Comparative Analysis: Resistance Of Klebsiella Pneumoniae to Fluoroquinolone and Carbapenem in European Countries.

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Abstract- ***K. pneumonia has been reported as a threat to human health due to the emergence of multidrug resistant isolates. This research was aimed at identifying the resistance rates of K. Pneumoniae to fluoroquinolones in 2021, its European age distribution and its resistance rates compared to carbapenems. The potential for K. Pneumoniae to increase or reduce susceptibility to fluoroquinolones in the next decade was determined by examining the resistance profile in 4 European countries for 16 years. Results observed highlighted that K. Pneumoniae isolates in Europe were more susceptible to Carbapenems compared to fluoroquinolones in the year 2021. The research also identified an over 50% resistance of K. Pneumoniae Europeans isolate for ages 19 and higher. The about 2 fold resistance increase observed to fluoroquinolones over16 years pose a high therapeutic threat to Europeans over the age of 19 over the next decade as K. Pneumoniae has shown tendencies to increase in their resistance rates. Thus European Health organisations need to create policies to curb the use of fluoroquinolones in the treatment of K. Pneumoniae infections and preserve administration to rare cases to limit rate of resistance development.***

I. INTRODUCTION

K. pneumonia has been reported as a threat to human health due to the emergence of multidrug resistant isolates linked to hospital outbreaks and virulent strains connected with community acquired infections (1). Though flouroquinolone is therapeutically effective against K. pneumonia, resistance to flouroquinolones has been observed in multiple microoraganiusms.

Resistance to flouroquinolone

DNA sequencing was used to determine mutations in the quinolone resistance-determining region of the gyrA and gyrB genes from clinical isolates of Escherichia coli with a range of MICs of ciprofloxacin from 0.007 to 128 micrograms/ml and of nalidixic acid from 2 to > 2,000 micrograms/ml. clinical isolates with a MIC of > or = 8 micrograms/ml (11 strains), a double change in Ser-83 and Asp-87 was found. All isolates with a MIC of nalidixic acid of > or = 128 micrograms/ml showed a mutation at amino acid codon Ser-83. Thus depicting that a change in Ser-83 is sufficient to generate a high level of resistance to nalidixic acid, whereas a second mutation at Asp-87 in the A subunit of DNA gyrase may play a complementary role in developing the strain's high levels of ciprofloxacin resistance (15). Similarly, a 2023 research abstract reported that genomic analysis identified Asp87Gly or Ser83Leu substitutions in the gyrA gene in the mutants of Escherichia coli K12 that obtained flouroquinolones resistance (12)

More so, 30 fluoroquinolone-resistant clinical isolates of Escherichia coli producing extended-spectrum β-lactamases were observed and mutations in the quinolone resistance-determining regions of gyrA, gyrB, parC, and parE were studied. Ten isolates showed a mutation in parE that was significantly associated with an increase in the MIC for fluoroquinolones (14).

Resistance to flouroquinolones in Flaviviruses such as Dengue and Zika virus were researched and Two putative resistance-conferring mutations were

detected in the envelope gene of ciprofloxacin and difloxacin-resistant DENV-4 (13)

Neisseria gonorrhoeae, the causative agent of gonorrhea was also observed and the effects of the fluoroquinolone ciprofloxacin on the catalytic and DNA cleavage activities of wild-type gyrase and topoisomerase IV and the corresponding enzymes that harbor mutations associated with cellular and clinical resistance to fluoroquinolones were determined. Research results indicate that ciprofloxacin interacts with both gyrase (its primary target) and topoisomerase IV (its secondary target) through a water–metal ion bridge that was previously observed in other species. Then, mutations in amino acid residues that anchor this bridge diminish the susceptibility of the enzymes for the drug, leading to fluoroquinolone resistance (11).

Then, Increased resistance of Fluoroquinolones in Enterobacteriaceae was reported in some countries causing community acquired or nosocomial urinary tract infections especially in Asia. One to two thirds of Enterobacteriaceae producing extended spectrum β-lactamases were reported to be resistant to Fluoroquinolone (4).

Resistance to flouroquinolone in Klebsiella pneumonia

Just as resistance has been observed in a lot of other microbes, Klebsiella pneumonia is not exempted. High prevalence resistance to ciprofloxacin in 89% of K. pneumoniae isolates was detected from a study at Iran. The higher prevalence of oqxA (95%) and oqxB (98%) was also detected, which are efflux pumps genes. There was a significant relationship between ciprofloxacin resistance and the oqxB gene as well as between ceftriaxone and chloramphenicol resistance and the oqxA gene. The expression of the oqxA gene was higher in ciprofloxacin-resistant isolates (10).

Fluoroquinolone sensitivity of K. pneumoniae was determined and of the tested isolates, 12% were observed to be reduced susceptible to fluoroquinolones, (2). This increasing resistance of K. pneumoniae to fluoroquinolones has been reported in multiple countries. In line with these, one hundred eighty four K. pneumoniae isolates from Iran were tested for their susceptibility to fluoroquinolones and increased resistance was observed of 2.1% - 31.5% to varying Fluoroquinolones (3).

K. pneumoniae blood isolates from Romania in 2015 were analysed for their susceptibility to a range of antibiotics including Fluoroquinolones, resistance were observed to Fluoroquinolones (27.02%) and one strain was resistant to Carbapenem (5). K. pneumoniae was stated to be the most prevalent cause of Carbapenem resistance in the US due to its production of Carbapenemase (6).

Same as Fluoroquinolones, resistance of K. pneumoniae to Carbapenem has also been reported in multiple countries.

From Jan 2006 - April 2007, 461 in-patients in a medical centre in Israel hospital facility were observed out of which 88 had Carbapenem resistant K. Pneumonia and were reported to be resistant to all commonly used antibiotics (7). Also, Clinical specimens were obtained from 6 hospitals in Ankara, Antalya, Istanbul, and Kayseri between 2010 and 2014 and 50 K. Pneumonia isolates were collected. The OXA48 Carbapenemase region was detected in 33 of the 50 isolates. Other resistant genes were also identified in the sample analysed (8). A 2017 research analysing K. Pneumoniae isolates from the UK and Ireland also identified multidrug resistant strains (9).

As previously stated, reports have shown K. pneumoniae resistance to Fluoroquinolones and Carbapenem in diverse countries, the present research aims to compare the resistance rates of K. pneumoniae resistance to Fluoroquinolones and Carbapenem reported in European countries.

II. METHODOLOGY

Data analysed in this paper was obtained and analysed from European centre for disease prevention and control (ECDC) surveillance atlas of infectious disease. Data obtained was also analysed using Excel. Comparison of % resistance year 2021 data of K. Pneumoniae to Fluoroquinolones and Carbapenems was carried out. Also, resistance profile of K. Pneumoniae to Fluoroquinolones association with age in the year 2021 was determined for 3 European countries. Then the potential of K. Pneumoniae to

become more or less susceptible to Fluoroquinolones in the next decade was determined by comparing resistance trends for 4 European countries in 16 years.

III. RESULTS

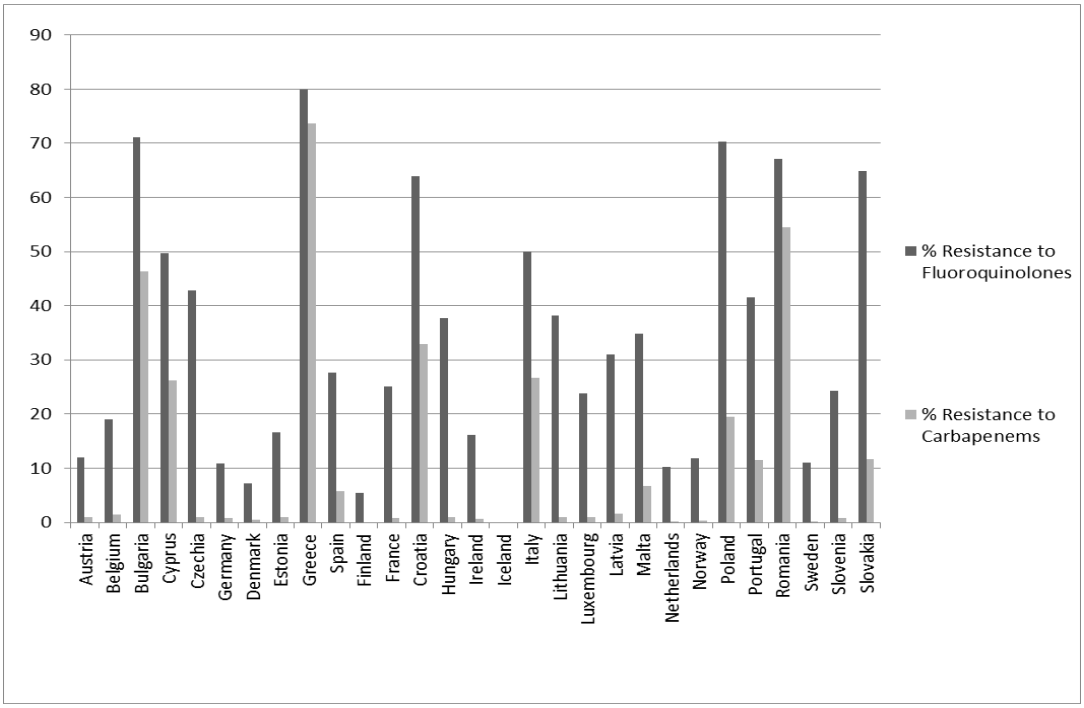

Fig.1. Antimicrobial % resistance of Klebsiella pneumoniae, to fluoroquinolones and Carbapenems, in European countries year 2021

Resistance profile of K. Pneumoniae isolates to Fluoroquinolone for 16 years in 4 countries and age distribution of resistance in 2021

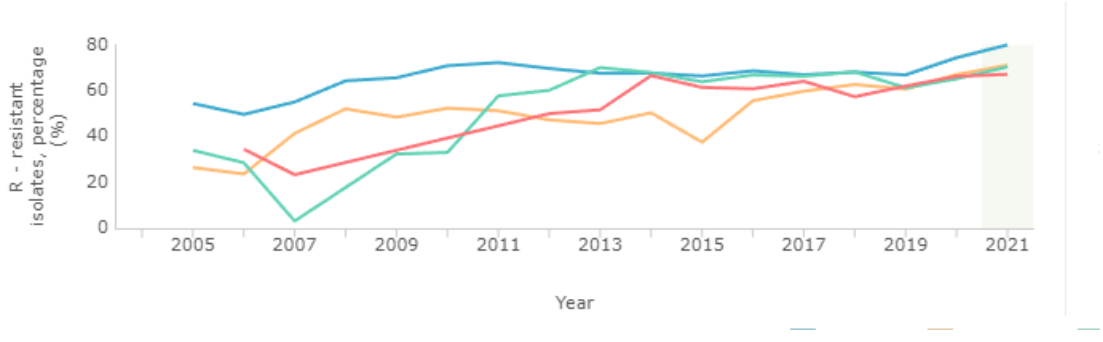

Fig. 2: Resistance profile of K. Pneumoniae isolates to Fluoroquinolone for 16 years in 4 countries

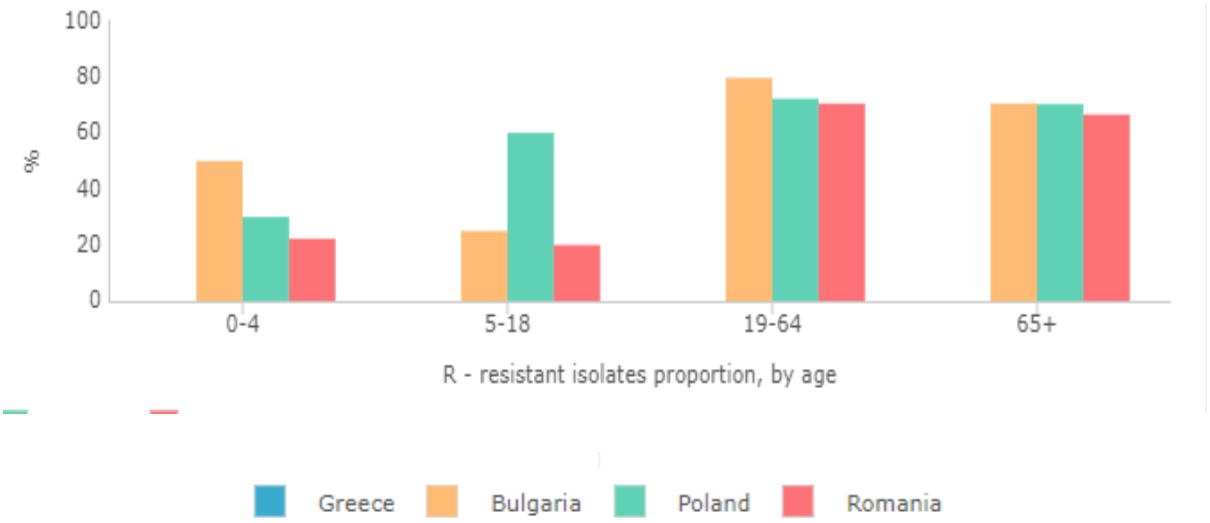

Fig. 3: Age distribution of resistance in 2021 in 4 European countries

IV. DISCUSSION AND CONCLUSION

Resistance to both antibiotics in 2021 were most predominant in Greece with resistance over 73% to both antibiotics as observed in Fig 1. No resistance was observed to both antibiotics in iceland. Fig 1. also showed for Countries with % resistance to Carbapenems less than or equal to 1, they showed a more than 10 fold higher resistance to Fluoroquinolone compared to Carbapanems. This large disparity was not observed in those of greater than 2% resistance to Carbapanems. It could be linked to the multidrug resistance earlier reported and observed in K. pneumoniae (1) and the genes or factors predisposing to these resistance.

Resistance at a level of over 50% to Fluoroquinolone were observed in 7 European Countries but only 2 countries had over 50% resistance to Carbapanems (Fig. 1).

Further analysis was done to observe the resistance profile for the 16 years of K. Pneumoniae to Fluoroquinolone for the 4 countries with highest resistance at 2021. As observed in Fig 2 above an increase over time from a range between 20-50% in the year 2015 to over 50% at 2021 for the 4 countries. This could aid us predict what could be expected in these European Countries in the next decade with respect to K. Pneumoniae resistance to Fluoroquinolones. An over 2 fold resistance could be

expected which is a therapeutic threat as countries like Greece already have reported K. Pneumoniae isolates with over 70% resistance to Fluoroquinolone. In addition resistance profile by age in the year 2021 was observed (Fig. 3)to be higher with increasing age thus those over 19 were observed to have more resistant isolates compared to those younger than 19. This was similar across 3 countries: Poland, Bulgaria and Romania. Though resistance to Fluoroquinolones and Carbapanems has been reported in multiple countries including Israel, Iran, US etc. (6, 7, 3), this research has highlighted that K. Pneumoniae isolates in Europe were more susceptible to Carbapenems.

The research also identified that risk of developing resistance might be more as Europeans complete their adolescent years. The about 2 fold resistance increase observed to Fluoroquinolones over 16 years pose a high therapeutic threat to Europeans over the age of 19 over the next decade as K. Pneumoniae has shown tendencies to increase in their resistance rates. Thus European Health organisations need to create policies to curb the use of Fluoroquinolones in the treatment of K. Pneumoniae infections and preserve its administration to rare cases to limit rate of resistance development.

Environmental organisations also require identifying lifestyle practices that increase the spread of K. Pneumoniae infection cases and introduce new practices to prevent the spread. Also since K. Pneumoniae is not only community acquired but also leads to nosocomial infection, these new lifestyle practices could also be adapted by medical centres.

CONFLICT OF INTEREST

No conflict of interest

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