The Epidemiology of Multidrug-resistant *Klebsiella pneumoniae* Isolated from Filipinos over a 10-year Period

Kristine Tamaray, Enrico Garcia
Bachelor of Science in Biology

ABSTRACT

Antimicrobial resistance (AMR) is characterized by the nonsusceptibility of certain species, especially bacterial species, to their respective antibiotics. Klebsiella pneumoniae, a gram-negative bacterium from the Enterobacateriaceae family and is one of the species (ESKAPE pathogens) that causes nosocomial infections. These bacteria are omnipresent in nature and can even be found inside the mouth flora but can cause pneumonia once they enter the respiratory tract. In this study, the researcher aimed to plot a decade trend (2010-2019) of the Philippine cases of pneumonia that were caused by the K. pneumoniae isolates. Moreover, nonsusceptibility patterns against antibiotics were also examined; both are analyzed and illustrated using Microsoft Excel. The increasing trends of MDR K. pneumoniae isolates every year are alarming as categorized antimicrobial agents seem to have little to no efficacy against these pathogens. , the researcher suggests an in-depth study inclusive of complete data from the main reference (i.e.: concentrations of the antibiotics used to examine resistance per region) and the morbidity and mortality reports of patients that suffered illnesses due to K. pneumoniae-induced infections as the plotted trends only supplement superficial information regarding the seriousness of resistant K. pneumoniae isolates.

Keywords: *Klebsiella pneumonia, ESKAPE pathogens, Philippine trends, pneumonia*

INTRODUCTION

Antimicrobial resistance (AMR) is a phenomenon that is characterized by the nonsusceptibility of microorganisms to antimicrobial agents that usually are the causative agents of infections and diseases (Gould & Bal, 2013). Bacterial resistance to antibiotics threatens worldwide public health. Due to this, several agencies such as the World Health Organization (WHO) have suggested recommendations for treatment and proposed initiatives for countries to follow (Ventola, 2015).

One of these disease-causing pathogens is a gram-negative bacterium called Klebsiella pneumoniae from the Enterobacteriaceae family. This bacterial species is present everywhere in nature even in the natural flora of humans. It is one of the major causes of urinary and respiratory tract infections and nosocomial/hospital-acquired infections. Isolates usually are present and obtained from respiratory samples, wounds, blood, and urine (Choby et al., 2020; Department of Health (DOH), 2019; Martin & Bachman, 2018). From 2010, it has been observed that the trend of nonsusceptible isolates of K. pneumoniae from human samples is becoming alarming as they become resistant to many antibacterial agents including beta-lactams, fluoroquinolones, aminoglycosides, carbapenems, and sulfonamides indicating its multidrug resistance (Ullah & Ali, 2017). The hypervirulence of this pathogen is not solely confined to this species but is shared along with different microorganisms as well that pose immense medical threats and dilemmas; Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species, the ESKAPE pathogens (Choby et al., 2020).

In this study, the researcher aims to assess the decade trend of AMR of K. pneumoniae isolates obtained from patients across regions in the Philippines by collated reports. All data are

downloaded and obtained under the publication panel on the official website. Investigating the decade trade of K. pneumoniae allows the monitoring of persistent pathogens against panels of antimicrobial agents by plotting trends and analyzing the results.

Review of Literature

Antimicrobial Resistance dilemma

Antimicrobial resistance (AMR) poses a threat to public health worldwide as it imperils antibiotic and modern medicine efficacy including transplant processes, surgical procedures, and even cancer treatment that only is possible because of antibiotics (World Health Organization, 2014; (Ventola, 2015). Sir Alexander Fleming, a Scottish microbiologist who discovered penicillin, has warned the society regarding the possible resistance of bacteria to antibiotics and had his prediction come to life as, within the decade of penicillin introduction, bacteria resistance started to emerge (Rosenblatt-Farrell, 2009). This health crisis is further heightened due to several reasons including antibiotic overuse, incorrect drug prescription, large-scale use in agriculture, lack of modern antibiotics, and gatekeeping drug regulation (Gould & Bal, 2013). Furthermore, several terminologies are coined to determine the level of resistance of bacteria right after the health crisis started to emerge. Multidrug-resistant (MDR) isolates are not susceptible to three or more categorized antimicrobial agents, extensively drug-resistant (EDR) isolates are resistant to two, at most, antimicrobial agents, and pan drug-resistant (PDR) isolates are impervious to all antibiotics (Li et al., 2019).

Klebsiella pneumoniae

Under the Enterobacteriaceae family, Klebsiella pneumoniae are gram-negative bacteria, omnipresent in nature, belonging to the natural flora of healthy species including animals and humans. This opportunistic pathogen is responsible for approximately one-third of all gram-negative infections to immunocompromised and at extreme age patients overall. Infections include urinary and respiratory tract infection, bacteremia, nosocomial infection (Choby et al., 2020; Martin & Bachman, 2018). Typically, these infections are medicated using antibiotics like β- lactam with a high sense of efficacy against Enterobacteriaceae (Martin & Bachman, 2018). Further, K. pneumoniae isolates that are no longer susceptible to carbapenems are referred to as carbapenem-resistant Enterobacteriaceae (CRE) (Choby et al., 2020).

ESKAPE pathogens

Moreover, the World Health Organization (WHO) included Klebsiella pneumoniae in the critical pathogen list of in need of new antibiotics (World Health Organization, 2017). According to Santajit and Indrawattana in 2016, the emergence of resistant bacteria poses a devastating burden in the field of healthcare. The weights of AMR comprise higher rates of morbidity and mortality, incorrect diagnosis, and society's distrust of concurrent medications. Due to the pathogens' hypervirulence and drug-susceptibility mechanisms, surveillance research studies recognized Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species as ESKAPE pathogens, constituting gram-positive and gram-negative bacteria that are usually the causative agents of nosocomial or hospital-acquired infections (HAI) (Sirijan Santajit & Nitaya Indrawattana, 2016).

Antimicrobial Susceptibility Testing

The advancement of medicine helped the researchers to unravel laboratory techniques in identifying bacterial resistance to panels of antimicrobial agents. Using a nutrient-rich growth medium where the pathogens are cultivated and subject to a series of tests to determine their susceptibility against specific drugs and for the primary care provider to prescribe patients appropriate medication (Bayot & Bragg, 2020). The most common methods of resistance test are broth dilution tests, antimicrobial gradient method, disk diffusion test, automated instrument systems. Broth dilution is a conventional test on which antimicrobial agents with different concentrations are dispensed in test tubes containing growth medium whilst being introduced to standardized suspension of bacteria. On the other hand, the antimicrobial gradient method utilizes plastic strips infused with dehydrated antibiotics with varying concentrations thus, the concentration gradient. The strips are then placed superficially on an agar plate with bacterial inoculum. Next is the disk diffusion method is the standard test in AST on which antibiotic paper disks are placed superficially on an agar plate inoculated with standard bacterial suspensions that can hold up to 12 disks. Lastly, the automated instrument system is characterized by the use of laboratory equipment that serves as an incubator and reader that can produce susceptibility results rapidly compared to the aforementioned three by detecting the smallest number of changes in microdilution trays or growth mediums. All methods exclusive of the last employ the minimum inhibitory concentration (MIC) that dictates and determines what concentration of the antimicrobial agent has the smallest amount that can inhibit the growth of the microorganism (Jorgensen & Ferraro, 2009).

Sentinel sites in the Philippines

Sentinel sites are hospitals, research laboratories, and research centers in the Philippines that follow the standard protocol from CLSI to collect, identify, test, and monitor AMR. Out of 17 regions comprising the archipelago, data are gathered from 16 of them. There are 15 sentinel sites in Luzon, inclusive of the National Capital Region. Mariano Marcos Memorial Hospital and Medical Center (MAR) in Region I; Cagayan Valley Medical Center (CVM) in Region II; Baguio General Hospital and Medical Center (BGH) in CAR; Jose B. Lingad Memorial Regional Hospital (JLM) in Region III; Batangas Medical Center (BRH) in Region IV-A (CALABARZON)*; Ospital ng Palawan (ONP) in Region IV-B (MIMAROPA)*; Bicol Regional Training and Teaching Hospital (BRT) in Region V. Followed by sentinel sites in NCR: Far Eastern University- Nicanor Reyes Medical Foundation (FEU); Lung Center of the Philippines (LCP); National Kidney and Transplant Institute (NKI); San Lazaro Hospital (SLH); University of Santo Tomas Hospital (STU); Philippine General Hospital (PGH); Rizal Medical Center (RMC); and Research Institute for Tropical Medicine (RTM). Located in the Visayas are 4 sentinel sites and 1 of the two gonorrhea surveillance centers. Corazon Locsin Montelibano Memorial Regional Hospital (MMH) for Region VI; Dr. Rafael S. Tumbokon Memorial Hospital (RTH) in Region VI**; Vicente Sotto Memorial Medical Center Governor Celestino Gallares Memorial Hospital (GMH) in Region VII; and Eastern Visayas Regional Medical Center (EVR) in Region VIII. In Mindanao is where 5 sentinel sites and the other gonorrhea surveillance center are localized. Zamboanga City Medical Center (ZMC) in Region IX; Zamboanga Del Norte Medical Center (ZPH) in Region IX**; Northern Mindanao Medical Center (NMC) in Region X; Southern Philippines Medical Center (DMC) in Region XI; Cotabato Regional and Medical Center (CMC) in Region XII; and Caraga Regional Hospital (CRH) in Region XIII (Department of Health (DOH), 2019).

Notes: *CALABARZON-Cavite, Laguna, Batangas, Rizal, and Quezon; MIMAROPA-Mindoro, Marinduque, Romblon, and Palawan; **The two gonorrhea surveillance centers in the Philippines

Objectives of the Study

This study aims to assess the prevalence of an antimicrobial-resistant bacterium *Klebsiella pneumoniae* in reported cases in the Philippines by plotting a decade trend of the cumulative count of the isolates tested against antibiotics and their respective resistance rates from 2010 to 2019.

METHODOLOGY

The research is a descriptive study employing a bibliographic approach. Data and reports were obtained via antimicrobial resistance surveillance reference laboratory page (https://arsp.com.ph/) and downloaded the executive summaries from their official publication panel.

K. pneumoniae isolates handed over the sentinel sites and gonorrhea surveillance centers are put through standard culture and resistance test methodology anchored in the manual provided by the WHO and Clinical Laboratory Standards Institute (CLSI). Most of the K. pneumoniae isolates are obtained from specimens including respiratory specimens, urine, blood, and cutaneous/wound while being present as well in other fluids, tissues, and genital samples. Results are then forwarded to the data management unit (DMU) of the reference laboratory. If isolates are presenting abnormal resistance patterns, these will be sent to in Department of Health- Antimicrobial Resistance Surveillance Laboratory (DOH-ARSL), the main surveillance site, to undergo genotypic and phenotypic evaluation.

Isolates that are suspected to be resistant to antimicrobial agents are re-determined by utilizing two approaches: minimum inhibitory concentration (MIC) and disk-diffusion agar method. To add, antimicrobial agents needed per sentinel site may differ from each other as proposed in the latest CLSI standards. The mentioned antimicrobial agents include drugs under these antibiotic classes: beta-lactams, fluoroquinolones, aminoglycosides, carbapenems, and sulfonamides.

Within 2010 through 2019, 24 sentinel sites (21 sentinel sites in 2010-2011; 21 in 2012 - 2013; 22 in 2014-2015; 24 in 2016-2017; 24 in 2018-2019) and 2 gonorrhea surveillance centers (1 gonorrhea surveillance center 2010-2011; 1 in 2014-2015; 2 in 2016-2017; and 2 in 2018-2019) across 16 regions in the Philippines are subject to data gathering for AMR of K. pneumoniae. The 24 sentinel laboratories and 2 gonorrhea surveillance centers receiving the routinely sent priority specimens are localized in the three major islands of the country: 15 sentinel sites in Luzon, 5 surveillance sites inclusive of 1 gonorrhea surveillance center in the Visayas, and 5 surveillance centers and the other gonorrhea surveillance in Mindanao. These hospitals and research facilities are responsible for the surveillance of AMR and hand in the reports to DOH annually.

Nonsusceptibility patterns of K. pneumoniae isolates against classes of antimicrobial agents from 2010 to 2019 are plotted and analyzed using Microsoft Excel.

RESULTS AND DISCUSSIONS

Table 1 shows the antibiotic classes utilized by experts to identify and determine antibiotic resistance patterns presented by K. pneumoniae isolates. Under six antibiotic classes are twenty medicaments following concentrations based on CLSI standards. Under aminoglycosides, binders to 30s ribosomal subunit of a bacterial cell and are responsible for incorrect code reading disrupting the synthesis of proteins (Krause et al., 2016), are amikacin, gentamicin, and tobramycin. Belonging to beta-lactam antibiotics, characterized by the rings on their structure

cores containing nitrogen that catalyze for bacterial self-digestion or autolysis (Cho et al., 2014), are amoxicillin-clavulanic acid, ampicillin-sulbactam, and piperacillin-tazobactam. Under carbapenems and cephalosporins, characterized by the similar mechanism as the beta-lactam antibiotics, are doripenem, ertapenem, imipenem, and meropenem and cefazolin, cefepime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, and cephalothin, respectively. Fluoroquinolones such as ciprofloxacin and levofloxacin are characterized by their mechanism of inhibiting DNA synthesis by targeting enzymes that overwind and under wind DNA called topoisomerase (Fàbrega et al., 2008). The last class is sulfonamides with a sole antibiotic under it, co-trimoxazole is responsible for inhibiting bacterial protein synthesis by hindering folic acid production (Ogbru, n.d.).

Table 1. Resistance rates against antimicrobial agents

Antiobiotic Classes		Years									
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Aminoglycosides		% Resistance									
AMK	Amikacin	8.20	7.50	5.70	7.00	6.10	6.80	5.50	7.00	6.00	4.90
GEN	Gentamicin	29.80	28.00	25.20	27.00	25.10	24.10	24.00	24.00	22.70	22.70
TOB	Tobramycin	*	*	*	*	*	*	*	*	22.00	16.40
Beta-Lactamese		% Resistance									
AMC	Amoxicillin-clavulanic	31.70	*	29.80	28.00	31.40	37.00	40.30	39.00	35.50	37.20
SAM	Ampicillin-sulbactam	33.00	29.00	32.30	*	*	*	*	*	*	*
TZP	Piperacillin-tazobactam	*	*	9.20	14.00	16.10	21.10	22.70	*	22.00	24.60
Carbapenems		% Resistance									
DOR	Doripenem	*	*	*	*	*	*	*	*	*	15.20
ETP	Ertapenem	5.70	*	5.10	9.00	11.80	15.30	9.10	* *	9.00	10.20
IPM	Imipenem	6.50	3.00	3.40	6.00	7.60	11.10	11.80	11.00	10.30	12.00
MEM	Meropenem	3.50	*	3.30	7.00	8.80	11.90	11.40		11.70	13.50
Cephalosporins		% Resistance									
CFZ	Cefazolin	*	*	*	*	*	*	*	*	51	50.90
FEP	Cefepime	25.70	13.50	11.50	16.00	28.10	26.10	30.40	33.00	34.00	34.70
CTX	Cefotaxime	*	*	*	*	*	*	*	*	49	46.30
CAZ	Ceftazidime	*	*	*	*	*	*	*	*	*	44.00
CRO	Ceftriaxone	36.70	34.00	35.50	40.00	39.40	40.60	40.90	46.00	45	46.60
CXM	Cefuroxime	29.70	40.00	38.70	46.00	45.70	49.10	40.30	50.00	48.00	52.20
CEP	Cephalothin	47.00	64.00	*	*	*	*	*	*	*	*
Fluoroquinolones		% Resistance									
CIP	Ciprofloxacin	30.00	29.00	26.00	28.00	26.30	24.40	26.00	23.00	22	44.80
LVX	Levofloxacin	*	*	*	*	* *	*	*	*	20	25.80
Sulfonamides		% Resistance									
CTM	Co-trimoxazole	*	*	*	*	* *	*	*	61	*	49.70

*Note: * Data not available/medicament is not used for a specific year*

Figure 1 exhibits the cumulative count of K. pneumoniae isolates against antibiotics classes from 2010 to 2019. The line graph shows the rising trends of isolates tested against panels of antimicrobial agents and depicts the emerging resistance of bacteria versus their respective medicaments. The percentage increase of cumulative isolate counts is measured using the formula: % Change = (Final Count - Initial Count)/|Initial Value| * 100 (Percentage Change Calculator, n.d.). The change is calculated utilizing the number cumulative number of isolates every two years. From 2010 to 2011, the percentage increase is ~8.4%, from 2012 to 2013, it rose to ~63%, from 2014 to 2015, 2.9%, from 2016-2017, 22.17%, and from 2018 to 2019, the percentage increase is 9.63.

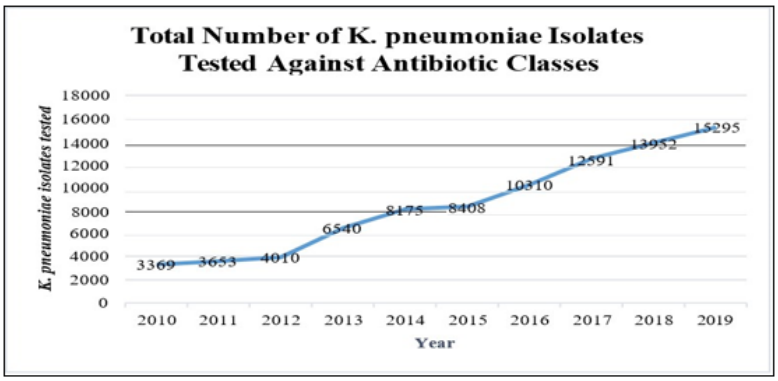

Figure 1. Total number of *K. Pneumoniae* Isolates Tested against Antibiotic Classes

Figure 2 exhibits the trends of amikacin, gentamicin, and tobramycin that belong to a broadspectrum class aminoglycoside inhibiting protein synthesis (Krause et al., 2016). Within a decade, K. pneumoniae isolates initially presented a high cumulative resistance percentage (29.8%) against gentamicin but slowly declined toward the succeeding years only rising abruptly in the year 2013. The Amikacin resistance line graph presents a fluctuating trend that shows a constantly increasing and decreasing pattern against the antibiotic. On the other hand, the biennial tobramycin data exhibits a decline of resistance peaking at its first time as an antimicrobial panel and plummeting in the succeeding year.

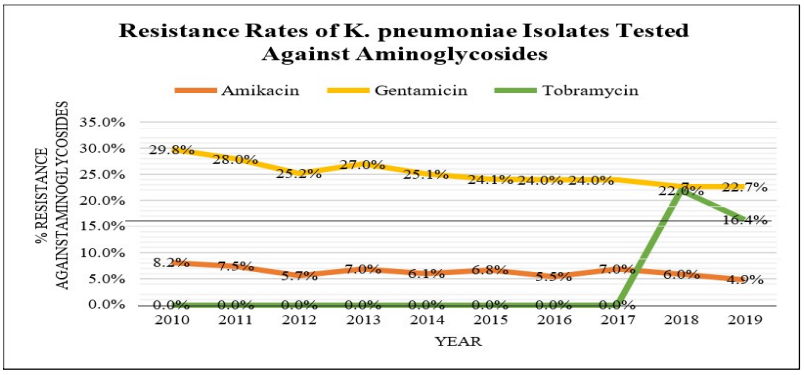

Figure 2. Nonsusceptibility Rates of *K. pneumoniae* Isolates Tested Against Aminoglycosides

Figure 3 represents the trends of three medicaments, amoxicillin-clavulanic acid, ampicillin sulbactam, and piperacillin-tazobactam, under beta-lactamase inhibitors of beta-lactam antibiotics that prevent the synthesis of the bacterial cell wall (Cho et al., 2014). Ampicillin-sulbactam served as one of the antibiotics for the initial three years within the study period garnering a 33.0% resistance rate on its first year, decreasing at 29.0% on the second, and increasing back at 32.3% on the third. Amoxicillin-clavulanic acid resistance presents a flowy trend starting at 31.7% resistance following a decreasing and increasing pattern peaking at 40% resistance percentage in the year 2016 although reports from the year 2011 seemed to be unavailable. Piperacillin-tazobactam nonsusceptibility trend presents an evident increase of K. pneumoniae resistance despite missing data in the year 2017 with a percentage increase of ~167%, from its initial to current use, only within eight years.

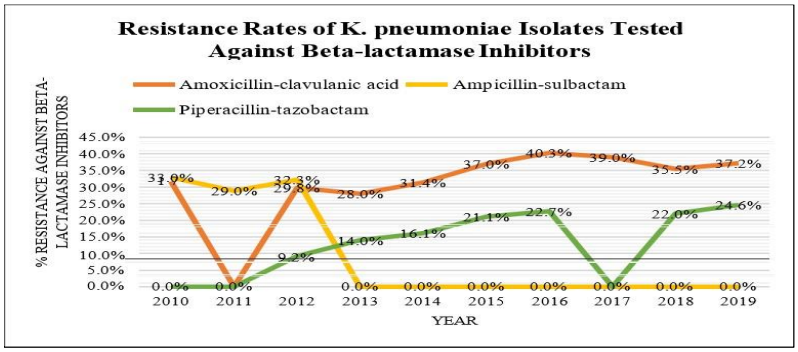

Figure 3. Nonsusceptibility Rates of *K. pneumoniae* Isolates Tested Against Beta-Lactamase Inhibitors

Figure 4 represents the following first to fourth generation cephalosporins: cefazolin, ceftriaxone, cefepime, cefuroxime, cefotaxime, cephalothin, and ceftazidime, under class cephalosporins that also prevent the synthesis of the bacterial cell wall (Fookes, 2018). Resistance against cefazolin is relatively high despite the biennial data provided peaking at 51% and decreasing at 50.9% with a minuscule percentage drop (~0.19%). Cefepime, one of the few antibiotics to complete a decade report, resistance presents a decreasing and increasing pattern of trend. Decreasing pattern is observed for the first three years, within the study period, of using the antibiotic and slowly increased on the succeeding ones only dropping in the year 2014 but continuously rose in the following years. Similar to cefazolin, the biennial data provided presents quite a high resistance rate against cefotaxime with 49% nonsusceptibility percentage in its first year and 46.3% in the second. K. pneumoniae isolates presented a constant resistance increase within a decade against ceftriaxone peaking in 2019 with a nonsusceptibility rate of 46.6% and lowest recorded percentage at 34% in 2011. Resistance against cefuroxime peaked in the last year with a 52.2% nonsusceptibility percentage and is low in 2010 with a 29.7% resistance rate. The trend exhibits an increasing and decreasing pattern as the years go by. Nonsusceptibility rates of K. pneumoniae isolates increased within the first two years of the study period, 2010 and 2011, with an increase from 47% in the initial year to 64% in the following.

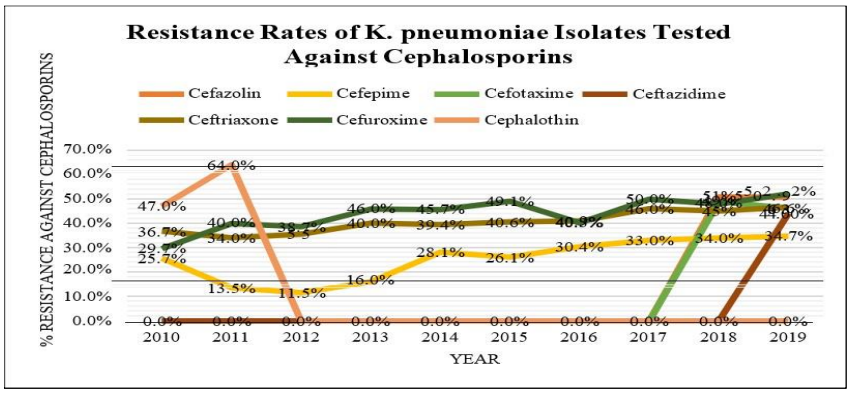

Figure 4. Nonsusceptibility Rates of *K. pneumoniae* Isolates Tested Against Cephalosporins

Figure 5 exhibits the resistance rates isolates of interest against ciprofloxacin and levofloxacin which are underclass fluoroquinolones, the sole antibiotic responsible for inhibiting DNA synthesis directly (Hooper, 2001). Resistance against ciprofloxacin is decreasing however, by the end of the study period, the nonsusceptibility rate rocketed to 44.8% from 22% in the

previous year. The biennial resistance data against levofloxacin from the last two years shows a brief increase from 2018 to 2019.

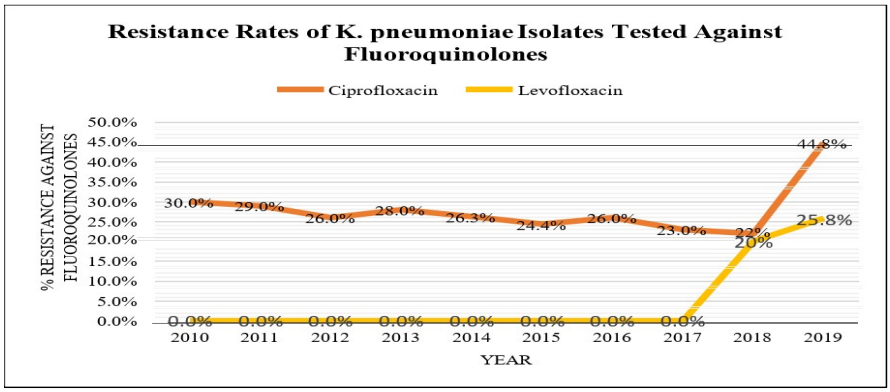

Figure 5. Nonsusceptibility Rates of *K. pneumoniae* Isolates Tested Against Fluoroquinolones

CONCLUSIONS

The increasing trends of MDR K. pneumoniae isolate every year is alarming as categorized antimicrobial agents seem to have little to no efficacy against these pathogens. People are oblivious as to how this health crisis would affect the future of medicine and the magnitude of it can bring the pre-antibiotic era back.

In conclusion, the researchers suggests an in-depth study inclusive of complete data from the main reference (i.e.: concentrations of the antibiotics used to examine resistance per region) and the morbidity and mortality reports of patients that suffered illnesses due to K. pneumoniae infection since the plotted trends only supplement superficial information regarding the seriousness of resistant K. pneumoniae isolates. Moreover, health awareness programs tackling antimicrobial resistance and its future undesirable outcomes must also be considered and implemented.

REFERENCES

Bayot, M.L. & Bragg, B.N. Antimicrobial Susceptibility Testing. [Updated 2020 Aug 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539714/

Cho, H., Uehara, T., & Bernhardt, T. G. (2014). Beta-lactam antibiotics induce a lethal malfunctioning of the bacterial cell wall synthesis machinery. Cell, 159(6), 1300–1311. https://doi.org/10.1016/j.cell.2014.11.017

Choby, J. E., Howard-Anderson, J., & Weiss, D. S. (2020). Hypervirulent Klebsiella pneumoniae - clinical and molecular perspectives. Journal of Internal Medicine, 287(3), 283–300. https://doi.org/10.1111/joim.13007

Department of Health (DOH). (2020). Antimicrobial Resistance Surveillance Program 2019 Annual Report. https://arsp.com.ph/

Department of Health (DOH). (2019). Antimicrobial Resistance Surveillance Program 2018 Annual Report. https://arsp.com.ph/.

Department of Health (DOH). (2018). Antimicrobial Resistance Surveillance Program 2017 Annual Report. https://arsp.com.ph/

Department of Health (DOH). (2017). Antimicrobial Resistance Surveillance Program 2016 Annual Report. https://arsp.com.ph/

Department of Health (DOH). (2016). Antimicrobial Resistance Surveillance Program 2015 Annual Report. https://arsp.com.ph/
Department of Health (DOH). (2015). Antimicrobial Resistance Surveillance Program 2014 Annual Report. https://arsp.com.ph/
Department of Health (DOH). (2014). Antimicrobial Resistance Surveillance Program 2013 Annual Report. https://arsp.com.ph/
Department of Health (DOH). (2013). Antimicrobial Resistance Surveillance Program 2012 Annual Report. https://arsp.com.ph/
Department of Health (DOH). (2012). Antimicrobial Resistance Surveillance Program 2011 Annual Report. https://arsp.com.ph/
Department of Health (DOH). (2011). Antimicrobial Resistance Surveillance Program 2010 Annual Report. https://arsp.com.ph/
Fàbrega, A., Madurga, S., Giralt, E., & Vila, J. (2008). Mechanism of action of and resistance to quinolones. https://doi.org/10.1111/j.1751-7915.2008.00063.x
Fookes, C. (2018, July 20). List of Cephalosporins + Uses, Types & Side Effects - Drugs.com. https://www.drugs.com/drug-class/cephalosporins.html
Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics (World Health Organization, 2017)
Gould, I. M., & Bal, A. M. (2013). New antibiotic agents in the pipeline and how they can help overcome microbial resistance. Virulence, 4(2), 185–191. https://doi.org/10.4161/viru.22507
Hooper, D. C. (2001). Mechanisms of action of antimicrobials: Focus on fluoroquinolones. Clinical Infectious Diseases, 32(SUPPL. 1), 9–15. https://doi.org/10.1086/319370
Jorgensen, J. H., & Ferraro, M. J. (2009). Antimicrobial susceptibility testing: A review of general principles and contemporary practices. Clinical Infectious Diseases, 49(11), 1749– 1755. https://doi.org/10.1086/647952
Krause, K. M., Serio, A. W., Kane, T. R., & Connolly, L. E. (2016). Aminoglycosides : An Overview. 1–18
Li, L., Yu, T., Ma, Y., Yang, Z., Wang, W., Song, X., Shen, Y., Guo, T., Kong, J., Wang, M., & Xu, H. (2019). The genetic structures of an extensively drug resistant (XDR) Klebsiella pneumoniae and its plasmids. Frontiers in Cellular and Infection Microbiology, 9(JAN), 1–11. https://doi.org/10.3389/fcimb.2018.00446
Martin, R. M., & Bachman, M. A. (2018). Colonization, infection, and the accessory genome of Klebsiella pneumoniae. Frontiers in Cellular and Infection Microbiology, 8(JAN), 1–15. https://doi.org/10.3389/fcimb.2018.00004
Ogbru, O. (n.d.). Sulfonamides: Drug Facts, Side Effects and Dosing. Retrieved March 20, 2021, from https://www.medicinenet.com/sulfonamides-oral/article.htm
Percentage Change Calculator. (n.d.). Retrieved March 20, 2021, from https://www.omnicalculator.com/math/percentage-change
Rosenblatt-Farrell, N. (2009). The Landscape of Antibiotic Resistance. Environmental Health Perspectives, 117(6). https://doi.org/10.1289/ehp.117-a244
Sirijan, S., & Nitaya, I. (2016). Mechanisms of antimicrobial resistance in Pasteurellaceae. PBioMed Research International, 2016(1155), 1–8
Ullah, H., & Ali, S. (2017). Classification of Anti-Bacterial Agents and Their Functions. Antibacterial Agents. https://doi.org/10.5772/intechopen.68695
Ventola, C. L. (2015). The antibiotic resistance crisis: causes and threats. P & T Journal, 40(4), 277–283. https://doi.org/Article
World Health Organization. (2014). Antimicrobial resistance: global report on surveillance. World Health Organization. https://apps.who.int/iris/handle/10665/112642

World Health Organization. (2017). Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics.