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Research Paper

Global trend of antimicrobial resistance in common bacterial pathogens in response to antibiotic consumption

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Abstract

The emergence of antimicrobial resistance (AMR) is a growing public health threat worldwide and antibiotic consumption is being increasingly recognized as the main selective pressure driving this resistance. However, global trend in antibiotic resistance in response to antibiotic consumption is not fully understood. In this study, we collected national resistance data on specific resistant pathogens considered by the World Health Organization (WHO) as priority and antibiotic consumption data for 61 countries to assess the global trends in antibiotic resistance of those common bacterial pathogens and their association with antibiotic consumption. The low- and middle-income countries (LMICs) represented the largest hotspots of resistance, which presented relatively higher resistance rates in common bacterial pathogens but lower antibiotic consumption rates compared to high-income countries (HICs). Specifically, we developed the Normalized Antibiotic Resistance/Consumption Index (NARCI) and produced global maps of NARCI to roughly assess the appropriateness of antibiotic consumption across countries and to indicate the potentially inappropriate antibiotic consumption in LMICs compared with HICs. Additionally, we linked antibiotic consumption rates and resistance rates of target pathogens, in conjunction with NARCI and the correlation analysis between antibiotic use and resistance, to inform strategies to alleviate the threat of antibiotic resistance worldwide.

Graphical Abstract
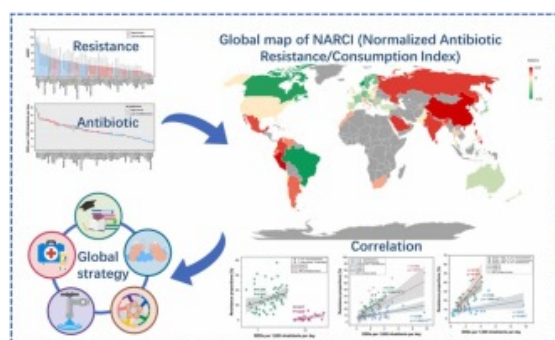
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Introduction

Since the discovery of penicillin in the 1920s, antimicrobial drugs have been regarded as the panacea to cure bacterial infections and have reduced the global burden of common infectious diseases (Van Boeckel et al., 2014, WHO, 2014); however, the widespread use of antimicrobial drugs is a major driving force for antibiotic resistance (Klein et al., 2018b). With the continuous increase in global antibiotic consumption over time (Klein et al., 2018b, Van Boeckel et al., 2014), the increasing trend in antimicrobial resistance (AMR) poses a serious threat to public health globally (Laxminarayan et al., 2016, WHO, 2014). According to the estimates by the World Health Organization (WHO), 700,000 deaths are attributable to AMR each year globally, and it has been estimated that 10 million people could die from resistant bacterial infections annually worldwide by 2050 if the current trend in rising AMR is not suppressed (Kupferschmidt, 2016, O'Neill, 2016).

Of particular concern is the developing resistance in those bacterial pathogens (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, nontyphoidal *Salmonella*) that cause the most common nosocomial, community-acquired infections, or both worldwide (WHO, 2014). Resistance to antibacterial drugs that are commonly used to treat infections caused by these common bacterial pathogens (e.g., *E. coli* resistance to third-generation cephalosporins and to fluoroquinolones, *K. pneumoniae* resistance to third-generation cephalosporins and to carbapenems, *S. aureus* resistance to methicillin, *S. pneumoniae* resistance to penicillin, and nontyphoidal *Salmonella* resistance to fluoroquinolones) has emerged and spread globally alongside the global increase in antibiotic consumption, posing a serious health risk worldwide, which is of particular concern to the WHO (WHO, 2014). The WHO published a series of global reports on the surveillance of resistance in those common bacteria-antibacterial drug combinations and global antibiotic consumption (WHO, 2014, WHO, 2018).

To date, in addition to investigating the global trends in antibiotic consumption (Klein et al., 2018a) and the global burden of bacterial antimicrobial resistance (Murray et al., 2022, Zhang et al., 2022), there have been increasing attempts to assess the association between antibiotic use and antibiotic resistance rates (Collignon et al., 2018, Goossens et al., 2005, Hu et al., 2014, Klein et al., 2019, López-Lozano and Lawes, 2019, Meyer et al., 2013). For instance, Goossens et al. (2005) showed a correlation between penicillin use and the prevalence of penicillin-nonsusceptible *S. pneumoniae* in Europe. Similarly, Meyer et al. (2013) found significant correlations for 3rd generation resistant *E. coli* or *K. pneumoniae* with 3rd generation cephalosporin use as well as with quinolone use in Europe. In addition, nonlinear relationships between antibiotic use and resistance have been more often reported (Austin et al., 1999, Haber et al., 2010, Kiffer et al., 2011, López-Lozano and Lawes, 2019). For instance, a prior study reported nonlinear relationships between fluoroquinolone use and resistant *E. coli* in Sao Paulo, Brazil (Kiffer et al., 2011). Using a nonlinear time-series analysis (NL-TSA) approach, López-Lozano et al. (2019) found empirical evidence of nonlinear

relationships between population antibiotic use and resistance rates in five European settings. However, these observations might only represent the tip of the iceberg given the complex relationships between population antibiotic use and resistance rates. Additionally, most of those studies are limited to specific countries or regions and only provide snapshots of antibiotic use–resistance relationships; the global AMR trends in relation to antibiotic consumption are not fully understood. Thus, additional study is needed to provide comprehensive insights into the antibiotic resistance genes in relation to antibiotic consumption on a global scale, providing a more accurate understanding of how modifying antibiotic use, infection control or other exposures is likely to affect resistance.

In this study, we focused on seven bacteria-antibacterial drug resistance combinations considered by the WHO as a priority, including *E. coli*/3rd generation cephalosporins, *E. coli*/fluoroquinolones, *K. pneumoniae*/3rd generation cephalosporins, *K. pneumoniae*/carbapenems, methicillin-resistant *S. aureus* (MRSA), *S. pneumoniae*/penicillin, and nontyphoidal *Salmonella*/fluoroquinolones (WHO, 2014). In total, we obtained national resistance data and antibiotic use data for 61 countries for 2009–2012 and assessed the global trends in antibiotic resistance in common bacterial pathogens in response to antibiotic consumption. Specifically, we developed a new index, the Normalized Antibiotic Resistance/Consumption Index (NARCI), to roughly assess the appropriateness of antibiotic consumption across countries. Then, we linked antibiotic consumption rates and resistance rates of target pathogens, in conjunction with NARCI and the correlation analysis between antibiotic use and resistance, to inform strategies to alleviate antibiotic resistance threats worldwide.

Section snippets

Global antibiotic use and resistance data collection

Antibiotic consumption data shown in defined daily doses (DDD) per 1000 inhabitants were obtained from Resistance Map (https://resistancemap.cddep.org/AntibioticUse.php) (The Center for Disease, 2020), a global repository of antibiotic consumption data obtained under license IQVIA's MIDAS database and Xponent information services. To compare antibiotic use across different countries, the antibiotic consumption rate for each country was calculated and expressed in DDDs per 1000 inhabitants per…

Global trends in bacterial-antibacterial resistance and antibiotic consumption

Among the seven selected bacteria-antibacterial resistance combinations in this study, significantly higher resistance rates were observed in four combinations (e.g., third-generation cephalosporin-resistant *K. pneumoniae*, fluoroquinolone-resistant *E. coli*, third-generation cephalosporin-resistant *E. coli*, and MRSA) compared to the other three combinations (e.g., fluoroquinolone-resistant nontyphoidal *Salmonella*, carbapenem-resistant *K. pneumoniae*, and penicillin-resistant *S. pneumoniae*) on a…

Global trends in antibiotic resistance in response to antibiotic consumption

In this study, we indicated the serious global health threat posed by third-generation cephalosporin-resistant *K. pneumoniae*, fluoroquinolone-resistant *E. coli*, third-generation cephalosporin-resistant *E. coli*, and MRSA compared to other combinations, as well as the significantly higher consumption rates for broad-spectrum penicillins compared to the other classes of antibiotics on a global scale. This observation was consistent with previous studies showing that the high occurrence of…

Conclusion

Overall, our study assessed the global trends in antibiotic resistance in common bacterial pathogens in response to antibiotic consumption and aimed to provide a data basis for developing and implementing strategies to mitigate the increasing trend of antibiotic resistance worldwide. In view of the increasing AMR issue worldwide and the current lack of new antimicrobials, international solidarity is called for to fight against antimicrobial resistance and to sustain the effectiveness of…

Environmental implications

Antibiotic resistance is the quintessential One Health and Global Health issue. Armed with a collection of antibiotic consumption and resistance data for 61 countries, we assessed the global trends in antibiotic resistance in response to antibiotic consumption. The low- and middle-income countries (LMICs) presented relatively higher resistance rates in common bacterial pathogens but lower antibiotic consumption rates, as well as the potentially inappropriate antibiotic consumption compared with …

CRediT authorship contribution statement

Jie Hou: Investigation, Visualization, Writing – original draft. **Xiang Long:** Investigation, Data curation. **Xiaolong Wang:** Investigation, Data curation. **Linyun Li:** Investigation. **Daqing Mao:** Supervision, Validation, Funding acquisition, Writing – review & editing. **Yi Luo:** Supervision, Validation, Conceptualization, Funding acquisition, Writing – review & editing. **Hongqiang Ren:**Supervision.…

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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1   Jie Hou and Xiang Long contributed equally to this work.

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