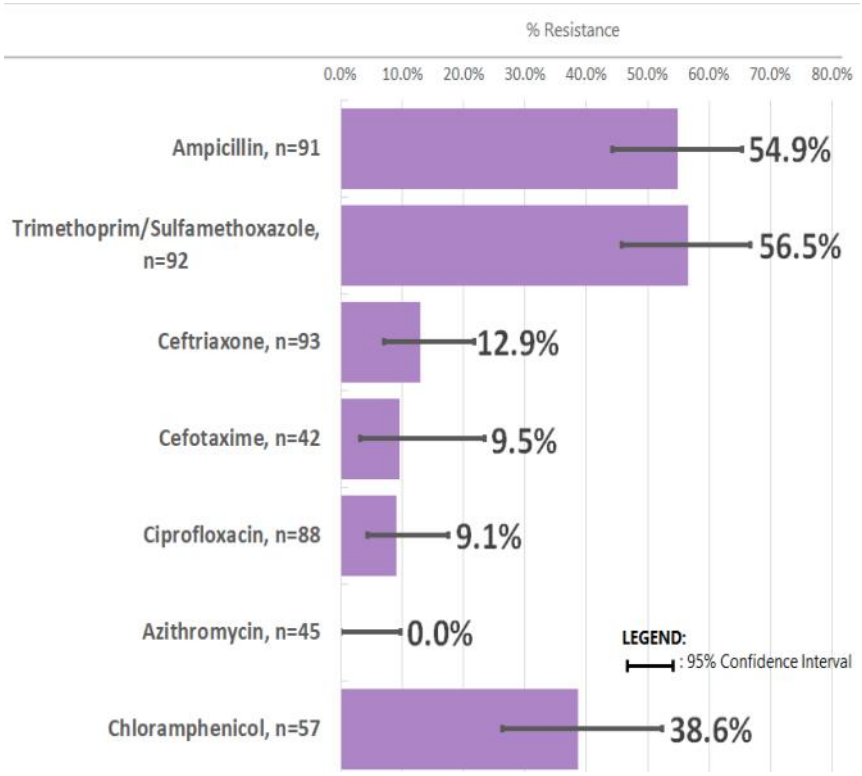


Figure 30. Resistance rates of *Shigella* species from all specimens, DOH-ARSP, 2019-2022

Figure 30 shows the cumulative resistance rates of *Shigella* species for all specimens from 2019-2022. Resistance to ceftriaxone was at 12.9%, to cefotaxime at 9.5%, ciprofloxacin at 9.1%, and zero for azithromycin. Ampicillin, co-trimoxazole and chloramphenicol resistance remained high at 54.9%, 56.5%, and 38.6%, respectively. Except for the increase in ceftriaxone, resistance rates decreased in 2022 when compared with rates in 2021; however, the changes were not statistically significant.

A comparison of the cumulative rates obtained from 2003 – 2022 (Figure 31) shows that changes in resistance rates for ciprofloxacin was not statistically significant but the increase in resistance rates for ceftriaxone over the past decade was statistically significant (p=0.0134).

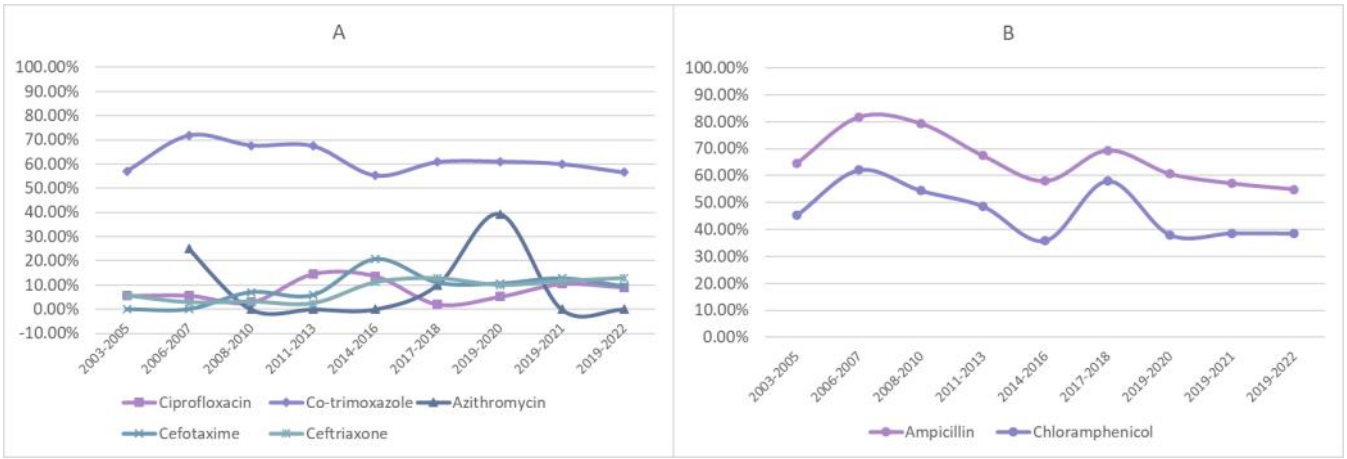


Figure 31. Yearly resistance rates of *Shigella* species isolates from 2003- 2022, DOH-ARSP

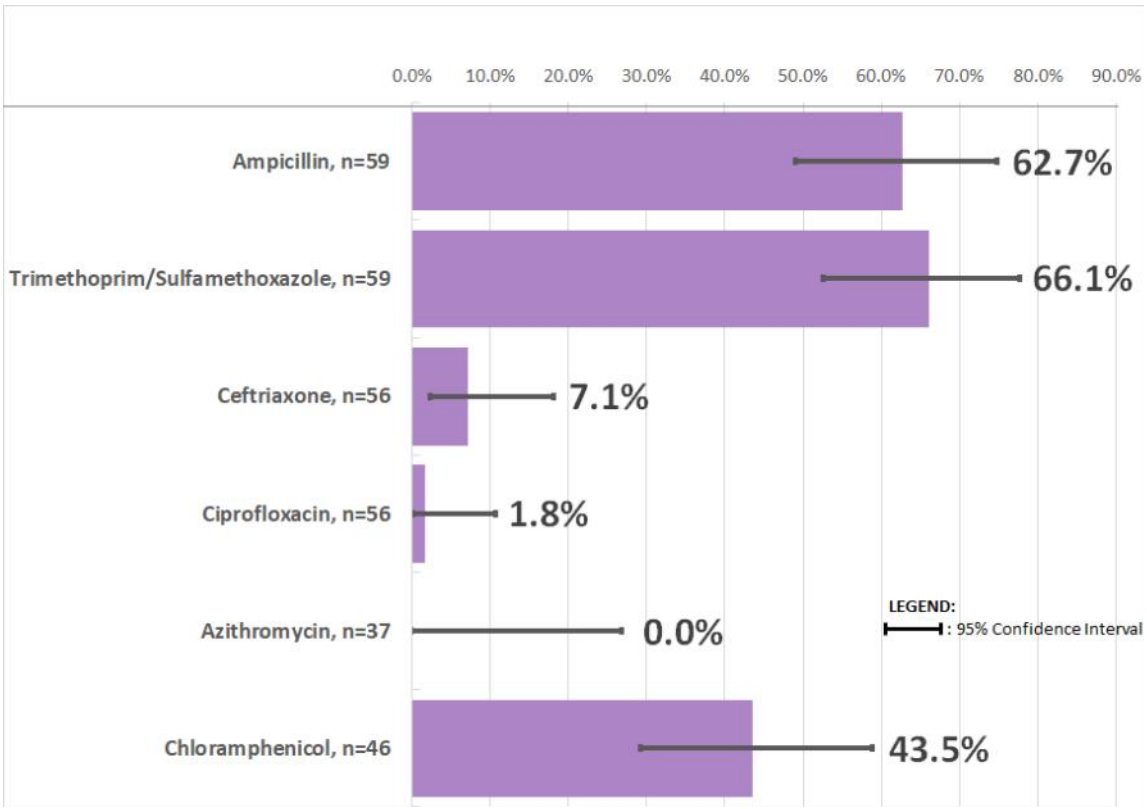


Figure 32. Resistance rates of *Shigella* species from stool isolates, DOH-ARSP, 2019-2022

Resistance rates for stool samples from 2019-2022 are shown in Figure 32. Resistances of *Shigella* isolates from stool samples for ceftriaxone was at 7.1%, to ciprofloxacin at 1.8% and azithromycin at zero. Resistance to ampicillin, cotrimoxazole and chloramphenicol remained high at 62.7%, 66.1%, and 43.5%, respectively. Compared with resistance rates for *Shigella* isolates from all samples, resistance of *Shigella* isolates from stool samples were lower for ceftriaxone and ciprofloxacin, higher for ampicillin, trimethoprim/sulfamethoxazole and chloramphenicol, and the same for azithromycin.

Table 6. *Shigella* serotypes per age group, DOH-ARSP, 2022

SEROTYPE	AGE													
	0-4				5-19				20-64				≥ 65	
	1	2	3		1	2	3		1	2	3		1	2	3
Shigella sonnei (n=1)															
Shigella sonnei Form I (n=1)															
Shigella flexneri serotype 1 (n=1)															
Shigella flexneri serotype 2a (n=1															
Shigella flexneri serotype 2b (n=5)															

There were 9 *Shigella* isolates referred to the reference laboratory for serotyping. Most of the isolates were *Shigella flexneri* serotype 2b (n=5), *Shigella sonnei* (n=1), *Shigella sonnei* Form I (n=1), *Shigella flexneri* serotype 1 (n=1), and *Shigella flexneri* serotype 2a (n=1) were also observed.

Vibrio cholerae

There were a total of **229** *Vibrio cholerae* isolates reported for 2022. (Figure 33). This is 136% higher than the reported isolates in 2021. Many of the isolates were from EVR at 31.0%, MMH at 29.7% and VSM at 13.1%. Distribution by island group shows the Visayas having the majority of isolates at 73.8%, Luzon at 17.0%, and Mindanao at 9.2%.

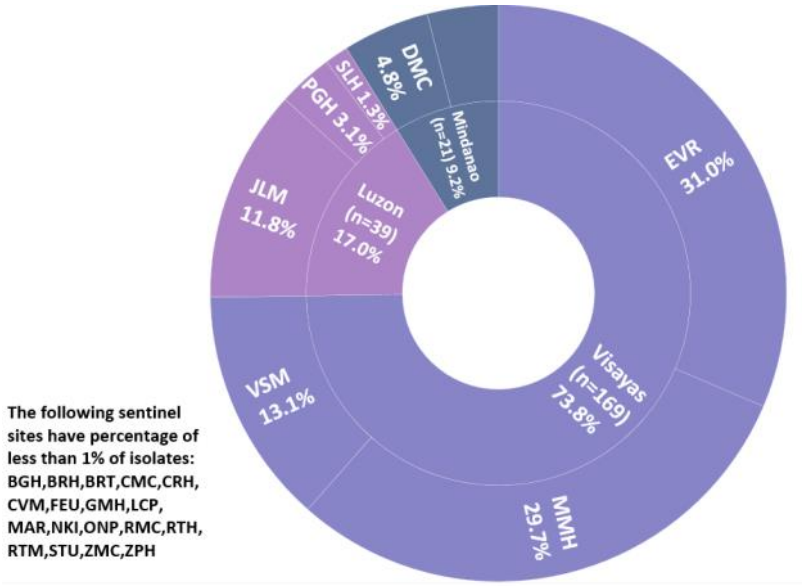


Figure 33. Isolate distribution of *V. cholerae* isolates, 2022, DOH-ARSP (n=229)

V. cholerae isolates reported were more frequently isolated in males (52.0%), in adult patients ages 20-64 (48.5%) from different hospital wards. (Figure 34). Majority (97.4%) were isolated from stool samples.

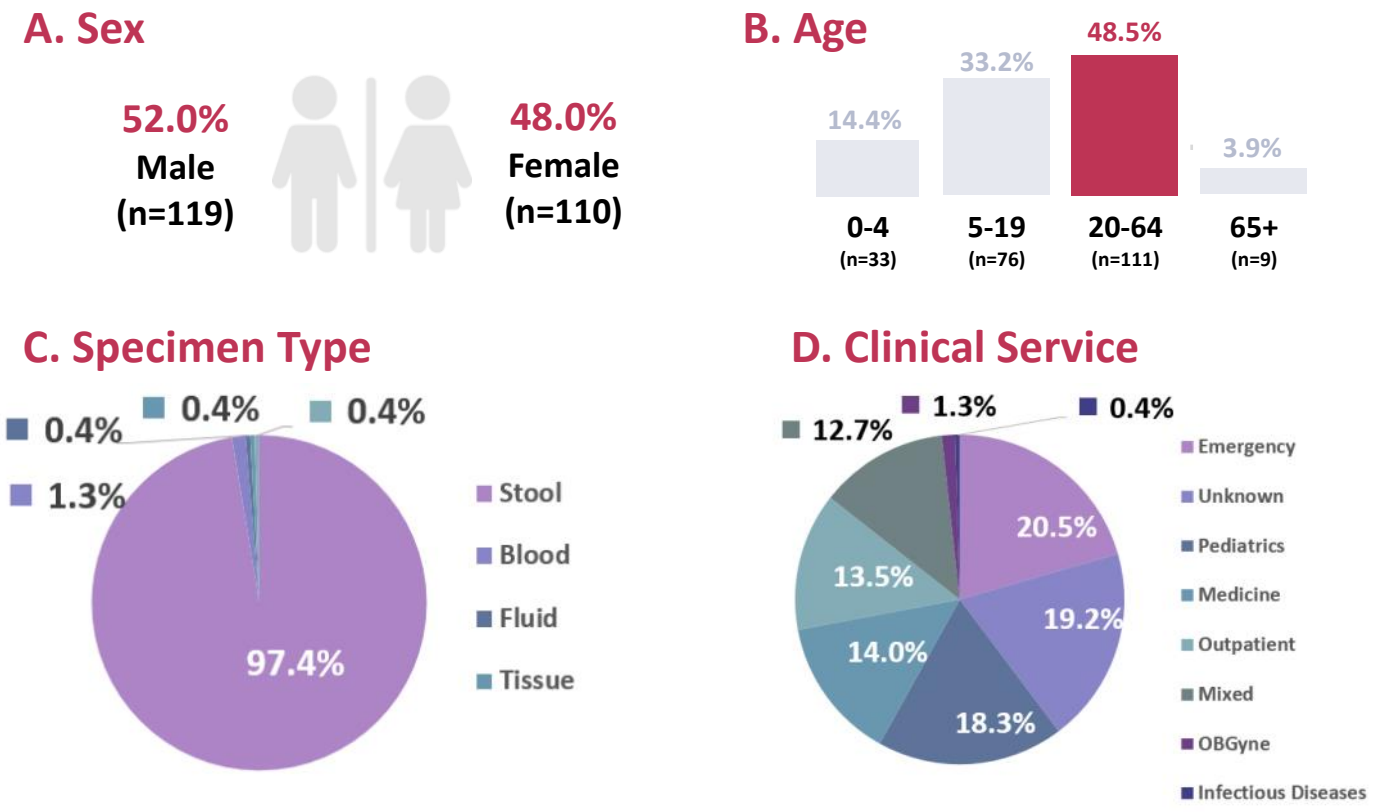


Figure 34. Patient characteristic of *V. cholerae* isolates, 2022, DOH-ARSP (n=229)

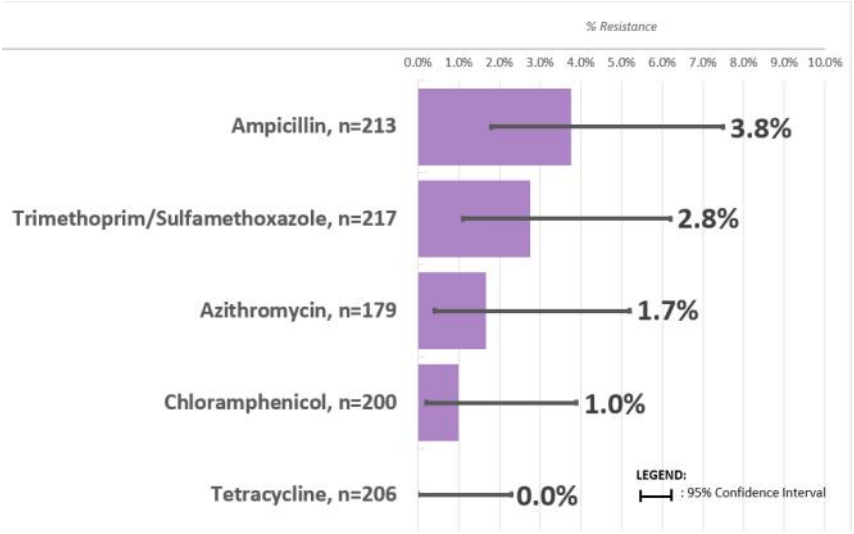


Figure 35. Resistance rates of *V. cholerae* isolates from all specimens 2022, DOH-ARSP

Resistance of *V. cholerae* isolates to all antibiotics used to treat infections due to these bacteria remained low for 2022 (Figure 35). Resistance to azithromycin and tetracycline was at 1.7% and zero, respectively. Resistance against ampicillin decreased from 9.6% in 2021 to 3.8% in 2022 (Figure 36) and the change was noted to be statistically significant. There was also decrease in resistance rates for co-trimoxazole while an increase in resistance was observed for azithromycin (1.7%) and chloramphenicol (1.0%).

One *V. cholerae* (serotype O1 Ogawa) isolate confirmed to be azithromycin resistant was reported from a stool specimen of a 67-year old male from VSM. The isolate also showed resistance to ampicillin, chloramphenicol, and co-trimoxazole but susceptible to tetracycline.

Molecular characterization of azithromycin resistant *Vibrio cholerae*

The growing concern over the emergence of antimicrobial resistance in *V. cholerae* strains has gained significant attention, particularly in low-income countries or endemic areas [1]. Surveillance of antibiotic resistance among this isolate is crucial to guide treatment options. Among the antibiotics used against *V. cholerae*, azithromycin was found to be one of the most effective and has added advantage of inhibiting colonization and shortened duration of symptoms [2, 3]. Further, it is a significant treatment option for severe cholera in pregnant women and children [5]. This report describes the molecular characteristics underlying antimicrobial resistance in an azithromycin-resistant *Vibrio cholerae* isolate identified in 2022.

The isolate was obtained from a stool specimen of a 67 year old male patient admitted to VSM (Table A). The isolate was identified as *Vibrio cholerae* O1 Ogawa based on phenotypic tests. Antimicrobial susceptibility testing (AST) showed resistance to ampicillin, azithromycin, chloramphenicol, and co-trimoxazole and was susceptible to tetracycline.

Table A. Characteristics of *Vibrio cholerae* isolate 2022

ID number	Hosp	Sex	Age	Specimen type	Lab ID	WGS ID	Antibiotic Tested	MIC Results	Resistance genes
22ARS_VSM0150	VSM	Male	67	Stool	Vibrio cholerae O1 Ogawa	Vibrio cholerae O1 Ogawa	Ampicillin (MIC)	>256 (R)	*bla*CARB-9
							Azithromycin (MIC)	64 (R)	*mph*(E), *msr*(E), *mph*(A)
							Chloramphenicol (MIC)	32 (R)	*cat*A2, *flo*R
							Co-trimoxazole(MIC)	>32 (R)	*sul*1, *sul*2, *dfr*A46, *dfr*A31
							Tetracycline (Disk)	26 (S)	

Whole genome sequencing identified the isolate as *Vibrio cholerae* O1 Ogawa. The identification of the strain is important for disease surveillance and control, particularly in the context of cholera outbreaks. The isolate is multidrug resistant harboring several antimicrobial resistance (AMR) genes conferring resistance to several antibiotics commonly used to treat infections caused by this pathogen (Table A). Resistance to azithromycin appears to be conferred by *mph*(E), *msr*(E) and *mph*(A) (Table A). Further analysis revealed the presence of *bla*NDM-1 in the isolate currently being described as well as the presence of *Inc*A/C plasmid, described in a previous study to carry multiple resistance genes among *V. cholerae* isolates [3]. The presence of *bla*NDM-1 in human as well as environmental isolates of *V. cholerae* [4] [5] may indicate wide distribution of this resistance gene among this pathogen. Detection of *bla*NDM-1 in the present isolate raises the need to determine to what extent *bla*NDM-1 gene is spreading among bacteria residing in the environment or clinical settings in the country.

References

1. Yuan XH, Li YM, Vaziri AZ, Kaviar VH, Jin Y, Jin Y, Maleki A, Omidi N, Kouhsari E. Global status of antimicrobial resistance among environmental isolates of Vibrio cholerae O1/O139: a systematic review and meta-analysis. Antimicrob Resist Infect Control. 2022 Apr 25;11(1):62. doi: 10.1186/s13756-022-01100-3. PMID: 35468830; PMCID: PMC9036709.
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3. Wang, R, Liu H., Zhao, X, Li, J, and Wan, Kanglin. IncA/C plasmids conferring high azithromycin resistance in Vibrio Cholerae International Journal of Antimicrobial Agents 51 (2018) 140–144 https://doi.org/10.1016/j.ijantimicag.2017.09.009
4. Elizabeth Darley, Janis Weeks, Lim Jones, Victoria Daniels, Mandy Wootton, Alasdair MacGowan, Timothy Walsh, NDM-1 polymicrobial infections including Vibrio cholerae, The Lancet, Volume 380, Issue 9850, 2012, Page 1358, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(12)60911-8.(https://www.sciencedirect.com/science/article/pii/S0140673612609118)
5. Diep TT, Nguyen NT, Nguyen TN, An HK, Nguyen TQ, Nguyen VH, Nguyen TV, Nguyen TN, Izumiya H, Ohnishi M, Yamashiro T, Nguyen LT. Isolation of New Delhi metallo-β-lactamase 1-producing Vibrio cholerae non-O1, non-O139 strain carrying ctxA, st and hly genes in southern Vietnam. Microbiol Immunol. 2015 May;59(5):262-7. doi: 10.1111/1348-0421.12248. PMID: 25683557.

Multi-year resistance rates illustrated in Figure 36 shows fluctuating resistance rates for chloramphenicol, co-trimoxazole and tetracycline.

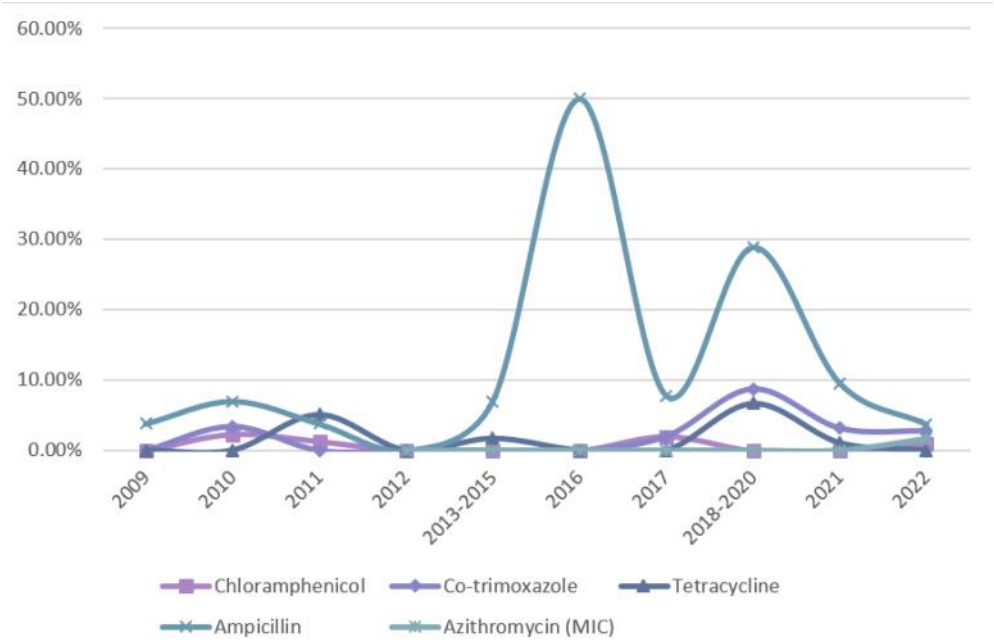


Figure 36. Multi-year cumulative rates of *V. cholerae* isolates from 2009-2022, DOH-ARSP

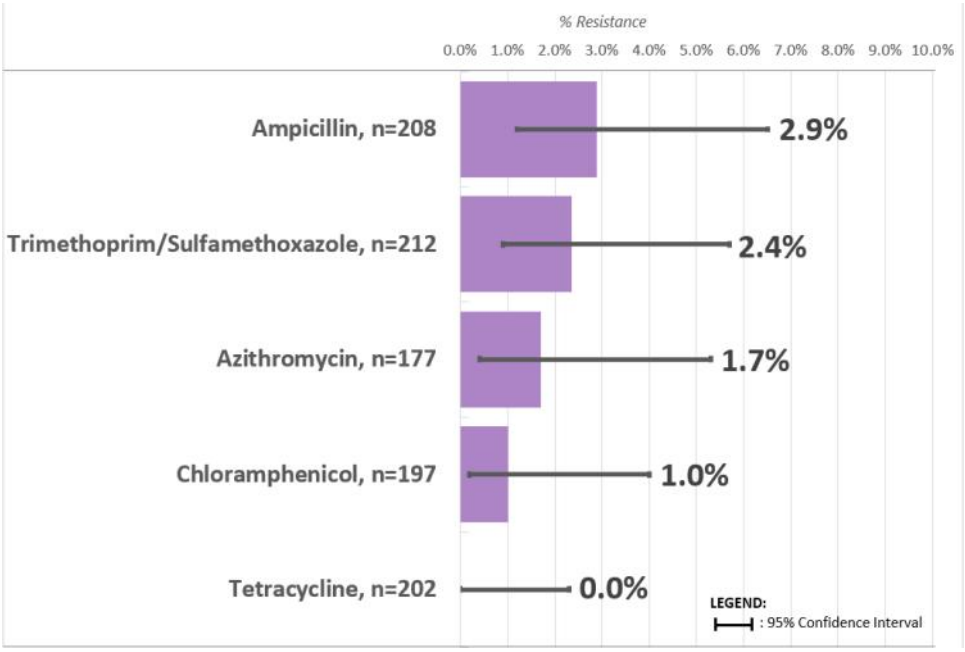


Figure 37. Resistance rates of *V. cholerae* isolates from stool specimens, 2022, DOH-ARSP

Resistance rates from stool specimens show a decreased resistance rate from 8.8% in 2021 to 2.9% in 2022 (Figure 37). Resistance to co-trimoxazole (2.4%), azithromycin (1.7%) and chloramphenicol (1.0%) increased in 2022 compared with rates in 2021. *V. cholerae* isolates from stool remained susceptible against tetracycline. Compared with resistance rates for *V. cholerae* isolates from all samples, resistance of *V. cholerae* isolates from stool samples were similar for tetracycline, azithromycin, & chloramphenicol and lower for ampicillin and trimethoprim/sulfamethoxazole.

Neisseria gonorrhoeae

There were 44 isolates of *Neisseria gonorrhoeae* reported for 2022 (Figure 38). This is 214% higher than the 14 isolates reported in 2022. The largest contributors were BGH at 27.3% (n=12), RTM at 18.2% (n=8) and VSM at 11.4% (n=5). Based on island group distribution, majority of isolates were from Luzon 63.6% (n=28), Visayas at 34.1% (n=15), and Mindanao at 2.3% (n= 1).

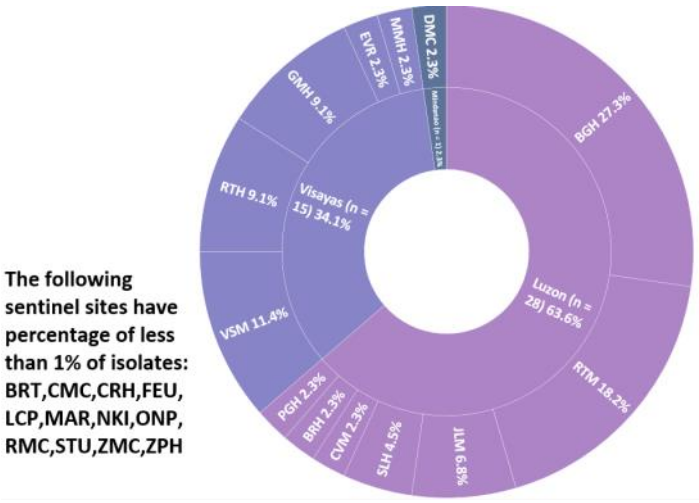


Figure 38. Isolate distribution of *N. gonorrhoeae* isolates, DOH – ARSP, 2022 (n=44)

Most isolates were from male patients (88.6%, n= 39). Isolates were mostly from adult patients aged 20-64 (63.6%, n= 28), and were from genital specimens (84.1%, n= 37).

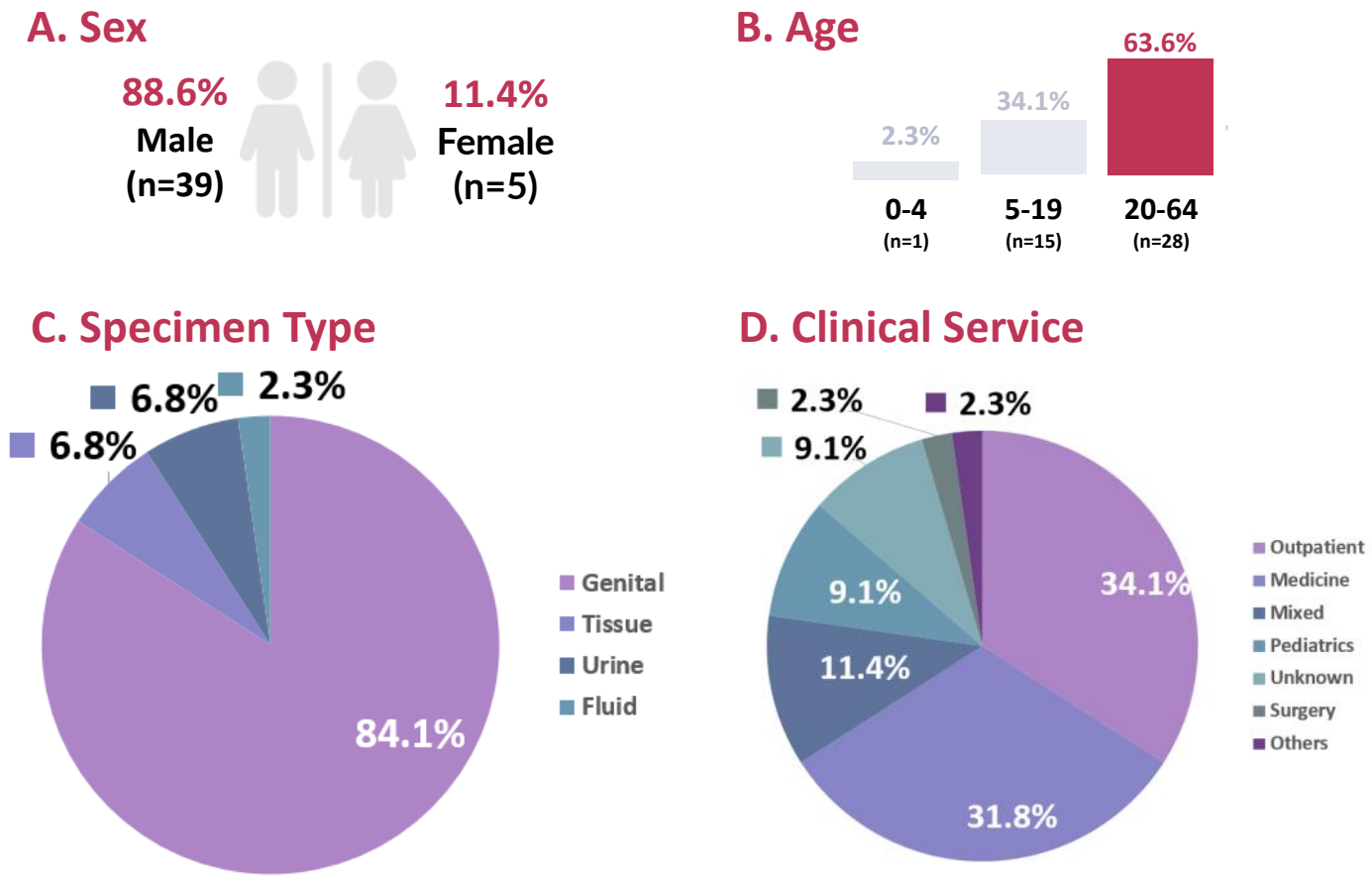


Figure 39. Patient characteristics of *N. gonorrhoeae* isolates, DOH-ARSP, 2022 (n=44)

Figure 40 shows the resistance rates of *N. gonorrhoeae* isolates in 2022. All isolates were susceptible to ceftriaxone, cefixime, azithromycin, and spectinomycin. Resistance to ciprofloxacin and tetracycline remained high at 76.3% and 71.8%, respectively.

Yearly resistance rates of *N. gonorrhoeae* from 2012-2022 are shown in Figure 41. Resistance rates for tetracycline was steadily increasing and this change is statistically significant (p=0.00768).

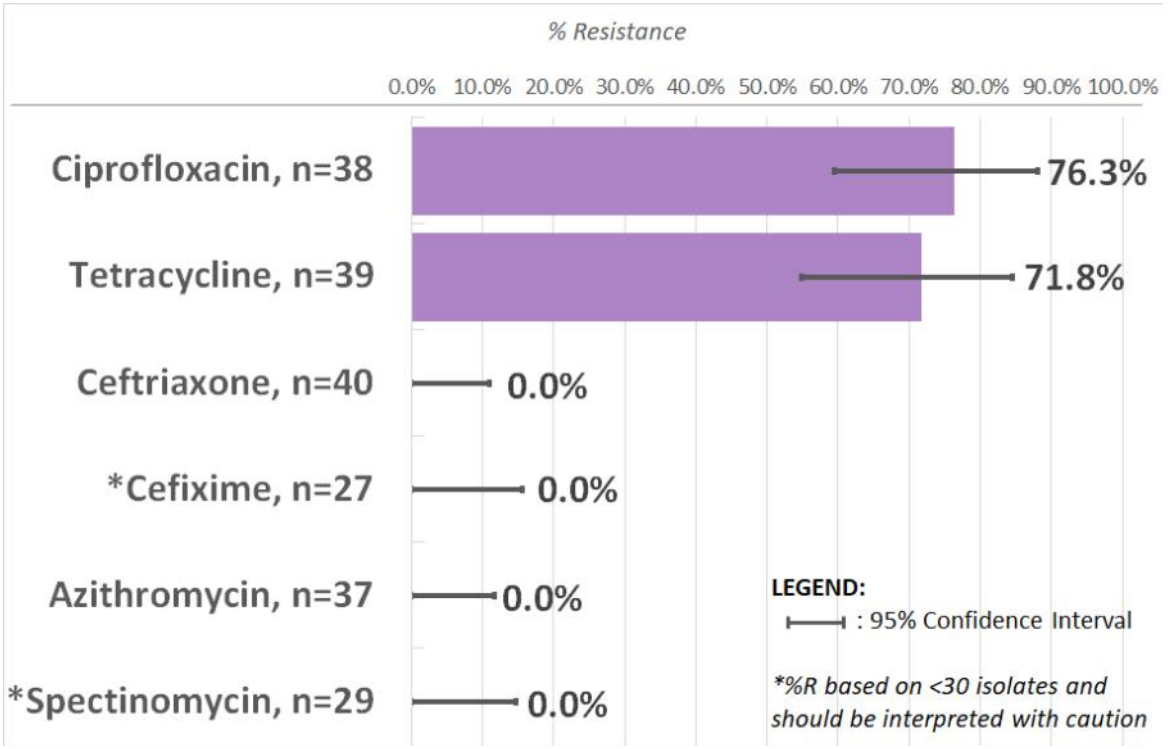


Figure 40. Resistance rates of *N. gonorrhoeae* isolates for all specimens, DOH-ARSP, 2022

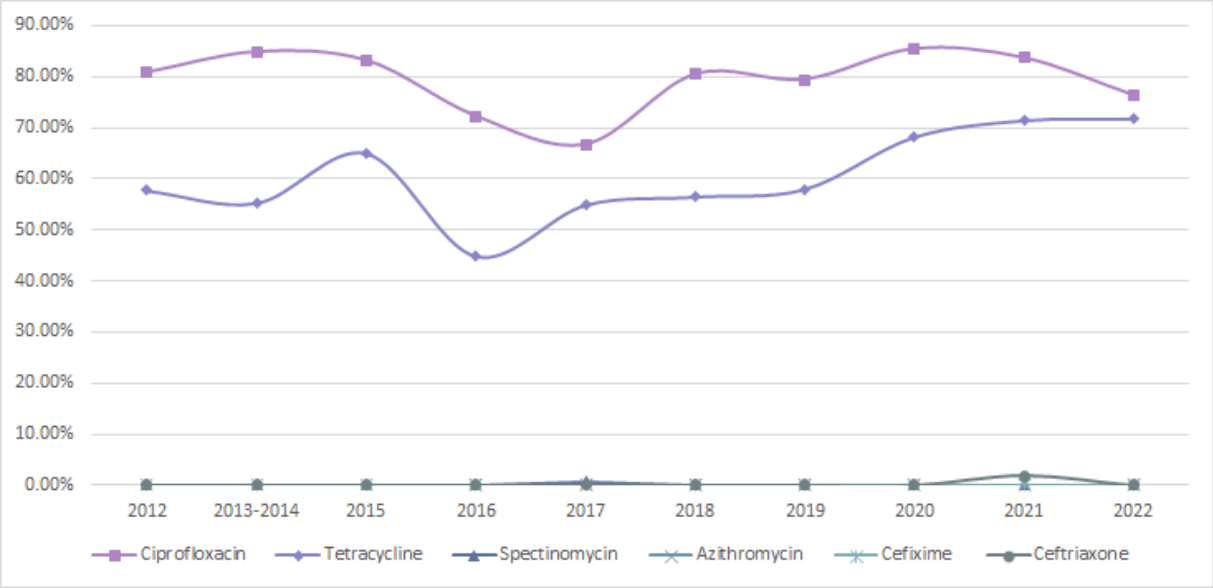


Figure 41. Yearly resistance rates of *N. gonorrhoeae* isolates from 2012-2022, DOH-ARSP

Staphylococcus aureus

There were **5,663** *Staphylococcus aureus* isolates reported for 2022. This is a 35% increase from the number reported in 2021 (n=4,198). The largest contributors were PGH (11.6%), DMC (10.9%), and JLM (9.27%) (Figure 42). Luzon showed the highest number of isolates at 61.2%, Mindanao at 23.3%, and the Visayas at 15.5%.

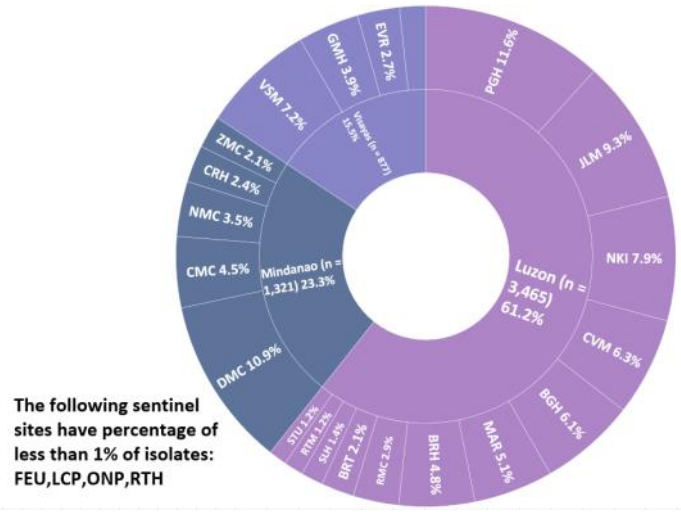


Figure 42. Isolate distribution of *S. aureus,* DOH-ARSP, 2022 (n=5,663)

Most (65.3%) of the isolates were from 20-64 years old patients and more frequently (55.6%) obtained from males (Figure 43). The highest percentage of the specimens were from wound (37.6%), followed by blood (25.9%), and respiratory (16.2%) samples. Majority of the isolates (81.8%) were from presumptive community-acquired infections.

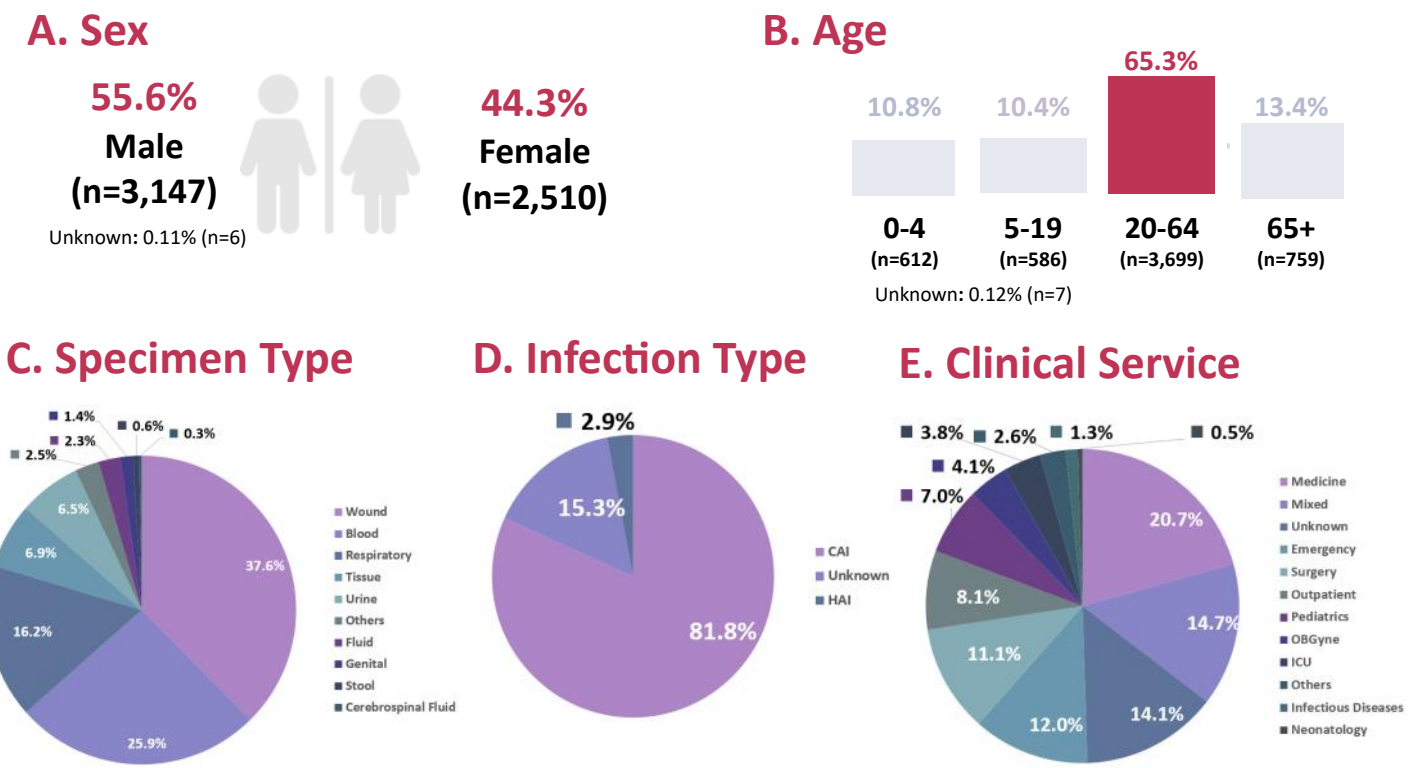


Figure 43. Patient characteristics of *S. aureus* isolates, DOH-ARSP, 2022 (n=5,633)

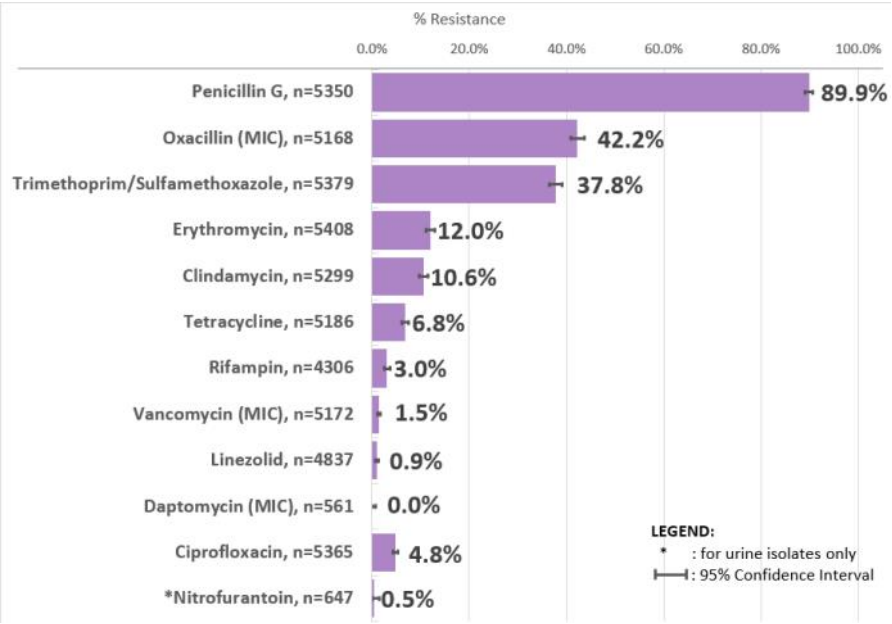


Figure 44. Resistance rates of *S. aureus* from all specimens, DOH-ARSP, 2022

The overall resistance rate of *S. aureus* from all specimens reported in 2022 is shown in Figure 44. Resistance to oxacillin was at 42.2%, to clindamycin at 10.6%, and co-trimoxazole at 37.8%. Resistance against erythromycin was 12.0%, and to tetracycline was 6.8%. Resistance to vancomycin and linezolid was 1.5% and 0.9% respectively. There had been a decrease in the resistance against vancomycin from 2.1% in the previous year to 1.5% in 2022 (Figure 45) which was statistically significant. All isolates tested against daptomycin were susceptible to this antibiotic.

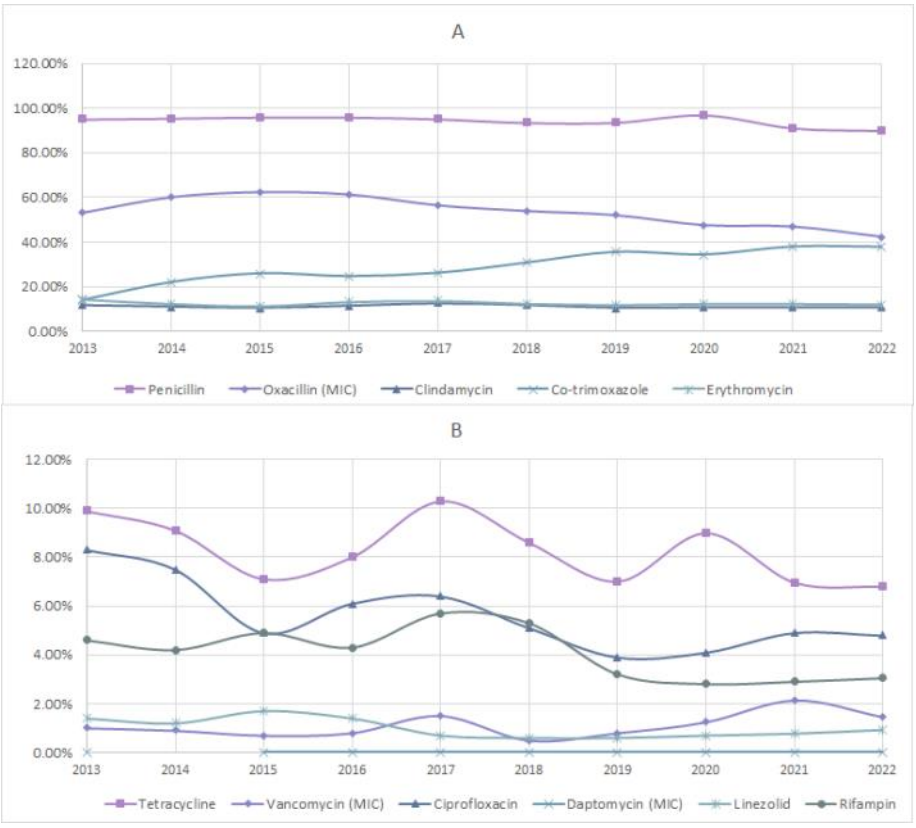


Figure 45. Yearly resistance rate of *S. aureus,* DOH-ARSP, 2013-2022

Yearly resistance rates for *S. aureus* is shown in Figure 45. Oxacillin resistance continue to decrease since 2016 and multiple year analysis showed that the noted changes in resistance rates were statistically significant (p=0.0000). Resistance rates for co-trimoxazole was noted to be increasing in the past 10 years and the increase was found to be statistically significant (p=0.0000). Vancomycin resistance rates over the past year were also found to be increasing since 2018 but decreased in 2022. Multiple year analysis has also shown changes in vancomycin resistance rates to be statistically significant (p=0.0000).

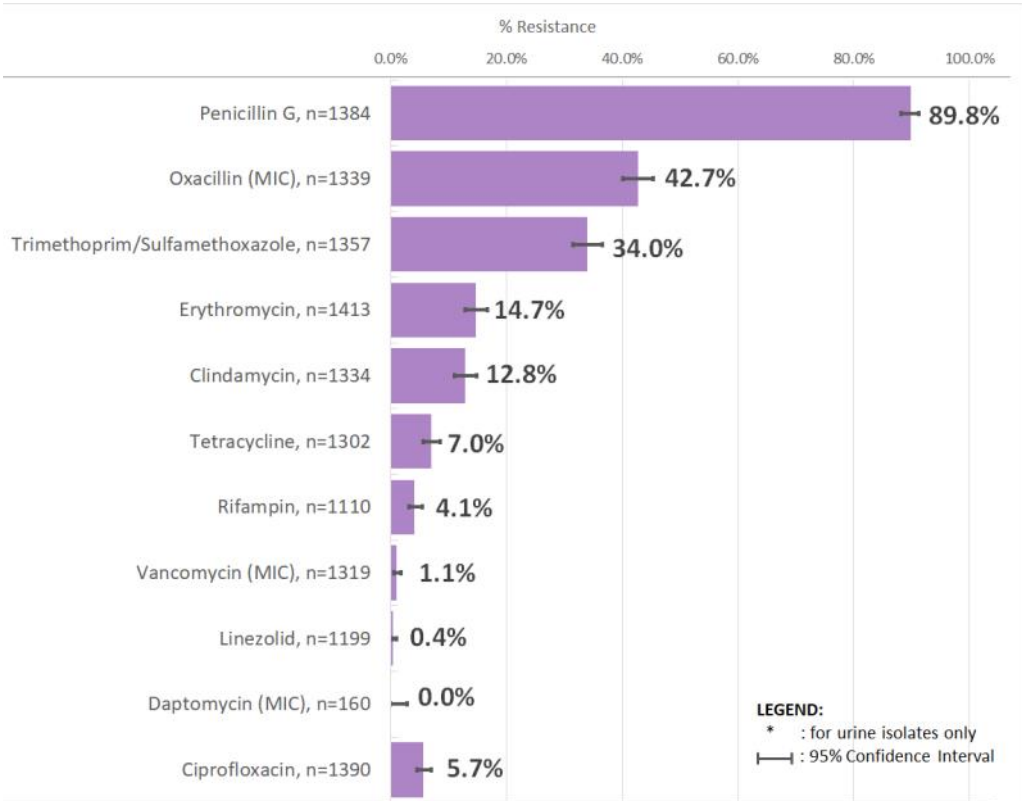


Figure 46. Resistance rates of *S. aureus* blood, DOH-ARSP, 2022

Figure 46 shows the resistance rates of *S. aureus* isolates from blood. Resistance against oxacillin was 42.7%, clindamycin at 12.8%, vancomycin at 1.1%, and linezolid 0.4%. No resistant isolate against daptomycin was reported. Compared with resistance rates of *S. aureus* isolates from all samples, resistance rates of *S. aureus* isolates from blood are higher for oxacillin, erythromycin, clindamycin, tetracycline, rifampin and ciprofloxacin; lower for co-trimoxazole, vancomycin and linezolid.

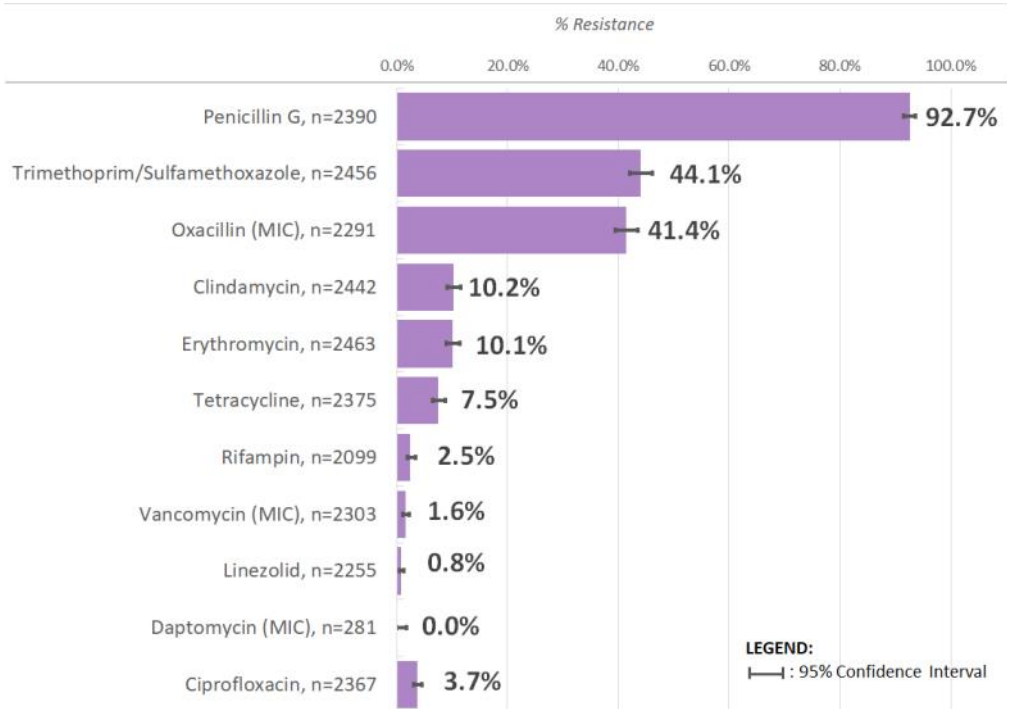


Figure 47. Resistance rates of *S. aureus* skin and soft tissues, DOH-ARSP, 2022

Figure 47 shows the resistance rates of *S. aureus* isolates from skin and soft tissues. Resistance against oxacillin was at 41.4%, against clindamycin at 10.2%, erythromycin 10.1%, tetracycline at 7.5%, vancomycin at 1.6%, and linezolid at 0.8%. No resistant isolates against daptomycin were reported. Compared with resistance rates of *S. aureus* isolates from all samples, resistance rates of *S. aureus* isolates from skin and soft tissues are higher for penicillin, co-trimoxazole, tetracycline, & vancomycin; lower for oxacillin, erythromycin, clindamycin, rifampin, ciprofloxacin and linezolid.

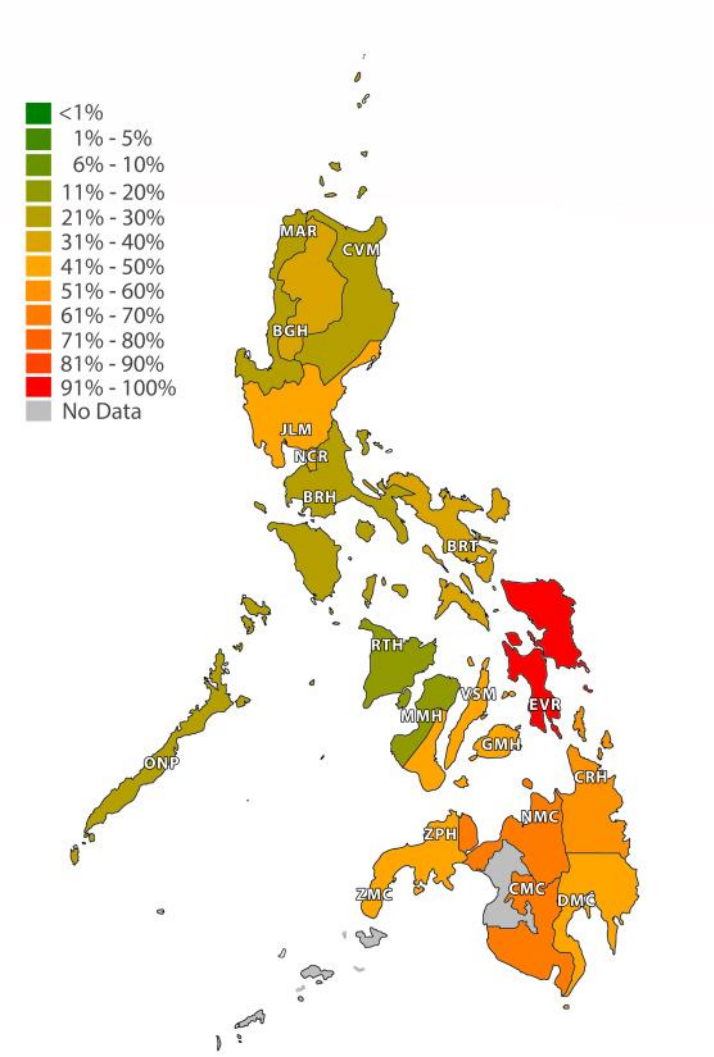


Figure 48. Geographic distribution of oxacillin-resistant *S. aureus* in the Philippines, DOH-ARSP, 2022

Figure 48 shows the oxacillin resistance rates across the different regions in the country. Sentinel sites from Mindanao have MRSA rates in the range of 51-71% while sentinel sites from Visayas ranges from 11-50% while in Luzon, sentinel sites have MRSA rates ranging from 21-40%.

Methicillin Resistant *Staphylococcus aureus*

There were **1,949** methicillin resistant *Staphylococcus aureus* (MRSA) isolates reported for 2022. Largest contributors for MRSA include DMC (13.1%), JLM (11.2%), and VSM (10.1%) (Figure 49).

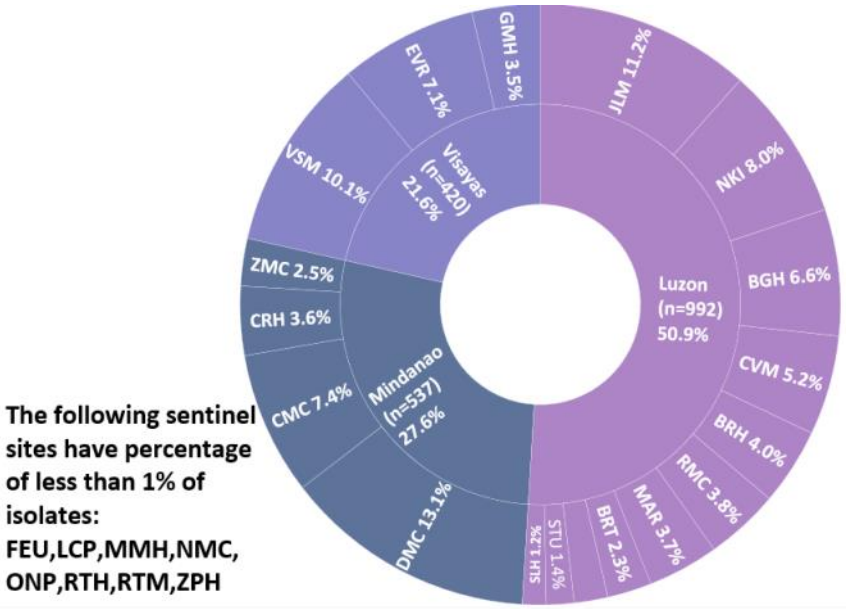


Figure 49. Isolate distribution of methicillin resistant *S. aureus*, DOH-ARSP, 2022 (n=1,949)

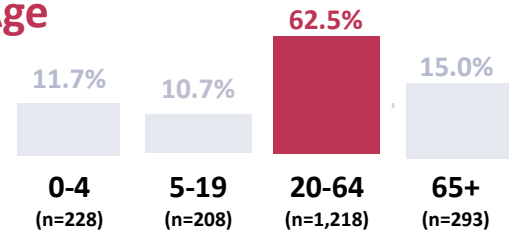
A. Sex

55.0% **Male (n=1,072)**

44.8% **Female (n=873)**

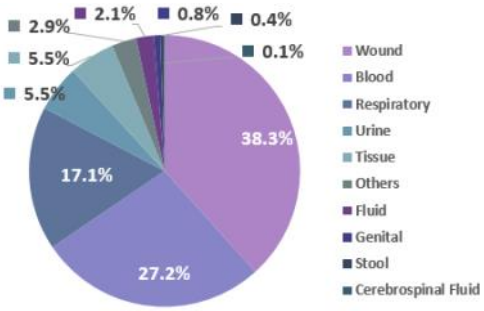
No data: 0.21% (n=4)

B. Age

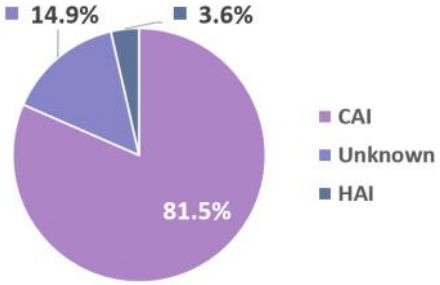


Unknown: 0.10% (n=2)

C. Specimen Type



D. Infection Type



E. Clinical Service

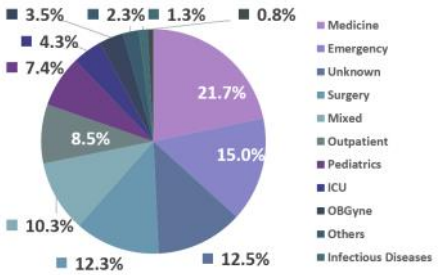


Figure 50. Patient characteristics of methicillin resistant *S. aureus*, DOH-ARSP, 2022 (n=1,949)

Most of the MRSA isolates were from males (55.0%) (Figure 50), and are adults aged 20-64 years old (62.5%). Majority of the MRSA isolates were received from wound specimens (38.3%), followed by blood (27.2%), and respiratory samples (17.1%).

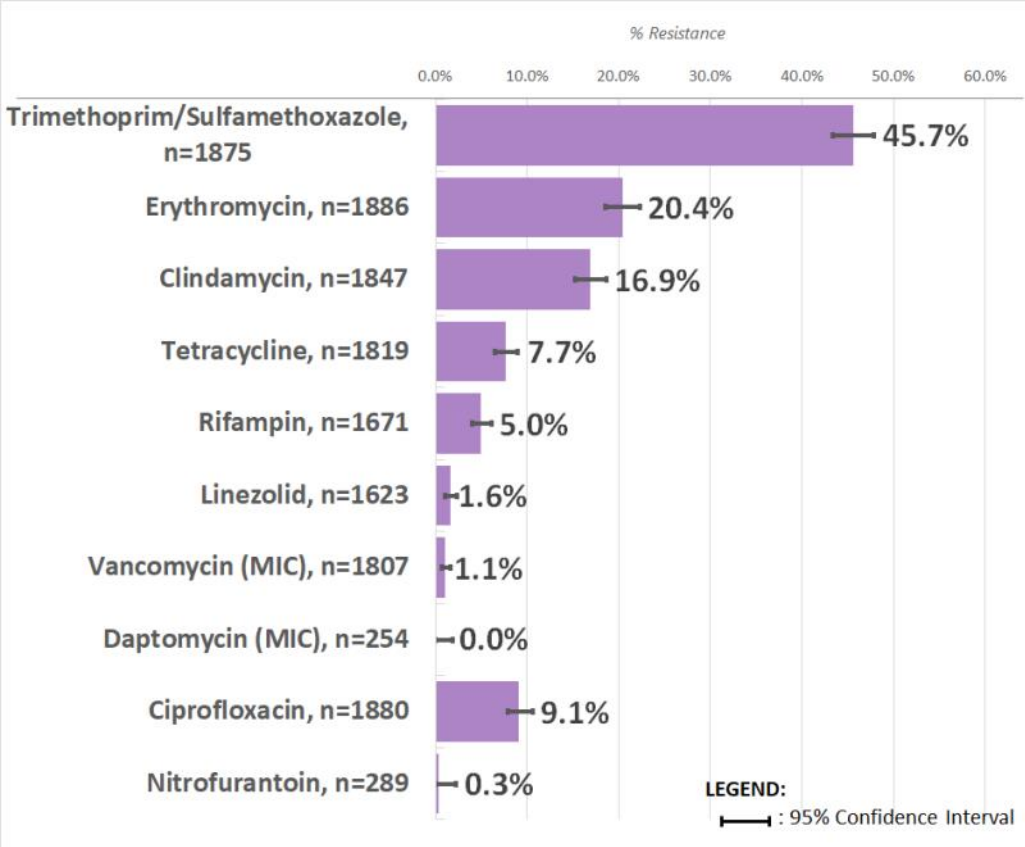


Figure 51. Resistance rates of methicillin resistant *S. aureus* from all specimens, DOH-ARSP, 2022

Resistance rates of MRSA isolates from all specimens are shown in Figure 51. The highest resistance was for co-trimoxazole at 45.7%, erythromycin at 20.4%, and clindamycin at 16.9%. Resistance rates for tetracycline, rifampin, linezolid, vancomycin, ciprofloxacin, and nitrofurantoin were less than 10%. No resistant isolate was reported for daptomycin.

One MRSA isolate from wound of a 70 -year old female from JLM was confirmed to be linezolid resistant. This isolate was noted to be susceptible to clindamycin, ciprofloxacin, co-trimoxazole, rifampicin, tetracycline, daptomycin and vancomycin but resistant to erythromycin.

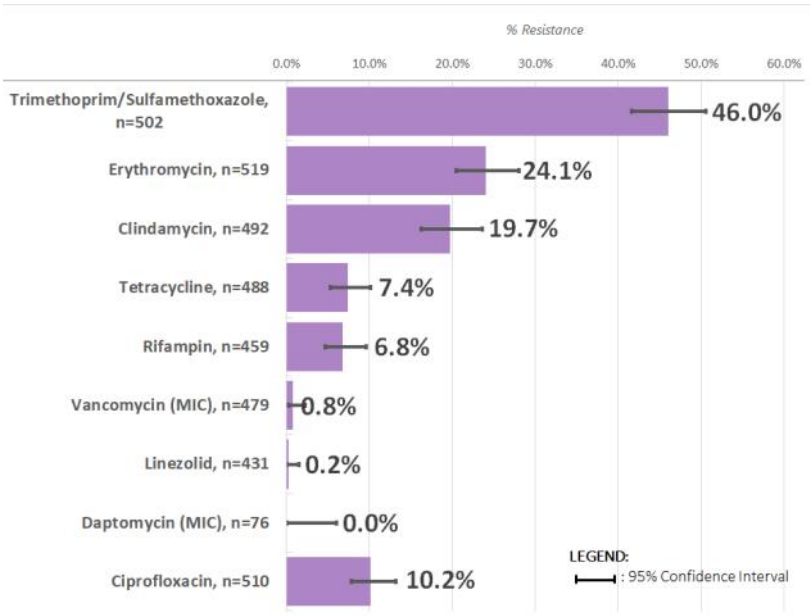


Figure 52. Resistance rates of methicillin resistant *S. aureus* from blood, DOH-ARSP, 2022

Figure 52 shows the resistance rates of MRSA isolates from blood. The highest resistance was for co-trimoxazole at 46.0%, erythromycin at 24.1%, and clindamycin at 19.7%. Resistance rates for tetracycline, rifampin, linezolid, vancomycin and ciprofloxacin, were less than 11.0%. No isolate was reported resistant to daptomycin. Compared with resistance rates of MRSA isolates from all samples, resistance rates of MRSA isolates from blood are higher for co-trimoxazole, erythromycin, clindamycin, rifampin, and ciprofloxacin; lower for tetracycline, vancomycin and linezolid.

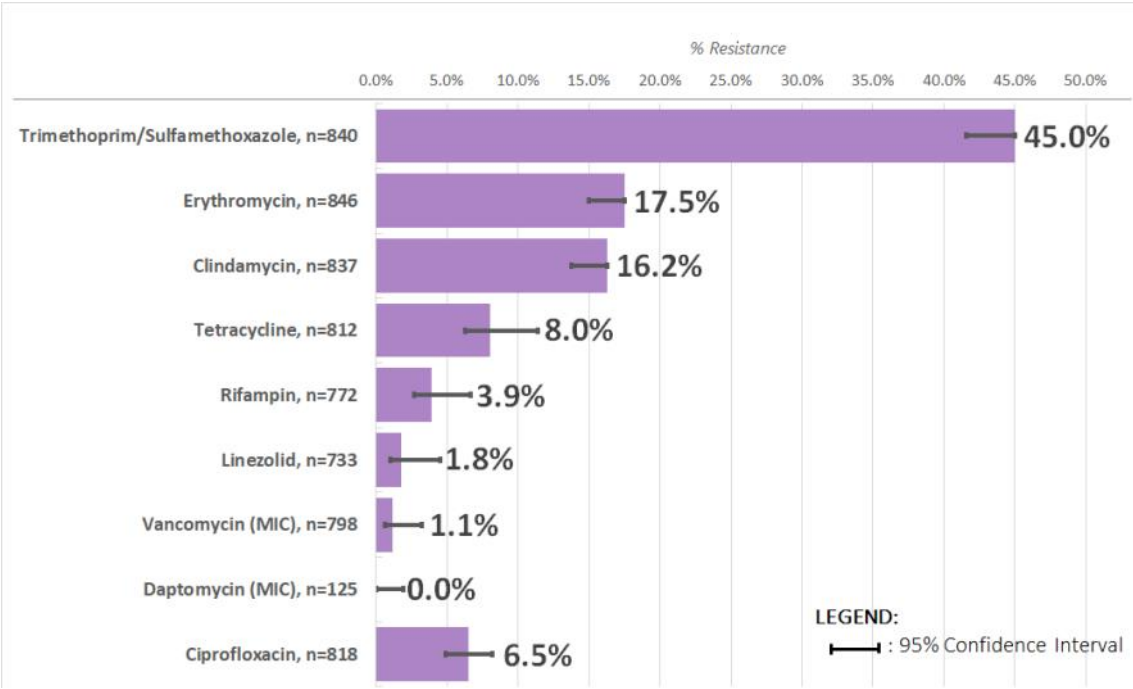


Figure 53. Resistance rates of methicillin resistant *S. aureus* from skin and soft tissues, DOH-ARSP, 2022

Figure 53 shows the resistance rates of MRSA isolates from skin and soft tissues. The highest resistance was for co-trimoxazole at 45.0%, erythromycin at 17.5%, and clindamycin at 16.2%. Resistance rates for tetracycline, rifampin, linezolid, vancomycin, and ciprofloxacin were less than 10%. No resistant isolate was reported for daptomycin. Compared with resistance rates of MRSA isolates from all samples, resistance rates of MRSA isolates from skin and soft tissues are lower for most antibiotics except for linezolid which had higher resistance rate.

Methicillin Susceptible *Staphylococcus aureus*

Cumulative resistance rates of methicillin susceptible *Staphylococcus aureus* (MSSA) from all specimens are shown in Figure 54. The highest resistance was for penicillin at 84.3% and co-trimoxazole at 33.8%. Resistance rates against erythromycin, clindamycin, and tetracycline were all less than 7.0% and resistance against vancomycin, rifampin , linezolid, ciprofloxacin, gentamicin and nitrofurantoin were less than 3%. No resistant isolate against daptomycin was reported.

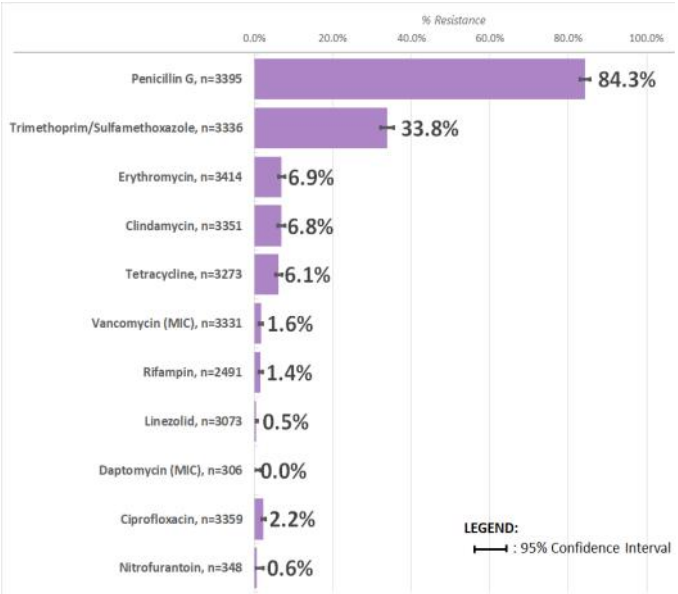


Figure 54. Resistance rates of methicillin susceptible *S. aureus* from all specimens, DOH-ARSP, 2022

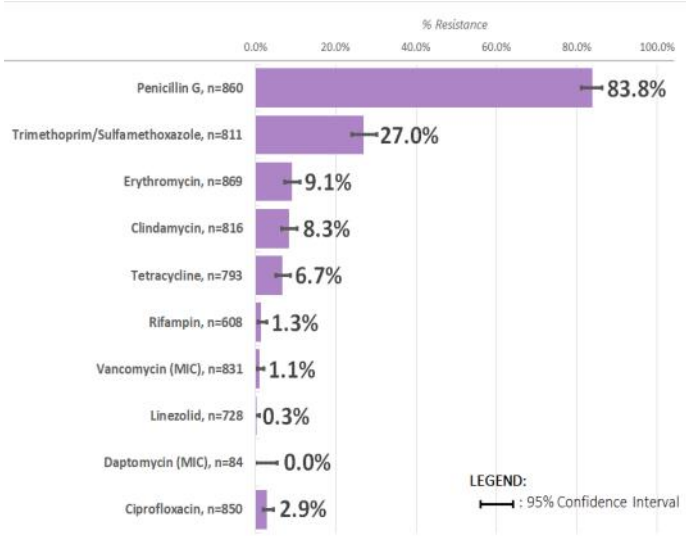


Figure 55. Resistance rates of methicillin susceptible *S. aureus* from blood, DOH-ARSP, 2022

Resistance rates of methicillin susceptible *Staphylococcus aureus* (MSSA) from blood specimens are shown in Figure 55. The highest resistance was for penicillin at 83.8% and co-trimoxazole at 27.0%. Resistant rates against erythromycin, clindamycin and tetracycline were less than 10%. Resistance rates against cefoxitin, rifampin, vancomycin, linezolid, gentamicin and ciprofloxacin were less than 3%. No resistant isolate against daptomycin was reported.

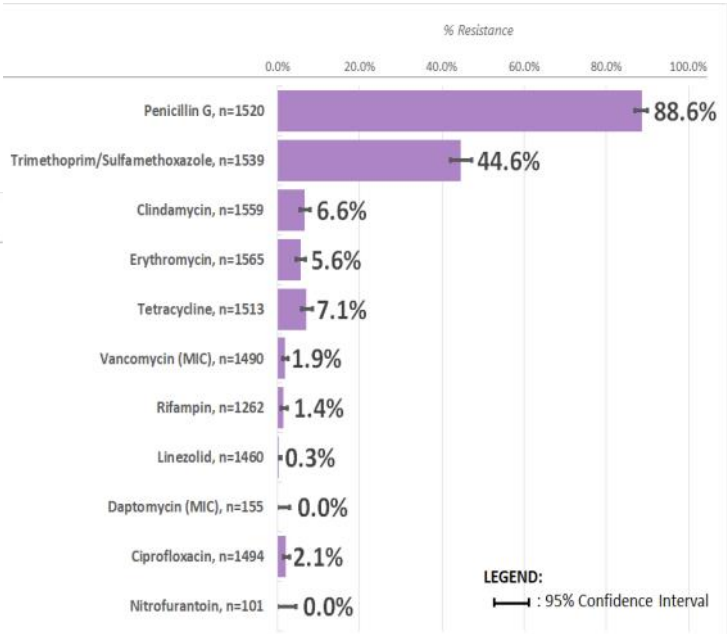


Figure 56. Resistance rates of methicillin susceptible *S. aureus* from skin and soft tissues, DOH-ARSP, 2022

Resistance rates of methicillin susceptible *Staphylococcus aureus* (MSSA) from skin and soft tissue samples are shown in Figure 56. The highest resistance was for penicillin at 88.6% and co-trimoxazole at 44.6%. Resistant rates against clindamycin, erythromycin, and tetracycline were less than 10%. Resistance rates against cefoxitin, vancomycin, rifampin, linezolid, and ciprofloxacin were less than 3%. No resistant isolate against daptomycin was reported.

Enterococcus species

For 2022, a total of **4,013** *Enterococcus* species were reported of which the most common were *Enterococcus faecalis* (63.9%) and *Enterococcus faecium* (36.1%).

Enterococcus faecalis

A total of **2,565** isolates of *Enterococcus faecalis* was analyzed for 2022. DMC (17.1%) contributed most of the data on *E. faecalis* followed by PGH (16.6%) and CVM (9.4%). The Luzon sentinel sites contributed the most (60.4%) number of isolates.

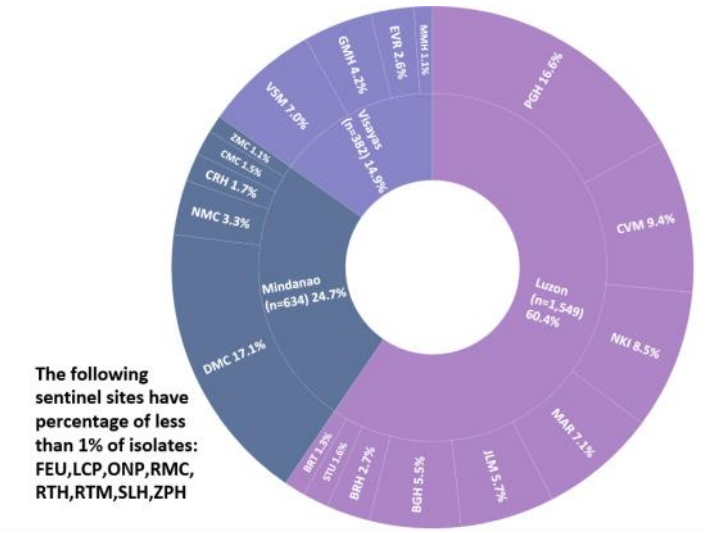


Figure 57. Isolate distribution of *Enterococcus faecalis*, DOH-ARSP, 2022 (n= 2,565)

Most (64.7%) of the isolates were from 20-64 age range and most (52.5%) were from female patients (Figure 58). *E. faecalis* isolates were mostly (48.7%) collected from urine specimens and most (81.9%) isolates were from presumptive community acquired infections.

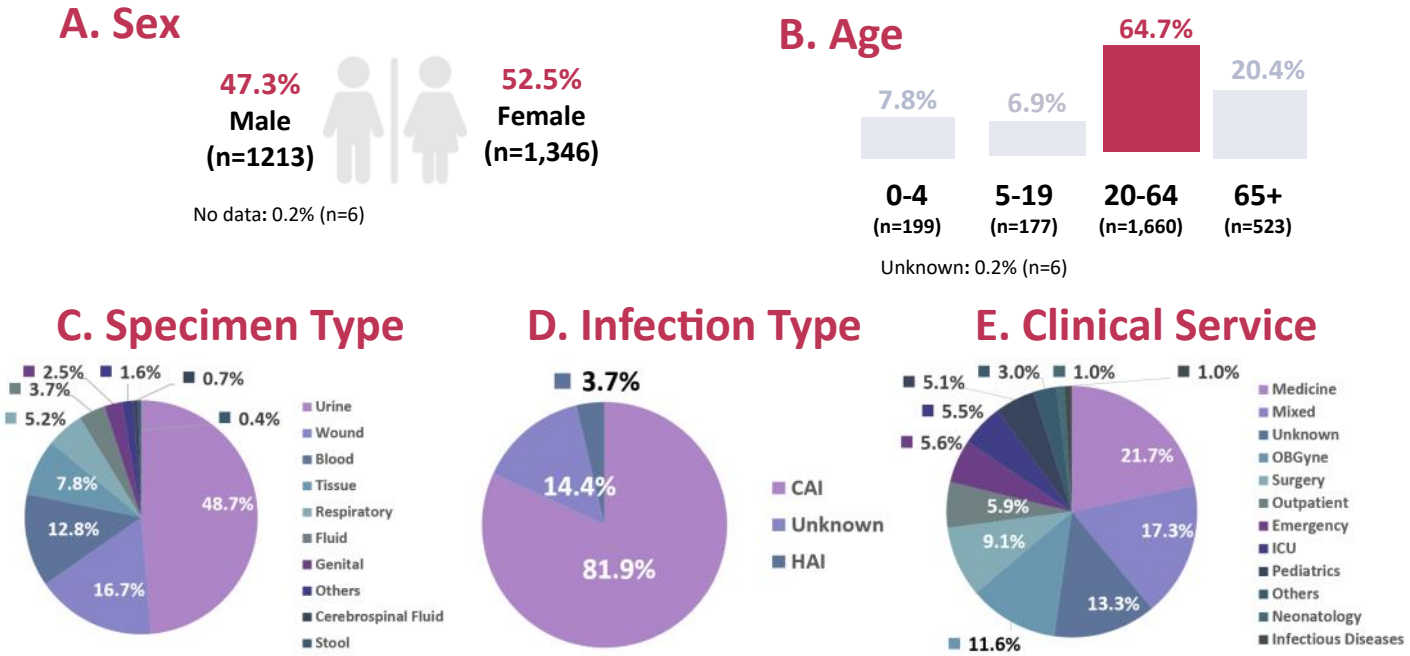


Figure 58. Patients characteristics of *E. faecalis*, DOH-ARSP, 2022 (n= 2,565)

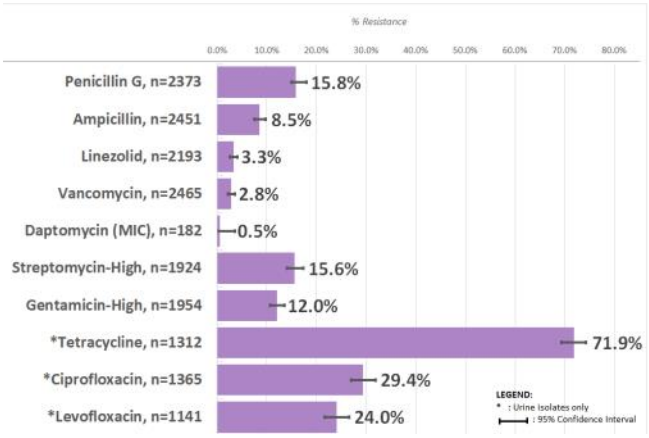


Figure 59. Resistance rates of *E. faecalis* from all specimens, DOH-ARSP, 2022

Resistance to penicillin was at 15.8%, ampicillin at 8.5%, vancomycin at 2.8%, linezolid at 3.3%, and 0.5% for daptomycin (Figure 59). High level resistance to gentamicin and streptomycin were at 12% and 15.6%, respectively. Percent resistance to penicillin and ampicillin decreased compared with resistance rates in 2021, however the changes were not statistically significant. Resistance rates to linezolid and vancomycin significantly decreased in 2022.

There were 2 confirmed linezolid resistant *E. faecalis* isolates from wound and blood samples of adult females reported by VSM. The isolates were susceptible to penicillin, ampicillin, vancomycin, gentamicin (HL), and streptomycin (HL).

Molecular characterization of linezolid resistant *Enterococcus faecalis*

E. faecalis is a highly adaptable pathogen ubiquituously found in the environment, in humans, and in animals. It is likewise an important opportunistic pathogen causing nosocomial infections with high incidence of multi-drug resistance.[1] Linezolid is a reserve antibiotic considered to be the last resort for treatment of severe infections due to vancomycin resistant *E. faecalis* (VRE)[2]. The emergence of linezolid resistance may reduce treatment of options for this important pathogen[3].

We report herein two *E. faecalis* isolates confirmed to be vancomycin susceptible but linezolid resistant. One isolate is from blood specimen of 45-year old hospitalized female (Isolate 1) and the other isolate from wound site of a 33 year old female (Isolate 2). Isolate 1 was presumptively nosocomial while isolate 2 was presumptively community acquired.

The characteristics of the 2 linezolid *E. faecalis* are shown in Table A.

Table A. Characteristics of linezolid resistant *E. faecalis* isolates

Isolate	Site	Sample Type	MLST	Linezolid MIC (µg/L)	Mechanism of linezolid resistance	Antimicrobial resistance phenotype	AMR genotype	Virulence genes
1	VSM	Blood	165	8	*optrA*	Lin	*optr*A, *erm*(B), *tet*(L), *tet*(M), *fex*A *lsa*(A)	*cad*, *cam*E, *c*CF10, *c*OB1, *ebp*A, *ebp*C, *efa*Afs, *fsr*B, *gel*E, *hyl*B, *Srt*A, *tpx*
2	VSM	Wound	16	8	*optrA*	Lin	*erm*(B), *tet*(M), *fex*A, *lsa*(A), and *lsa*(A)	*agg*, *cad*, *cam*E, *c*CF10, *c*OB1, *cyl*A, *cyl*L, *cyl*M, *ebp*A, *ebp*C, , *efa*AFs, *Elr*A, *Srt*A, *tpx*

Isolate 1 was noted to be susceptible to ampicillin, penicillin, high level gentamicin, high level streptomycin and vancomycin and intermediate against daptomycin. Isolate 2 was susceptible to tested ampicillin, penicillin, daptomycin, vancomycin, high level gentamicin, and high level streptomycin.

Mechanisms of oxazolidinone resistance and molecular characterization

The two isolates both have linezolid MICs of 8 µg/mL. The *optr*A gene is the resistance gene noted to confer the linezolid resistance on both isolates. Isolate 1 was noted to be of ST 165 and, in addition to *optr*A gene, was found to also carry the genes *erm*(B), *tet*(L), *tet*(M), *fex*A *lsa*(A) which confer resistance to erythromycin, and chloramphenicol respectively. No phenotypic test results were available for erythromycin, tetracycline and chloramphenicol as testing for these are indicated only for isolates from urine specimens. Isolate 2 was ST 16 and also carried the resistance genes *erm*(B), *tet*(M), *fex*A, *lsa*(A), and *lsa* (A) which confer resistance to erythromycin (not tested phenotypically), tetracycline (phenotypic testing indicated for urine isolates only), and chloramphenicol (phenotypic testing indicated for urine isolates only), respectively.

The *optr*A gene is the known main mechanism which confers linezolid resistance among *E. faecalis*.[4] This gene encodes an ATP-binding cassette F (ABC-F) protein which either effect antibiotic efflux or ribosomal protection.[5] While it can be located in the chromosomal DNA, it is often located on conjugative plasmids found frequently in combination with the *fex*A gene, a resistome enabling resistance against chloramphenicols. Using Mobile Element Finder[6], the *optr*A gene was identified to harbored in plasmid *rep9c*, and in Isolate 2, it was located in a transposon (*Tn558*). In both isolates, *optr*A gene was in combination with the *fex*A gene in the same transmissible genetic element.

In both isolates, virulence factors[7] associated with conjugative transfers (*came, c*CF10*, cad, c*OB1*, fsr*B), endocarditis and biofilm formation (*ebp*A*, ebp*C), and protection from oxidative stress genes (*tpx*) were found. Isolate 1 was also found to harbor the virulence factors associated with biofilm formation as well as *gel*E which is a factor which was significantly associated with infections of clinical origin.[8] In Isolate 2, *ElrA* gene associated with macrophage persistence, *agg* for production of aggregation substances, and cytolysin toxin genes (*cyl*A*, cyl*L*, cyl*M*)* were noted.

In the country, linezolid is indicated for treatment of life threatening infections of Gram positive bacteria including *Enterococcus faecalis*. Resistance against this antibiotic remains low and local efforts to preserve its effectiveness is reflected in its categorization as currently one of the restricted antibiotics listed in the Philippine National Formulary (8th ed)[9]. The steady increase in resistance against vancomycin[10] over the past 10 years warrants access and judicious use of linezolid as an alternative drug. The present report documents the presence of local linezolid resistance among *E. faecalis* that is likely due to a transmissible gene *optr*A. Although there are no evidence of continued occurrence of these resistant isolates in the hospital from where it was identified, the cases underline the importance of a real-time detection of resistance genes against linezolid, including environmental sources[11] and food animals[8], in order to elicit timely interventions.

References:

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Resistance rates of gentamicin high level were observed to be decreasing since 2020 (Figure 60) and multiple year analysis revealed that the overall changes was statistically significant (p=0.0000). On the other hand, streptomycin high level showed an increase in resistance rate in 2022 apart from its decreasing trend from 2019-2021, the changes in resistance rates for ten years was noted to be statistically significant (p=0.0003) for this antibiotic. It is likewise noted that multiple year analysis of the changes in resistance rates to vancomycin was statistically significant (p=0.0000).

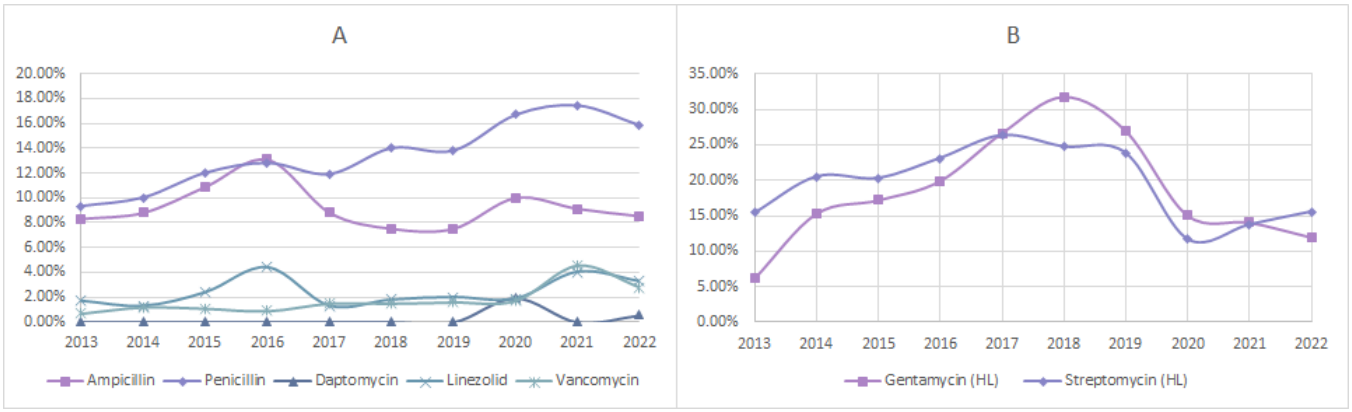


Figure 60. Yearly resistance rates of *E. faecalis*, DOH-ARSP, 2013-2022

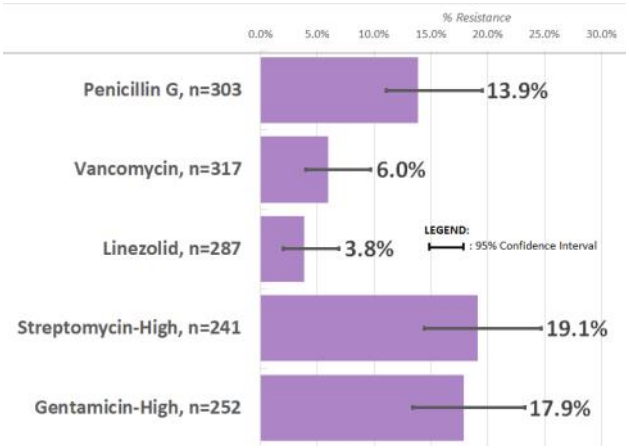


Figure 61. Percent resistance of *E. faecalis* blood isolates, DOH-ARSP, 2022

Figure 61 shows the resistance rates of *E. faecalis* isolates from blood specimens. Resistance to penicillin was at 13.9%, vancomycin at 6.0% and linezolid at 3.8%. High level resistance to streptomycin was at 19.1% and to gentamicin at 17.9%. Compared with resistance rates of *E. faecalis* isolates from all samples, resistance rates of *E. faecalis* isolates from blood are higher for all antibiotics except for penicillin.

Figure 62 shows the resistance rates of *E. faecalis* isolates collected from urine specimens. Resistance to penicillin was 19.8%, to ampicillin 11.1%, vancomycin 2.9%, and linezolid 3.1%. Gentamicin resistance (high level) was at 12.9% and streptomycin resistance (high level) was at 15.1%. Resistance to levofloxacin was at 26.8% and to nitrofurantoin 4.5%. Compared with resistance rates of *E. faecalis* isolates from all samples, resistance rates of *E. faecalis* isolates from urine are higher for all antibiotics except for linezolid and streptomycin.

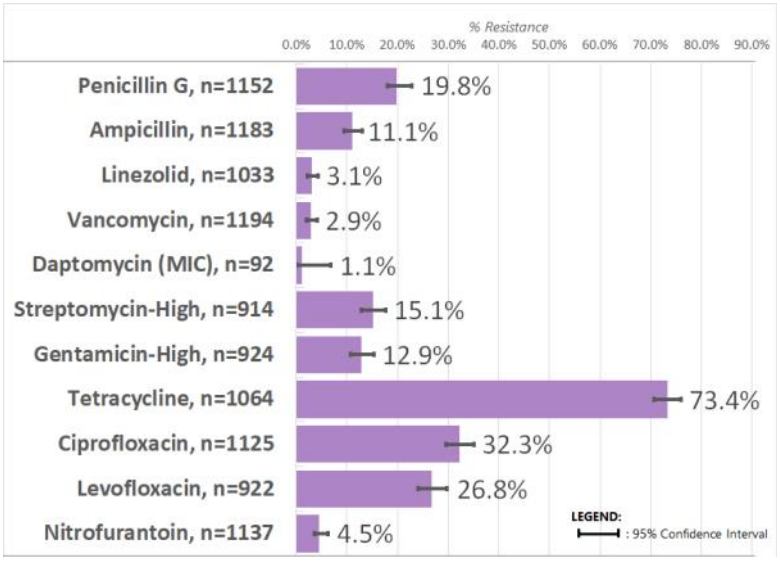


Figure 62. Percent resistance of *E. faecalis* urine isolates, DOH-ARSP, 2022

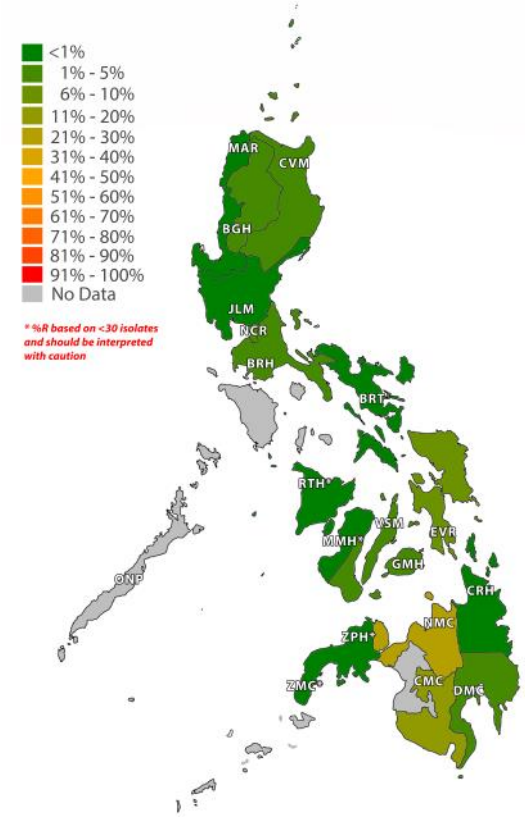


Figure 63. Geographic distribution of vancomycin-resistant *E. faecalis* in the Philippines, DOH-ARSP, 2022

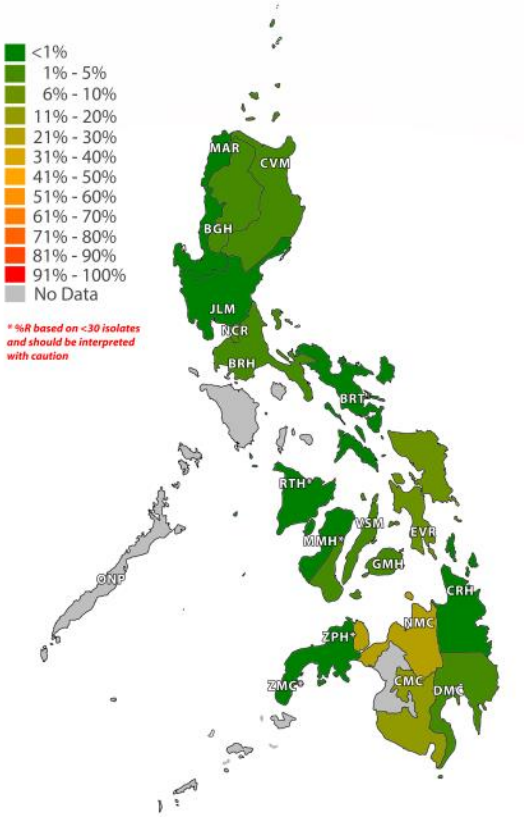


Figure 64. Geographic distribution of linezolid-resistant *E. faecalis* in the Philippines, DOH-ARSP, 2022

Figure 63 shows the geographical distribution of vancomycin-resistant *E. faecalis* isolates across the country. NMC and CMC have vancomycin resistance rates from 6-30% range. While BGH, MAR, CVM, BRH, NKI, PGH and VSM were within 1-5% range.

Figure 64 shows the geographical distribution of linezolid-resistant *E. faecalis* isolates across the country. PGH, RTM and NMC have linezolid resistance rates from 6-20% range. While BGH, MAR, CVM, PGH, VSM and DMC were within 1-10% range.

Enterococcus faecium

There were **1,448** *Enterococcus faecium* reported for 2022. Highest contributors of data for E. faecium were PGH (25.7%), DMC (22.0%) and VSM (10.0%) (Figure 65). The sentinel sites from Luzon contributed most (52.1%) of the data with 33.7% coming from the NCR.

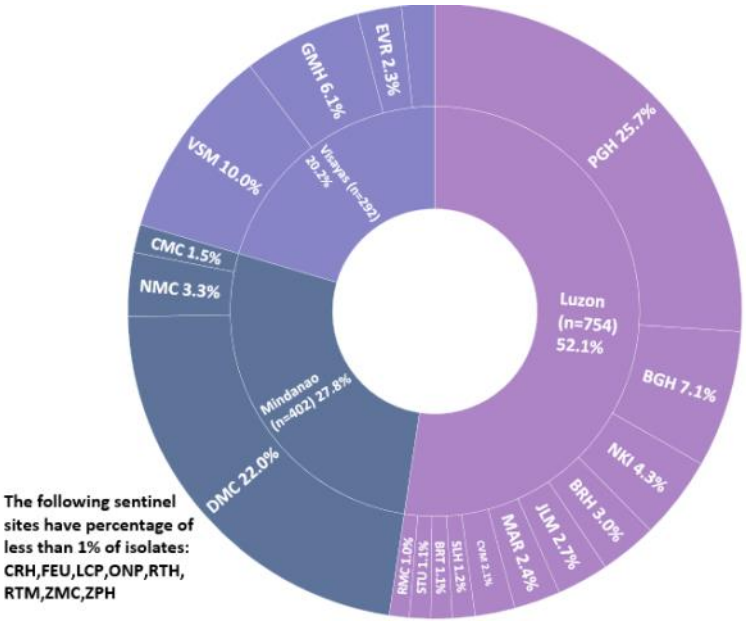


Figure 65. Isolate distribution of *E. faecium*, DOH-ARSP, 2022

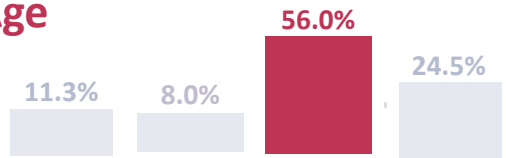
A. Sex

42.3% **Male (n=612)**

57.7% **Female (n=835)**

No data: 0.1% (n=1)

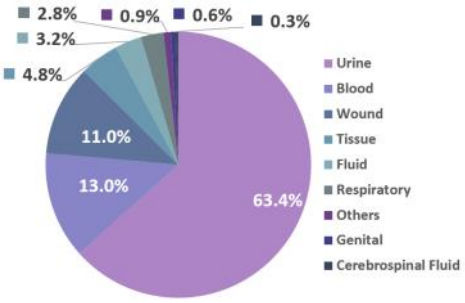
B. Age



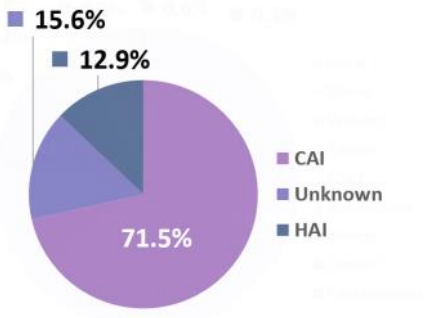
0-4 (n=164) **5-19 (n=116)** **20-64 (n=811)** **65+ (n=355)**

Unknown: 0.1% (n=2)

C. Specimen Type



D. Infection Type



E. Clinical Service

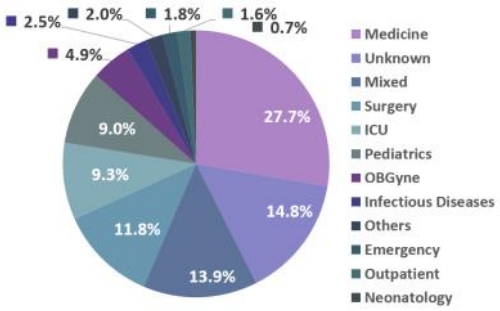


Figure 66. Patients characteristics of *E. faecium* isolates, DOH-ARSP, 2022

Most (56.0%) of the isolates were from 20-64 years old and were collected mostly (57.7%) from female patients (Figure 66). More than half (71.5%) of the isolates were from presumptive community acquired infections and most (63.4%) were from urine specimens.

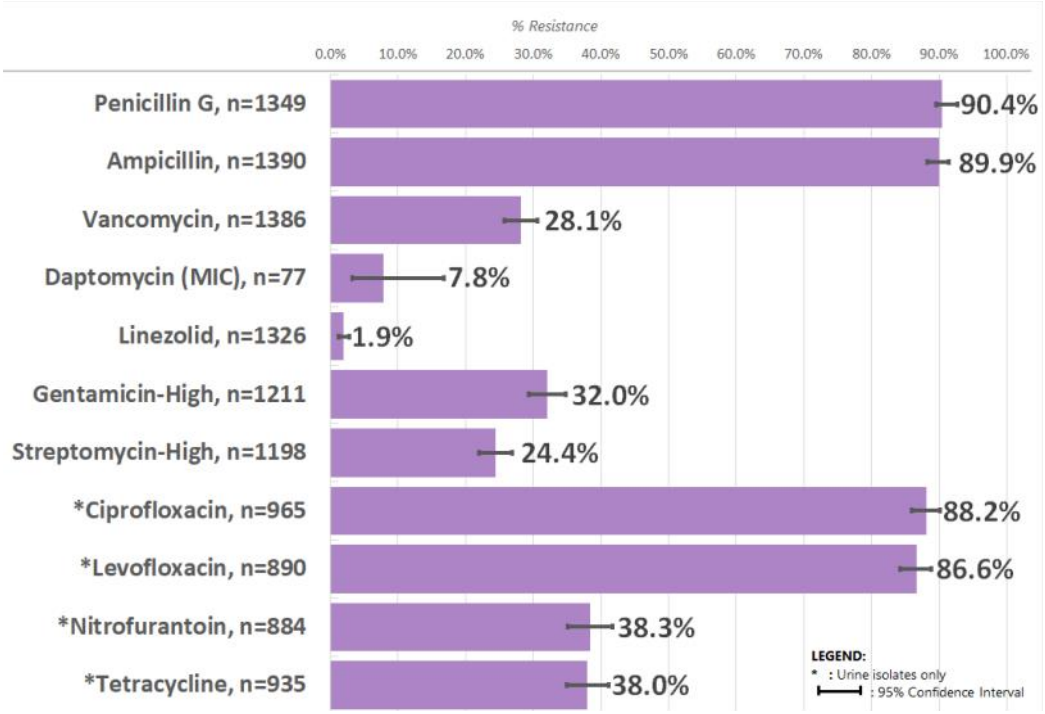


Figure 67. Resistance rates of *E. faecium* from all specimens, DOH-ARSP, 2022

Cumulative resistance rates of *E. faecium* are shown in Figure 67. Percent resistance to penicillin was high at 90.4%, ampicillin at 89.9% and levofloxacin at 86.6%. The resistance rates to vancomycin and daptomycin were both less than 30%. Resistance to linezolid was 1.9%. High level resistance to gentamicin and streptomycin were at 32% and 24.4%, respectively.

The increase in percent resistance in 2022 compared with rates in 2021 for gentamicin high level (p=0.0067) and streptomycin high level (p=0.0008) were statistically significant. Further, the decrease in percent resistance for linezolid from the previous year was also noted to be statistically significant (p=0.0000).

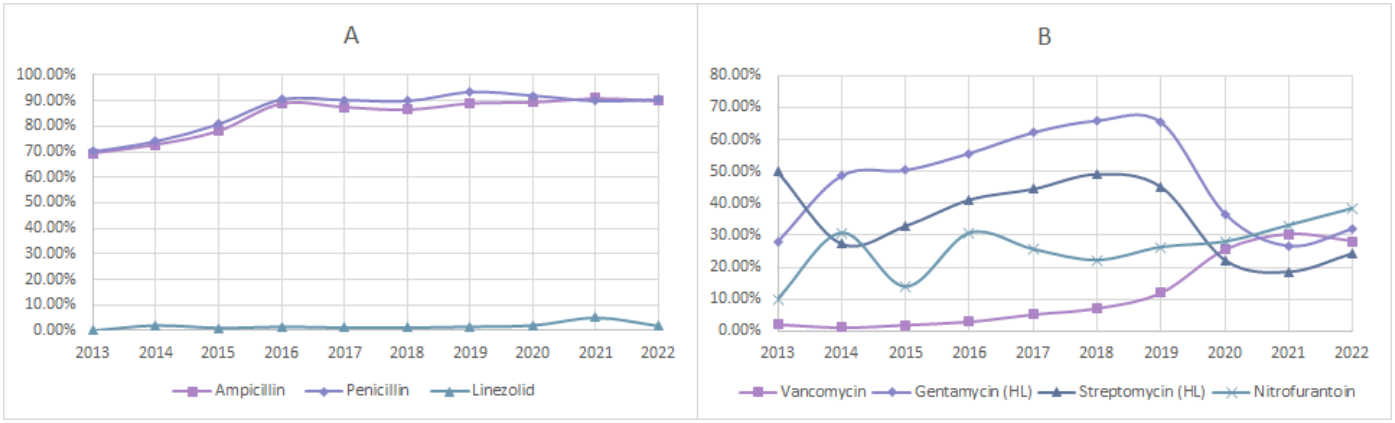


Figure 68. Yearly resistance rates of *E. faecium*, DOH-ARSP, 2013-2022

Penicillin and ampicillin resistance were at high level in the past ten years (Figure 68). The observed increased in resistance rates for vancomycin and linezolid from 2017 to 2021 was interrupted with the decrease in resistance rates for these two antibiotics in 2022, these changes over the years were both statistically significant for vancomycin (p=0.0000) and linezolid (p=0.0000). The decreasing resistance for gentamycin high level (p=0.0000) and streptomycin high level (p=0.0000) were likewise noted to be statistically significant.

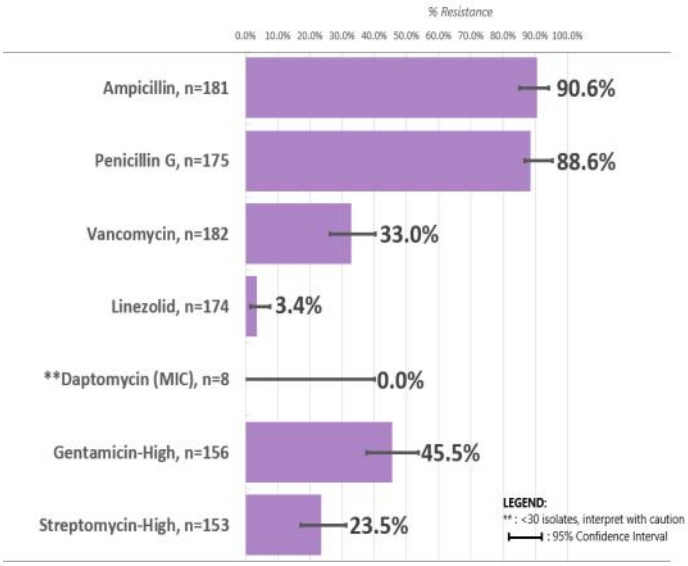


Figure 69. Percent resistance of *E. faecium* blood isolates, DOH-ARSP, 2022

Figure 69 shows the percent resistance rates of *E. faecium* isolates from blood specimens. Ampicillin and penicillin resistance were high at 90.6% and 88.6%, respectively. Percent resistance to gentamicin high level and streptomycin high level were noted at 45.5% and 23.5% respectively while linezolid resistance was at 3.4%. Compared with resistance rates of *E. faecium* isolates from all samples, resistance rates of *E. faecium* isolates from blood are higher for all antibiotics except for ampicillin and streptomycin.

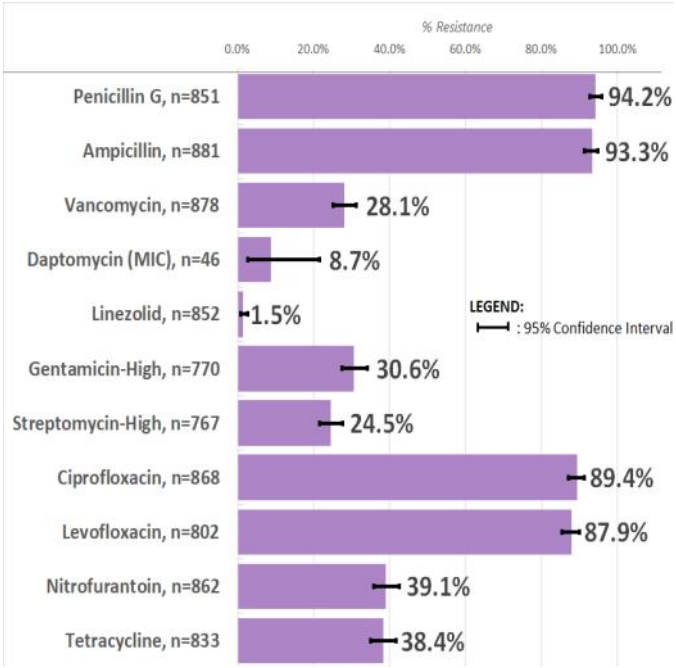


Figure 70. Percent resistance of *E. faecium* urine isolates, DOH-ARSP, 2022

Figure 70 shows the percent resistance of *E. faecium* isolates from urine specimens. Penicillin resistance was at 94.2%, ampicillin resistance at 93.3%, ciprofloxacin at 89.4% and levofloxacin at 87.9%. Resistance rates to nitrofurantoin, tetracycline and gentamicin high level were less than 40%. Resistance rates to vancomycin and streptomycin high level were all less than 30%. Resistance to daptomycin was 8.7% and linezolid 1.5%. Compared with resistance rates of *E. faecium* isolates from all samples, resistance rates of *E. faecium* isolates from urine are higher for all antibiotics except for linezolid and gentamicin (HL).

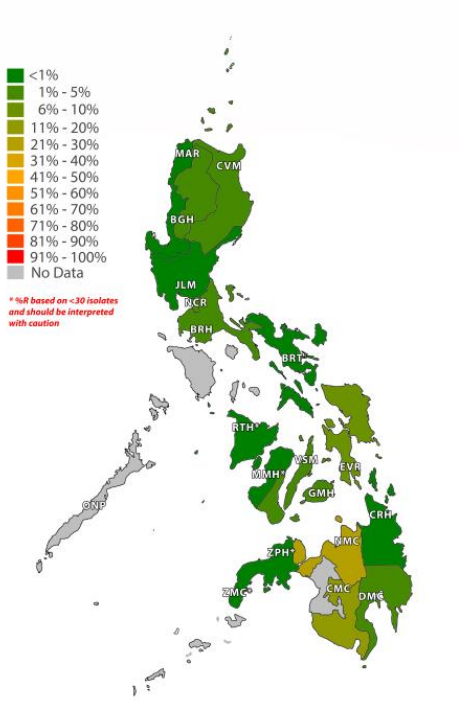


Figure 71. Geographic distribution of vancomycin-resistant *E. faecium* in the Philippines, DOH-ARSP, 2022

Figure 71 shows the geographical distribution of vancomycin-resistant *E. faecium* isolates across the country. JLM, NKI, RMC, VSM PGH and BRH have vancomycin resistance rates from 20-53% range. While SLH, GMH and EVR showed resistance rates of less than 10%.

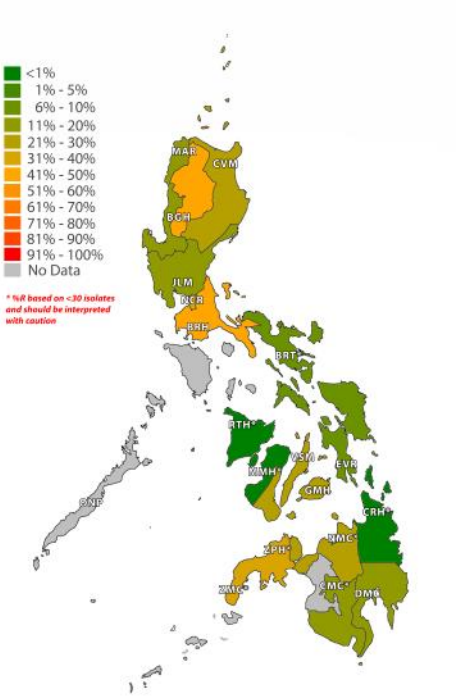


Figure 72. Geographic distribution of linezolid-resistant *E. faecium* in the Philippines, DOH-ARSP, 2022

Figure 72 shows the geographical distribution of linezolid-resistant *E. faecium* isolates across the country. NMC showed linezolid resistance rate at 8.11%. While, sentinel sites from PGH, BRH, BGH, and RMC showed resistance rates of less than 10%.

Escherichia coli

A total of **10,451** isolates of *E. coli* were reported and analyzed for 2022. PGH contributed most (15.7%) to the number of isolates followed by DMC (8.8%) and NKI (7.9%). Based on island group distribution, 59.4% were from Luzon with 29.7% from NCR sentinel sites (Figure 73).

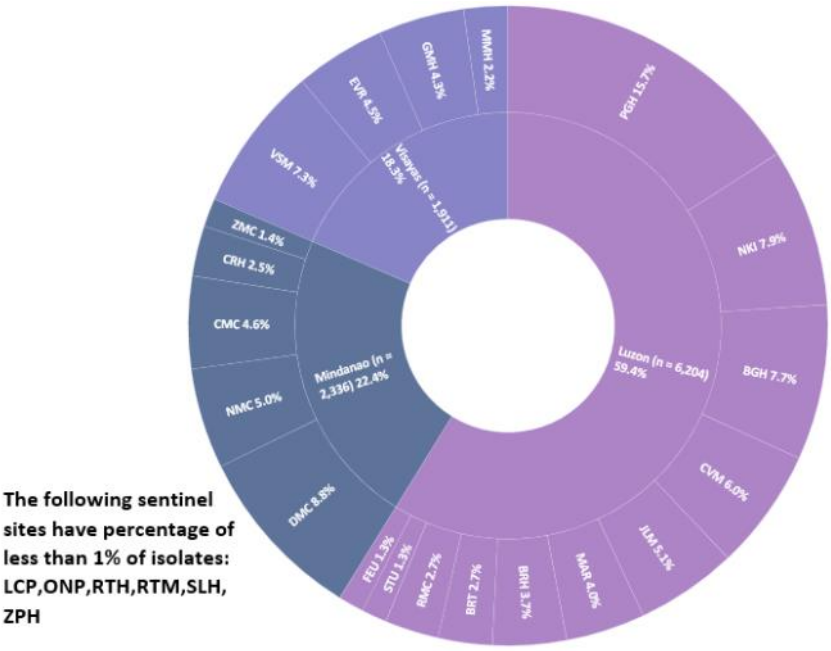


Figure 73. Isolate distribution of *E. coli*, DOH-ARSP, 2022

More than half (62.4%) of the isolates were from patients aged 20-64 years old and most (61.0%) were from female patients (Figure 74). Many (50.7%) of *E. coli* isolates were from urine specimens and most (81.7%) were presumptive community acquired infections.

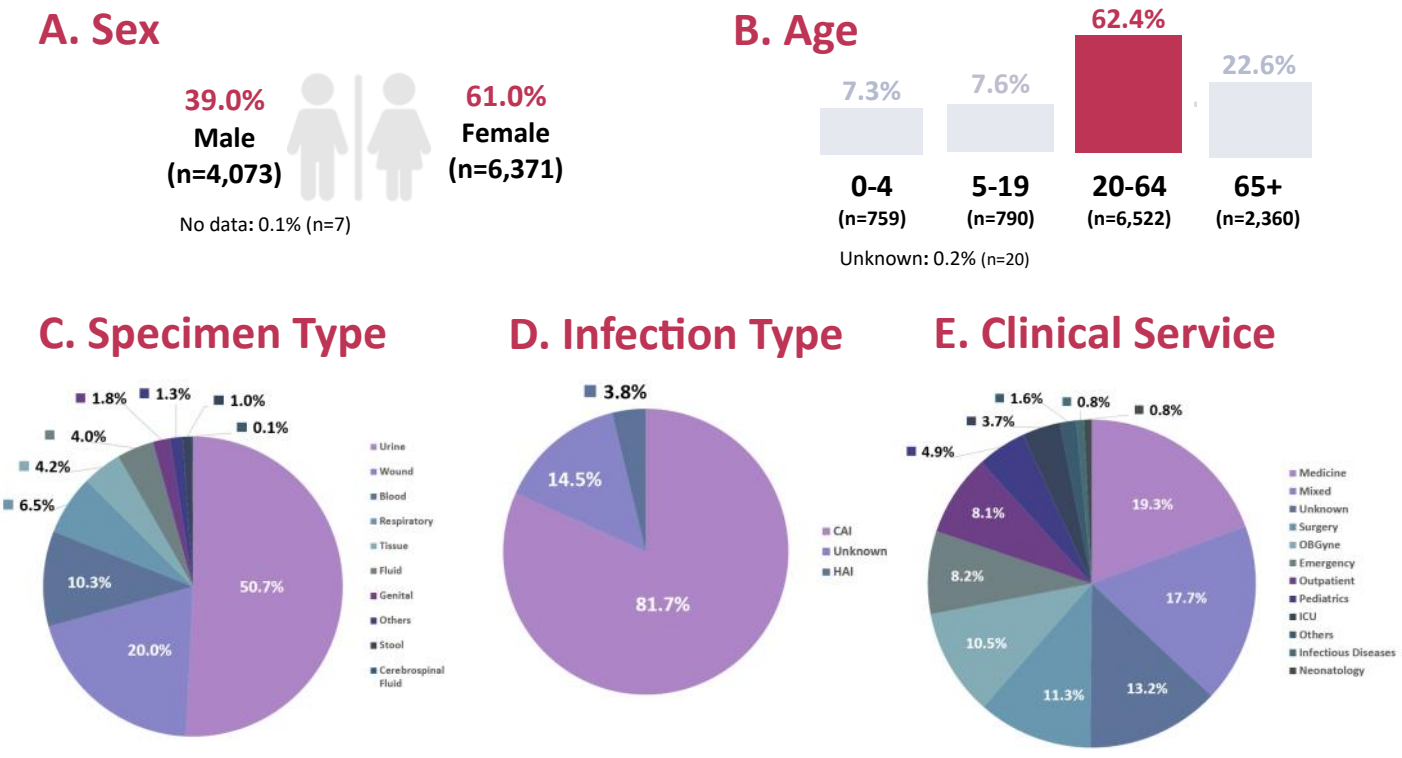


Figure 74. Patient characteristics of *E. coli* isolates, DOH-ARSP (n= 10, 451)

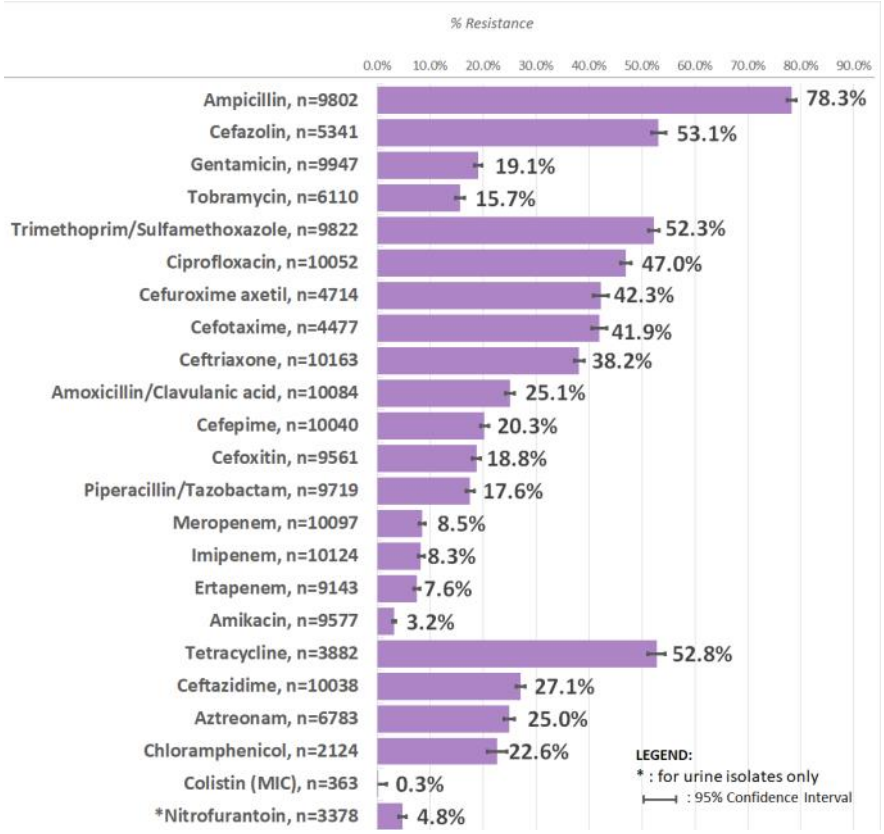


Figure 75. Resistance rates of *E. coli* from all specimens, DOH-ARSP, 2022

Cumulative resistance rates of *E. coli* for 2022 is shown in Figure 75. Resistance rates of *E. coli* to almost all of the antibiotics were above 15%. There were significant increase in the resistance rate of the following antibiotics from 2021 compared with 2022 rates: cefazolin (p=0.0000), piperacillin/ tazobactam (p = 0.0000), and ertapenem (p = 0.0328). There were also significant decrease in the resistance rate of the following antibiotics from the previous year compared with 2022 rates: tobramycin (p= 0.0000), co-trimoxazole (p= 0.0046), cefepime (p=0.0000), cefoxitin (p=0.0241), amikacin (p=0.0157), ceftazidime (p=0.0000) and aztreonam (p=0.0000). Lowest resistance rates for 2022 were amikacin (3.2%), imipenem (8.3%) and meropenem, (8.5%).

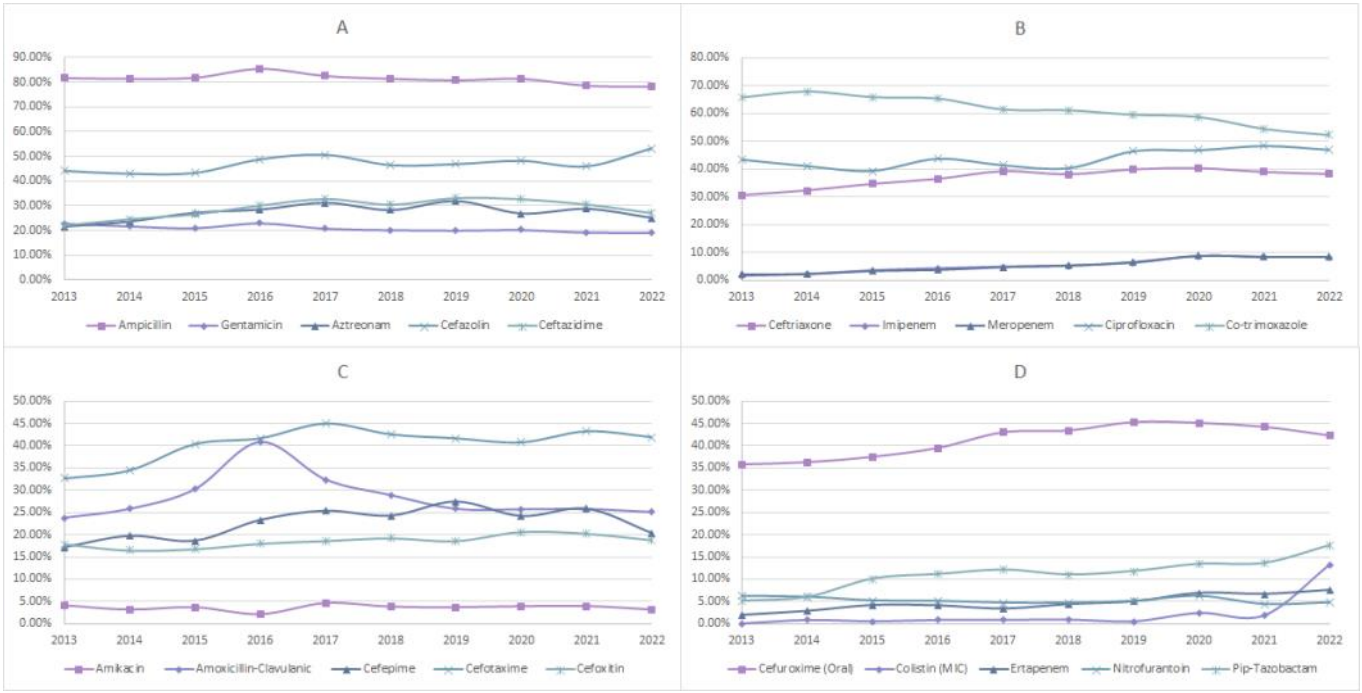


Figure 76. Yearly resistance rates of *E. coli,* DOH-ARSP, 2013-2022

The yearly resistance rate of *E. coli* is shown in Figure 76. Multiple year analysis revealed that the increase in resistance rates for the carbapenem antibiotics, ertapenem (p= 0.0000), meropenem (p=0.0000) and imipenem (p=0.0000) were all statistically significant.

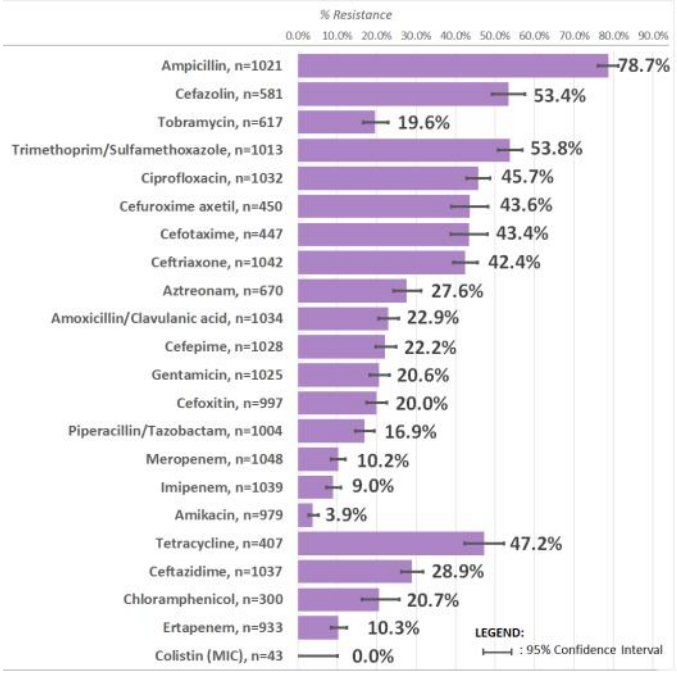
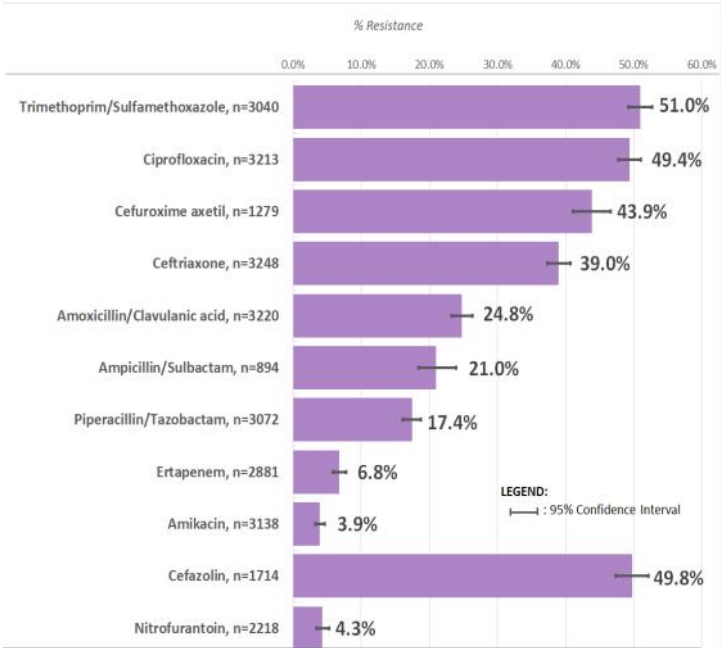


Figure 77. Percent resistance of *E. coli* blood isolates, DOH-ARSP, 2022

Figure 77 shows the resistance rates of *E. coli* isolates from blood. Resistance rates to most antibiotics were above 20% with the resistance to ampicillin at 78.7% and 22.9% for amoxicillin/clavulanic acid. Resistance to cephalosporins ranged from 20% for cefoxitin to 53.4% for cefazolin. Resistance rates to meropenem, imipenem and ertapenem were 10.2%, 9% and 10.3%, respectively and to amikacin 3.9%. Compared with over-all resistance rates, relatively higher rates were seen for most antibiotics except for piperacillin/tazobactam (16.9%), amoxicillin/clavulanic acid (22.9%), ciprofloxacin (45.7%), and tetracycline (47.2%) which had lower rates.

In-patient



Out-patient

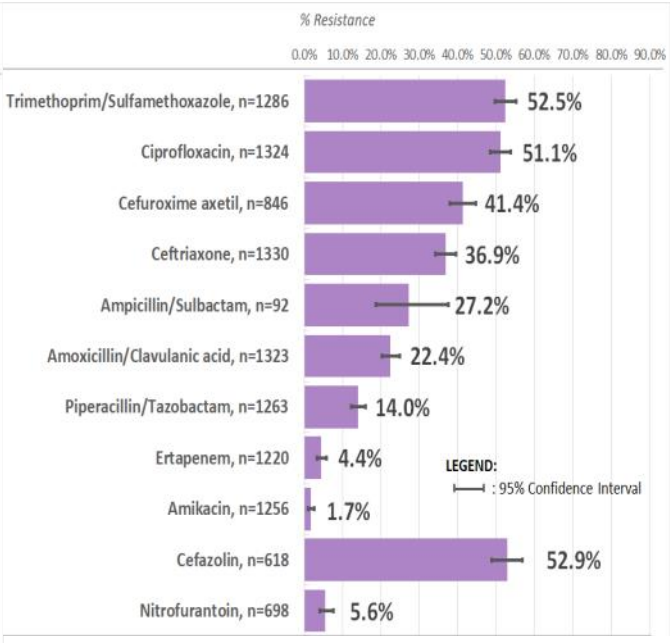


Figure 78. Percent resistance of *E. coli* isolates from in-patients and out-patients, DOH-ARSP, 2022

Resistance rates of in-patient and out-patient *E. coli* urine isolates against commonly used antibiotics are shown in Figure 78. Among urinary *E. coli* from in-patients, co-trimoxazole resistance was highest at 51% followed by cefazolin at 49.8%. Resistance to ceftriaxone, cefuroxime, ciprofloxacin, and cefazolin ranged from 35 to 50%. Resistance to carbapenem antibiotics ranged from 6.8 to 8.1%. Among urinary *E. coli* isolates from out-patients, resistance to cefazolin was highest at 52.9%, and co-trimoxazole at 52.5%.

One *E. coli* isolate from urine specimen of a 64 year-old male patient from JLM was confirmed at ARSRL to be colistin resistant for 2022. The isolate was presumptively nosocomial. The isolate was noted to be ESBL positive and showed resistance to ampicillin, aztreonam, cefazolin, cefepime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin. It was noted to be susceptible to amikacin, cefoxitin, co-trimoxazole and the three carbapenem antibiotics.

Molecular characterization of multidrug-resistant ESBL E. *coli* with colistin resistance

Colistin is a last resort antibiotic for treating multidrug-resistant bacterial infections, and the emergence of colistin-resistant bacteria is a major public health concern. Given that *E. coli* is a common bacterium that causes various infections, the detection and reporting of colistin resistance in *E. coli* isolates is essential for monitoring the spread of antibiotic resistance and developing effective treatment strategies [1].

We report here the identification of an ESBL+ colistin resistance *E.coli* from a urine specimen of a 64-year old male patient admitted to the medicine department of JLM. Antimicrobial susceptibility testing revealed resistance to multiple antibiotic subclasses, including polymyxins (colistin), penicillins (ampicillin), monobactams (aztreonam), first-generation cephalosporins (cefazolin), fourth-generation cephalosporins (cefepime), third-generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone), second-generation cephalosporins (cefuroxime), fluoroquinolones (ciprofloxacin), aminoglycosides (gentamicin, tobramycin), but susceptibility to cephamycins (cefoxitin), trimethoprim-sulfamethoxazole (co-trimoxazole), carbapenems (imipenem, meropenem, ertapenem), tetracyclines (tetracycline), and penicillin/beta-lactamase inhibitor combination (piperacillin-tazobactam).

Whole genome sequencing of the isolate revealed it to be *E. coli* sequence type 90 and of O8:H9 serotype. The isolates carried AMR genes which conferred resistance to polymyxins, penicillins, cephalosphorins, fluoroquinolones and aminoglycosides (Table A).

Table A. Antibiotic resistance genes of the ESBL+ colistin-resistant *E. coli*

Antibiotic class	Resistance	AMR gene/mutation
Polymyxins	Colistin	mcr-1.1
Penicillin	Ampicillin	*bla*TEM-1B, *bla*CTX-M-123
Monobactam	Aztreonam	-
Cephalosphorins	Cefepime, Cefotaxime, Ceftazidime, Ceftriaxone, Cefuroxime, Cefazolin	*bla*CTX-M-123
Fluoroquinolones	Ciprofloxacin	*gyr*A (p.S83L)
Aminoglycosides	Gentamicin, Tobramycin	*aac(3)-IId*

Of particular interest was the detection of mcr-1.1 which confers resistance to colistin. The mcr-1 gene was first identified in China in 2015 and has since been found in bacterial isolates worldwide. The identification of the presence of this resistance gene in a local isolate is of particular concern as colistin is considered a last-resort antibiotic for the treatment of infections caused by multidrug-resistant bacteria. [2]. Additionally, a *pmrB*_Y358N mutation was detected in this isolate. This mutation has been associated with colistin resistance in other bacteria, suggesting that it may play a role in *E. coli* resistance[3]. However, the presence of this mutation in both resistant and susceptible *E. coli* suggests that it may not be the only mechanism involved in colistin resistance in this bacterium. In 2018, two isolates of *E. coli* isolates obtained from clinical samples in the Philippines were found to harbor the mcr-1 gene[4]. The detection of *mcr*-1.1 in report is a major concern as its presence indicates a potential for the spread and dissemination of the resistance gene among local bacterial population. A spread of this resistance genes could compromise the effectiveness of colistin as a last-resort antibiotic. It is also noteworthy that the *mcr*-1 gene has been found in bacterial isolates from various sources worldwide, including humans, animals, and the environment [5]. This observation highlights the need for a One Health approach, which recognizes the interconnectedness of human, animal, and environmental health in tackling of the spread of AMR.

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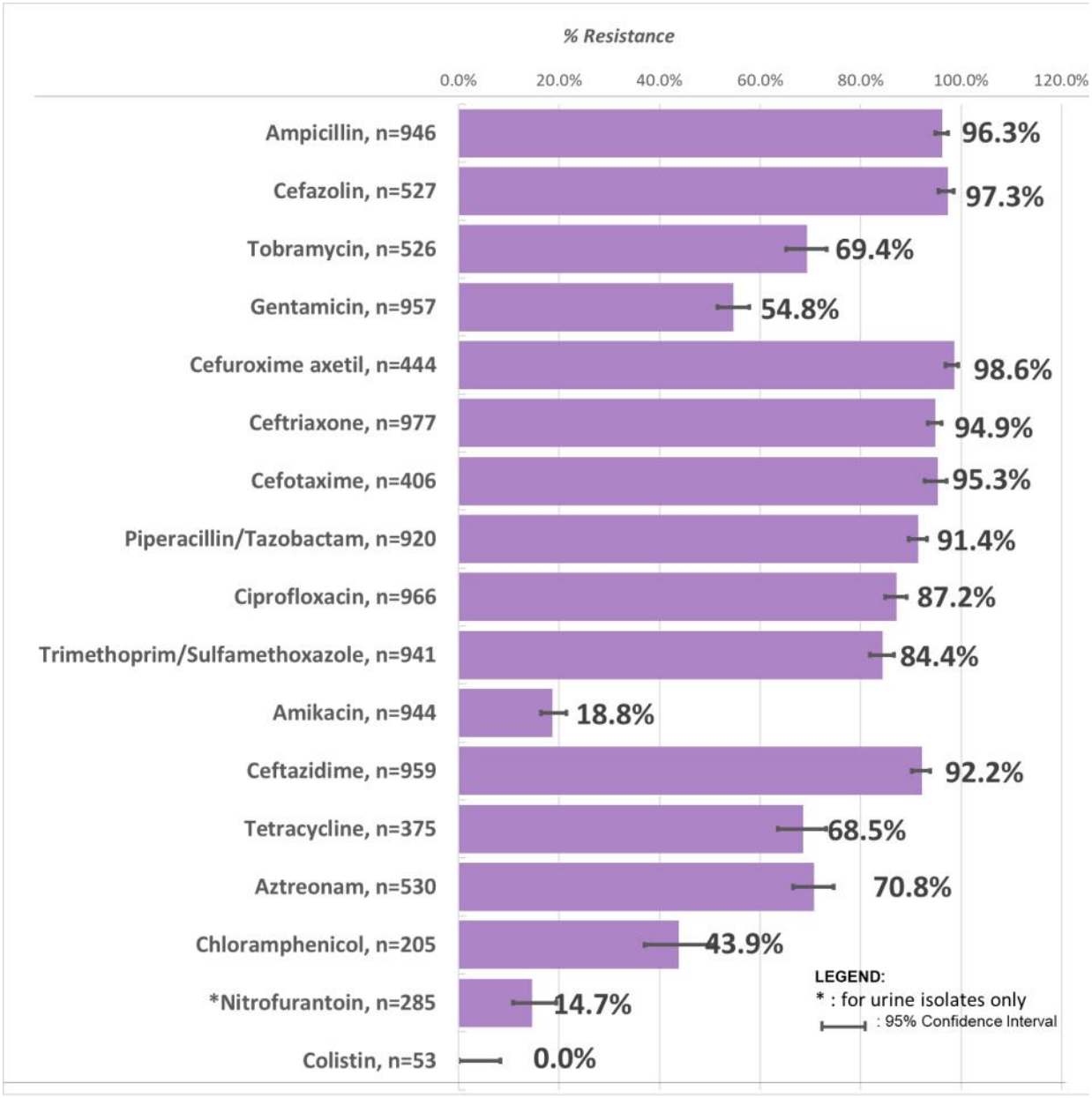


Figure 79. Percent resistance of *E. coli* (carbapenem- resistant), DOH-ARSP, 2022

Figure 79 shows the percent resistance of *E. coli* isolates found to be resistant to at least one of the carbapenems. Among these isolates, resistance to most antibiotics were high ranging from 50-90%. Cefuroxime resistance was at 98.6%, cefazolin at 97.3%, ampicillin at 96.3% and cefotaxime at 95.3%. Resistance rate for amikacin was 18.8% and no observed resistance for colistin.

From the subset of 2022 *E. coli* isolates screened phenotypically for ESBL production (n=6,078), ESBL positivity rate was at 43.8% (Figure 80).

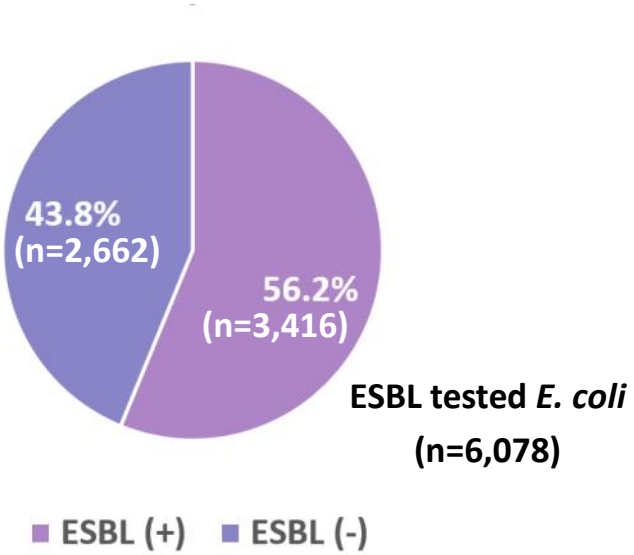


Figure 80. Percentage of ESBL positive and negative isolates among ESBL tested *E. coli* in the Philippines, DOH-ARSP, 2022

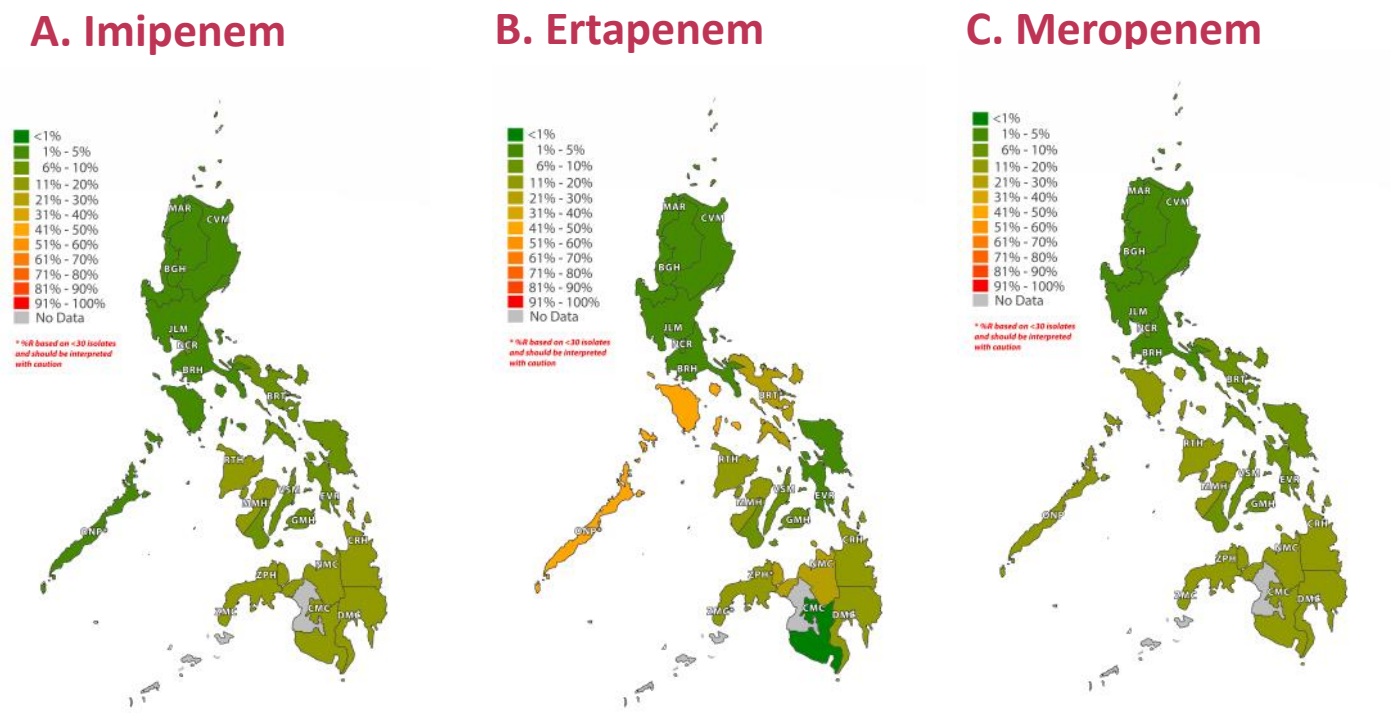


Figure 81. Resistance maps of *E. coli* for (A) imipenem, (B) ertapenem, and (C) meropenem DOH-ARSP, 2022

Figure 81 shows the carbapenem resistance rates of *E. coli* across regions represented by sentinel sites. The carbapenem resistance of *E. coli* isolates from Luzon sentinel sites mostly are below 10% while rates for most of the sentinel sites from Visayas and Mindanao were in the 11-40% range.

Klebsiella pneumoniae

A total of **12,255** *K. pneumoniae* isolates were reported in 2022. PGH (16.1%) contributed the most number of isolates followed by VSM (12.3%) and DMC (8.1%). Based on island group distribution, more than half (50.7%) were from Luzon with 23.4% coming from NCR sentinel sites, 30.5% from Visayas and 18.9% from Mindanao (Figure 82).

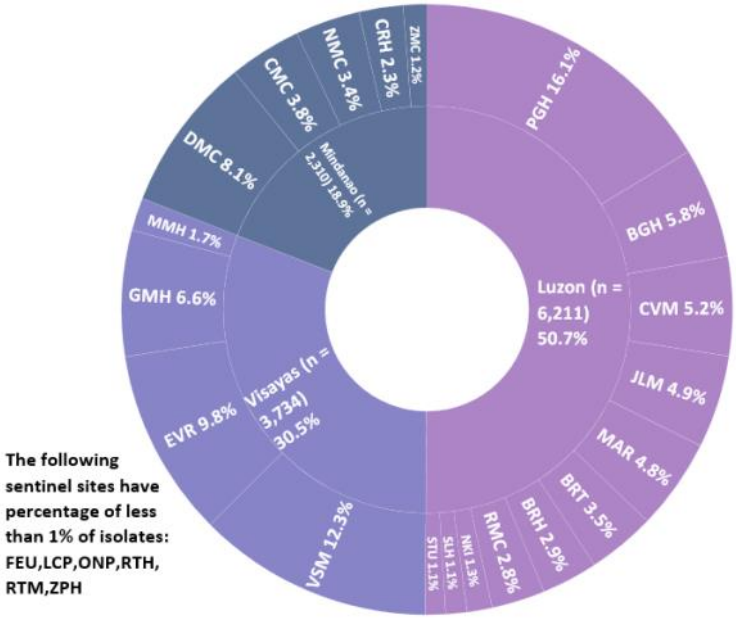


Figure 82. Isolate distribution of *K. pneumoniae*, DOH-ARSP, 2022 (n= 12,255)

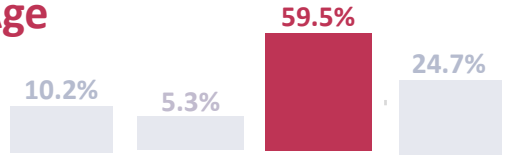
A. Sex

54.7% **Male (n=6,701)**

45.1% **Female (n=5,526)**

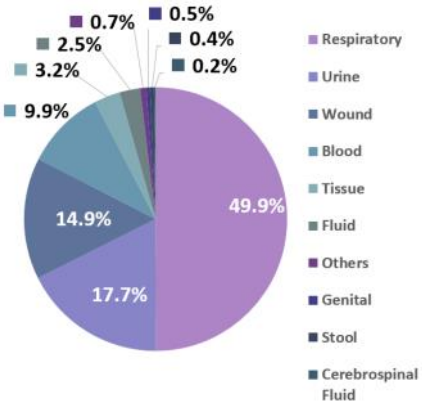
No data: 0.2% (n=28)

B. Age

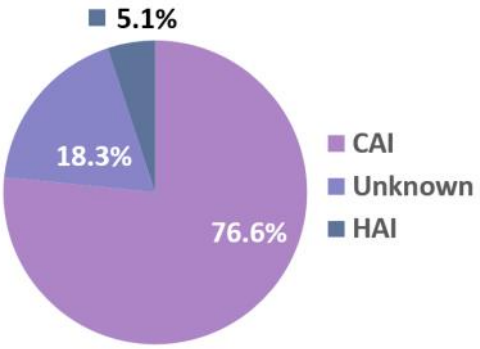


Unknown: 0.3% (n=31)

C. Specimen Type



D. Infection Type



E. Clinical Service

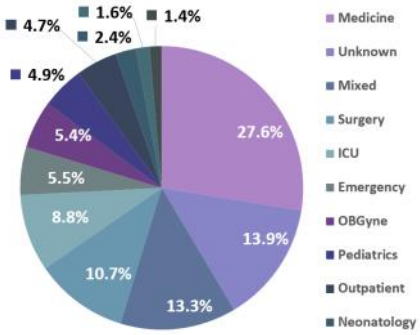


Figure 83. Patients characteristics of *K. pneumoniae* isolates, DOH-ARSP, 2022 (n= 12,255)

More than half (59.5%) of the isolates were from 20-64 years age group and most (54.7%) were from male patients. Many (49.9%) of the isolates were collected from respiratory specimens, urine (17.7%) and wound (14.9%). Most (76.6%) of the isolates were from presumptive community acquired infections (Figure 83).

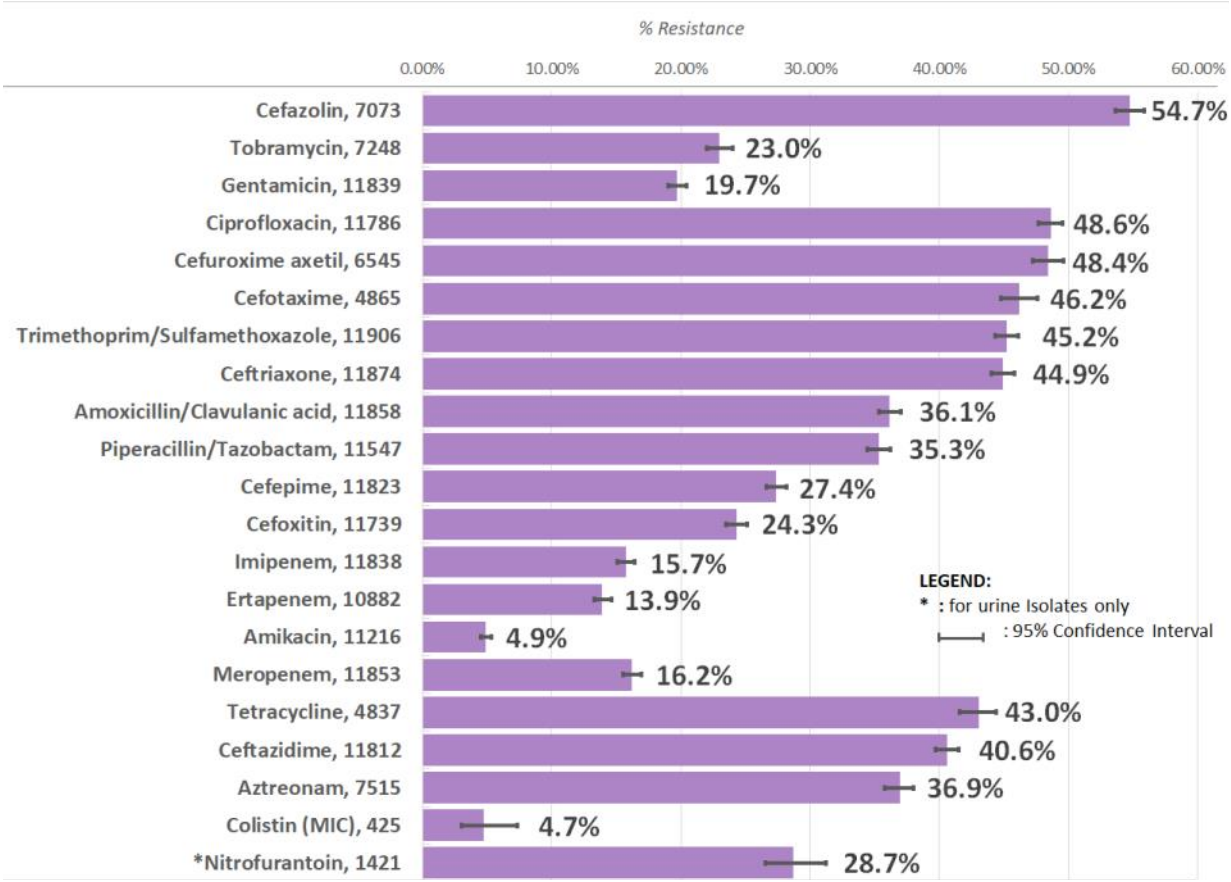


Figure 84. Resistance rates of *K. pneumoniae* from all specimens, DOH-ARSP, 2022

Cumulative resistance rates of *K. pneumoniae* from all specimens are shown in Figure 84. As known to be commonly resistant to multiple antibiotics, *K. pneumoniae* antimicrobial rates to most antibiotics were above 20%. Resistance to amoxicillin-clavulanic acid was at 36.1% and piperacillin-tazobactam at 35.3%. Resistance to meropenem, imipenem and ertapenem were 16.2%, 15.7% and 13.9% respectively. There was significant increase in the resistance rates of the following antibiotics from 2021 compared with 2022 rates: cefazolin (p= 0.0000), piperacillin/ tazobactam (p=0.0000), meropenem (p= 0.0412), imipenem (p= 0.0123), and ertapenem (p= 0.0000). There was also significant decrease in the resistance rates of the following antibiotics from previous year compared with 2022 rates: tobramycin (p = 0.0003), cefepime (p= 0.0000), amikacin (p= 0.0000) and aztreonam (p= 0.0000).

There were **20 confirmed** colistin *K. pneumoniae* isolates for 2022. Half of the isolates were from the 20-64 age group. Most (60%) of the isolates were detected from respiratory isolates. Most of the isolates were susceptible to amikacin and cefoxitin, while, these isolates were resistant to ampicillin, amoxicillin/ clavulanic acid and ciprofloxacin. Eighteen isolates were further characterized using whole genome sequencing.

Molecular characterization of multidrug-resistant *K. pneumoniae* with colistin resistance

Klebsiella pneumoniae is among the most commonly isolated bacteria among many health care institutions. These bacteria are commonly resistant to a wide range of antimicrobial agents with some isolates noted to have resistance against colistin, an antibiotic of last resort to treat infections caused by highly resistant bacteria in humans. The emergence of colistin resistance in *Klebsiella pneumoniae* and other multidrug-resistant bacteria is a significant clinical and public health concern that requires urgent attention towards the preservation of the effectiveness of this antimicrobial agent. Efforts to control the emergence of antimicrobial resistance to this antibiotic among many pathogens and multidrug-resistant bacteria are crucial to maintaining effective treatment for infectious diseases[1].

We investigated 18 colistin-resistant *Klebsiella pneumoniae* isolates collected in 2022. The specimens from which the isolates were recovered were respiratory sources (tracheal aspirate (n=5) and sputum (n=3)), wound (n=4), urine (n=4), and catheter (n=1). The patients included 8 females and 10 males with ages ranging from of 2 months to 82 years old.

Table A. Characteristics of colistin resistant *K. pneumoniae* isolates ARSP 2022

Isolate	Hospital	Type of specimen	In silico species ID	MLST	Colistin MIC (mg/L)	Mutations associated with colistin resistance	Antimicrobial resistance phenotype	Antimicrobial resistance genotype
22ARS-BGH0107	BGH	Wound	*K. pneumoniae*	464	8	*pmrB*_T157P	ESBL+, cephalosphorin, aminoglycoside, quinolone	*bla*CTX-M-15, *bla*OXA-1, *gyrA*_D87A, *gyrA*_S83Y, *parC*_S80I, *qnrB6*,aac(6')-Ib-cr5, *aac*(3)-IIe
22ARS-BGH0169	BGH	Wound	*K. pneumoniae*	147	4	*pmrB*_R256G, *crrB*_S195N	cephalosphorin, carbapenem, aminoglycoside, quinolone	*bla*CTX-M-15, *bla*OXA-1, *bla*OXA-48, *bla*NDM-1, *aac*(6')-Ib-cr5, *aph*(3')-VI, *gyrA*_S83I, *parC*_S80I, *qnrS1*
22ARS-BGH0171	BGH	Wound	*K. quasipneumoniae*	No predicted	4		ESBL+, cephalosphorin, quinolone	*bla*CTX-M-15, *qnrS1*
22ARS-BRT0038	BRT	Sputum	*K. quasipneumoniae*	367	4		ESBL+, cephalosphorin, aminoglycoside, quinolone	*bla*CTX-M-15, *aac*(6')-Ib-cr5, *qnrB6*
22ARS-CMC0019	CMC	Urine	*K. quasipneumoniae*	No predicted	4			
22ARS-CRH0035	CRH	Tracheal aspirate	*K. quasipneumoniae*	No predicted	8		ESBL+, cephalosphorin, quinolone	*bla*CTX-M-15, *qnrS1*
22ARS-CVM0040	CVM	Catheter	*K. quasipneumoniae*	1822	4		cephalosphorin, carbapenem, aminoglycoside, quinolone	*bla*CTX-M-15, *bla*OXA-1, *bla*NDM-1, *aac*(6')-Ib-cr5, *qnrB1*
22ARS-EVR0008	EVR	Urine	*K. quasipneumoniae*	1525	32		ESBL+, cephalosphorin, aminoglycoside, quinolone	*bla*CTX-M-15, *aac*(6')-Ib-cr5, *aac*(3)-IId, *qnrB6*
22ARS-EVR0019	EVR	Sputum	*K. pneumoniae*	45	8	*pmrB*_R256G	ESBL+, cephalosphorin, aminoglycoside, quinolone	*bla*CTX-M-15, *aac*(6')-Ib-cr5, *aac*(3)-IId, *qnrS1*
22ARS-EVR0108	EVR	Tracheal aspirate	*K. pneumoniae*	273	32	*pmrB*_R256G	cephalosphorin, carbapenem, aminoglycoside, quinolone	*bla*CTX-M-3, *bla*KPC-2, *aac*(3)-IId, *aac*(6')-Ib-cr5, *gyrA*_S83I, *parC*_S80I, *qnrS1*
22ARS-EVR0125	EVR	Tracheal aspirate	*K. pneumoniae*	273	16	*pmrB*_R256G	cephalosphorin, carbapenem, aminoglycoside, quinolone	*bla*CTX-M-3, *bla*KPC-2, *aac*(6')-Ib-cr5, *gyrA*_S83I, *parC*_S80I, *qnrS1*
22ARS-EVR0127	EVR	Wound	*K. pneumoniae*	273	8	*pmrB*_R256G	cephalosphorin, carbapenem, aminoglycoside, quinolone	*bla*CTX-M-3, *bla*KPC-2, *aac*(6')-Ib-cr5, *gyrA*_S83I, *parC*_S80I, *qnrS1*
22ARS-JLM0018	JLM	Tracheal aspirate	*K. pneumoniae*	86	4			
22ARS-JLM0037	JLM	Urine	*K. pneumoniae*	5297	8		ESBL+, cephalosphorin, quinolone	*bla*CTX-M-15, *aac*(6')-Ib-cr5, *qnrB1*
22ARS-MAR0008	MAR	Urine	*K. variicola*	697	4			
22ARS-SLH0009	SLH	Wound	*K. variicola*	695	32			
22ARS-VSM0078	VSM	Sputum	*K. variicola*	697	8			
22ARS-VSM0173	VSM	Tracheal aspirate	*K. quasipneumoniae*	2133	8			

Bacterial species identification and typing

Whole-genome sequencing (WGS) of the 18 colistin-resistant *Klebsiella pneumoniae* isolates enabled the *in silico* species identification of 8 *Klebsiella pneumoniae*, 7 *Klebsiella quasipneumoniae* and 3 *Klebsiella variicola* strains. These *Klebsiella* species are closely related, and their differentiation in genetic terms is based on multiple factors. They can be genetically classified based on their core genome, accessory genome, virulence factors, and antibiotic resistance genes, with *Klebsiella pneumoniae* showing higher levels of antibiotic resistance and virulence factors. *Klebsiella variicola*, on the other hand, has a smaller core genome and a larger accessory genome, suggesting greater variability in genetic content. These information can be valuable in the development of effective diagnostic, treatment, and preventive strategies for infections caused by these organisms. [2]. The inability of conventional laboratory techniques to definitively differentiate the species of *Klebsiella* may be due to the overlapping biochemical phenotypes and lack of a stable classifier among these closely related species [3].

Multilocus sequencing typing (MLST) is a molecular typing method which makes use of the nucleotide sequence variations in several housekeeping genes to identify and differentiate between different strains of bacteria [4]. In this report, there were 13 unique sequence types (STs) identified through MLST. For *K. pneumoniae*, the sequence types identified were ST 273, 147, 45, 464, 5297, and 86 (Table B). For *K. quasipneumoniae*, the STs were 1525, 1822, 2133, and 367, and three novel STs. Additionally, the analysis identified sequence types 697 (n=2) and 695 (n=1) for *K. variicola*.

Table B. In silico species identification and sequence types

Bacterial identification and ST	Number
Klebsiella pneumoniae	**8**
ST273	3
ST147	1
ST45	1
ST464	1
ST5297	1
ST86	1
Klebsiella quasipneumoniae	**7**
Novel	3
ST1525	1
ST1822	1
ST2133	1
ST367	1
Klebsiella variicola	**3**
ST697	2
ST695	1

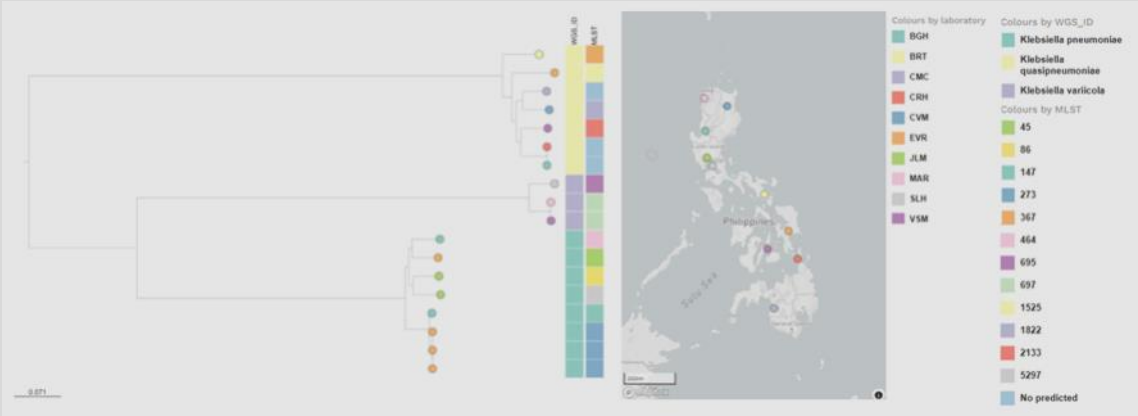


Figure A. Phylogenetic tree of colistin resistant *K. pneumoniae* isolates

Colistin resistance

The AMR gene prediction analysis identified mutations in the *pmrB* gene in six out of eight *K. pneumoniae* isolates and a mutation in the *crrB* gene in one other isolate. The mobile colistin resistant (mcr) gene was not detect in any of the isolates. Mutations in the *pmrB* gene, which regulates the biosynthesis of lipopolysaccharides in *Klebsiella pneumoniae*, have been linked to resistance to polymyxins due to alterations in the lipid A component of the bacterial cell wall resulting in decreased binding affinity of colistin[5]. The occurrence of a point mutation in *pmrB*(T157P) has been shown in previous studies to result in an increase in the expression of *pmrCAB* and *pmrHFIJKLM* operons, which subsequently lead to the development of resistance to polymyxins among isolates of *Klebsiella pneumoniae*[6]. In the present report, the *pmrB*(T157P) mutation was identified in one strain (22ARS-BGH0107) while the *pmrB*(R256G) mutation was found in five strains. The presence of the *pmrB* mutation in R256G, however, is not definitively known to confer resistance to colistin as studies have shown that it can be found in both colistin resistant and susceptible *Klebsiella pneumoniae* isolates[7]. One isolate which carried the *pmrB*(R256G) (22ARS-BGH0169) was noted to also carry *crrB*(S195N), a mutation due to a novel individual amino acid substitution previously identified to also confer colistin resistance[8]. Thus in this report, colistin resistance appears to be conferred by *pmrB*(T157P) and *crrB*(S195N) in two out of the 8 *Klebsiella pneumoniae* isolates while it is possible that *pmrB*(R256G) conferred colistin resistance to 4 out of the 8 *Klebsiella pneumoniae* isolates. Our analysis, however, did not show presence of known chromosomal mutation targets for colistin resistance in 2 *Klebsiella pneumoniae* isolates, 7 *Klebsiella quasipneumoniae* isolates and 3 *Klebsiella variicola* isolates. The noted absence of known specific genetic alterations conferring colistin resistance among these isolates suggests the possibility of the presence of alternative mechanisms for resistance to colistin among these isolates. It is acknowledged that, although mutations in the mgrB, pmrCAB, and phoPQ genes are commonly associated with resistance, other unidentified mechanisms may also contribute to this phenotype, including an overexpression of capsule polysaccharides in some isolates[9]. Other factors and additional tests, along with clinical and epidemiological context, should be considered to determine the isolate's susceptibility to colistin and to make treatment decisions for infected patients.

Table C. *pmrB* distribution of ST273, ST147, ST45 and ST464

pmrB distribution	ST273	ST147	ST45	ST464
***pmrB*(R256G)**				
BGH	-	1	-	-
EVR	3	-	1	-
***pmrB*(T157P)**				
BGH				1

Colistin resistant *K. pneumoniae* ST273 cluster

Phylogenetic analysis showed that the 18 colistin resistant *Klebsiella pneumoniae* isolates collected in 2022 were genetically diverse. However, a cluster of three presumptive nosocomial *Klebsiella pneumoniae* ST273 isolates from elderly female patients in the medical ICU of EVR was observed (Figure A). The isolates were collected within a range of 39 days, with two from tracheal aspirate and one from a wound. Susceptibility testing showed that all the three isolates were resistant to cephalosporins, carbapenems, beta-lactam+inhibitor, and quinolones, but were susceptible to aminoglycosides, such as amikacin. The isolates had *pmrB*(R256G) mutation, *bla*CTX-M-3, and *bla*KPC-2 genes as well as other antimicrobial resistance genes conferring resistance to quinolones and co-trimoxazole. The isolates had a minimal difference of 0-1 single nucleotide polymorphism (SNP), suggesting the possibility of intra-hospital transmission. A previous study investigated the emergence of ST273 carbapenem-resistant *Klebsiella pneumoniae* in two Manila hospitals reporting the first cases of *bla*NDM pathogen in the Philippines[10] which highlights the need for ongoing surveillance to monitor the spread of this strain.

These findings are significant as it suggests the emergence of nosocomial infections caused by highly resistant *K. pneumoniae* strains with potential for rapid intra-hospital transmission. The co-occurrence of resistance to colistin, carbapenems, and other broad-spectrum antibiotics, as well as the findings from the whole-genome sequencing analysis, underscores the significance of this observation. This report also emphasizes the importance of ongoing surveillance of isolates with unusual susceptibility patterns, as well as the need for effective collaboration between the reference laboratory and the sentinel sites during investigations.

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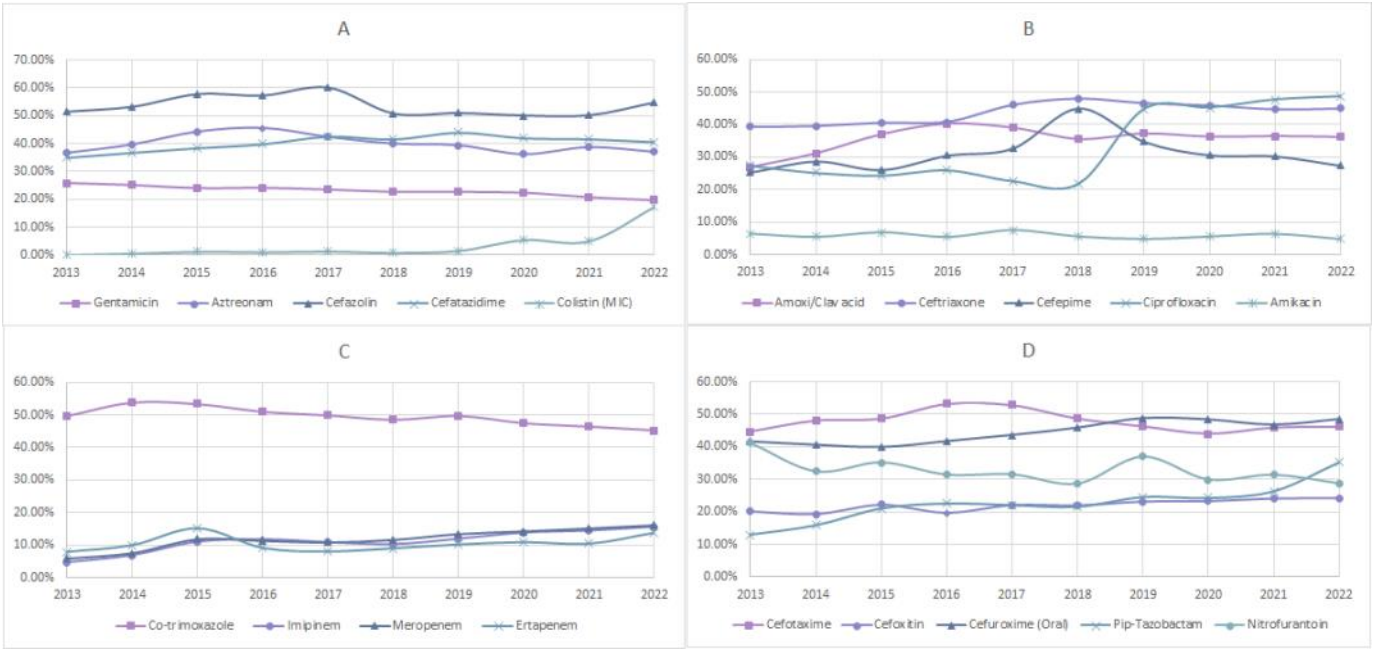


Figure 85. Yearly resistance rates of *K. pneumoniae*, DOH-ARSP, 2022

Figure 85 shows the yearly resistance of *K. pneumoniae*. Cefotaxime, cefoxitin, ceftazidime and cefuroxime showed relatively constant rates over the years. The multiple year analyses showed that the changes in the resistance rates over the years for carbapenem antibiotics, meropenem (p= 0.0000), ertapenem (p= 0.0000), meropenem (0.0000), and ciprofloxacin (p= 0.0000) were all statistically significant.

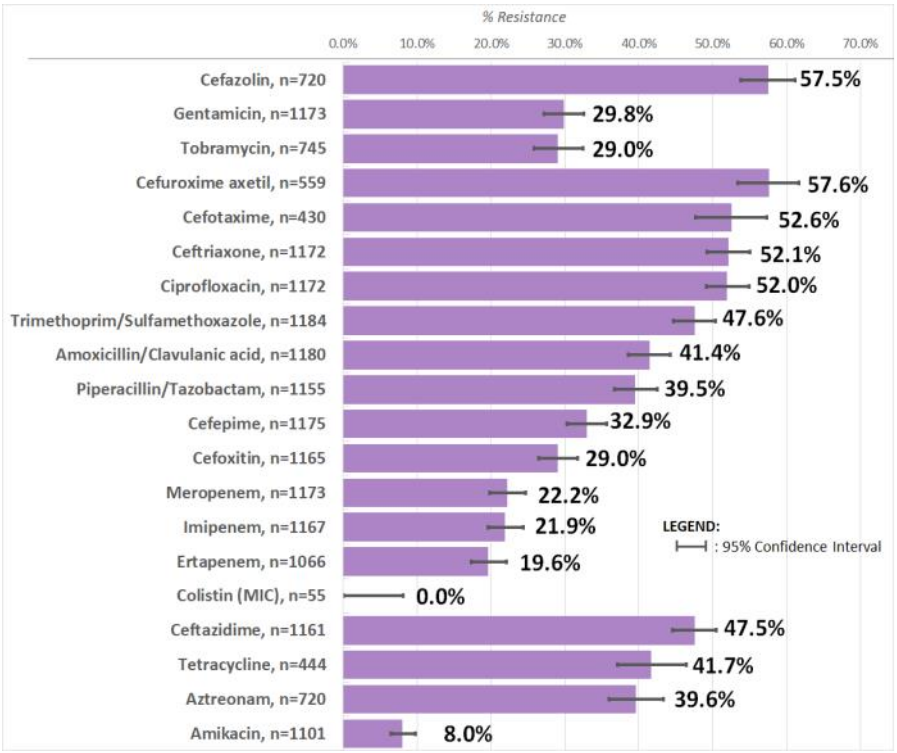


Figure 86. Percent resistance of *K. pneumoniae* blood isolates, DOH-ARSP, 2022

Figure 86 shows the percent resistance rates of *K. pneumoniae* isolates from blood specimens. Resistance rates for most antibiotics were above 20%. Resistance to amoxicillin/ clavulanic acid was at 41.4% and 39.5% for piperacillin/tazobactam. Resistance to meropenem, imipenem and ertapenem were 22.2%, 21.9% and 19.6% respectively. No colistin resistance was observed among *K. pneumoniae* blood isolates. Compared with over-all resistance rates, relatively higher rates were seen for *K. pneumoniae* blood isolates for most antibiotics except for tetracycline (41.7%).

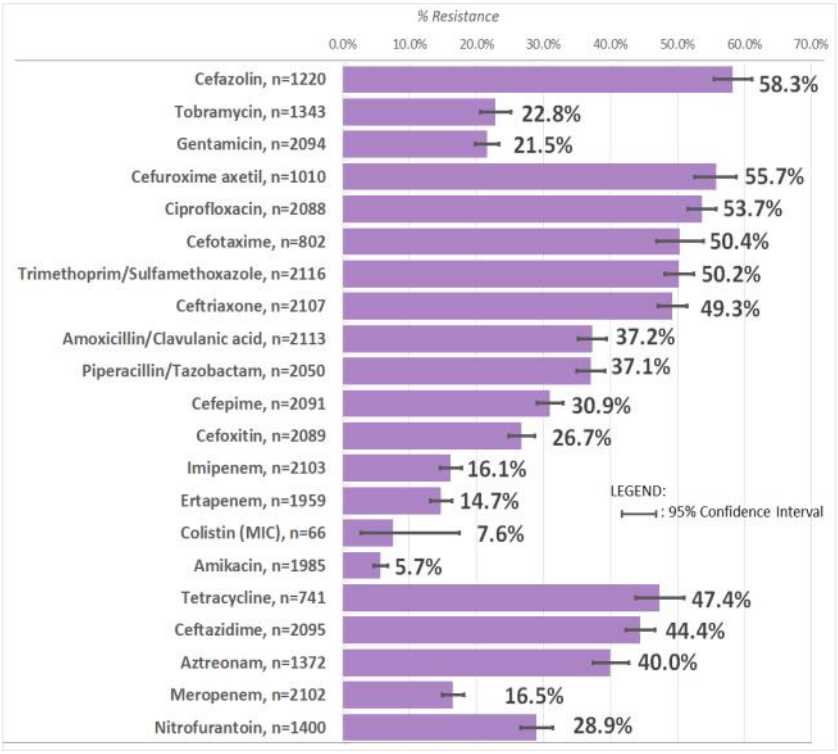


Figure 87. Percent resistance of *K. pneumoniae* urine isolates, DOH-ARSP, 2022

Figure 87 shows the percent resistance of *K. pneumoniae* isolates from urine specimens. Resistance to combination antibiotics amoxicillin/clavulanic acid and piperacillin/tazobactam were at 37.2% and 37.1% respectively. Resistance rates to carbapenem antibiotics ranged from 14-16.5%. Compared with over-all resistance rates from all samples, relatively higher rates were seen for *K. pneumoniae* urine isolates for most antibiotics except for tetracycline (47.4%).

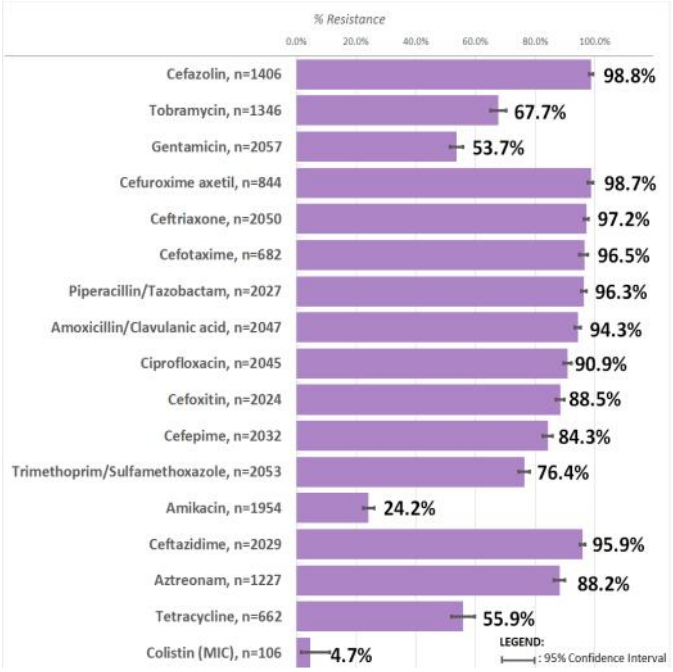


Figure 88. Percent resistance of *K. pneumoniae* (carbapenem-resistant) isolates, DOH-ARSP , 2022

Figure 88 shows the percent resistance of *K. pneumoniae* isolates found to be resistant to at least one of carbapenems. Among these isolates, resistance rates to most antibiotics were high ranging from 59-90%. Cefazolin resistance was at 98.8%, tobramycin at 67.7%, gentamicin at 53.7% and ceftriaxone at 97.2%. Resistance to amikacin and colistin were relatively low at 24.2% and 4.7% respectively.

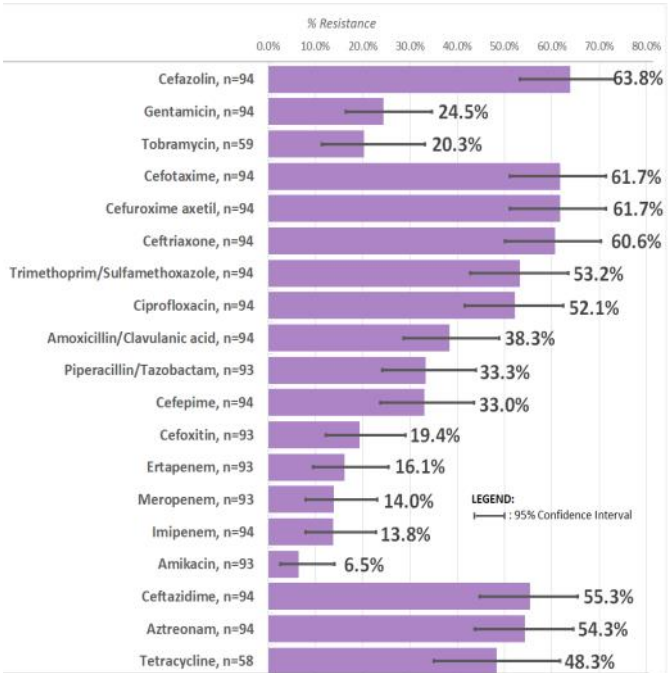
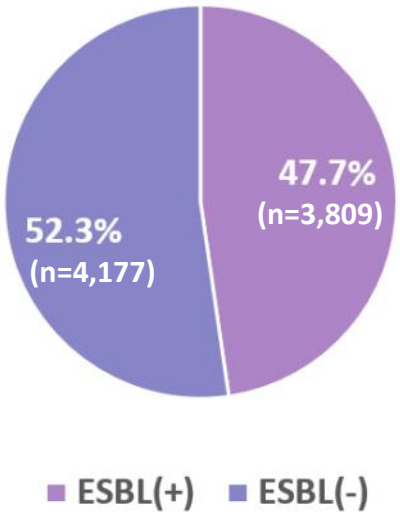


Figure 89. Percent resistance *of K. pneumoniae* (colistin-resistant) isolates, DOH-ARSP, 2022

There were **94 confirmed** colistin-resistant *K. pneumoniae* isolates analyzed from 2021 to 2022. Percent resistance of these isolates are shown in Figure 89. Resistance to most antibiotics were more than 20%. Relatively lower resistance for this group of isolates was for amikacin (6.5%) and carbapenem antibiotics, meropenem (14.0%), imipenem (13.8%) and ertapenem (16.1%) (Figure 89).

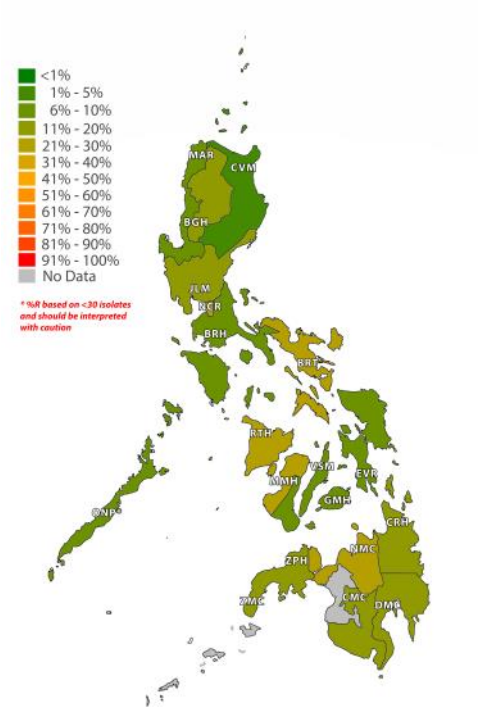
From the subset of 2022 *K. pneumoniae* isolates screened phenotypically for ESBL production,(n=7,986) ESBL positivity rate was at 47.70% (Figure 90).



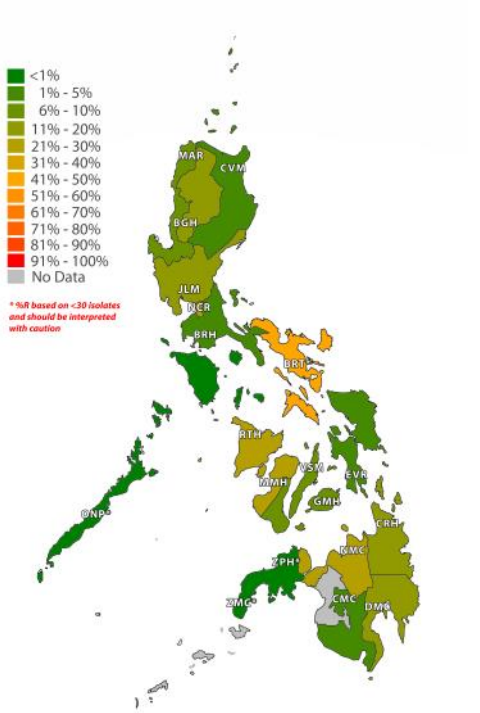
ESBL tested *K. pneumoniae* (n=7,986)

Figure 90. Percentage of ESBL positive and negative isolates among ESBL tested *K. pneumoniae* in the Philippines, DOH-ARSP, 2022

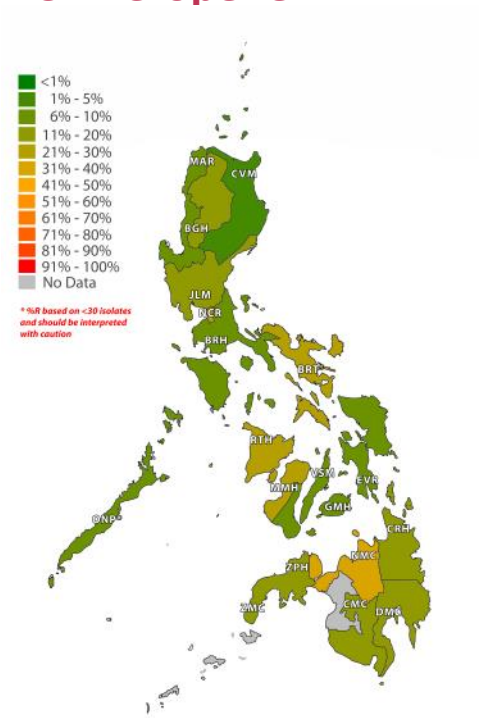
A. Imipenem



B. Ertapenem



C. Meropenem



D. Colistin

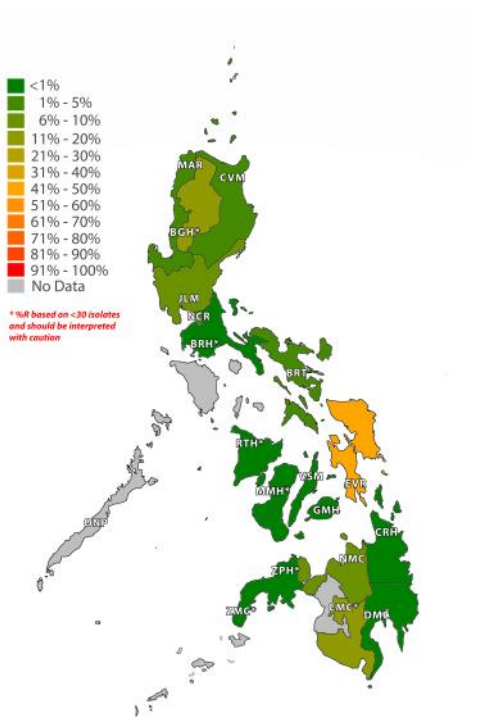


Figure 91. Resistance maps of *K. pneumoniae* for (A) imipenem, (B) ertapenem, (C) meropenem and (D) colistin , DOH-ARSP, 2022

Figure 91 shows the carbapenem and colistin resistance rates of *K. pneumoniae* across different regions as represented by the sentinel sites. The carbapenem resistance of *K. pneumoniae* isolates from Luzon sentinel sites ranged from 1-20%. The rates for most of the sentinel sites from the Visayas ranged from 11-50% while the rates for Mindanao sentinel sites were mostly in the 21-40%. Confirmed colistin resistant isolates have been reported from almost all of the sentinel sites except for RMC and ONP.

Pseudomonas aeruginosa

A total of **7,561** *Pseudomonas aeruginosa* isolates for 2022. Large contributors of *P. aeruginosa* data were PGH (14.2%), DMC (12.3%) and VSM (10.7%). Sentinel sites from Luzon contributed 56.2% of the isolates, 23.6% from Visayas and 20.2% from Mindanao (Figure 92).

Figure 92. Isolate distribution of *P. aeruginosa*, DOH-ARSP, 2022 (n= 7,561)

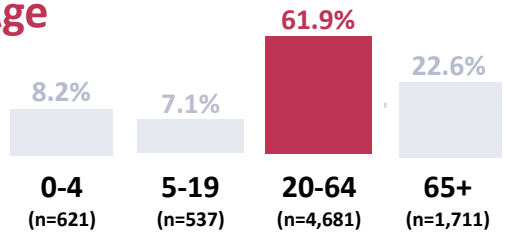
A. Sex

56.9% **Male** **(n=4,304)**

42.9% **Female** **(n=3,247)**

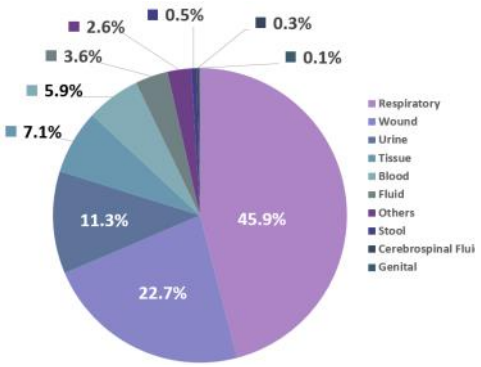
No data: 0.1% (n=10)

B. Age

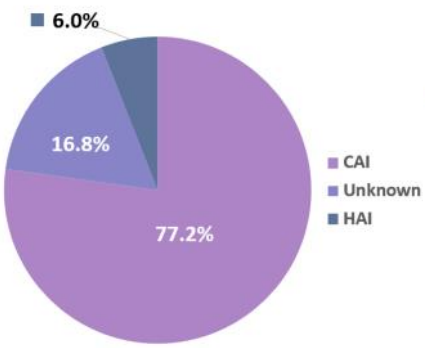


Unknown: 0.1% (n=11)

C. Specimen Type



D. Infection Type



E. Hospital Department

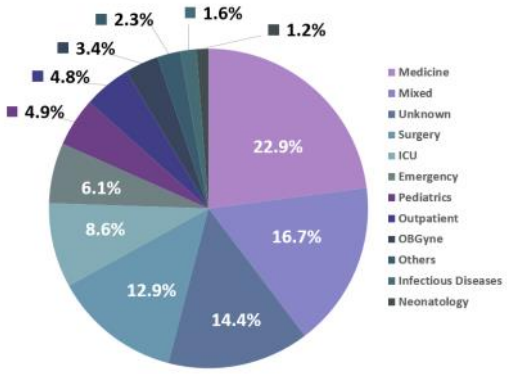


Figure 93. Patients characteristics of *P. aeruginosa* isolates, DOH-ARSP, 2022 (n=7,561)

Most (61.9%) of the isolates were from patients within 20-64 years old and most (56.9%) were from male patients. Most (45.9%) of the *P. aeruginosa* isolates were from respiratory specimens followed by wound (22.7%) and urine (11.3%). Most (77.2%) cases were presumptive community acquired infections (Figure 93).

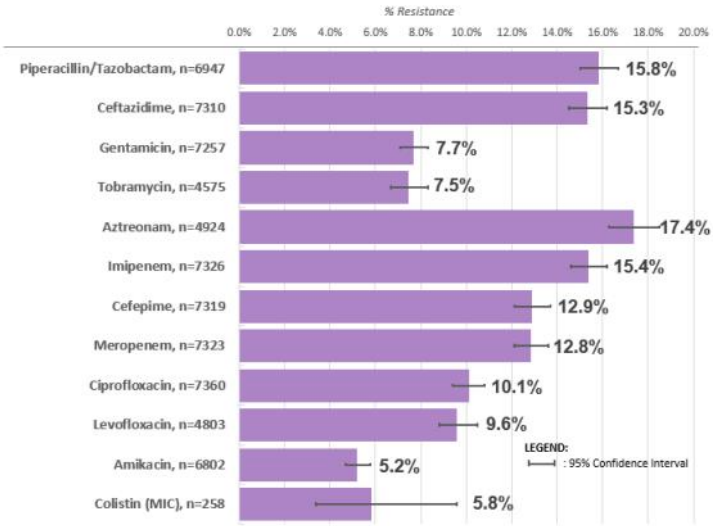


Figure 94. Resistance rates of *P. aeruginosa* from all specimens, DOH-ARSP, 2022

Figure 94 shows the cumulative resistance rates of *P. aeruginosa* isolates in 2022. Resistance to beta lactam agents are as follows: ceftazidime was 15.3%, cefepime at 12.9%, aztreonam at 17.4%, and piperacillin/tazobactam 15.8%. For flouroquinolones resistance are at 10.1% for ciprofloxacin and 9.6% for levofloxacin. There were significant increase in the resistance rate of the following antibiotics from 2021 compared with 2022 rates: piperacillin/tazobactam (p=0.0000), and aztreonam (p=0.0000). There were also significant decrease in the resistance rate of the following antibiotics from 2021 compared with 2022 rates: tobramycin (p=0.0002) and meropenem (p= 0.0000).

There were **15 confirmed** colistin-resistant *P. aeruginosa* isolates for 2022. Most (n=6, 40%) were from the 20-64 age group. Most (n=10, 66.7%) of the isolates were detected from respiratory isolates. Most of the isolates were susceptible to amikacin, aztreonam, cefepime, ceftazidime, gentamicin and tobramycin. Twelve isolates were further characterized using whole genome sequencing.

Molecular Characterization of Colistin Resistant *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a Gram-negative opportunistic pathogen, which is ubiquitous in nature. This bacterium is an important nosocomial pathogen capable of causing both acute and chronic infections.[1] One of the main concern in dealing with patients infected with *P. aeruginosa* is the multi-drug resistance characteristic of this bacterium to several antibiotic classes, coupled with significant adaptation capacity of the pathogen. This bacterium synthesizes various toxic products that promotes host invasion, colonization and spread throughout its host.[2] Of the 15 confirmed colistin resistant *Pseudomonas aeruginosa* for 2022, 12 were available for WGS. We describe in this report the molecular characteristics of twelve *Pseudomonas aeruginosa* isolates, which exhibited resistance to colistin, a crucial last resort drug option for MDR pathogens.

The twelve isolates were collected from nine Antimicrobial Resistance Surveillance Program (ARSP) sentinel sites representing nine regions of the county. The isolates were mostly detected from respiratory specimens including tracheal aspirate (n =5), sputum (n=2) and bronchial (n=1) (Table A). *P. aeruginosa* isolates were likewise detected from wound, tissue and catheter line of patients. It was noted that 10 out of the 12 isolates, though resistant to colistin, were susceptible to aminoglycosides (amikacin, tobramycin and gentamicin), cephalosphorins (ceftazidime and cefepime), quinolones (ciprofloxacin and levofloxacin), carbapenem (imipenem and meropenem), monobactam (aztreonam), and beta-lactamase inhibitor (piperacillin/ tazobactam).

Table A. Characteristics of colistin-resistant *Pseudomonas aeruginosa* isolates ARSP 2022

Isolate	Hospital	Specimen Type	MLST	Colistin MIC (mg/L)	Mechanism of Colistin Resistance	AMR Phenotype	AMR Genotype
22ARS-BRH0027	BRH	Wound	ST357	4	--		mexA,catB7,aph(3')-IIb,blaPDC-11,fosA,blaOXA-846,mexX,mexE
22ARS-BRT0012	BRT	Tracheal aspirate	ST970	8	--	CAZ, CIP, LEV, IPM, MEM, ATM, PIP/TAZ	aph(3')-IIb,blaPDC-1,catB7,blaOXA-50,mexA,fosA,crpP, mexX,mexE
22ARS-CRH0026	CRH	Tracheal aspirate	ST234	4	--		mexA,blaOXA-486,fosA,blaPDC-31,aph(3')-IIb,catB7,crpP,mexX, mexE
22ARS-DMC0116	DMC	Bronchial	ST357	4	--		fosA,blaOXA-846,catB7,blaPDC-11,aph(3')-IIb,mexX,mexA,mexE

Isolate	Hospital	Specimen Type	MLST	Colistin MIC (mg/L)	Mechanism of Colistin Resistance	AMR Phenotype	AMR Genotype
22ARS-EVR0014	EVR	Tracheal aspirate	ST236	8	--		mexA,catB7,blaOXA-486,blaPDC-31,aph(3')-IIb,fosA,mexE,mexX
22ARS-GMH0131	GMH	Wound	ST316	4	--		mexE,fosA,mexA,blaOXA-395,blaPDC-36,aph(3')-IIb,catB7,mexX
22ARS-JLM0131	JLM	Tissue	ST292	4	--		mexA,blaOXA,catB7,fosA, blaPDC-45,mexE,aph(3')-IIb,mexX
22ARS-MAR0018	MAR	In-line catheter	No ST predicted	4	--	TOB, GEN, CAZ, FEP, IPM, MEM	mexA,aph(3')-IIb,blaPDC-11,fosA,blaOXA-846,mexX,catB7,mexE, blaIMP-4,aac(6')-Ib4,blaOXA-2,aadA1,sul1
22ARS-MAR0082	MAR	Tracheal aspirate	No ST predicted	4	--		mexA,blaOXA-486,mexE,fosA,catB7,blaPDC-24,aph(3')-IIb,mexX
22ARS-MAR0116	MAR	Sputum	No ST predicted	4	--		mexA,crpP,fosA,blaOXA-1131,catB7,mexE,blaPDC-260,aph(3')-IIb,mexX
22ARS-SLH0012	SLH	Tracheal aspirate	ST357	4	--		catB7,mexA,mexE,fosA,blaOXA-846,blaPDC-11,aph(3')-IIb,mexX
22ARS-SLH0051	SLH	Sputum	No ST predicted	4	--		blaOXA-486,blaPDC-3,aph(3')-IIb,fosA,catB7,mexA,mexE,mexX

Multilocus Sequencing Type (MLST), a DNA- based typing method that identifies bacterial strains through variations in housekeeping genes, characterized the isolates into six sequence types (ST), with ST357 (n= 3) being the most common. Other sequence types were ST970, ST234, ST236, ST316, and ST292. ST357 is one of the international high risk clone identified from comprehensive review studies of *P. aeruginosa* diversity and distribution of resistance markers. WGS also revealed that there were five O polysaccharide types among the isolates including O3, O4, 06, 011 and 012. All of the three ST357 were identified as 011. The O antigen/ O polysaccharide, together with the hydrophobic lipid A region and central core, makes up the lipopolysaccharide (LPS), which is an important virulence factor for *P. aeruginosa*. Phylogenetic analysis revealed that there was a clustering of ST 357 isolates from SLH, DMC and BRH (Figure A). The zero to one single nucleotide polymorphisms (SNPs) difference among the three isolates implies single origin. The possible transmission pattern among the three sentinel sites requires further investigation.

Figure A. Phylogenetic tree of colistin resistant *P. aeruginosa* isolates

Known antimicrobial resistance (AMR) genes that confer resistance to carbapenems among *P. aeruginosa* such as the metallo beta lactamases VIM, IMP and NDM were not observed among the isolates in this present report. Resistance genes to chloramphenicol (*cat*B7), aminoglycoside (*aph*(3')-IIb) and fosfomycin (fosA) were seen on twelve isolates but no single gene that mediates colistin resistance was detected. Mechanism of antibiotic resistance among bacteria, including, *P. aeruginosa* can be intrinsic or acquired.[3] Intrinsic resistance among *P. aeruginosa* can be characterized with decrease in of specific porin and overexpression of efflux pumps.[4] Evidently, all isolates possess at least two efflux genes such as *mex*A, *mexE* and *mex*X. The *mex* efflux pumps of *P. aeruginosa* are of particular interest because of their exceptionally broad substrate specificity. In addition, there were 12 potential efflux systems of this gene family have been identified in the *P. aeruginosa* genome.[5] The absence of plasmids on all isolates, which has the capacity to carry antimicrobial resistance genes, further substantiate the possibility of intrinsic mechanism of resistance among these colistin-resistant isolates.

Multi-drug Colistin- Resistant Pseudomonas aeruginosa

The first isolate that showed resistance to carbapenems and other antibiotics was detected from the tracheal aspirate specimen of a 60-year old male from the intensive care unit of BRT, moreover, the isolate was not considered as nosocomial. The *P. aeruginosa* isolate belongs to ST970 and O4 serogroup. This particular isolate was resistant to aztreonam, ciprofloxacin, ceftazidime, levofloxacin, piperacillin/tazobactam and the two carbapenem antibiotics, meropenem and imipenem but susceptible to amikacin, cefepime, gentamicin and tobramycin. Next, the second isolate was collected from the in-line catheter of a 62-year old female from MAR. The isolate showed similar resistance profile with the first isolate with additional resistance to tobramycin and gentamicin. Interestingly, WGS analysis revealed the presence of bla_{IMP-4}, which is a highly mobile genetic element that is generally embedded in integrons flanked by transposons within plasmids, which facilitate its horizontal dissemination and intercontinental spread.[6] In line with the presence of bla_{IMP-4}, this *P. aeruginosa* from catheter also carries stress genes including mercury resistance operons (merR, merT, merP, merA, merD, merE) and genes conferring resistance to quaternary ammonium compounds (qacG), which were the typical gene cassette array of bla_{IMP-4} found across Australia, Hong Kong, Singapore, Japan and Malaysia.[6] It is important to mention that quaternary ammonium products was considered by World Health Organization for routine cleaning in hospital facilities including non-critical surfaces such as floors, bed-rails, walls, and partitions.[8] This posited a public a public health concern as there are mobile bacterial pathogens that can evade disinfectant substances usually utilized in the hospital. This report highlights the significance of whole-genome sequencing (WGS) to uncover transmission patterns, identify known AMR mechanisms, and pinpoint the source of acquired infections specifically in the hospital settings. Notwithstanding the non-detection of mobile colistin resistance genes among the *P. aeruginosa* isolates in this report, there is a need for a continued surveillance of resistance to this last resort antibiotics. Continued implementation of effective infection control measures in hospital settings is paramount especially with the identification of the presence of highly mobile genetic elements conferring resistance to antibiotics such as carbapenems which facilitate dissemination of AMR genes and the potential for bacterial pathogens to evade commonly used disinfectants.

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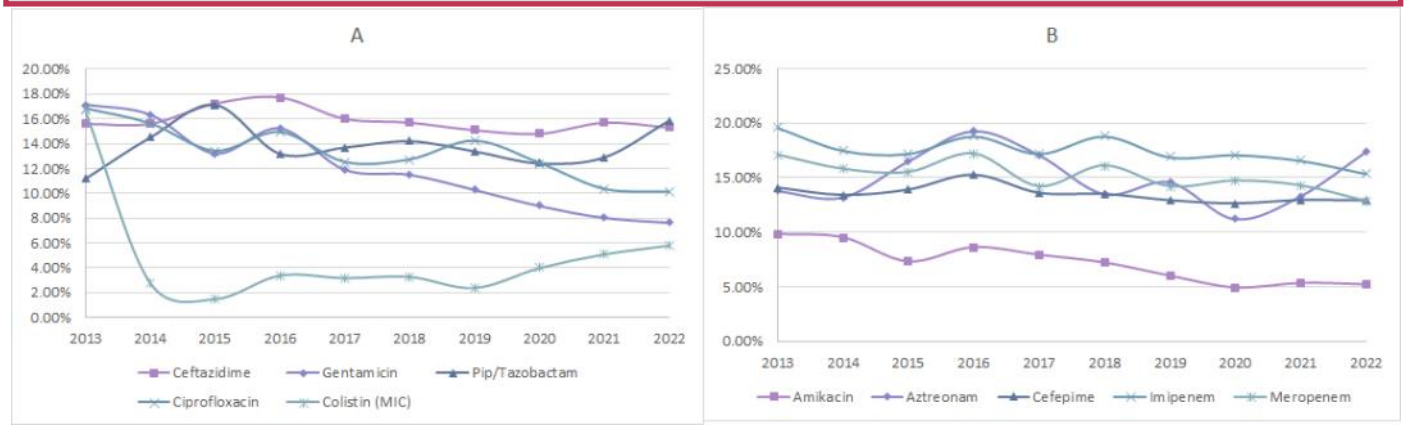


Figure 95. Yearly resistance rates of *P. aeruginosa*, DOH-ARSP, 2013-2022

Figure 95 shows the yearly resistance rates of *P. aeruginosa*. Multiple year analysis revealed that changes in resistance rates for two carbapenem antibiotics, meropenem (p=0.0000) and imipenem (p=0.0000) and colistin (p=0.0000) were statistically significant.

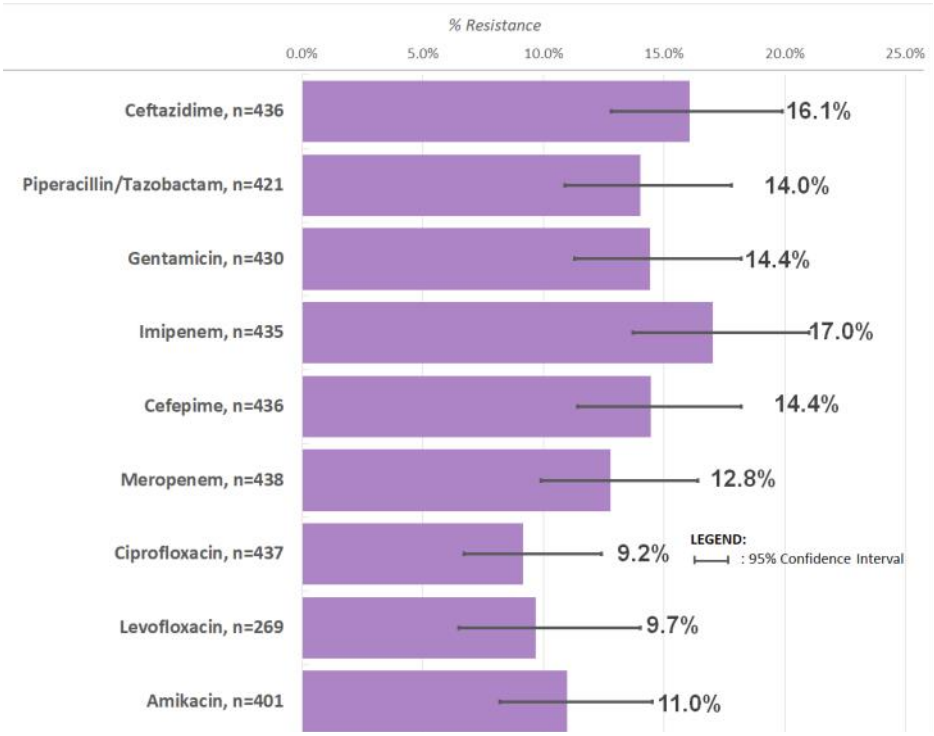


Figure 96. Percent resistance of *P. aeruginosa* blood isolates, DOH-ARSP, 2022

Figure 96 shows the antibiotic resistance rates of *P. aeruginosa* from blood samples. Highest resistance rates were for imipenem (17%) and ceftazidime (16.1%). Compared to cumulative rates of resistance for all isolates combined, invasive *P. aeruginosa* had relatively higher rates of resistance for almost all antibiotics except for ciprofloxacin (9.2%) and piperacillin/tazobactam (14%) and similar rate for meropenem (12.8%).

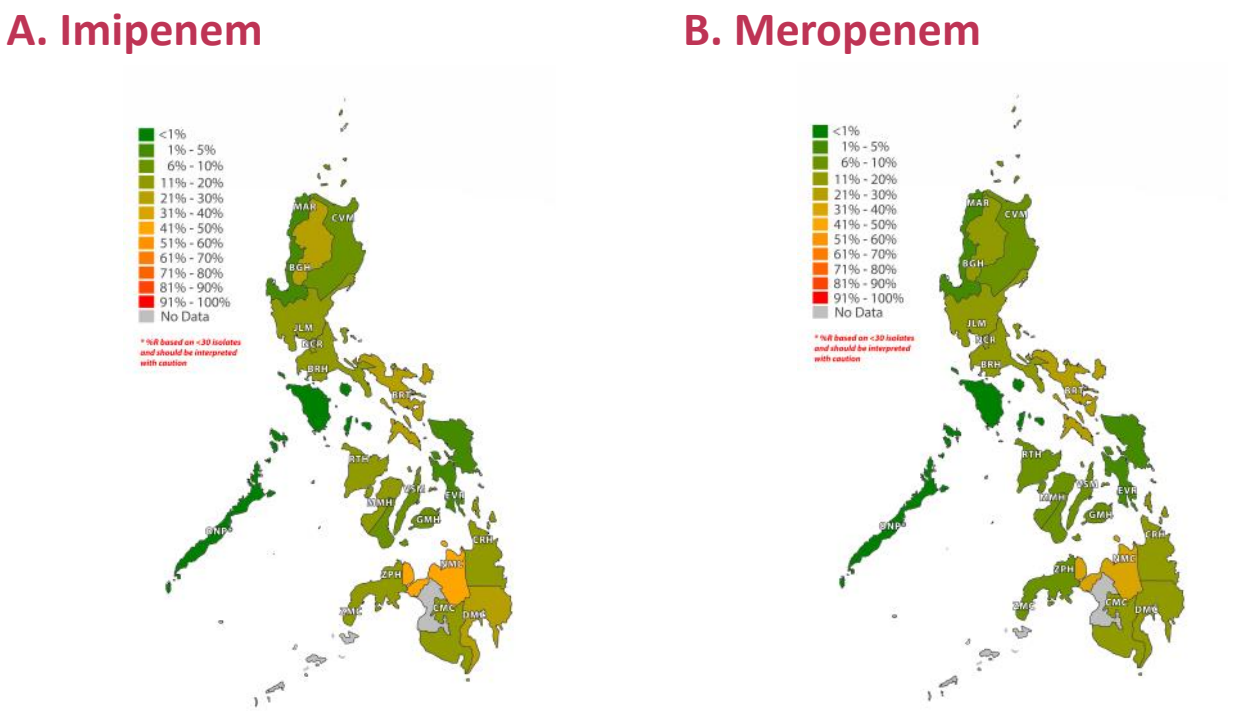


Figure 97. Resistance maps of *P. aeruginosa* for (A) imipenem and (B) meropenem, DOH-ARSP, 2022

Figure 97 shows the carbapenem resistance rates of *P. aeruginosa* across different regions represented by the sentinel sites. The *P. aeruginosa* isolates from most of the regions have carbapenem resistance rates in the range of 11-20%. NMC has relatively higher resistance to carbapenems with rates higher than 40%.

Acinetobacter baumannii

There were **4,870** *Acinetobacter baumannii* reported for 2022, which was higher than the number of isolates reported in 2021. Largest contributors of *A. baumannii* isolates were PGH (20.6%), DMC (13.7%) and VSM (10.2%) (Figure 98).

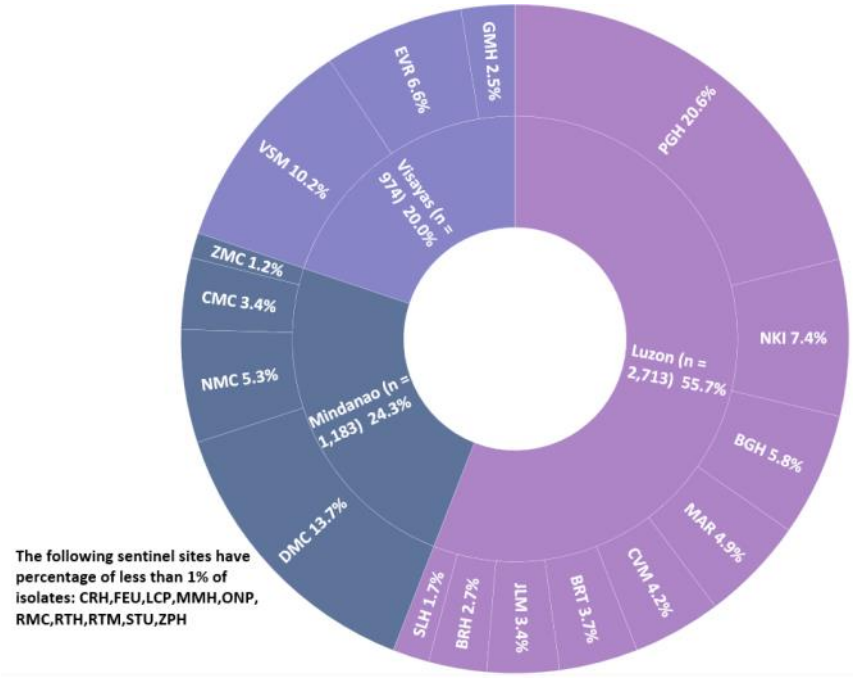


Figure 98. Isolate distribution of *A. baumannii*, DOH-ARSP, 2022 (n= 4,870)

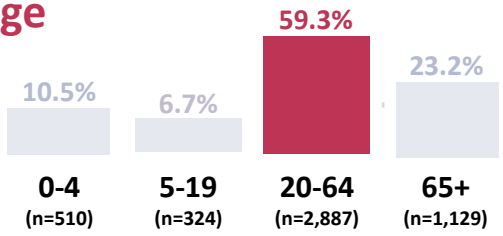
A. Sex

54.9%
Male
(n=2,675)

44.9%
Female
(n=2,184)

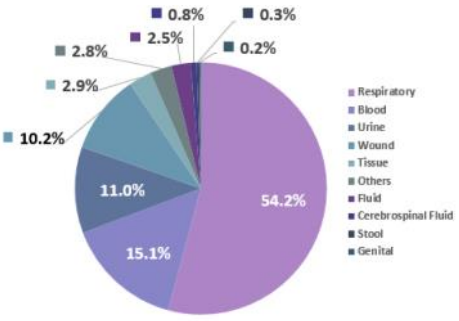
No data: 0.2% (n=11)

B. Age

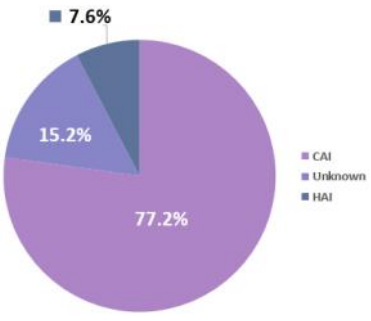


Unknown: 0.4% (n=20)

C. Specimen Type



D. Infection Type



E. Hospital Department

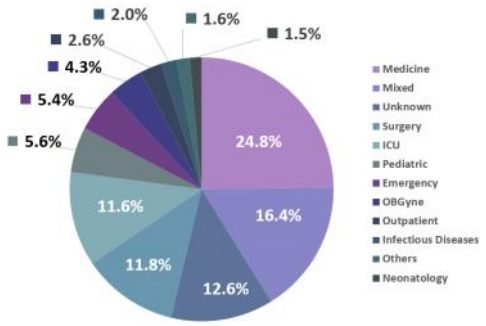


Figure 99. Patient characteristics of *A. baumannii* isolates, DOH-ARSP, 2022 (n= 4,870)

Most (59.3%) of the isolates were from 20-64 years old and mostly (54.9%) were from male patients. Most (54.2%) of the isolates were collected from respiratory samples and most (77.2%) were from presumptively community acquired infections (Figure 99).

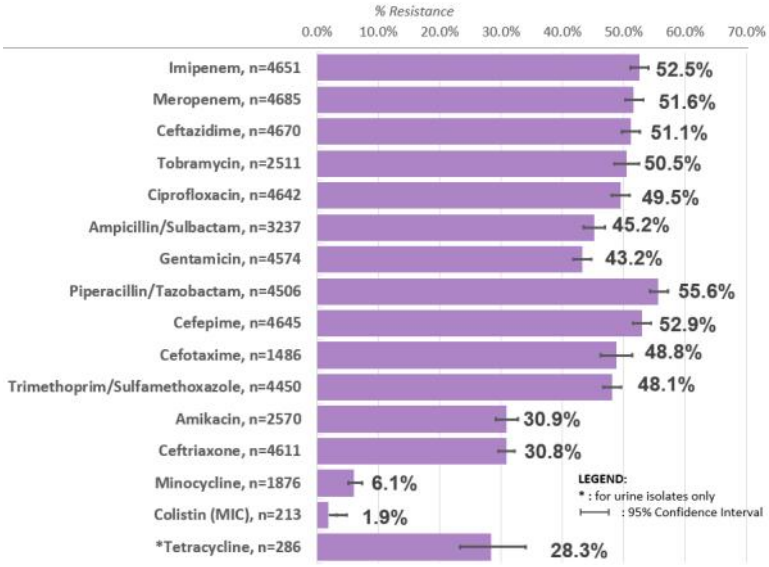


Figure 100. Resistance rates of *A. baumannii* from all specimens, DOH-ARSP, 2022

Figure 100 shows the cumulative resistance rates of *A. baumannii* isolates for 2022. More than 50% of all reported *A. baumannii* isolates were resistant to the β-lactam antibiotics, piperacillin/tazobactam (55.6%), cephalosporins cefepime (52.9%), ceftazidime (51.1%), carbapenems imipenem 52.5% and meropenem (51.6%), and aminoglycoside tobramycin (50.5%). Lowest resistance was noted for minocycline (6.1%), ceftriaxone (30.8%) and amikacin (30.9%).

There were **4 confirmed** colistin resistant *A. baumannii* isolates for 2022. The four isolates were from patients aged 28-71 years old. All isolates were detected from respiratory specimens. Three out of the 4 isolates were resistant against all antibiotics tested (presumptive XDR) while one of the 4 isolates was resistant to most of the antibiotics tested except aminoglycosides gentamicin and tobramycin. All 4 isolates were not tested for doxycycline, minocycline and cefiderocol. Three isolates were further characterized using whole genome sequencing.

Molecular Characterization of Colistin Resistant *Acinetobacter baumannii*

Multidrug resistant (MDR) *Acinetobacter baumannii* is one of the rapidly emerging pathogen in health care setting which possess a great public health concern. The intrinsic ability of this bacterium to survive under a wide range of environmental conditions within extended period of time makes it a frequent cause of outbreaks specifically in medical facilities. We describe in this report, three multidrug resistant *Acinetobacter baumanii* isolates which exhibits resistance to colistin, a crucial last resort drug option for MDR pathogens.

The first isolate was from the blood sample of a 33-year old female patient from intensive care unit (ICU). While the two isolates were detected from tracheal aspirates of two female adult patients (56 and 70 years old). The two patients stayed in a common ward. All of the isolates were considered nosocomial (hospital-acquired) as the specimens were collected on the third day of hospitalization or later. The three isolates shared uniform resistance profile which shows resistance to third generation cephalosphorins (cefotaxime, ceftazidime, and ceftriaxone); aminoglycosides (amikacin and tobramycin); carbapenemns (imipenem and meropenem); fourth generation cephalosphorin (cefepime); beta-lactamase inhibitor (ampicillin-sulbactam); fluoroquinolone (ciprofloxacin) and sulfonamide (trimethoprim-sulfamethoxazole).

Multilocus Sequencing Type (MLST), a DNA- based typing method that identifies bacterial strains through variations in housekeeping genes, characterized the three isolates into a single sequence type (ST 2). It can be noted that even as the three isolates shared a single sequence type, they have varying clusters of genes at the K locus located between *fkpA* and *lldP* genes in the *A. baumannii* chromosome which drives capsular polysaccharide synthesis.[1] WGS revealed three K cluster types including KL2, KL3 and KL32. Several studies have highlighted the structural pliability of the *A. baumannii* genome, revealing very poor correlation between KL and outer core locus types and other genomic features including ST. In contrast, a single type (OCL1) was identified among the isolates. OCL is located between the flanking genes *aspS* and *ilvE*, which directs the synthesis of outer core component of lipopolysaccharide.[2] Information on these loci clusters are important determinants for identification and virulence of *A. baumannii.*

Table A shows the list of antibiotics to which the isolates were resistant to alongside with the antimicrobial resistance (AMR) genes detected. Amikacin resistance were mediated by aph(3')-Via, and aph(3')-Ia genes, while resistance to cephalosphorins were mediated by blaADC-73 and blaADC-30 genes. Further, non-susceptibility to ciprofloxacin was conferred by specific mutations in gyrA and parC genes. The AMR gene sul2, on the other hand drives resistance to sulfonamide such as trimethoprim-sulfamethoxazole. Moreover, resistance to carbapenem antibiotics were correlated with the presence of blaOXA-23, blaOXA-66, ftsI_A515 genes. WGS analysis showed the presence of various replication initiation plasmids (r3-T3,rP-T1,r3-T60) that have the capacity to carry antimicrobial resistance genes.[3] Plasmids can incorporate and deliver genes by recombination or transposition, thus favoring genetic exchanges in bacterial populations.

Table A. Characteristics of colistin resistant *A. baumannii*, (n=3)

Isolate	Hospital	Sample Type	*In silico* ID	MLST	K locus	O locus	Colistin MIC (mg/L)	Mechanism of Colistin Resistance	AMR Phenotype	AMR Genotype
22ARS-VSM0139	VSM	Tracheal aspirate	*A. baumannii*	ST2	KL2	OCL1	4	--	Aminoglycoside Cephalosphorin Quinolone Sulfonamide Carbapenem	*aph(3')*-Via, *aph(3')*-Ia, *bla*ADC-73, *bla*ADC-30, *gyr*A (p.S81L), *par*C (p.S84L), sul2 *bla*OXA-23, *bla*OXA-66, *fts*I_A515
22ARS-VSM0377	VSM	Blood	*A. baumannii*	ST2	KL3	OCL1	> 32	--		
22ARS-VSM0382	VSM	Tracheal aspirate	*A. baumannii*	ST2	KL32	OCL1	16	--		

It can be noted that no known AMR gene nor mechanism which confers resistance to colistin was detected among the three isolates. It was noted there were several efflux genes seen among the isolates, including *ade*C and *amv*A which were identified in other studies to enhance colistin resistance among *A. baumannii*.[4] The noted absence of known specific genetic alterations conferring colistin resistance among these isolates suggests the need for further studies including efforts to determine the possibility of the presence of alternative mechanisms for resistance to colistin among these isolates. This highlights the importance of continued monitoring and surveillance of AMR patterns and the need for alternative strategies to combat infections caused by this multi-drug-resistant bacteria.

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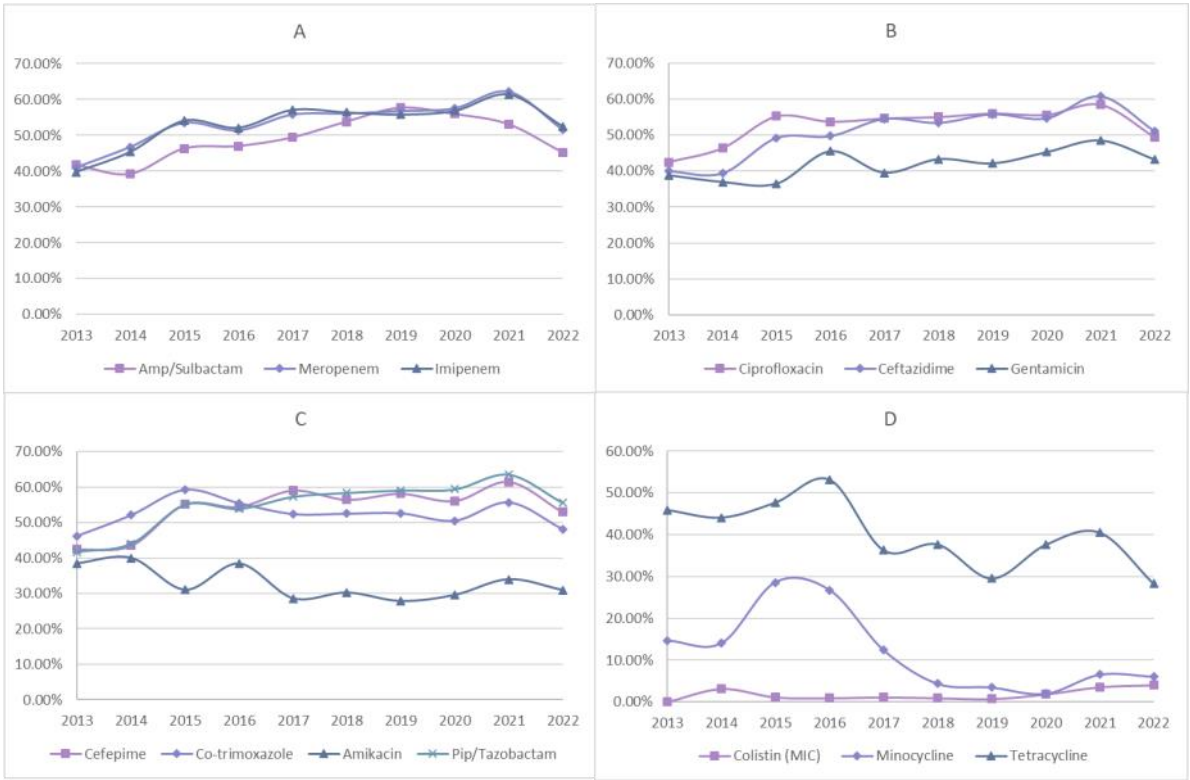

Figure 101. Yearly resistance rates of *A. baumannii*, DOH-ARSP, 2013-2022

Resistance to most antibiotics were noted to decrease in 2022. There were significant decrease in the resistance rate of the following antibiotics from 2021 compared with 2022 rates: meropenem (p=0.0000), ceftazidime (p=0.0000), imipenem (p=0.00), ceftazidime (p=0.0000), ciprofloxacin (p=0.0000), tobramycin (p=0.0000), cefepime (p=0.0000), co-trimoxazole (p=0.0000), ceftriaxone (p=0.0000) and amikacin (p=0.0000). The decrease in the resistance rate of the combination antibiotics, ampicillin/sulbactam and piperacillin/tazobactam were both significant at p= 0.0000.

Figure 101 shows the yearly resistance rate of *A. baumannii* over the years. Multiple year analyses revealed that the changes in resistance rates over the years were significant for meropenem (p=0.0000), imipenem (p=0.0000), and ceftazidime (p=0.0000).

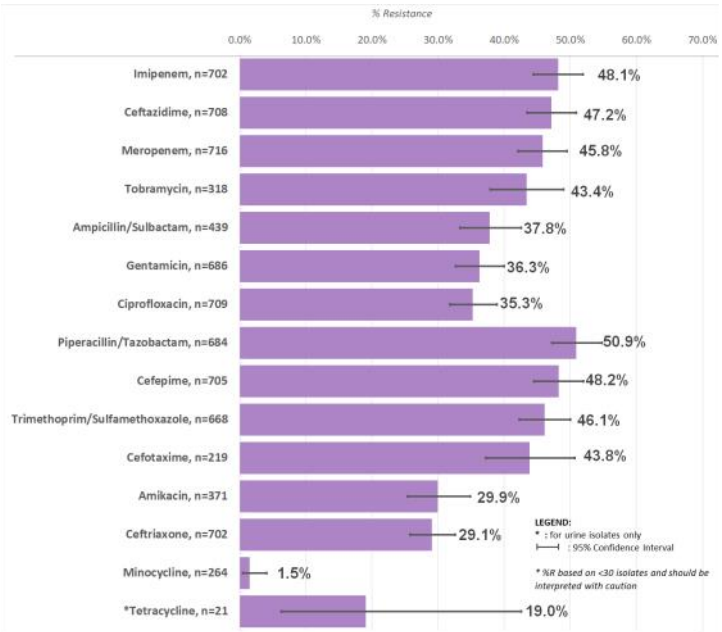

Figure 102. Percent resistance of *A. baumannii* blood isolates, DOH-ARSP, 2022

Figure 102 shows the resistance rates of *A. baumannii* isolates from blood specimens. Most of the resistance rates were above 35%. Resistance rate to amikacin was at 29.9% which is higher than 28.7% in 2021 (p= 0.0632). Compared to cumulative rates of resistance for all isolates combined, invasive *A. baumannii* had relatively lower resistance rates for all antibiotics.

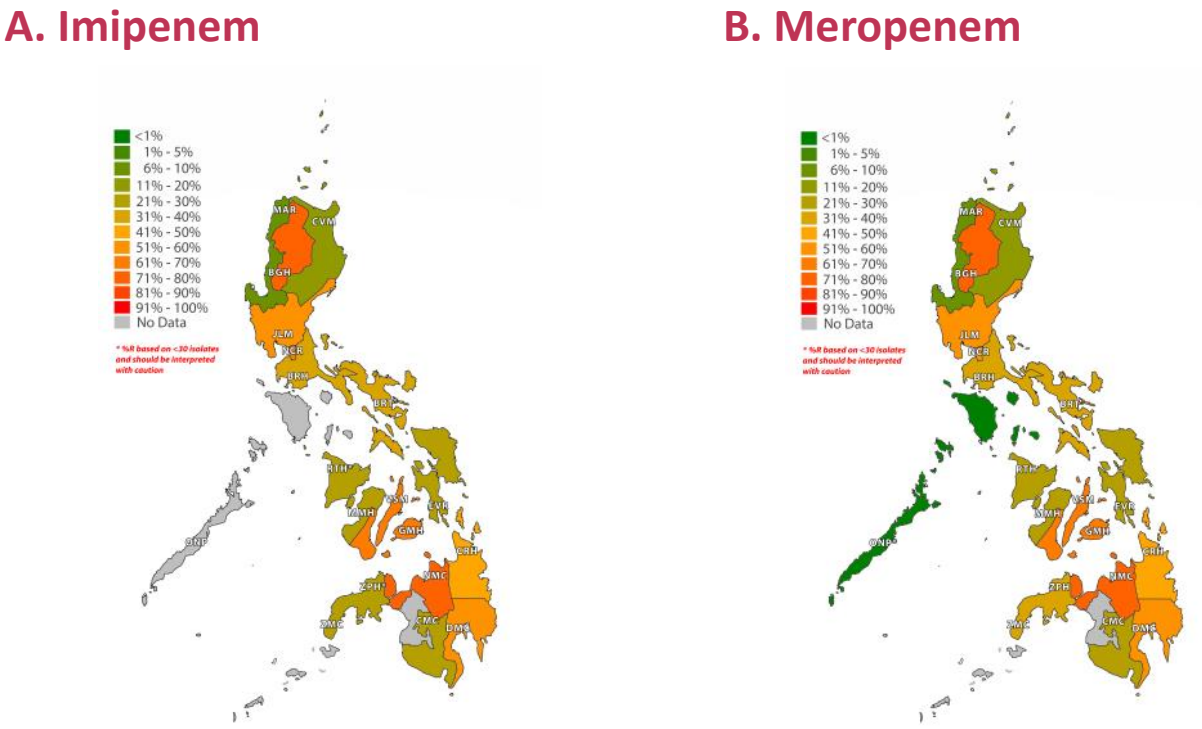

Figure 103. Resistance maps of *A. baumannii* for (A) imipenem and (B) meropenem, DOH-ARSP, 2022

Figure 103 shows the carbapenem resistance rates of *A. baumannii* across regions as represented by the sentinel sites. Carbapenem resistance among many sentinel sites varies but most rates are high.

Multidrug Resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

Multidrug- resistant pathogens are increasingly recognized globally. Terminologies are summarized in Table 7.

Among the 2022 *P. aeruginosa* isolates from all specimen types, 23% were MDR and 14% were possible XDR. Among *P. aeruginosa* blood samples, 22% were MDR and 15% were possible XDR (Table 8).

Among the 2022 *A. baumannii* isolates from all specimen types, 60% were MDR and 50% were possible XDR. Among *A. baumannii* blood samples, 56% were MDR and 46% were possible XDR (Table 8).

Table 7. Multidrug resistant, extensively drug resistant and pandrug-resistant bacteria in an international expert proposal interim standard definitions for acquired resistance.

Term	Definition
MDR Multidrug-resistant	Acquired non-susceptibility to at least one agent in three or more antimicrobial categories
XDR Extensively drug-resistant	Non-susceptibility to at least one agent in all but two or fewer antimicrobial categories
PDR Pandrug-resistant	Non-susceptibility to all agents in all antimicrobial categories

Table 8. MDR and possible XDR *P. aeruginosa* and *A. baumannii*, DOH-ARSP, 2022

	Number of isolates tested	Percentage MDR	Percentage Possible XDR
Pseudomonas aeruginosa			
All isolates	7,561	23%	14%
Blood isolates	448	22%	15%
Acinetobacter baumannii			
All isolates	4,870	60%	50%
Blood isolates	735	56%	46%

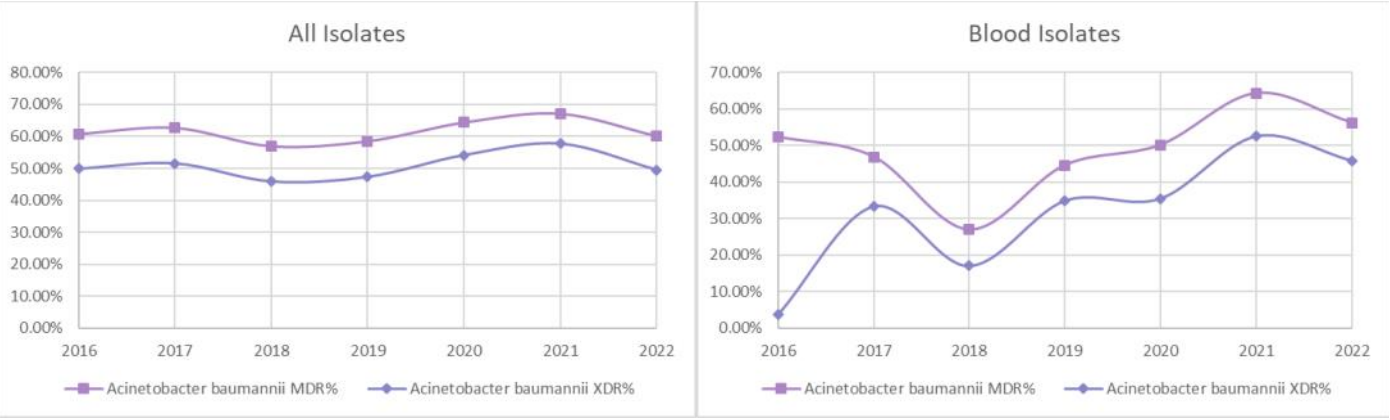

Figure 104. Yearly percentage of MDR and XDR isolates of *A.baumannii*, DOH-ARSP, 2016-2022

Figure 104 shows the yearly resistance rates of MDR and XDR isolates of *A. baumannii*. Among isolates from all sample type, following an increase in the past 3 years, the percentage of MDR and XDR *A. baumannii* isolates as well as percentage of MDR isolates for blood decreased in 2022. Multiple year analysis revealed that the changes over the years were statistically significant for all three class definition. Continued increase in the percentage of XDR *A. baumannii* was noted in the past 4 years.

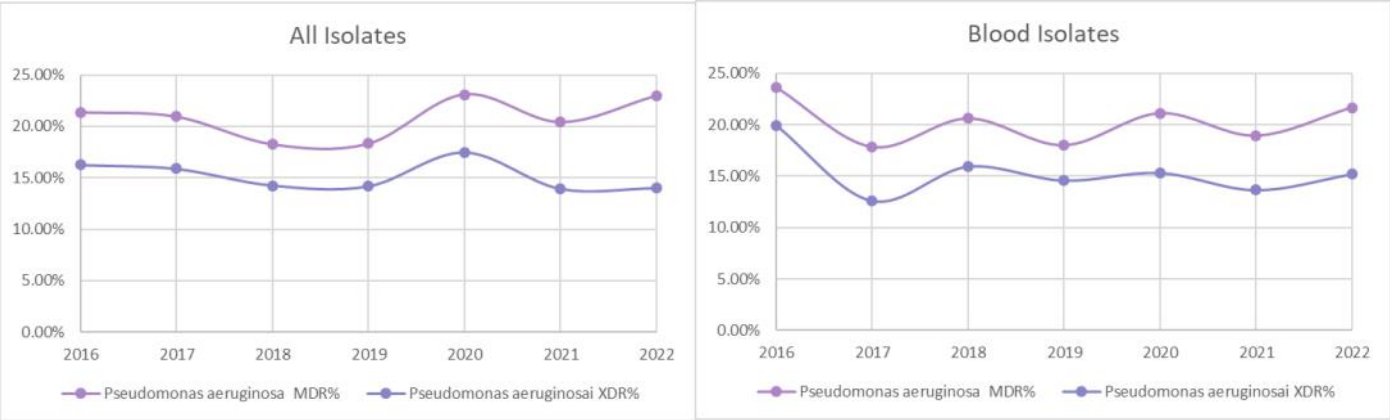

Figure 105. Yearly percentage of MDR and XDR isolates of *P. aeruginosa*, DOH-ARSP, 2016-2022

Figure 105 shows the yearly percentage of MDR and XDR isolates *of P. aeruginosa*. Both the MDR and XDR rates for *P. aeruginosa* isolates from all samples as well as from blood samples appear to be decreasing in the past 6 years but was noted to increase for 2022. The MDR and XDR percentage change over the years in were found to be statistically significant (p= 0.0003).

Conclusions, Recommendations and Future Directions

Antimicrobial resistance continues to increase for most of the bacterial pathogens considered of public health importance included in this surveillance.

Recommendations based on the reported 2022 data:

Penicillin may still be used to treat non-meningitis infections secondary to *Streptococcus pneumoniae,* notwithstanding the need to monitor the shifting patterns of resistance among pneumococci. The use of extended spectrum macrolides and penicillin for meningitis secondary to *Streptococcus pneumoniae* may be best guided by susceptibility data given the ongoing rise in resistance to erythromycin and penicillin using meningitis breakpoint. Better monitoring and evaluation of the government's immunization program for this disease that is vaccine preventable will be possible by expanding AMR surveillance of *Streptococcus pneumoniae* isolates to include pneumococcal serotyping.

The empiric treatment for suspected *H. influenzae* infections may include extended spectrum oral cephalosporins and beta-lactam-beta-lactamase inhibitor combinations due to high resistance rate of *H. influenzae* to ampicillin.

Chloramphenicol or co-trimoxazole or amoxicillin/ampicillin may still be used as empiric treatment for suspected uncomplicated typhoid fever. It is recommended that microbiological data be used to support pathogen-directed therapy in light of the growing reports of ciprofloxacin resistance, which could lead to clinical treatment failures.

Limited resistance data on *Shigella* sp in the past 4 years show emerging resistance to the quinolones and extended spectrum cephalosporins. A more vigilant surveillance of the resistance pattern of this bacteria should be pursued by encouraging clinicians to send specimens for culture.

Tetracycline, chloramphenicol and co-trimoxazole remain good treatment options for cholera cases. With the report of the first azithromycin resistant *V. cholerae* isolate for 2022, continued vigilant AMR surveillance among *V. cholerae* isolates is warranted to guide control and prevention of the spread of resistant *V. cholerae* isolates.

With the limited available data on *Neisseria gonorrhoeae*, ceftriaxone remains as empiric antibiotic of choice for gonococcal infections. More vigilant surveillance of the resistance patterns of this organism should be pursued by encouraging clinicians to send specimens for culture to their local laboratory and the sentinel sites to send isolates to the reference laboratory for confirmatory testing.

The use of oxacillin as empiric treatment option for *S. aureus* infections remains limited by continued high rates of oxacillin resistance even as statistically significant decrease in MRSA rates is noted beginning in 2017 until 2022. With the noted relatively lower resistance rates to clindamycin and the macrolides, these antibiotics could be considered as alternative options. Judicious use of the reserve antibiotic vancomycin remains paramount in order to preserve the effectiveness of this antibiotic in treating *S. aureus* infections.

Multidrug resistance among the bacterial organisms *Escherichia coli, Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* continues to be a public health concern because of the limited treatment options and infection control challenge in containment. Real time data analysis, and genotyping to establish linkages will allow for implementation of timely patient isolation and infection control measures to prevent spread of these superbugs. Institute specific and stratified antibiograms will allow clinicians to identify the best empiric antibiotic options for suspected infections due to these superbugs.

Program Future Directions

- Pursue continuous and expanded integration of whole genome sequencing into ARSP through fostering continued growth of technical expertise and skills in molecular diagnostics and bioinformatics within the reference laboratory as well as through advocacy for requisite fund and resource requirements.
- Improve detection of clustering of cases in ARSP sentinel sites through the use of WHONET SaTScan analysis on ARSP data by encouraging prompt data transfer from sentinel sites. Enhance the investigation of possible outbreaks in the sentinel sites through close coordination with the Infection and Prevention Committee of sentinel sites and through the use of WGS.
- Actively engage in the One Health approach to AMR surveillance together with relevant stakeholders from the food chain and environmental sectors.
- Advocate for and implement relevant AMR surveys, studies and researches to inform the policies towards the control and prevention of the emergence and spread of AMR in the country. Generate more relevant collaborative and investigator-initiated researches.
- Actively contribute and participate in the implementation of the Philippine Action Plan to Combat Antimicrobial Resistance. Explore and pursue the establishment of a case-based AMR surveillance in line with the objectives of the Philippine Action Plan to Combat Antimicrobial Resistance (2019-2023) to enable the gathering of quantifiable burden of disease due to resistant infections.
- Continue to ensure the high quality of surveillance data through active capacity building of sentinel site and reference laboratory staff, robust efforts to improve facilities, and safeguard availability of resources, equipment and services.
- Incorporate the technology of geographic information system and mapping in the surveillance.
- Pursue ISO 15189 accreditation for the reference laboratory.

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