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RESEARCH ARTICLES

Understanding the Trend and Distribution of Antimicrobial Resistance Using Event Based Surveillance System: EpiWatch

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Abstract

Background: Antimicrobial Resistance (AMR) is a significant public health threat in many countries around the world, endangering the control of infections and infectious disease. AMR related illness has been responsible for annual global mortality of 700,000. Besides health outcomes, they bear an adverse impact on economic development. However, the lack of comprehensive global AMR surveillance data and an over-reliance on an indicator-based surveillance system has limited the early detection of emerging AMR threats and trends.

Methods: The EpiWATCH outbreak database has been used to retrieve AMR outbreak reports between August 2016-March 2020 using keywords such as 'resistance', 'resistant', 'superbug', 'bugs', 'MRSA' and 'VRE'. Cases were grouped according to geolocation and time to conduct a descriptive epidemiologic analysis of the outbreak.

Results: A total of 60 reports of outbreaks involving 18,275 cases of AMR were identified from 14 countries between August 2016 and March 2020. Over half of the reports were from the United States of America. The most common reported pathogen was MRSA, followed by drug-resistant Salmonella which includes Salmonella Typhi and non-Typhi Salmonella serovars. The majority of the infections were caused by gram-negative bacteria. Drug-resistant Klebsiella, Acinetobacter and New Delhi Metallo-β-lactamase-1 (NDM-1) Carbapenemase-producing Enterobacteriaceae acquired in hospitals were associated with reported mortality. Schools and universities were at-risk locations in the community for Methicillin-resistant Staphylococcus Aureus (MRSA) outbreaks and in hospital settings, the neonatal units were at risk. EpiWATCH identified reports of AMR for pathogens not captured by the WHO AMR surveillance system, GLASS.

Conclusion: EpiWATCH identified reported AMR outbreaks quickly compared to an indicator-based surveillance system. It detected outbreaks by pathogens, including some not monitored by the World Health Organization. Also, it identified information on both colonised and infected cases. Thus, open source data from EpiWATCH can complement an indicator-based surveillance system for strengthening AMR surveillance.

Key words: Antimicrobial-resistance, AMR, outbreak surveillance, hospital acquired infections

Background

AMR is a global public health issue and the rapid spread of AMR between continents makes it a health threat internationally. The global annual mortality from AMR related illness exceeds 700,000 and is projected to steeply rise to 10,000,000 by 2050, associated with costs (1). Drug-resistant microbes have been isolated from the human and animal population in all the seven continents, including international space stations. In high-income countries, increased antimicrobial usage in humans, farming, livestock and agriculture has facilitated the development of AMR (2). In low and middle-income countries rising antibiotic consumption, increased hospitalisation and prevalence of hospital-acquired infections along with inadequate hygiene, poor sanitary measures and an already existing burden of bacterial infections have contributed to the rapid growth of AMR (3).

The injudicious use of antibiotics in human medicine, veterinary, horticulture, aquaculture and agriculture, and the release of nonmetabolized antibiotic residue into the environment contribute to the emergence of AMR (4). Emergence and spread of AMR reduce the efficacy and limit the choice of antibiotics administered (5). By making antimicrobials ineffective, AMR jeopardises the achievements of modern medicine and could potentially result in situations wherein common infections and minor injuries could lead to death (7).

The past decades have witnessed indiscriminate use of antibiotics in human and livestock for therapeutic and prophylactic purpose. Globally, within a span of fifteen years, from 2000 to 2015, human health care has witnessed a 65% rise in intake of antibiotics from 21.1 to 34.8 billion daily doses (6). This widespread use has led to the emergence of Multi-Drug and Extremely-Drug Resistant (MDR & XDR) pathogens most of which fail to respond to conventional treatment and even to last-resort antibiotics (7).

A rising elderly population, accompanied by comorbidities and the increased usage of complex medical procedures with a risk of infection, will increase the requirement for antimicrobials (8). However, since

1968 only two classes of antibiotics have been developed. Developing a new drug requires $800,000,000 over 10 years. The high cost of production and the short term of antibiotic use disincentivises the pharmaceutical industries from launching new antibiotics (7). The majority of medical procedures rely heavily on effective antibiotics (9). The less potent antibiotics increase the length of hospitalisation and have an unfavourable outcome on surgical and immunosuppressive treatments. Of lately, there has been an increased administration of older drugs like Fosfomycin, Pristinamycin and Colistin, which may have serious adverse effects (8). The current situation highlights the need to preserve the efficacy of currently available antimicrobials by using them cautiously to prevent AMR.

Surveillance has been recognised as an important strategy to contain AMR. Surveillance data on AMR aids clinical decision making on empirical prescriptions and infection prevention policies in hospitals. They also guide public health actions (10). Global surveillance has become a requisite as the ease of international travel and medical tourism have facilitated the resistant strains to cross-national and international boundaries (11). However, the present surveillance systems are disconnected and underdeveloped, and there is no global surveillance data available. This limits quantification of AMR related morbidity and mortality.

The WHO acknowledges the gaps in knowledge of magnitude and distribution of AMR and has launched an indicator-based surveillance system, the Global Antimicrobial Resistance Surveillance System (GLASS) in 2015, to collect country reported AMR data, and has 68 countries voluntarily reporting to it (3). However, GLASS currently does not capture comprehensive data. Indicator based surveillance is the oldest, commonest and widely used method used by public health agencies for collecting and analysing structured data based on established protocols (12). Though GLASS employs reliable methods, its ability to quickly detect potential threats and completeness of reporting are deficient. Importantly, due to predefined structure and surveillance pathogens, it is poorly equipped to identify new or unpredicted disease occurrence. The use of open source data to gain a more comprehensive overview of AMR globally is another approach to surveillance.

Aim

To assess the pattern of reported AMR at a global level using EpiWATCH, an event-based open-source surveillance system.

Methodology

EpiWATCH is a "semi-automated outbreak data collection and analysis observatory that monitors and provides critical analysis of global outbreaks and epidemics of public health significance using publicly available sources. It is created and run by The NHMRC Centre for Research Excellence, Integrated Systems for Epidemic Response (ISER)". The database has over 10,000 outbreaks from 2016 onward that can be searched on disease, date, location and other keywords.

Media reports on antimicrobial resistance globally were retrieved from EpiWATCH between August 2016-March 2020. The outbreak database was searched using keywords such as 'resistance', 'resistant', 'superbug', 'bugs', 'MRSA' and 'VRE'. The process was repeated twice to ensure all reports relating to AMR were extracted accurately. Inclusion criteria were articles reporting AMR outbreaks from 1 August 2016 to 30 March 2020. All the retrieved articles were assessed thoroughly, and duplicates were removed.

For the analysis, data from all reported outbreak AMR cases were grouped according to geolocation and time in which they occurred. Descriptive epidemiologic analysis of the outbreaks has been conducted and additional public domain data was sought where necessary.

The EpiWATCH data was compared to the WHO's AMR surveillance system, GLASS. GLASS has 68 countries voluntarily providing national AMR data. Thus, to fairly present comparison in data between the two systems, only three countries providing the maximum number of resistant isolates and specimen have been chosen for each WHO region. Similarly, in measuring resistance of pathogens to antibiotics, only those isolates or specimen from either blood or urine culture more than 75% resistant to the antibiotic have been nominated. However, all the reporting countries to the WHO were included in measuring pathogen resistance to antibacterial.

The GLASS surveillance system gathers data on selected bacteria of international concern, responsible for infection in humans such as Acinetobacter spp., Escherichia coli, Klebsiella pneumoniae, Neisseria gonorrhoeae, Salmonella spp., Shigella spp., Staphylococcus aureus, and Streptococcus pneumoniae. GLASS monitors DR Mycobacterium Tuberculosis separately.

Results

There was a total of 60 reports on AMR outbreaks between August 2016 and March 2020. We detected AMR outbreak reports from 14 countries and regions. The distribution of reporting is shown in figure 1. The most frequently reporting country was the United States of America, with a total of 33 reports. The most common reported pathogen was MRSA, followed by drug-resistant Salmonella which includes *Salmonella typhi* and non-Typhi Salmonella serovars.

There were 18,275 cases of AMR infection reported in the four-year period and is represented in the graph below (Figure 2). Among the 18,274 AMR cases, 64.8% (11,851) of the AMR infections were caused by drug-resistant Salmonella Typhi, 27.6 % (5,060) by MRSA, 2.1% (384) by Non-typhoid Salmonella and 2.2% (412) by the drug-resistant fungus Candida Auris. The rest of the pathogens together constituted less than 3.5% of the total infections. Further, 12,767 (69.8%) of these infections were caused by gram-negative bacilli, 5,071

(27.7%) by gram-positive cocci and six (0.03%) by gram-negative cocci.

Among the gram-positive cocci, all VRE infections were acquired in hospitals. Unlike VRE, MRSA presented in communities and hospitals. There were 18 reports on MRSA from USA, and England constituted 60 cases. Most of the MRSA infections affected children and young people. In 13 reports, the MRSA outbreaks surfaced from schools and universities. Primarily contact sports participants like wrestlers and footballers were at risk. The rest of the cases were outbreaks in hospital wards. Additionally, the majority of hospital-acquired MRSA infections were in neonatal units.

Of gram-negative bacilli, the majority (92.8%) of infections were due to Salmonella Typhi, 3.71% by non-Typhi-Salmonella and 1.4% by DR Shigella. Around 4% of the gram-negative infections (DR Campylobacter & MDR Salmonella) were zoonotic, linked to the consumption of poultry products or contact with livestock. There were repeated and considerable outbreaks of drug-resistant non-typhoidal Salmonella serovar surfacing from the USA and 31.2 % of these reported cases of non-typhoid Salmonella required hospitalisation.

All cases of (NDM-1) Carbapenemase-producing Enterobacteriaceae, DR Acinetobacter and DR Klebsiella were acquired in the hospitals. NDM-1 colonised the medically compromised patients and had a case fatality rate of 40%. All the documented cases of DR Klebsiella were linked with frequent outbreaks in neonatal wards. Carbapenem-resistant Klebsiella proved lethal for 47.6 % of the infant patients in South Africa and in Kenya the mortality rate was 48% in the neonatal unit. DR Acinetobacter infections reported from Japan (58-97 year old patients), Mexico and Belgium were all hospital-acquired. But the case fatality rate varied across regions. In Japan, it was a staggering 94.7%, in contrast to 30.7 % in Mexico and 33% in Belgium. No HAIs were generated or fatalities reported from infections caused by gram negative cocci.

Figure 1. Number of reports by distribution of pathogens in reporting countries and regions.

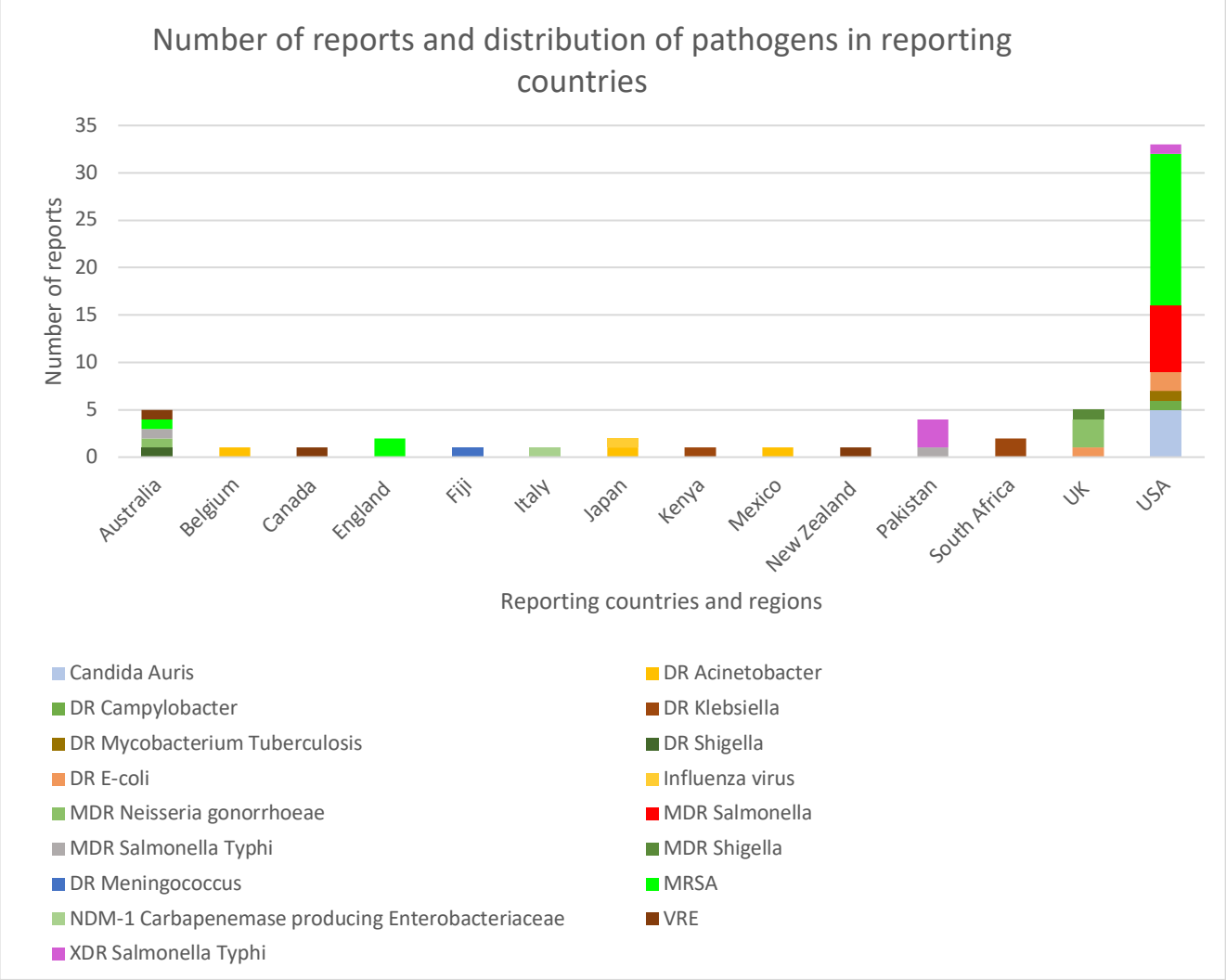
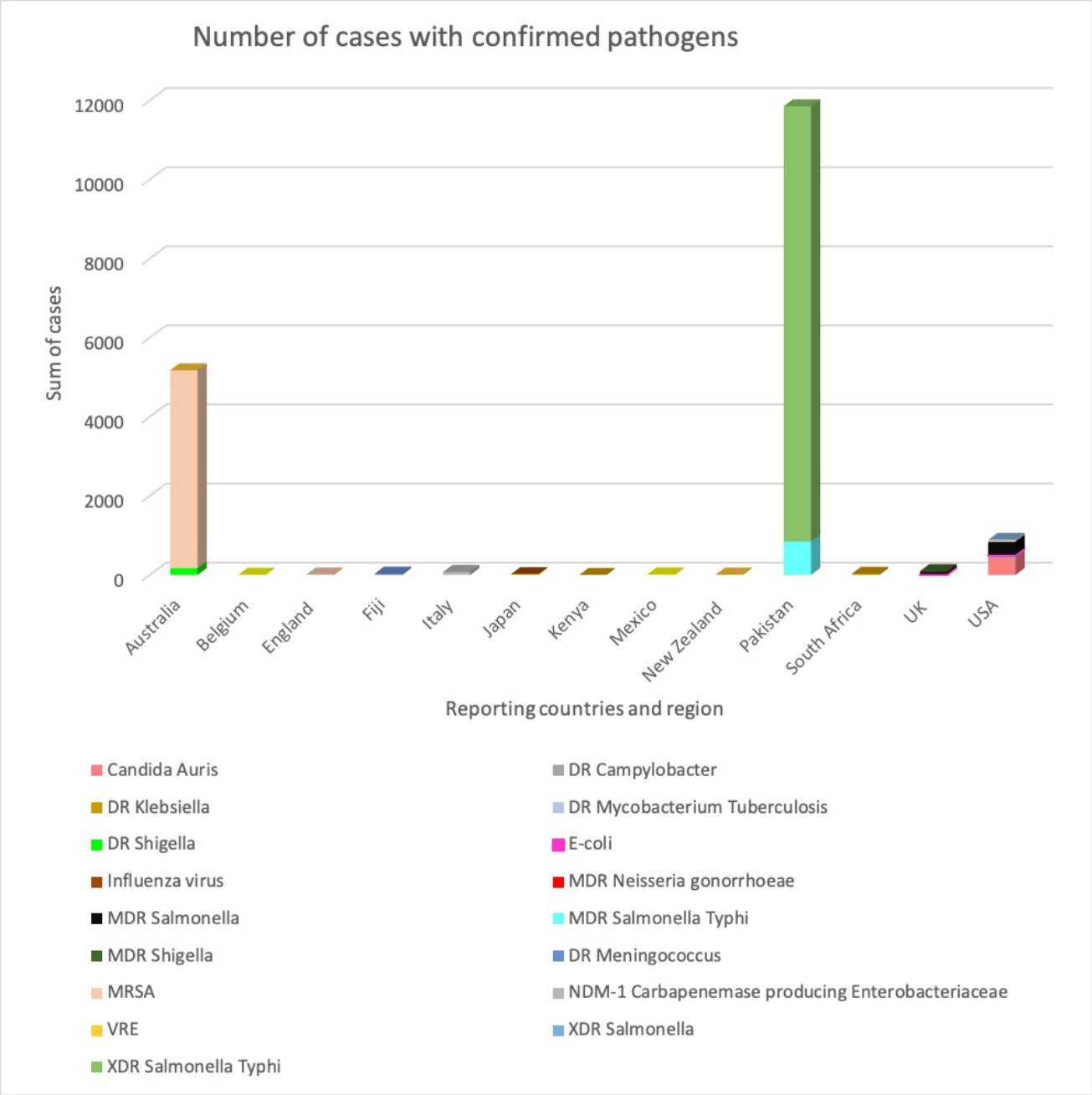


Figure 2. Number of cases by pathogens and reporting countries.



Note: Canada was excluded from figure 2 as the number of infections during VRE outbreak in Canada was not reported.

Table 1. Summary of the aggregated data, EpiWATCH

Pathogens	Number of reports	Number of cases	Number of hospitalisations	Number of HAIs	Number of deaths
Gram +ve cocci	**22**	**5,071**	**-**	**47**	**1**
MRSA	19	5,060	NR	36	1
VRE	3	11	NA	11	0
Gram -ve bacilli	**27**	**12,767**	**164**	**145**	**76**
NDM-1 Enterobacteriaceae	1	75	NA	75	30
DR Acinetobacter	3	36	NA	36	18
DR Campylobacter	1	55	13	0	0
DR Klebsiella	3	45	NA	45	27
MDR Shigella	2	188	NR	0	0
E-coli	3	9	3	0	0
MDR Salmonella	8	474	148	0	1
MDR Salmonella - typhi	3	851	NR	NR	NR
XDR Salmonella - typhi	2	11,000	NR	NR	NR
DR Meningococcus	1	34	NR	NR	NR
Gram -ve cocci	**4**	**6**	-	**0**	**0**
MDR Neisseria-gonorrhoeae	4	6	NR	0	0
Others	**7**	**431**	-	**270**	**40**
Candida Auris	5	412	NR + NA	270	40
DR Mycobacterium -Tuberculosis	1	17	NR	0	0
Influenza virus	1	2	NR	0	0
Total	60	18,275	164	462	117
*NR-not reported, *NA-not applicable as the infections were acquired in hospitals.					

There were recurrent outbreaks of a drug resistant fungus, Candida Auris in USA. A significant proportion (>60%) of these resistant fungal infections were contracted in health facilities and largely among the already compromised candidates. On the whole, most transmissions were occurring from spread of pathogens in health facilities. Mortality was strongly associated with patients acquiring the drug-resistant organisms in the hospital, especially with gram-negative bacilli like DR Klebsiella and Acinetobacter. Infants, elderly and medically compromised patients were the most vulnerable to MDR microorganisms. Additionally, among bacteria, gram-negative bacilli were primary causative agents of healthcare-associated infections.

Comparing pathogen resistance to antimicrobials (Figure 3), a greater number of pathogens were resistant to antimicrobials inhibiting the synthesis of cell wall or interfering with the protein synthesis of the target bacteria. E-coli with the mcr gene and Salmonella had developed resistance to almost one antibiotic among the various categories. Also, within the cell wall inhibiting group the resistance to βlactam producing antibiotics is notable, especially to Penicillin, Cephalosporins and Carbapenems. Importantly resistance was developing beyond bacterial domain to include viruses and fungi.

Further, gram-negative bacilli were resistant to almost all the classes of antibiotics. Between the cell wall inhibitors, gram-negative bacilli had lesser susceptibility

to non-lactam producing drugs and Glycopeptides (which includes vancomycin and colistin). Further, gram-negative cocci were being lesser susceptible to cephalosporins and macrolides, such as Azithromycin. Majorly gram-negative bacilli, gram-positive cocci and gram-negative cocci were gaining resistance to Cephalosporins (Figure 4).

The EpiWATCH data was compared to the WHO's AMR surveillance system, GLASS, which has 68 countries voluntarily providing national AMR data (13). GLASS gathers data on selected bacteria of international concern (Acinetobacter spp., Escherichia coli, Klebsiella pneumoniae, Neisseria gonorrhoeae, Salmonella spp., Shigella spp., Staphylococcus aureus, and Streptococcus pneumoniae). With the exception of Streptococcus Pneumonia, EpiWATCH has captured reports in all the WHOs "selected bacteria" categories as well as Campylobacter and Meningococci. Campylobacter is listed as a priority pathogen in the WHO, but the GLASS report contains no surveillance data on campylobacter.

In all the regions except American and African regions, E-coli was the most common pathogen from the WHO's AMR surveillance, 2016 to 2018. In EpiWatch Salmonella Typhi followed by Staphylococcus aureus were the commonly reported drug resistant pathogens. EpiWATCH was consistent with GLASS in capturing Salmonella from the American region and Klebsiella from the African region as causing maximum resistance burden (Appendix A, figure 5 & 6). Additionally, in both GLASS and EpiWATCH, majority of the resistant infections reported were caused by the gram-negative bacilli.

Corresponding to EpiWATCH data, there was predominance of pathogenic resistance towards the cell wall inhibitor class of antibiotics in GLASS and none of the Staphylococcus isolates from the world were more than 75% resistant to antibiotics, highlighting that gram-positive cocci infections were not as lethal as the gram-negative bacilli infections. This result is consistent with the EpiWATCH findings.

Figure 3. Pattern of pathogen resistance to antimicrobial drugs from EpiWATCH data

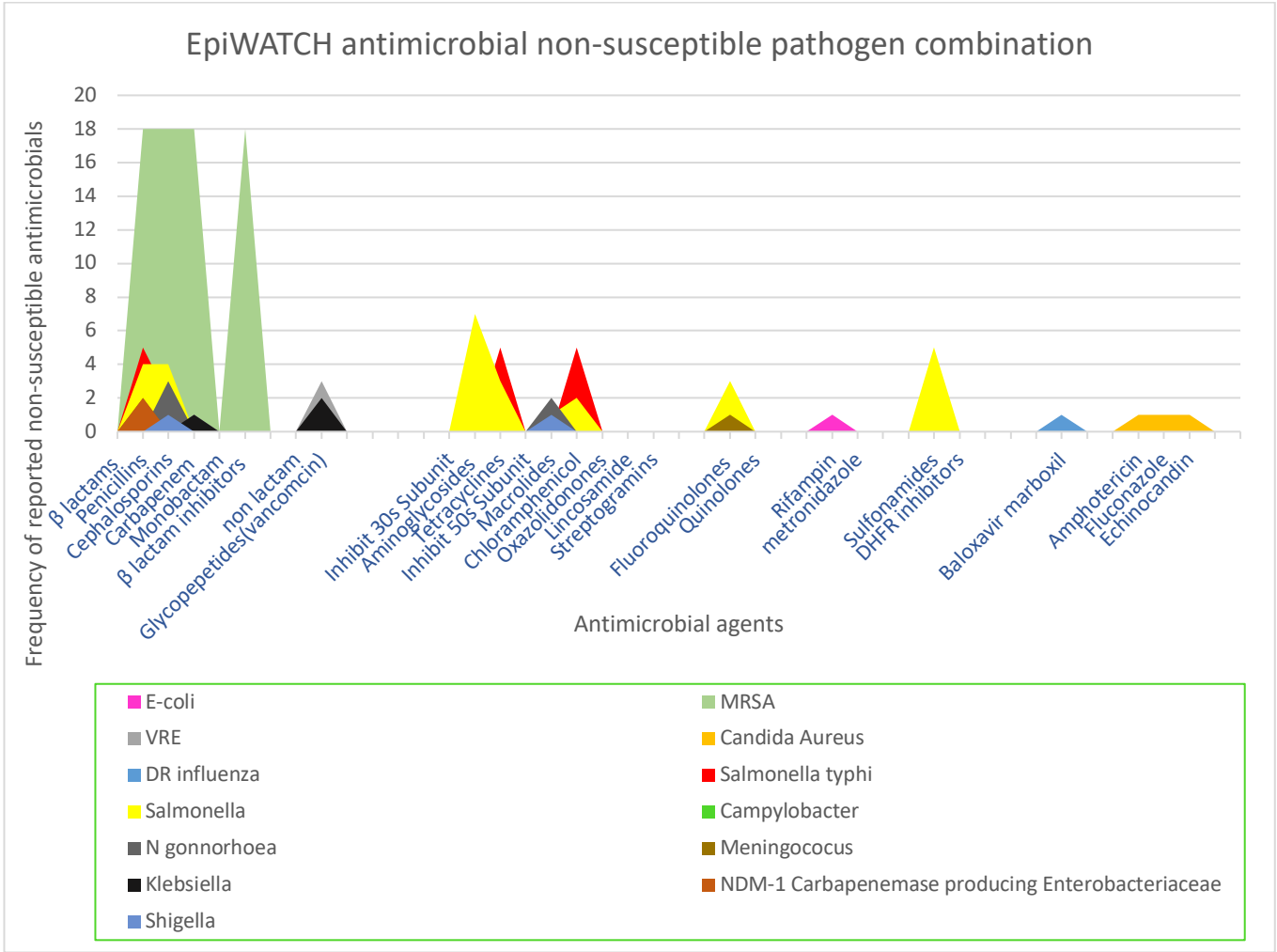
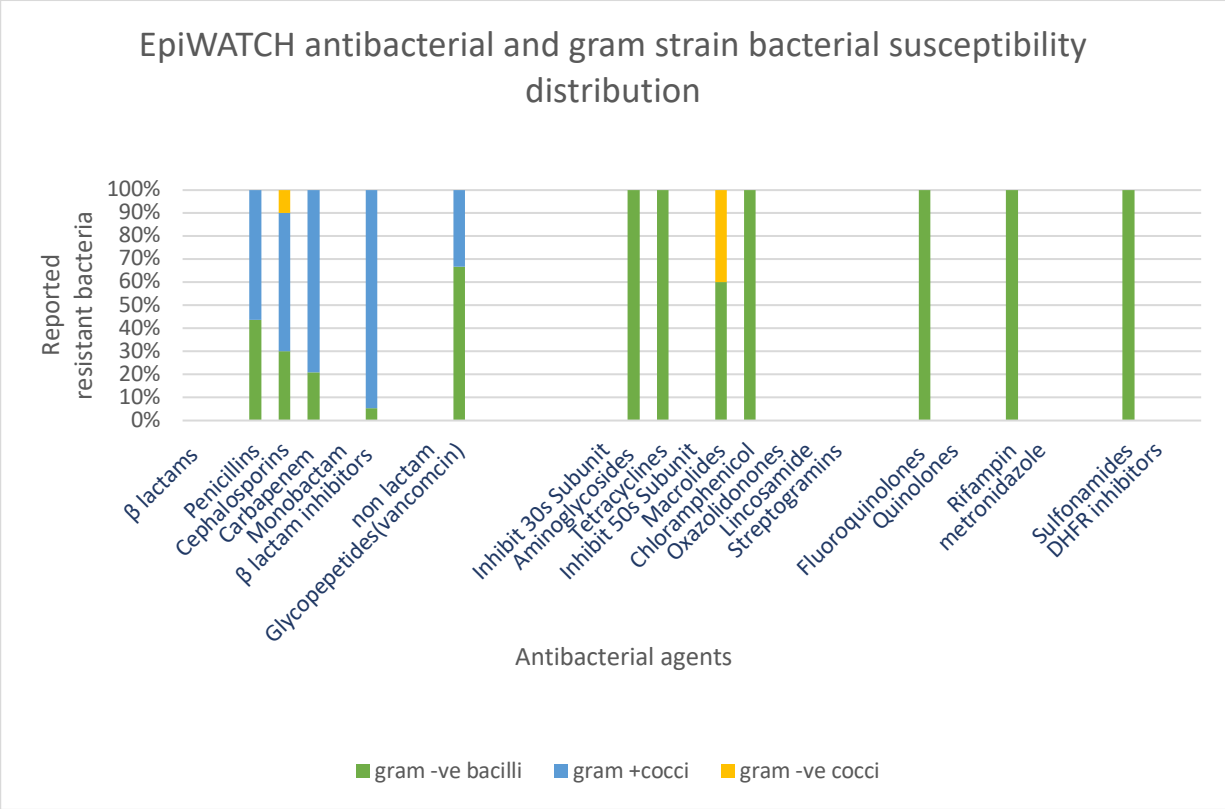


Figure 4. Proportion and distribution of resistance to antibacterial agents according to bacterial morphology and gram strain



Discussion

EpiWATCH provided AMR data from open source reports from 14 countries. Information on AMR collected in the study is not validated or complete, but provides an overview of AMR globally, including on pathogens not reported in GLASS. EpiWATCH identified medically important gram-negative and gram-positive bacteria along with other pathogens that have caused outbreaks and needed to be looked out for in health centres and communities.

All VRE cases were reported from hospital wards. The ability of MRSA and VRE to spread from hospital and universities were a risk factor for MRSA transmission. Also, from the US, there were MRSA cases among police coming in contact with homeless people. It indicates that poverty is also a determinant for community-acquired MRSA (17). Staphylococcus Aureus isolates designated as MRSA are categorised as MDR (18). It underscores the threat that could be caused by gram positive bacteria (19).

The growing community spread of MRSA is ascribed to the lack of general awareness among the public and inadequate knowledge among health professionals, and also to the persistent and evolving ingenuity towards survival among the pathogenic strains (17). Hence, building awareness among public and health care workers should be a strategy to reduce the resistance along with environmental decontamination, disinfection of universities and schools, hand hygiene education for environment to the patients as well as from other infected or colonised patients/ health care workers (14, 15), coupled with immature immunologic functions in neonates (15), explains the frequent outbreaks in neonatal wards. Crowded schools and universities might create an environment to facilitate the spread of MRSA (16). MRSA was the predominant pathogen causing nosocomial and community transmissions in the US, England and Australia. Schools were an at-risk location in the community for MRSA transmission and in the hospitals, infants were at risk in neonatal wards. In addition, the data suggested sporting events at school students (16), and hospital designs providing for sufficient washrooms (14).

Drug-resistant Klebsiella Pneumonia, NDM-1 Enterobacteriaceae and Acinetobacter (Baumanii and Bachmannii) were all hospital-acquired and were reported from both high- and middle-income countries. Most of reports of Acinetobacter and Klebsiella infections were outbreaks in neonatal intensive care units. All three pathogens have been responsible for causing serious infections in patients admitted due to pre-existing conditions and were largely fatal. The reported Klebsiella Pneumonia and NDM1 pathogens were resistant to key antibiotics Carbapenem and Colistin. Carbapenem resistance is of concern in Klebsiella infections, since Carbapenems are last-resort antibiotics for treating MDR Klebsiella Pneumoniae (20). Combination therapy with Polymyxins, Fosfomycin, Tigecycline, Rifampin, and Carbapenems

have met with success. Importantly, strict adherence to infection control measures along with patient isolation or cohorts could help in control of resistant strains (20).

Acinetobacter baumanii is the most virulent (21), and a significant nosocomial pathogen due to its potential to withstand major antibacterial agents, disinfectants and desiccation (22), and to evade rapid clearance by the immune system (21). β-lactam is the first choice for Acinetobacter infections, but in XDR cases combination carbapenem-polymyxin therapy is the preferred choice (21). Other than being present on environmental surfaces, Acinetobacter have also been reported to be transmitted as aerosols. Early airborne precautions, adequate ventilation, high-efficiency particulate air (HEPA) filtration (23), and patient cohorting along with surface disinfection could prevent the spread of resistant pathogens (21).

All cases of MDR non-typhoidal salmonella were foodborne or were a result of contact with livestock. They are a common cause of foodborne illnesses in industrialised countries. In a span of four years, there were multiple outbreaks of Salmonella in the US and most of them were MDR. In the reported outbreaks, more than a hundred people were hospitalised. MDR Salmonella and Campylobacter infections in humans may occur as a result of consumption of animals that were administered antibiotics as growth promoters (24, 25). Monitoring bacterial resistance in animal products will safeguard human health (26).

The MDR Salmonella typhoid outbreak was reported in a low-income country, due to poor water and sanitation facilities. It gradually evolved to XDR strain, resistant to 5 classes of antibiotics. Two imported cases were reported in the US and Australia of MDR and XDR Salmonella Typhi associated with a history of travel to the affected country. In drug-resistant typhoid endemic areas, mass awareness campaigns, particularly targeting practitioners for appropriate use of diagnostic procedures and antibiotic use (27) along with the issue of travel alert could curb the spread of resistance.

Overall, a thorough understanding of the mechanism of resistance towards commonly used antibiotics could help inform prescription. Clinician's cognisance of the intrinsic and acquired resistance mechanism of the pathogens to antibiotics could facilitate accurate prescriptions. They should also be aware of the newer antibacterial β-lactams and β-lactamase–inhibitor combinations like Meropenem/Vaborbactam or Ceftolozane/Tazobactam as alternatives for treatment of complicated AMR cases (28, 29). Lastly, the development of acquired resistance by pathogens, could largely be prevented by treating with the highest dose a patient will be able to withstand, for the shortest duration required to terminate the infection (30).

A limitation of this study is that EpiWATCH exclusively relies on English in gathering data. The selection of articles in English introduces reporting bias, and could explain the predominance of reports from the USA. Besides language bias, some reports presented incomplete data, in particular for variables like the age and gender of patients, together with omission of relevant clinical details. Moreover, there is also a potential for inter and intraobserver bias with the investigator conducting data entry, varying over the recording of AMR news events during extraction, filtration and presentation of reports.

In conclusion, open source data is useful as an adjunct to attain complete and comprehensive information on AMR at a global level. EpiWATCH is user friendly, timely, rapid, flexible and low maintenance. The data is readily available and can be easily exchanged, compared and analysed. A system like EpiWATCH can be amalgamated with indicator-based surveillance systems to capture and disseminate data, for identifying action areas, especially in low resource countries, which lack the capacity to establish and maintain a surveillance system on AMR.

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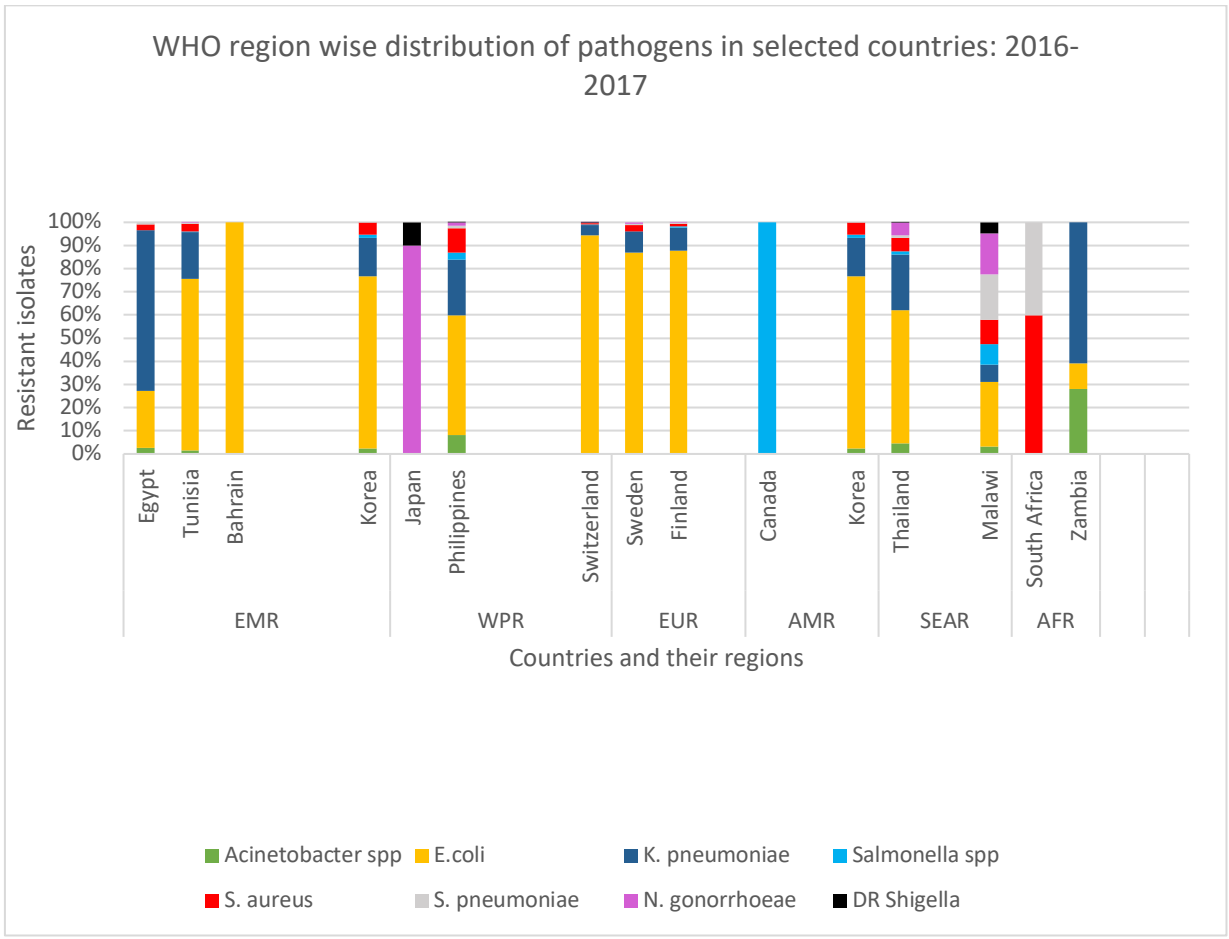
Appendix A

Figure 5. Profile of the region wise distribution of pathogens in selected countries, 2016-2017, WHO



*EMR -Eastern Mediterranean Region, WPR- Western Pacific Region, EUR – European Region, AMR- American Region, SEAR- South East Asia Region, AFR- African Region

Figure 6. Profile of the region wise distribution of pathogens in selected countries, 2017-2018, WHO