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Review article

Meta-Analysis of Economic Impact of Antibiotic Resistance in Developing Countries

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ABSTRACT

Background and Objectives: Antimicrobial resistance is associated with substantive health and financial consequences that lead to economic and clinical impact in both developed and developing countries. This review analyzed economic impacts of antimicrobial resistance in terms of lengthening recovery time, expensive medicines and specialized care for patients. **Materials and Methods:** A systematic search was carried out via PubMed and Web of Science using a combination of Boolean operators and pre-defined keywords. **Results and Conclusion:** Determining the true economic impact of antimicrobial drug resistance is a challenge because so many variables and perspectives are involved. The economic interests surrounding this matter are paramount and have to be adequately addressed. Furthermore, optimization of rational antibiotic use at regional and national levels is essential to ensure a high quality and effective of therapeutic options.

Keywords: Antimicrobial resistance, economic impact, antibiotic use, multidrug resistant strains.

INTRODUCTION

Antimicrobial resistance is the ability of microorganisms to multiply and spread in the presence of antimicrobial compounds which are normally inhibit/kill them. The resistance is associated with modified antimicrobial target, drug efflux mechanisms, enzymatic degradation, presence of diverse resistance genes and inappropriate use of antibiotics[1,2]. Resistance among microorganisms is considered a significant threat to the public health systems not just in developing countries but throughout the world. Patients undergoing chemotherapy, dialysis, surgery and joint replacement are more vulnerable as antibiotic resistance compromises a human immune system's capacity. Furthermore, people with chronic conditions like diabetes, asthma and rheumatoid arthritis will be heavily impacted by antibiotic resistance.Several national and international working groups have proposed actions to mitigate its further development, with recommendations including novel funding structures for new antibiotic research and development, development and use of technologies like diagnostics and vaccines that may reduce the need for antibiotics, education to enhance antibiotic stewardship as well as better infection control practices[3-5]. Various organizations refer antimicrobial resistance as a global public health issue and a threat to the modern health-care system that could hamper the control of many infectious diseases and dramatically set back the modern medicine.

Among the hospitalized patients, one of the public health threatsacross the globe isantimicrobial resistance. Antimicrobial resistance is also associated with substantive health and financial consequences that lead to economic and clinical impact in both developed and developing countries[6,7]. The economic analysis of antimicrobial resistance has adopted different approaches to get a better understanding of the impact of the problem for the health care sector and for society as a whole, usually segmenting it by type of resistant bacteria, by jurisdiction or by antibiotic family. Economic impacts of antimicrobial resistance involve, lengthening recovery time, expensive medicines and specialized care for patients[8,9]. Other indirect costs associated with AMR include productivity losses due to excess morbidity and premature mortality. This review is aimed at analyzing the economic features and economic information regarding antibiotic resistance.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed in this study[10,11]. A systematic search was carried out via PubMed andWeb of Science from June 2020 to August 31, 2020 using a combination of Boolean operators (AND/OR) and pre-defined keywords.Peer-reviewed papers in English on the clinical and/or economic impacts of antibiotic resistance in developing countries were retrieved and evaluated for eligibility based on titles and abstracts.Earlier studies of impact have also included estimates of increased hospital or other institutional stay, incremental specific treatments and additional diagnostic tests needed for a patient infected with a resistant organism compared with a patient infected with a strain of the same organism that is drug susceptible[12-14].

Efficacy of Antibiotics

There are two main problems affect the efficacy of antibiotics. The first is that following the introduction of a new antibiotic, resistance to it will arise sooner or later. As bacteria keep developing resistances against existing antibiotics, one potential solution is to develop new antibiotics so that the older ones can be replaced by new ones with a more complex mechanism of action that makes it difficult for bacteria to develop such resistances. The second is the growing gap being recognized between the increased antimicrobial resistance and the development of new molecules[15].

Patients who do not receive appropriate treatment promptly are at increased risk for a longer disease course or fatal outcome and remain infectious for longer periods, increasing the likelihood of transmission of the resistant microorganisms if infection control measures are not implemented. Some antibiotics are given prophylactic ally to patients particularly susceptible to infections such as pregnant women[16] and cancer or surgical patients[17]; loss of antibiotic effectiveness will decrease prophylaxis effectiveness and worsen patient outcomes[18]. These effects can be translated into costs and have impact on a country's economy.

Longer Stay

Resistance frequently leads to delays in the administration of effective therapy and a mismatch between empirical therapy and subsequent antibiotic susceptibility test results is the most significant factor in delaying effective therapy. Infections caused by resistant bacterial strains lead to up to two-fold higher rates of adverse outcomes compared with similar infections caused by susceptible strains[19]. Patients with laboratory-confirmed antibiotic-resistant urinary and respiratory-tract infections are more likely to experience delays in clinical recovery after treatment with antibiotics[20]. Patients suffering from antimicrobial resistant nosocomial infections or who become sick due to the consumption of food contaminated by resistant pathogens experience longer recovery and a higher frequency of septicemic infections and mortality[21,22]. In this situation, health-care costs are higher, due to extended hospital stays and the use of more expensive drugs.Developing countries need to optimize their management of communicable and non-communicable diseases, implement infection, prevention and control measures, as well asantimicrobial stewardship programs in both hospital and community settings to reduce morbidity, mortality and the costs associated with antibiotic resistance[7]. If antibiotic resistance results in longer hospital stays and more complex procedures, then thismay increase household out-of-pocket costs such as co-payments for treatment, transport costs,caregiver accommodation costs and childcare costs. Patients and caregivers may miss workand lose income. These costs may be especially large for poorer patients, especially those incountries without universal health coverage[23].

Obligation to Use More Expensive Antibiotics

One of the major consequences of resistant bacterial infections is the obligation to use antibiotics with extended spectrums andincreased expense. For example, in the case of

methicillin-susceptible *S. aureus*/methicillin-resistant susceptible *S. aureus* the treatment options turn from cefazolin/β-lactam plus β-lactamase combinations to vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin; in vancomycin-susceptible *Enterococcus*/vancomycin-resistant susceptible *Enterococcus*; penicillin or vancomycin to linezolid and quinopristin/dalfopristin, in extended-spectrum β-lactamase-Enterobacteriaceae: cephalosporins or β-lactam/β-lactamase inhibitor combinations to carbapenems[24-28].

Cost of drug therapy is a major concern while treating multi drug resistant strains. Though there is product diversity in drugs, they do not seem to bring price reductions to the same extent[29]. Generic drugs typically enter the market at a significantly discounted price compared to the innovator drug. If a patient is prescribed medicines which are two to ten times more expensive than a generic alternative, it severely hampers their ability to complete treatment courses[30]. The economic burden of treatment of infections on patients can be significantly reduced by including pharmacoeconomic analyses in treatment recommendations, and elimination of cost variations arising out of branded or generic prescribing[31].

Delayed Appropriate Therapy

Patients who receive delayed appropriate therapy are more likely to have an infection due to antibiotic-resistant pathogens. Some portion of excess mortality/cost/duration of hospitalization in some of the resistant bacterial infections is due to delayed appropriate or inappropriate antimicrobial therapy. Starting inappropriate therapy affects not only mortality but also duration of hospitalization. MRSA bacteremia patients also have an increased risk of delayed treatment and delayed therapy[32]. Mortality rates are higher among patients with ventilator-associated pneumonia who receive inappropriate empirical treatment[33]. Delayed appropriate therapy was associated with worse outcomes including ~70% increase in length of stay, ~65% increase in total in-hospital costs and ~20% increase in the risk of in-hospital mortality/discharge[34]. Delayed appropriate therapy is the primary factor that influenced clinical and economic outcomes, suggesting that timely initial therapy coverage impacts clinical and economic outcomes more than the specific pathogen.Lodise*et al*.[35] indicated that delayed appropriate therapy increases the risk of mortality, due to bloodstream infections by *K. pneumoniae* or *E. coli* especially when appropriate treatment is delayed by

> 48 hrs.Similarly, delayed appropriate therapy is a more important driver of outcomes than carbapenem-resistance[36].

Morbidity and Mortality

The economic cost of antimicrobial resistance is narrowly defined as the incremental cost of treating patients with resistant infections as compared with sensitive ones and the indirect productivity losses due to excess mortality attributable to resistant infections.The direct economic cost refers to the direct medical cost attributable to the treatment of a resistant infection as compared with the costs of treating a susceptible strain of the pathogen and the indirect cost refers to the cost to society due to productivity losses attributable to premature excess deaths due to resistance.Mortality figures are converted into productivity losses taking the human capital approach, by multiplying them by an assumed ten productive life years lost per death[37].

Conclusion

There are many variables and perspectives involved while determining the economic impact of antimicrobial drug resistance. Nevertheless, feasible policies can be adopted at a local level to overcome the problems identified above. Such policies must be adapted to the specificities of each health care system to have a chance of success.While adapting those policies, economic impacts needs to be addresses adequately. One of the major initiatives to address the issue is optimization of antibiotic use at regional and national levels which ultimately lead to high quality and effective therapeutics.

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