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Review Article

A Review of Antimicrobial Surveillance Networks Across the Globe

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A B S T R A C T

Introduction: Antimicrobial Resistance (AMR) poses a global public health threat with a wide gap between the knowledge and mechanism of resistance acquired by the pathogens. This increasing hazard of AMR has been recognized by the different geographical regions and responded to by implementing tough restrictions and AMR strengthening AMR surveillance systems for monitoring and prediction.

Methodology: We searched data using National and International databases of different geographical AMR surveillance networks and extracted information from them.

Results: In India, AMR surveillance reported fluoroquinolones and Aminoglycosides as the major group against which microbes develop resistance followed by Cephalosporins and Carbapenem whereas the WHO European Region, EU/EEA noted decreasing trend of AMR during 2016-2020 for several bacteria although an increasing trend was reported for Carbapenem-resistance in Klebsiella pneumoniae and represents region's most serious concern.

Conclusion: India currently has two independent AMR surveillance networks, whereas the European Surveillance system presents a trajectory of resistance data based on consumption data.

Keywords: Antimicrobial Surveillance, Antimicrobial Resistance, Antimicrobial Consumption

Introduction

New AMR mechanisms are evolving as a result of improper antimicrobial usage that are posing a danger to the treatment of infectious diseases, resulting in prolonged sickness, disability, and death, as well as growing healthcare expenses.[1] Lord Jim O'Neill's published a report in 2016 predicting that antimicrobial resistance might cause 10 million deaths per year globally by 2050.[2]

This increasing hazard of AMR has been recognized by the different geographical regions and responded to by implementing an Integrated AMR surveillance which has also been emphasized in previous research as a significant tool for guiding policy and regulating reactions.[3]

In 2015, World Health Organization established the Global Antimicrobial Resistance Surveillance System (GLASS), the first global collaborative effort to standardize AMR surveillance[4] which has collaborated with already existing large regional AMR surveillance networks.

India has a huge infectious diseases burden and a lack of countrywide data on estimates of drug resistance prevalence severely restricting its coordinated response to AMR.[5] To address this need, the Indian Council of Medical Research (ICMR) in New Delhi launched Antimicrobial Resistance Surveillance & Research Network (AMRSN)[6] in 2013, and in 2017, the Government of India instituted another comprehensive surveillance network, the National Antimicrobial Resistance Surveillance Network (NARS-Net),[7] which is coordinated by National Centre for Disease Control (NCDC), Delhi for tackling AMR and implementation of National Action Plan on AMR (NAP-AMR).

Based on the above background we planned a review study to have a better comparative knowledge of geographical AMR surveillance networks and trends for priority pathogens, with specific attention to surveillance networks in India.

Methodology

This study was conducted in two parts; a review of regional AMR surveillance networks and a comparative analysis of India and Europe's AMR surveillance networks.

Results

Review of Regional Antimicrobial Surveillance Networks.

WHO European Region, 2016-2020:

The European Antimicrobial Resistance Surveillance Network (EARS-Net) and the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network are the two main international AMR surveillance networks in the WHO European Region.

Every year, countries and areas report routine Antimicrobial Susceptibility Testing (AST) results collected from one or more medical microbiology laboratories to both networks. Only data from invasive (blood and cerebrospinal fluid) isolates are included in surveillance with a focus on invasive isolates of eight key bacterial species:

1. Staphylococcus aureus
2. Enterococci species
3. Escherichia coli
4. Klebsiella species
5. Pseudomonas species
6. Acinetobacter species
7. Enterococcus faecalis (E. faecalis) and Enterococcus faecium (E. faecium)
8. Streptococcus pneumoniae

In E. coli, Carbapenem resistance trend increased significantly between 2016 and 2020 whereas trends for aminopenicillin, third-generation cephalosporin, fluoroquinolone, and aminoglycoside resistance all decreased slightly.

The trend of carbapenem, third-generation cephalosporin, fluoroquinolone, and aminoglycoside resistance all increased significantly during 2016-2020 in Klebsiella pneumoniae.

In Pseudomonas aeruginosa, the trend of Piperacillin-tazobactam, Ceftazidime, carbapenem, and fluoroquinolone resistance, all increased significantly during 2016-2020, whereas the trend against Aminoglycoside and Carbapenem resistance decreased sharply in the same period.

Acinetobacter spp. is the least commonly reported bacterial species under EARS-Net surveillance, with the greatest intercountry variation in AMR percentages. Between 2016-2020, the trend of Carbapenem, Aminoglycosides, and Fluoroquinolone resistance all significantly increased.

The resistance trend against Methicillin-Resistant Staphylococcus Aureus (MRSA) decreased considerably from 2016(17.7%) to 2020(16.7%). In Streptococcus pneumoniae, no significant trend was found for Macrolide resistance in 2016-2019, however, indicated a relatively large annual resistance of 16.9% in 2020.

In Enterococcus faecalis, Gentamicin resistance decreased significantly from 2016(31.8%) to 2020(29.0%) and in Enterococcus Faecium, resistance against Vancomycin represented a significant increase from 2016(12.3%) to 2020(16.8%).

Pan America Health Organization (PAHO), 2014-2016

PAHO is a network of 19 countries in Latin America and launched the Red Latinoamericana de Vigilancia de la Resistencia a Los Antimicrobianos (ReLAVRA by its Spanish acronym) surveillance network in 1996. The officially designated national reference laboratory receives data on isolates with overall resistance percentages and intermediate resistance annually from sentinel sites.

The surveillance system provides analyses of data on six selected bacteria:

1. Klebsiella pneumoniae,
2. Escherichia coli,
3. Acinetobacter Baumannii,
4. Staphylococcus aureus,
5. Pseudomonas aeruginosa, and
6. Neisseria gonorrhoeae.

For Klebsiella pneumonia, the major concern is the emergence of Carbapenem-resistant bacteria which limits therapeutic options. Between 2014 and 2016, the percentage of nonsusceptibility to carbapenems increased significantly at the regional level.

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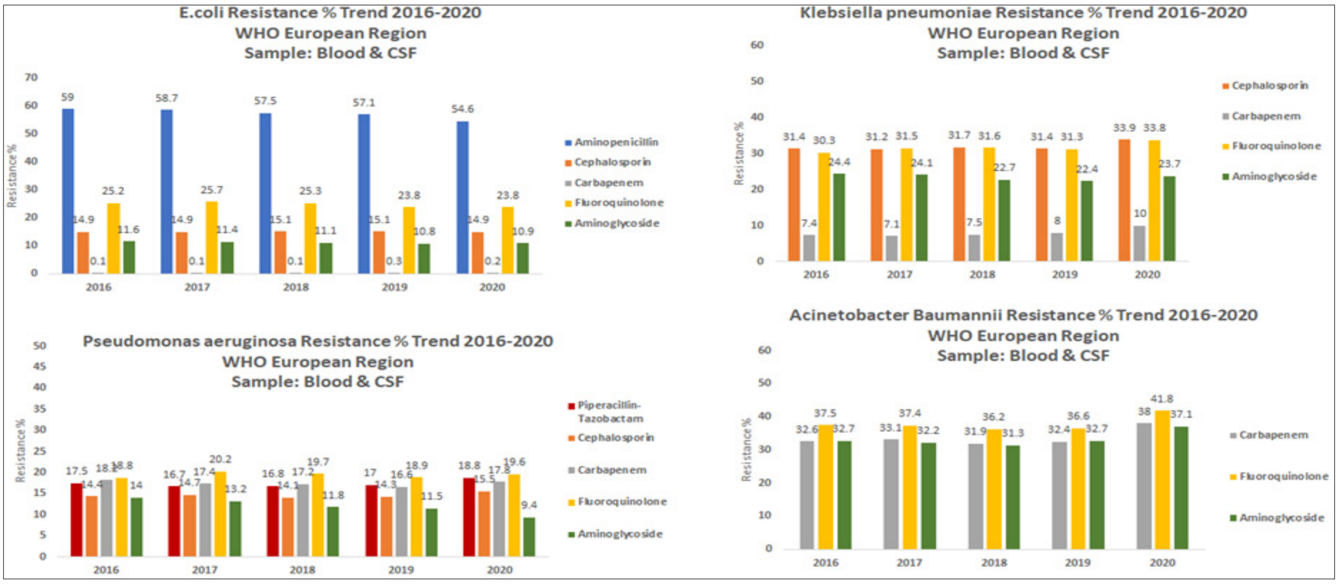

Figure 1.Resistance Trends of Priority Pathogens in WHO European Regions Over the Years 2016-2020

The percentage of Extended-Spectrum-Beta Lactamase (ESBL)-producing Escherichia coli ranged from 10% to 30% with the concern of carbapenemase-producing strains spreading all over the world. In 2016, the proportion of third-generation cephalosporin nonsusceptibility ranged from 21% in Argentina to 60% in the Dominican Republic out of 12 countries.

In Acinetobacter Baumannii, nonsusceptibility to Carbapenems varied from 29% in Honduras to 89% in Peru. Overall, the region's countries have exhibited considerable resistance to carbapenems, with nonsusceptibility levels above 50%.

Between 2014 and 2016, three countries (Bolivia, Ecuador, and Paraguay) had large increases in MRSA percentages, whereas five nations (Argentina, Brazil, Colombia, Guatemala, and Panama) showed decreases out of 15 countries. For Pseudomonas aeruginosa, the rate of carbapenem nonsusceptibility ranged from 20% in the Dominican Republic to 69 % in Peru and compared to other pathogens, information on susceptibility against Neisseria gonorrhoea is scarce in this region.

Indian Antimicrobial Surveillance Networks

- **Indian Council for Medical Research (ICMR), 2016-2020.**

Antimicrobial Resistance Research & Surveillance Network (AMRSN) is the first national AMR surveillance network established by ICMR in 2013 to understand spread and pattern of AMR in India and to strategize control measures.[8] It focuses mainly on six pathogenic groups from thirty hospitals:

1. Enterobacterales causing sepsis
2. Gram-negative non-fermenters
3. Typhoidal Salmonella
4. Diarrhoeagenic bacterial organisms,
5. Gram-positives: staphylococci and enterococci, and
6. Fungal pathogens.

Six nodal Centres are formed across the country assigned with responsibility of Antimicrobial Susceptibility Testing (AST) and are managed by coordinating center of ICMR, Delhi.[9] Molecular characterization and whole-genome sequencing are techniques utilized to detect resistance mechanism against major priority pathogens in network sites.[10]

Imipenem susceptibility in E. coli declined steadily from 86% in 2016 to 63% in 2019 and showed a slight recovery to 72% in 2020, whereas Klebsiella pneumoniae susceptibility dropped slowly from 65% in 2016 to 46% in 2019 and remained at 45% in 2020.

Sensitivity to cephalosporins, carbapenems, monobactams, and -β-lactamase inhibitors was reduced by 10-20% in A. Baumannii.

In Pseudomonas aeruginosa, the least susceptibility of 40% was observed for fluoroquinolones and 60-70% for cephalosporins, carbapenems, and aminoglycosides.

Staphylococcus aureus has shown rising resistance to most antibiotics over the years, with Teicoplanin and linezolid resistance found at very low rates of 0.5 and 1%, respectively in Methicillin-Resistant Staphylococcus Aureus (MRSA) isolates.

Isolation of MDR (Multiple Drug Resistance) strains in Salmonella typhi has dropped from 8% to 3% between 2016 and 2020. The sensitivity to Ampicillin has increased from

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92% in 2016 to 98% in 2020. Chloramphenicol sensitivity has increased from 91% in 2016 to 97% in 2020, with Trimethoprim-sulfamethoxazole sensitivity increasing from 92% in 2016 to 96% in 2020.

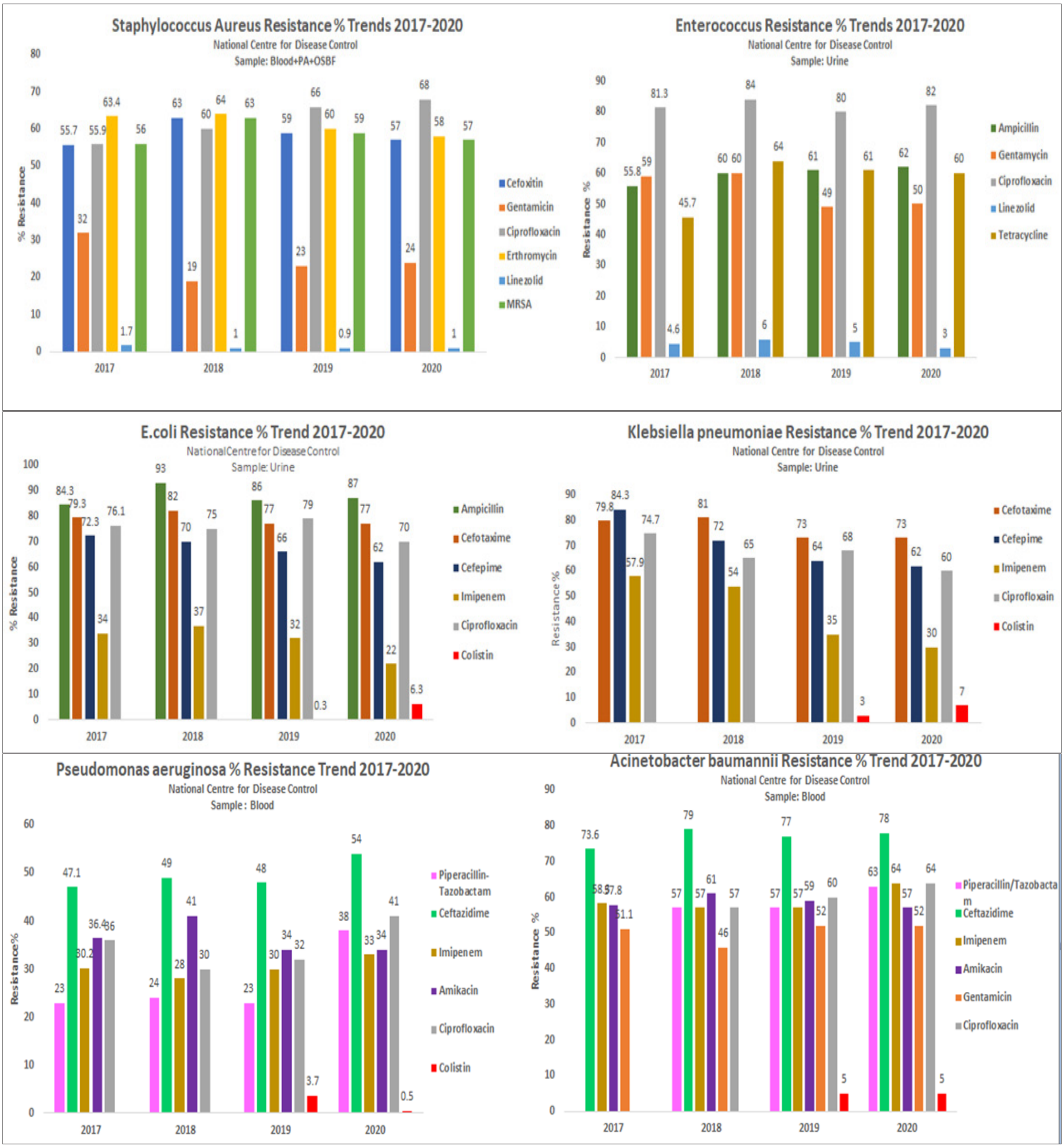

Figure 2.Resistance Trends of Priority Pathogens in NARS-Net India Over the Years 2017-2020

- **National Centre for Disease Control (NCDC), India 2017-2020.**[11]

NCDC is the site of Coordination for the "National Programme on AMR Containment" established by the Government of India during the 12th five-year plan (2012-2017). Under this program, National Antimicrobial Resistance Surveillance Network (NARS-Net) has been established and currently includes 30 state medical college labs in 24 states. The Surveillance System under this network presently includes seven priority bacterial pathogens:

1. Staphylococcus aureus
2. Enterococci species

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3. Escherichia coli
4. Klebsiella species
5. Pseudomonas species
6. Acinetobacter species
7. Salmonella enterica serotype Typhi and Para-Typhi isolated from five clinical samples; Blood, Urine, Pus Aspirates (PA), Stool and Other Sterile Body Fluids.

This Network uses WHONET software for data collection and techniques like AST with disk diffusion/ broth microdilution/ automated systems are used to detect microbial resistance in sites.

Staphylococcus aureus in blood samples showed maximum resistance against Ciprofloxacin in 2020(68%) followed by Erythromycin (64%) in 2018. The resistance trend for Ciprofloxacin increased from 2017(55.9%) to 2020(68%) and MRSA showed maximum resistance in 2018(63%).

Enterococcus isolates had maximum resistance against Ciprofloxacin in 2018(84%) and Erythromycin in 2020(84%) and displayed resistance to Linezolid (Reserve drug) decreased from 2017(4.6%) to 2020(3%) with a peak in 2018(6%). The resistance trend against Ampicillin was increasing from 2017(55.8%) to 2020(62%).

Isolates of E. coli showed maximum resistance against Ampicillin in 2018(93%) followed by Cefotaxime in 2018 (82%) and Ciprofloxacin in 2019(79%),[12] Resistance trend for cefepime was steadily decreased during 2017-2020 whereas resistance trend against Colistin was increasing from 2019 (0.3%) to 2020(6.3%) which is a reserve category drug.

Klebsiella isolates exhibited maximum resistance against Cefepime in 2017(84.3%) followed by Cefotaxime in 2017 (79.8%), resistance trend for Ertapenem and Imipenem was decreasing significantly during 2017-2020 whereas the resistance against Colistin increased from 2019(3%) to 2020(7%).

Isolates of Pseudomonas showed maximum resistance against Ceftazidime in 2020(56%) followed by Ciprofloxacin in 2020(54%) and Ceftazidime in 2019(54%). The resistance trend for Ceftazidime increased gradually from 2017(52.3%) to 2020(56%). The resistance against Colistin was increasing from 2018(7%) to 2020(8%).

Acinetobacter isolates displayed maximum resistance against Ceftazidime in 2018 (87%)[13] followed by Ciprofloxacin in 2020(81%) and Imipenem in 2018(76%). The resistance trend for Minocycline declined sharply from 2017[14] (52.2%) to 2020(25%) and maximum resistance against Colistin was shown in 2019(7%).

Comparison of AMS data Globally and Nationally:

To have a comparison of surveillance data of AMR globally and nationally, we have compared the EARS-Net of Europe with the NARS-Net of India because:

- EARS-Net and NARS- Net directly provide information based on the resistance pattern of bacteria whereas AMRSN (India) provides the data on susceptibility to measure resistance indirectly
- We have resistance data from PAHO but the data is not combined rather there are separate data for different countries. Comparing all the data will be a cumbersome task

EARS-Net Versus NARS-Net

The surveillance systems of EARS-Net (Europe) versus NARS-Net (India) are compared in this section of the study, with a focus on five priority pathogens: E. coli, Klebsiella, Pseudomonas, Acinetobacter, and Staphylococcus aureus, which were isolated from blood samples and are resistant to antibiotic classes like the third-generation cephalosporin, fluoroquinolone, aminopenicillin, aminoglycoside, and Carbapenem.

1. Escherichia Coli

The data from EARS-Net and NARS-Net figure 3, showed a consistently increasing trend of resistance in E. coli against the Aminopenicillin group of antibiotics followed by a high resistance trend for both Fluoroquinolone and third-generation Cephalosporin. Resistance to Carbapenem is a major concern for India with a peak of 33% in 2019 whereas in Europe resistance for carbapenem is rare (0.2%).

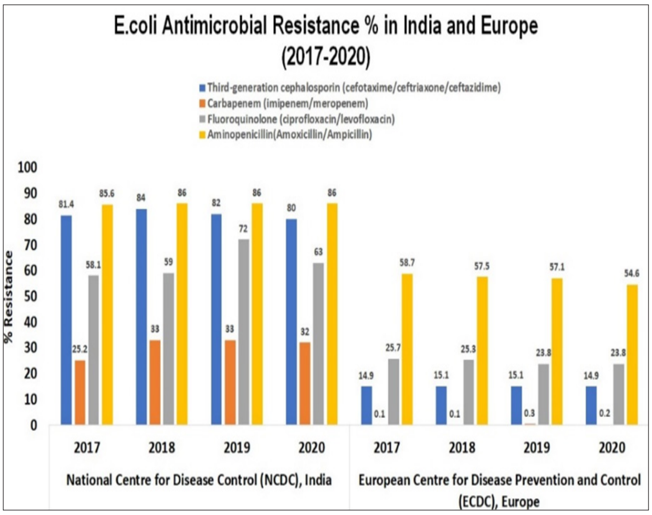

Figure 3.Comparison of E. Coli Resistance patterns in Europe and India (2017 -2020)

2. Klebsiella Pneumoniae

As shown in Figure 4, the rise of carbapenem-resistant klebsiella was identified as a major concern in both regions, with a growing trend in Europe and India exhibiting peaks of 90.2% and 10%, respectively. Fluoroquinolone resistance in India has shown an overall upward trend since 2017(54.6%), peaking in 2019(74%), and slightly decreasing in 2020(68%), whereas in Europe there is a steady increasing trend from

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2017(31.55%) to 2020(33.8%), and both regions have seen a significant increase in Third Generation Cephalosporin resistance since 2017.

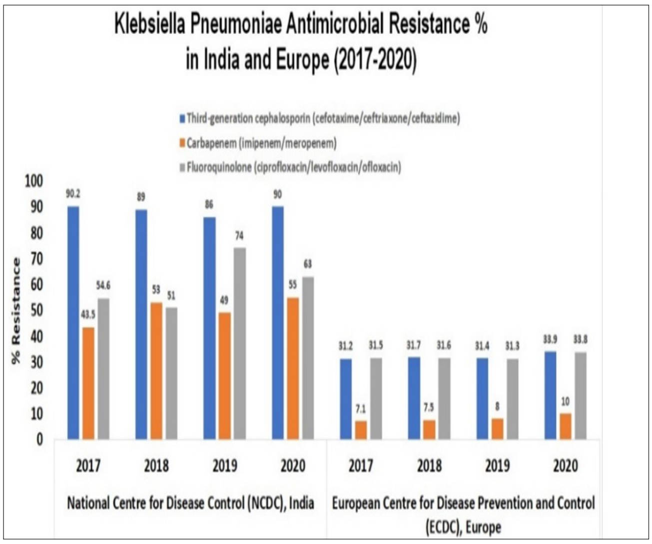

Figure 4.Comparison of Klebsiella Resistance Patterns in Europe and India (2017-2020)

3. Pseudomonas Aeruginosa

EARS-Net data Figure 5, shows the resistance trend decreases significantly for P. aeruginosa to Aminoglycosides during the period 2017-2020 whereas resistance for Fluoroquinolone (19.6%) is increasing followed by Carbapenem (17.8%) and Ceftazidime (15.5%) reaching maximum in 2020. On the other hand, NARS-Net data shows maximum resistance for Ceftazidime attaining a peak at 54% in 2020 followed by a significant increasing trend for Fluoroquinolone, Carbapenem, and Aminoglycosides.

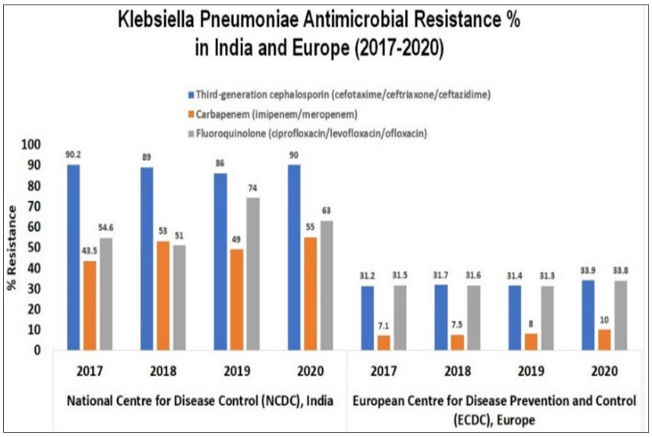

Figure 5.Comparison of Pseudomonas Resistance Patterns in Europe and India (2017-2020)

4. Acinetobacter Baumannii

As shown in Figure 6, data revealed that Carbapenem-resistant Acinetobacter is the leading issue in both India and Europe as the trend against carbapenem resistance is increasing followed by Fluoroquinolone and Aminoglycosides resistance.

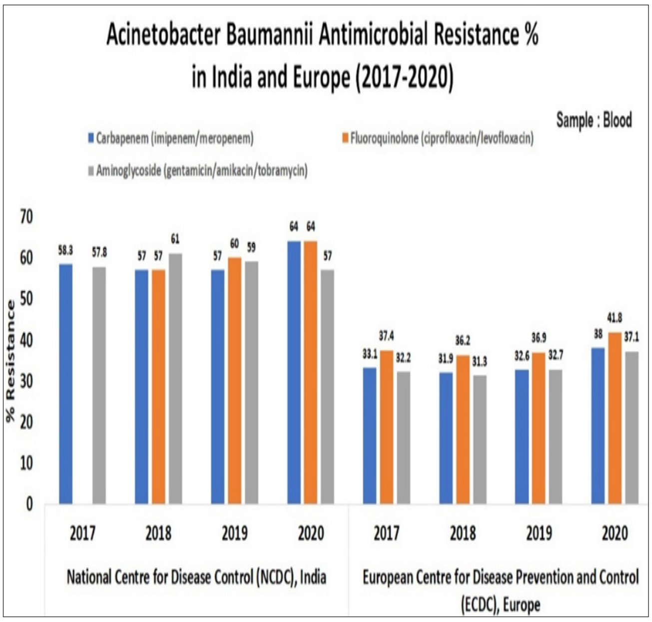

Figure 6.Comparison of Acinetobacter Resistance Patterns in Europe and India (2017-2020)

5. Staphylococcus Aureus

Data showed that the resistance of MRSA among Staphylococcus continued to be high over the past years. In India, the Trend for MRSA first increased from 56% in 2017 to 63% in 2018 and then decreases to 57% in 2020 whereas, In Europe, the trend first decreased from 16.8% in 2017 to 15.7% in 2019 and then increases to 16.7% in 2020.

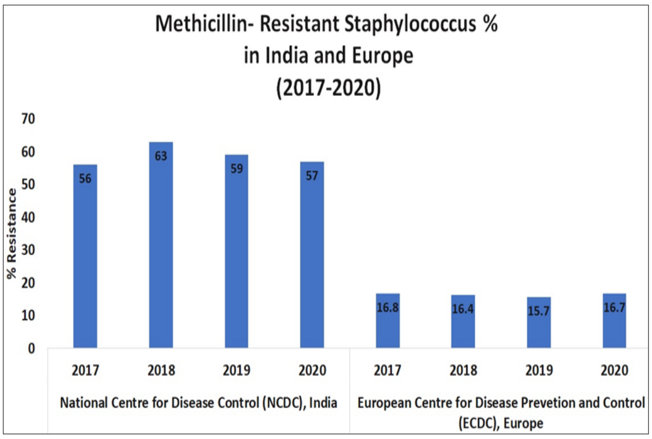

Figure 7.Comparison of MRSA Resistance Patterns in Europe and India (2017-2020)

Discussion

Reliable surveillance data is necessary for defining the AMR global burden and tracking effectiveness of measures to combat it.[15] The present study reviewed a

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few surveillance networks collaborated with WHO GLASS for the comprehensive work to eliminate hazardous effect of AMR.

Different AMRSSs have a difference in monitored bacterial species, choices of antibiotics, methods of antimicrobial susceptibility, and different objectives which necessitate the adoption of different techniques oriented to their goals for example some use only invasive clinical samples (CSF & Blood) to investigate while others sampling collection also include stools, urine, etc. The other aspect is different coverage areas of AMRSSs like EARS-Net, AMRSN and NARS-Net cover only tertiary care hospitals in countries and give the general estimate of specific pathogens resistance trends whereas PAHO provides data from both tertiary and Community Health centers.

WHO European Region, EU/EEA noted decreasing trend of AMR during 2016-2020 for several bacteria[16] evidently with a large decrease in community antibiotic consumption reported by Europe Surveillance of Antimicrobial Consumption Network (ESAC-Net) 2020,[17] although an increasing trend was reported for Carbapenem-resistant in Klebsiella pneumoniae and represents region's most serious concern.

In PAHO, there has been a significant increase in the resistance pattern of hospital pathogens since 2014, such as Klebsiella pneumoniae, which has an average resistance rate of 21% against carbapenem,[18] and Staphylococcus aureus, which is another most frequently isolated bacterium and has a 25% resistance proportion to methicillin.[19]

In India, National Database collected by both AMR surveillance indicated fluoroquinolones and Aminoglycosides as the major group against which microbes develop resistance followed by Cephalosporins and Carbapenem.

Like AMRSN and NARS-Net, EARS-Net and PAHO do not monitor colistin resistance[20] while this antibiotic is a last resort for treatment of carbapenem-resistant Gram-negative bacteria and is categorized as a reserve antibiotic by WHO Aware classification which should be monitored carefully. Studies revealed novel resistance mechanisms have emerged in recent years across the globe.[21]

The limitations of these AMRSSs are related to a lack of global coordination, insufficient standardization of terminology used in epidemiology, samples and data gathered, culture medium used, microbiological testing procedures, and dissemination of reports for years after the data was obtained.[22]

Recommendations

- India currently has two independent AMR surveillance networks. It is recommended that the Government of India may link the work of these two surveillance networks so that a national picture of antimicrobial resistance can be obtained
- However, so far, no national data on antimicrobial consumption has been gathered and correlated with AMR in Indian surveillance networks. European surveillance systems give AMC data along with demonstrating the trajectory of AMR

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Conflict of Interest: None

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