

Antimicrobial resistance gene distribution: a socioeconomic and sociocultural perspective

Verteilung mikrobieller Resistenzgene: ein sozioökonomischer und soziokultureller Ausblick

Abstract

The appearance of resistance to many first-line antimicrobial agents presents a critical challenge to the successful treatment of bacterial infections. Antimicrobial resistant bacteria and resistance genes are globally distributed, but significant variations in prevalence have been observed in different geographical regions. This article discusses possible relationships between socioeconomic and sociocultural factors and regional differences in the prevalence of antibiotic-resistant bacteria and their associated resistance genes. Findings indicate that the few studies that have been conducted to understand relationships between socioeconomic and sociocultural factors and antimicrobial resistance have focused on patterns of phenotypic antibiotic resistance. Yet, a critical need exists for molecular studies of human influences on bacterial resistance and adaptation. We propose that the results of these studies, coupled with well-coordinated culturally appropriate interventions that address specific socioeconomic and sociocultural needs may be necessary to reduce the scourge of antimicrobial resistance in both developing and developed countries.

Keywords: antimicrobial resistant bacteria, resistance genes, gene distribution, socioeconomic, sociocultural

Zusammenfassung

Das Auftreten von Resistenzen gegen viele First-Line Antibiotika ist eine schwierige Herausforderung, um bakterielle Infektionen erfolgreich zu behandeln. Zwar sind resistente Bakterien und folglich deren Resistenzgene global verteilt, jedoch sind deutliche Unterschiede bezüglich des Auftretens in verschiedenen geografischen Regionen beobachtet worden. In diesem Artikel werden mögliche sozioökonomische und soziokulturelle Faktoren sowie regionale Unterschiede in Bezug auf das Auftreten von resistenten Bakterien und ihren dazu gehörigen Resistenzgenen diskutiert. Untersuchungen zeigen, dass sich die wenigen Studien, die bisher durchgeführt worden sind, um Beziehungen zwischen sozioökonomischen sowie soziokulturellen Faktoren und Resistenzen zu verstehen, bisher auf phänotypische Antibiotikaresistenzen konzentriert haben. Daher werden molekular-basierte Studien des menschlichen Einflusses auf bakterielle Resistenz und Anpassung benötigt. Wir schlagen vor, dass die Ergebnisse dieser Studien gekoppelt mit gut koordinierter, kulturell angemessener Berücksichtigung sozioökonomischer sowie soziokultureller Bedürfnissen notwendig ist, um die Geißel antimikrobieller Resistenzen sowohl in entwickelten als auch in Entwicklungsländern zu reduzieren.

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Introduction

Antimicrobial resistance is a global emergency of the highest magnitude. The increasingly limited number of effective antimicrobial medications poses a critical barrier to the successful treatment of bacterial infections [1]. Resistance to many new agents develops soon after their introduction into clinical practice and agriculture settings, thus reducing their value to human and veterinary medicine [1], [2], [3]. Several studies have demonstrated a significant association between antimicrobial use and the emergence of resistance traits on local scales [4], [5], [6], [7]. However, relationships between the use of antimicrobials and the development of resistance in different geographical regions are made more complex by the interplay of socioeconomic and sociocultural factors [3], [8], [9], [10], [11]. Synergism between these factors and bacterial evolutionary processes, including gene transfer events and mutations, may explain the enormous variations in the speed at which resistance to antimicrobials emerges in different geographical regions.

Socioeconomic and sociocultural factors and the biology of resistance genes

To date, few clinical and public health microbiologists have addressed the possible influences of socioeconomic and sociocultural factors upon the development and spread of antibiotic resistance genes. A review of the documentation of bacterial resistance patterns in different countries however showed that cultural and economic factors could be at play in the distribution of bacterial resistance determinants [10], [11]. A 2005 global epidemiological survey for instance, revealed that the prevalence of extended spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* isolates from patients in intensive-care units may be decreasing in France (7.9%), Sweden (3%), the United States (6.1%), Australia (5%), and Japan (5%), while continuing to increase in comparatively less wealthy nations elsewhere in Asia (20–50%), and in Brazil, Colombia, Venezuela, Poland, Portugal, Turkey and South Africa (30–60%) [6]. Similar trends were reported for ESBL-producing *E. coli* isolates [7]. Although these differences in phenotypic resistance rates are consistent with the socioeconomic disparities among these countries [12] it is difficult to establish causality based on these ecological data. Nevertheless, this is an important hypothesis that requires close examination from clinical, public health and agricultural experts, particularly given the severity and magnitude of the problem.

Biological Aspects

Higher prevalence of resistance has consistently been attributed to antibiotic selective pressures and the availability of transferable resistance genes. Following this line of thought, one would expect lower prevalence rates of ESBL resistance (and ESBL resistance genes) in poorer populations that do not have broad access to beta-lactams such as the newer and more expensive cephalosporins that select for ESBL-producers. However, substrate specificity of ESBLs is not restricted to newer generation cephalosporins but includes narrower spectrum beta-lactams such as ampicillin. Thus, the expected lower prevalence rates from limited use of agents normally expected to select for ESBL-producers can be amplified by the heavy and unregulated use of narrower spectrum drugs. Similarly, the genetic environments around most ESBL determinants have been speculated to induce mobilization of these genes from the chromosome to plasmids that carry multiple genes encoding resistance to many antibiotics, including aminoglycosides, chloramphenicol, sulfonamides, trimethoprim, and tetracyclines [13]. Recent findings indicate that bacterial species have only a small barrier to overcome for the exchange of a resistance determinant once it has been integrated into auxiliary mobile DNA. This scenario perhaps explains the high prevalence of plasmid-borne ESBL genes [6]. We should of course be reminded that specific resistance genes can persist even in geographic regions with no direct selective pressures from the use of their respective drugs if the genes are linked with other genetic determinants associated with antimicrobials that are heavily used in the area [14]. Thus, the unorthodox, unregulated use of cheaper and readily available beta-lactams like ampicillin, ampicillin-cloxacillin combinations, aminoglycosides, chloramphenicol, sulfonamides, trimethoprim, and tetracyclines effectively provides an example of social forces that could influence the co-selection and reported higher prevalence of ESBL-producing genes in developing countries like Bolivia, Peru [15], Nigeria [16], Cameroon [17], India [18], Colombia [19], Puerto Rico [20] and Vietnam [21] compared to developed countries such as Canada [22], Spain [23], Switzerland [24], France [25] and the UK [26].

Sociocultural Factors

Recent trends in Nigeria highlight the type of unorthodox, sociocultural-influenced antimicrobial usage patterns that may be driving increases in resistance rates and the spread of resistance genes. In Southwestern Nigeria, young female college students are increasingly using over the counter antimicrobials during their menstrual periods to prevent perceived risks of infections from feminine sanitary products and to “treat” menstrual symptoms such as cramps and bloating [27]. The choice of antimicrobial varies between ampicillin, ampicillin-cloxacillin combinations, metronidazole or tetracycline depending on socioeconomic ranking and other physiological condi-

tions such as menstrual flow rate, color and general appearance of flow, and onset of cramps [27]. Moreover, due to the strong social stigmas associated with any infections of the female urogenital system, whether they are sexually transmitted diseases or other unrelated infections, a significant number of female University dormitory residents are using one or more self-prescribed antibiotics in combination with miconazole or clotrimazole regularly to prevent or manage "toilet" diseases (candidiasis) that are perceived to be associated with community restrooms in campus housing. The consequences of such inappropriate uses of drug compounds include higher rates of antimicrobial resistance and have been widely discussed [4], [5], [6], [7].

Socioeconomic Factors

Higher prevalence of obtainable resistance genes and overall resistance rates in regions such as Africa, the Caribbean, South Asia and Latin America could also be influenced by the high burdens on public health systems as a result of the HIV/AIDS epidemic, Ebola viruses and other infectious diseases. Several countries in these regions, especially Africa, spend huge percentages of their public health budgets on epidemics such as HIV at the expense of other illnesses and needed upgrades of hospital equipment [28].

A case in point is Uganda which spends about \$ 1 billion per year on HIV-related problems out of a total GNP of about \$ 6 billion [29]. Moreover, there are countries within the African continent that spend more than half of their national budgets to service external debts while losing sight of the long term gains and effective interventions that could be obtained from surveillance of antibiotic resistance, general improvements in community based sanitary welfare and other previously described public health interventions [30]. For instance, Niger spends three times more money servicing its international debt than on the health and education sector of the economy. As a result, there are little or no antibacterial drugs/medications in hospitals because, on average, annual health spending on the continent of Africa ranges between \$ 13 and \$ 21 per person and there are simply not enough funds available to purchase antimicrobials [28], [31]. In comparison, this equates to approximately 0.3% of the annual per person healthcare expenditures in North America. In Canada alone, about \$ 4,400 was spent per person in 2005 [32].

However, even when funds are available, glitches in the organizational machinery of hospitals due to a combination of factors – such as: 1) lack of active participation in surveillance and control of infections; 2) management's need to save (or reallocate) money; and 3) reductions in the number of maintenance staff which could lead to poorer hygiene and cleanliness in patients' rooms – may increase the risk of drug resistant bacterial outbreaks, such as multiple antibiotic-resistant *Clostridium difficile* hospital outbreaks, which occur in both developed and developing countries. In fact, these outbreaks have re-

cently become more rampant in Canada. Between 2003 and 2007, outbreaks of multiple antibiotic-resistant *C. difficile* have claimed an estimated 2,000 lives in the province of Quebec [33], [34]. Some outbreaks also have occurred in the province of Ontario, which made drastic cuts to its health-care funding/budget between 2000 and 2003. We suggest that a consequence of underdeveloped and under-funded systems of surveillance, research, healthcare and infection control in both developed and developing countries could be the silent but rapid movement of mobile genetic elements and the reshuffling of antibiotic resistance genes [35].

Brain drain is another problem. Many medical professionals in developing countries have been lured away to better working conditions and salaries in Western countries. As a consequence, there are less health professionals per population in developing countries. For example, in Ethiopia, the physician-to-population ratio is 1:38,619 and the pharmacist-to-population ratio is 1:3,671,327 [36]. Unlike people in many developing countries, citizens of nations with higher per capita incomes enjoy increased access to health professionals which can lead to more appropriate uses of antimicrobials and a greater variety of available antibacterial drugs. These two factors independently, as well as their interactions, might explain the lower overall patterns of antimicrobial resistance observed in these high resource countries. However, significantly higher rates of drug resistance also have been observed in resource-depleted micro-communities within those high-income nations indicating that other social, cultural and/or behavioral factors may be influencing resistance rates. Population-based studies have revealed correlations between the incidences of infectious diseases and educational attainment, per capita income and behavioral patterns [37]. Poor patient compliance and self-medication (as described above) aided by the availability of over the counter drugs, are behaviors that worsen treatment options which are already very limited [3], [9].

Genetic flexibility and adaptation of bacteria to changes in the environment

Under the intense selective pressures of antimicrobial use and abuse, genetic mutations and recombination events associated with drug resistance are selected among bacterial populations. The sophistication and complexity of these resistance mechanisms, as well as the ease with which they can be disseminated, are inversely related to the level of caution applied in antimicrobial use within a region being studied. Although specific mechanisms of action and gene dissemination are widely known and have been analyzed in great detail [38], [39], [40], the scientific community must keep pace with the rapidity and flexibility of resistance gene exchanges between bacterial genomes of the same species or members of mixed populations. A comprehensive genetic engineering process has evolved which allows bacteria to remodel, mix and match genes [40] and to integrate

them into auxiliary and mobile genetic elements. The direct consequence of this reassortment is greater ease of bacterial genetic mobility. Whether via conjugation, transduction, or transformation, genetic mobilization may occur between similar or diverse bacterial genera. This pool of resistance determinants is distributed across the bacterial kingdom worldwide. However, there are significant variations in the patterns of resistance gene spread from region to region, and the reasons for these variations are not yet clear.

High population densities and poor living and sanitary conditions are underlying social forces which have been directly linked with high densities of mixed bacterial populations [3], within which rapid exchange of mobile genetic elements can occur. However, additional unappreciated socioeconomic factors discussed in this article may be at play. The potential for unrestricted exchange of DNA encoding antimicrobial-compromising proteins constitutes a great challenge for the assurance of therapeutic antibacterial drug efficacy. This is a serious public health concern on both local and global scales.

Suggestions for improvement and conclusions

In 2001 the World Health Organization published its global strategy for the containment of antimicrobial resistance [30], a landmark position paper that focused international attention on this crucial problem. The Infectious Diseases Society of America has recently published its own excellent guidelines for antimicrobial stewardship [41]. We applaud these efforts, and concur with many of their recommended interventions. However, these interventions have not yet been implemented on a broader scale – either in industrialized societies or in developing nations, where many consumers of antibacterial drugs earn approximately \$ 1.00/day. Thus, we should take into account the major economic impacts of apparently simple interventions [42]. Worse yet, political corruption is often endemic in areas that are hardest hit by rising rates of resistance. Corruption dampens socioeconomic activities and perpetuates unemployment, illiteracy, and the collapse of transportation, education and health care systems [12]. For all of these reasons, we need to design thoughtful non-generic programs/interventions aimed at the containment of resistance that address specific socioeconomic and sociocultural factors and accommodate the current needs of specific populations. These interventions should include, but not be limited to, health communication programs that educate people about the proper use of antimicrobials.

We are troubled by the current state of knowledge regarding the global epidemiology of antimicrobial resistance. The little research that has been conducted to understand relationships between socioeconomic and sociocultural factors and antimicrobial resistance has focused on patterns of phenotypic antibiotic resistance. Yet, there is a real need for qualitative and quantitative measurements of human influences upon the molecular biology of bac-

terial resistance and adaptation. If researchers focus more attention towards understanding the influence of socioeconomic and sociocultural factors on genotypic resistance determinants, perhaps we will develop a clearer understanding of the ways in which our socioeconomic and sociocultural environment contributes to shifts in the microbial ecology of antimicrobial resistance. If our social and cultural experiences influence the molecular adaptation and spread of resistance genes in the microbial world, then precisely which of those experiences should we seek to change? This information would allow us to formulate rational, locally-effective interventions to quell this problem.

Charitable institutions and centers of higher learning have begun to emphasize the importance of this type of research. We are encouraged by the University of Washington's recent creation of the Department of Global Health and the Institute for Health Metrics and Evaluation [43]. It remains to be seen whether research from these and other programs around the world will focus on ways to contain antimicrobial resistance by explaining the impacts of human behaviors upon bacterial molecular phenomena.

An intervention which is effective in one part of the world might be entirely inappropriate elsewhere. We suggest a more integrated culturally appropriate approach. We submit that the escalating problem of antimicrobial resistance is not a single human health problem, but a manifestation of an array of problems rooted in the complex evolution of bacteria and greatly influenced by multifaceted sociocultural and socioeconomic factors, as well as the human and veterinary use of antimicrobials. A well-coordinated and rational response to this global crisis is clearly overdue.

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Conflicts of interest

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