Response to antimicrobial resistance in a globalized world

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Abstract
Antimicrobial resistance is a major challenge for public health in the current globalized trade-based environment. Antimicrobial drugs are susceptible to obsolescence due to inappropriate use. This relates to use of these drugs in humans and use of antimicrobials in developing food products: plant, animal and aquaculture, etc. Antimicrobial resistance-related issues are becoming important in the work of a range of multilateral bodies such as World Health Organization’s International Health Regulations, World Trade Organization’s Trade Related Aspects of Intellectual Property Rights and Sanitary and Phytosanitary Measures Agreements, the Food and Agriculture Organization, Office International des Epizooties, and the Codex Alimentarius Commission, etc. Norm-setting at a global level is being undertaken by these multilateral organizations in their own capacity and through joint collaboration. This paper argues that regulatory and policy measures distinguished from drugs in general are imperative to preserve the efficacy of antimicrobials. It also argues that multilateral acceptance needs to develop synergy with norm-setting measures at regional/national levels in order to achieve an effective response to antimicrobial resistance.

Background
In the twentieth century, antimicrobial drugs, antibiotics and antivirals provided a critical breakthrough in man’s successful fight against disease. Penicillin, the first truly safe antibiotic agent, was discovered by Sir Alexander Fleming in 1928. In 1942, penicillin was made available to some members of the public and in 1944 to the general public. Currently, though many antibiotics are available, there are only about twelve classes of antibiotics. The most recently approved new class of antibiotics, the Oxazolidinones, was approved in 2000. It is the only new antibiotic class to be introduced into a clinical setting in thirty years. By 2001, clinical resistance to this drug was observed.

Antimicrobial drugs are susceptible to obsolescence by overuse. This happens when the target of the antimicrobial drug develops resistance, a process that can occur with alarming rapidity. According to Dawkins, “life results from the non-random survival of randomly varying replicators. Resistance to antimicrobials is a result of such evolution. Given a sufficient amount of time and a large enough population, a particular life-form will find some way to adapt to a particular environmental stimulus.” Unnecessary use of an antimicrobial occurs when the compound is administered to treat a condition for which the compound is wholly unsuited or is genuinely irrelevant. The tendency of patients to consume sub-therapeutic doses, partial courses, or to under-use the antimicrobials is problematic.

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1 On November 29, 1942, the Cocoanut Grove, a Boston, Massachusetts bar, was the scene of a horrible fire. Several hundred people were killed and many survivors were severely burned. The United States Government released a substantial quantity of penicillin to the victims and in what was the largest clinical trial of the compound, nearly every patient treated with the penicillin avoided infection.
The adaptive potential of the microbial world is such that for each new antibiotic that is introduced, several escape mechanisms are soon devised. According to a forecast by the University of California at San Francisco, the United States of America, this dynamic will lead to the exhaustion of all antimicrobial drug options by 2070. Many developing countries have inadequate or non-existent regulatory controls over antimicrobial use for human and animal health purposes. Regulatory and policy measures are imperative to preserve the efficacy of these “wonder drugs” for coming generations in the current fast-paced, globalized and trade-centred national and international environment.

Legal developments

The advent of antibiotics has had a profound impact on the societal response to communicable diseases. These drugs changed the hitherto prevalent quarantine-based response. A leading case in quarantine law occurred in 1902 when a public health resolution was upheld prohibiting the entry of any person in any city or town in quarantine, regardless of whether the person was healthy or infected with disease. Antibiotics made coercive personal control mechanisms unnecessary and legal decisions shifted the focus to the due process in law. It was held that a person alleged to have tuberculosis (TB) must be accorded procedural due-process rights. However, in the 1980s, the courts upheld the substantive authority of public health authorities in responding on behalf of a community. They also reaffirmed the historical public health legal concepts.

The delicate balance between individual liberty of action and community public health interests is at the forefront in discussion on antimicrobial resistance (AMR). On the one hand is the necessity for promotion of use of antibiotics for containment of disease and on the other, containment of use of antimicrobials to make certain that they do not lose efficacy through indiscriminate use. This has engaged national and international entities and resulted in certain directives governing such use as is the case in the European Union (EU). One of the only antimicrobial agents available for treatment of multidrug-resistant enterococci and methicillin-resistant Staphylococcus aureus (MRSA) infections was vancomycin. The Danish Minister of Agriculture and Fisheries banned the use of avoparcin nationally because scientific evidence showed that avoparcin used as a growth promoter in food animals constituted a potential threat to human health. In July 1995, the ban became effective in all countries in the EU. The avoparcin ban called attention to the wide array of antimicrobial substances being used in food animals for growth promotion or disease control and to the risk for transfer of other resistant bacteria or resistance genes from animals to humans through the food chain. It was decided that all use of antimicrobial growth promoters should be terminated within the EU starting 1 January 2006. This EC Regulation 2821/98 came up for adjudication and President of the Court of First Instance of the European Court of Justice (CFI) held that the documents before him confirmed that bacteria resistant to virginiamycin in animals were transmissible to humans.

The importance of preserving these drugs has led courts in the EU to exercise the precautionary principle in law. The mere existence of this potential risk was enough in

2 Antibiotics and antimicrobials are used interchangeably in this text.
itself to exercise the precautionary principle and justify taking the protection of human health into account in the balancing of interests. Thus it has been reiterated at national and international forums that the “protection” of the efficacy of antimicrobial drugs is of vital importance.

Trade and intellectual property issues

Trade and globalization have contributed to international and national movement in medicines, food products and persons. The globalization of the food industry is having enormous health (and regulatory) effects. The term “globalization of public health” has emerged in policy discourses to express the transnational or globalized nature of public health threats (including the spread of communicable diseases) in an interdependent world and de-emphasizes the “territorialization” or “nationalization” of diseases. This process has fostered AMR. It has been stated that easy access to cheap antibiotics under the globalised trade regime in the third world has furthered antimicrobial resistance. This can occur both by human consumption of antimicrobial drugs and in animal and plant use. Overuse of antimicrobials in livestock and poultry production can lead to the rapid development of resistant strains of food-borne pathogens like Campylobacter jejuni.4

Antimicrobial resistance is relevant in international trade and public health in issues related to intellectual property rights (patents), compulsory licensing, parallel trade, counterfeit drugs and internet (web-based) procurement of different food and drug products.

Of all intellectual property rights, the pharmaceutical industry relies primarily on patents. The pharmaceutical industry’s dependence on the patent system as a panacea of all problems has resulted in the approach to find a “patent” solution for all problems. The intellectual property law including on patents, that endows drug makers with a temporary monopoly on new drugs, can make effective preventive medications inaccessible to poor countries.

The Infectious Diseases Society of America (IDSA) correctly identifies the need for effective antibiotic therapies, but has mistakenly called for significant changes in patent law to remedy the problem, including patent extensions and wildcard patent extensions for antibiotics.5 It is assumed that apart from the direct stimulation of resistance by increasing consumption, AMR has resulted in retardation of innovation and research efforts in this genre of drugs. According to surveys conducted in 1999 and 2003 by the Pharmaceutical Research and Manufacturers Association, the trade organization for the pharmaceutical industry in the United States, the number of drugs in development for AIDS and related conditions declined from 102 to 83, respectively. Similarly, the supply of antibiotics is threatened by high levels of antibiotic resistance, an uneven supply of novel classes of antibiotics over the last few decades, and a dramatic reduction in the number of pharmaceutical companies engaged in research and development (R&D) in the area of antibiotics. Despite the critical need for new antimicrobial agents, the development of these agents is declining. Steps are therefore needed to encourage and facilitate the development of new antimicrobial agents.

Although knowledge is a classic public good, in practice the enormous cost of R&D means that patents are used to transform it into a private good thus providing the incentive for private sector investment.

4 C. jejuni became resistant to fluoroquinolone once that antimicrobial was approved for use in poultry

5 A wildcard patent extension grants additional years of patent life on any drug of a company’s choice if the company achieves some socially desirable goal, in this case, development of a novel antibiotic. Wildcard patent extensions have generated sharp academic exchanges in recent years.
However, market-based pricing is an important element of the patent system and its absence in pharmaceuticals is intriguing. For dealing with AMR, the most effective and immediate solutions might be based on conservation rather than production, and on reimbursement rather than patent law.

Several methods have been suggested to avoid or remedy this problem, including transferring the responsibility for research funding to the public sector, requiring all drug manufacturers to pay into a research and development fund, and increasing the drug patent term. Perhaps a total rethinking of how antibiotic funding is handled is in order.

Collective action on a number of fronts is therefore necessary, including the reform of international patent laws and the coordination of licensing and regulatory requirements. Conservation and issues of reimbursement in the current globalized trade-dependent milieu thus call for concerted national and international intervention tailored specifically to prevent AMR.

The debate on compulsory licensing and AMR illustrates the dichotomy of accessibility of drugs on the one hand and their overuse on the other. Compulsory licensing is one of the flexibilities permitted under the Trade Related Aspects of Intellectual Property Rights Agreement (TRIPS) under the World Trade Organization (WTO). A compulsory licence is granted by a government to allow the use of a patented product without the permission of the patent holder and is one of the major safeguards for access to medicine in a public emergency. Opposition to compulsory licensing is based on concerns about the potential misuse and abuse of antimicrobial drugs in developing countries. It has been stated that lack of control over the prescription and distribution of antimicrobial drugs has contributed to the irrational use of such drugs and the resulting development of AMR. Antimicrobial resistance in diseases such as TB and malaria has resulted from the undisciplined use and misuse of pharmaceutical drugs in developing countries. With some strains of the human immunodeficiency virus (HIV) already developing resistance to HIV/acquired immunodeficiency syndrome (AIDS) therapies, concern exists that widespread compulsory licensing of HIV/AIDS therapies in developing countries could increase the potential for the development of resistant strains of HIV. While some developing countries may have the public health infrastructure to administer HIV/AIDS drugs properly on a large scale, the historical problems encountered in the developing world with the irrational use of antimicrobials suggests that compulsory licensing of HIV/AIDS therapies might have a significant long-term downside. Therefore, opponents of compulsory licensing advocate restricted access to antimicrobial drugs to developing countries.

Instead of preventing access, it is important to address the constraints of effective drug use in developing countries such as the lack of infrastructure etc. Disease knows no boundaries as has been observed in the H1N1 and H5N1 epidemics. Hence, rather than restricting accessibility to antimicrobial drugs, availability of drugs in countries with high disease burdens should be ensured combined with appropriate national regulatory mechanisms especially designed to address AMR.

Parallel imports, or grey-market goods, are imported copies of a product protected by some class of intellectual property, which are legitimately and legally purchased in a foreign jurisdiction. Parallel imports are likely to increase the improper use of antimicrobials by increasing both unnecessary consumption and underconsumption. Underconsumption may increase as a secondary effect of price, and is likely a result of patient capriciousness. On the other hand, patients may encourage overconsumption themselves merely on the ground of information that an antimicrobial
may help. Both parallel imports and drug subsidies function by lowering the cost of drugs to consumers. Rather than restricting parallel imports that ensure accessibility to much needed drugs, both patients and doctors need to be sensitized to AMR. This calls for enhanced communication to the public on AMR and its implications. This process may be given a stimulus through appropriate national regulation on communications measures specifically designed for AMR.

Antimicrobial resistance is a matter of serious concern in counterfeit medicines. Counterfeit medicines are more commonly found “in countries with weak drug regulation control and enforcement, scarcity in the ... supply of basic medicines, unregulated markets, and unaffordable prices. Counterfeit drugs pose a serious risk to the safety of patients who take them as they are unsafe and ineffective. Counterfeit medicines also affect the health of the public at large by increasing the risk of producing more antimicrobial-resistant organisms. In view of their importance, counterfeit antimicrobials need to be addressed differently from other counterfeit products or drugs. Hence, it is necessary to have national and international regulations on counterfeits that distinguish this class of drugs from the others. This would help focus attention on AMR and thereby preserve the efficacy of this genre of drugs.

Internet and web-based transactions (and parallel imports through the web) enhance the ability of patients to order medications from pharmacies and suppliers from all over the world. More complicated, however, is the purchase of drugs from overseas pharmacies, when the exporting jurisdiction does not require a prescription for export, or where the pharmacies can easily avoid the regulations that exist. It has been suggested that in these cases, parallel importing jurisdictions should require that all imported medication be screened by the respective border control agency, and every prescription drug matched with a valid prescription. Without curbing the freedom of communication and information in internet transactions, suitable mechanisms to address AMR are the need of the hour. Hence, it may be advisable to encourage the development/use of nationally/internationally recognized antimicrobial provider indicators e.g. trademark/ logos/ certification marks on web sites. These indications on the source of drugs would encourage discerning use through widespread dissemination and communication among doctors and patients and assist in containing AMR.

International developments

Issues related to AMR have assumed importance in a range of multilateral organizations such as WHO’s International Health Regulations (IHR), WTO’s Trade Related Aspects of Intellectual Property Rights (TRIPS) and Sanitary and Phytosanitary Measures (SPS) Agreements, the Food and Agriculture Organization (FAO), Office International des Epizooties (OIE), and the Codex Alimentarius Commission Standards on Food Safety, etc.

The role of WHO: The genesis of WHO’s role in containment of communicable diseases is the nineteenth-century international sanitary

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6 CEO of the Centre for Mental Health in the United Kingdom, stated that, “...potent substances are freely available on the Internet and can be ordered easily without any prescription and any authentication of sources, making the public vulnerable to health hazards and public health vulnerable to growing antimicrobial and drug resistance.”

7 Julian Mount, Diminishing the Risk of Counterfeit Drug, World Pharmaceutical Frontiers, http://www.worldpharmaceuticals.net/articles/wpf007_Pfizer.htm. Mount notes that “the website Paypill.com had been found to be selling counterfeit medicines for the second time. Paypill.com has stated, ‘We purchase drugs directly from the same parallel imported sources as the NHS, so if we are selling fakes, then the NHS is selling/dispensing fakes too.’ Mount notes that parallel trade also introduces the potential for error at the repackaging stage, and makes recall difficult when particular problems are identified.
conferences initiated by France in 1851 and attended by eleven European states. From 1851 to the end of the nineteenth century, ten such international sanitary conferences were convened. Surveillance was an important part of the mandate of the Pan American Sanitary Bureau, Office International d’Hygiène Publique, Health Organization of the League of Nations, and the OIE. In 1951, WHO adopted the International Sanitary Regulations, the product of the nineteenth-century international sanitary conferences, which were re-named the International Health Regulations (IHR) in 1969, and modified in 1973, 1981 and 2005. The IHR are a set of regulations for the control and sharing of epidemiological information on the transboundary spread of cholera, plague and yellow fever; to ensure “maximum security against the international spread of diseases with a minimum interference with world traffic”. The IHR (2005) are legally binding on virtually all (i.e. 194) States worldwide, and impact governmental functions and responsibilities across many ministries, sectors and governmental levels.

The role of WTO: The role of WTO and TRIPS in communicable diseases was brought into focus by the situation presented by HIV/AIDS in developing countries, especially South Africa. The complexity of striking a balance between intellectual property rights and access to essential medicines by vulnerable populations has placed TRIPS at the centre of global public health policy in recent years. The exceptions under TRIPS (commercial licensing and parallel importation of generic drugs) could be exploited to protect public health. Despite these exceptions, thirty-nine multinational pharmaceutical companies initiated litigation against the Government of South Africa in 1998. In another case, the United States filed a complaint against Brazil at the WTO in 2001. These interventions challenged the aspects of South African and Brazilian legislations as infringing the TRIPS obligations. This revealed the complexity of balancing intellectual property rights with access to drugs. As a result in November 2001, a WTO Ministerial Conference adopted the Doha Declaration and stated that “the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health”.

Apart from TRIPS, the Agreement on the Application of Sanitary and Phytosanitary Measures (“the SPS Agreement”) of the WTO sets out the basic rules for food safety and animal and plant health requirements while allowing countries to set their own standards. However, SPS also specifies that regulations must be based on scientific findings and should be applied only to the extent that they are necessary to protect human, animal or plant life or health; they should not unjustifiably discriminate between countries where similar conditions exist.

The SPS Agreement was the subject of legal interpretation in the WTO Dispute Settlement mechanism in a major international dispute relating to AMR. In EC-Hormones, the challenged measures were EC regulations prohibiting the sale and importation of meat and meat products that had been treated with growth hormones. The WTO dispute Appellate Board (AB) found that the different levels of sanitary protection set by the EC for meat (beef) treated with growth hormones as compared with meat (pork) treated with antimicrobial agents were unjustifiable. Although they all involve the same health risk (carcinogenicity), growth hormones were banned while antimicrobial agents were allowed. Notably, the EC allowed carbadox and olaquindox to be used as antimicrobial feed additives that promoted the growth of pigs; yet the EC banned the use of hormones as growth promoters in cows although the hormones resulted in similar (or lower) risks to humans. However, the AB observed that the

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EC regulations had legitimate purposes and were genuinely designed to protect its population from the risk of cancer. Thus the normative role of Member states to set up their own standards and regulations under SPS is relevant for AMR issues.

Role of the Office International des Epizooties (OIE), Food and Agriculture Organization (FAO) and the Codex Alimentarius Commission: The Office International des Epizooties (OIE) established in 1924 is the international organization designated to fight animal diseases at the global level. The OIE’s standard-setting activities in this field focus on eliminating potential hazards existing prior to the slaughter of animals or the primary processing of their products (meat, milk and eggs, etc.) that could be a source of risk for consumers. FAO has been concerned with antimicrobial resistance, related to the use of antimicrobials in agriculture (including aquaculture) and veterinary medicine.

The Codex Alimentarius Commission was created in 1963 by FAO and WHO to develop food standards, guidelines and related texts such as codes of practice. The Joint FAO/WHO Food Standards Programme aims to protect health of consumers and ensure fair trade practices in the food trade. Use of antimicrobial agents in animals in the food chain has long-term implications. As a result many noncommunicable diseases may have their base in communicable diseases. Codex, WHO and FAO are currently engaged in risk analysis of food-borne antimicrobial resistance-specific interventions and implementation strategies to control and contain antimicrobial resistance in various areas, including animal husbandry.

Hence, a number of international organizations are currently engaged in AMR prevention under their mandates and their activities augment norm-setting at international level.

Conclusion

International and national movement of persons coupled with global trade in food items mandates examination of crossborder effects of policies and regulations for rational use of antimicrobials. Due to the challenges posed by movement of pathogens in this globalized trade environment and paucity of new drug development through research, the need to preserve antibiotics is more important than ever before. Since the sum of actions by individual nations does not equal the optimal global response, some element of collective action is required. Collective action to address AMR at international level is seen in the collaboration among WHO, FAO, OIE and Codex, etc. The AMR issues are engaging international courts and WTO is increasingly relying on standards set up under such collaborations in settlement of trade disputes.

Certain work has been carried out to develop international standard treatment guidelines, which are similar, for example, to current WHO AMR surveillance standards, WHO guidelines for the treatment of MDR-TB, and WHO protocols for the detection of drug-resistant malaria. WHO has begun development of a global strategy to contain AMR.

This strategy follows the historical preference of WHO and other international bodies for operating through recommendations and guidelines, relying largely on ad hoc harmonization of individual national mechanisms, legislation and strategies, rather than on formal international legislation. Unfortunately, evidence suggests that this may be inadequate to contain AMR in the long run. In view of the importance of this genre of drugs, developing sustained mechanisms to contain AMR through formal norm-setting is imperative. Formal norm-setting to contain AMR that is binding both nationally and internationally should be encouraged at national and regional levels.
WHO, FAO, OIE and Codex, etc. are undertaking norm-setting at the global level. Multilateral acceptance at this level needs to develop synergy with norm-setting measures at regional/national level. For these responses to yield tangible results, it is necessary to extend the global collective action at regional and national forums in order to have a comprehensive approach to AMR. Such collective action must be initiated not only in single-line WHO programmes at national and regional levels but also be sustained in horizontal formal collaboration with organizations responsible for plant and animal health. A dialogue-exchange mechanism should be established at global, regional and national levels. These forums could then develop national, regional and international normative action that encourages optimal use of antimicrobials. This would lead to acceptance of measures to contain antimicrobials and development of national and international norms in synergy with practical requirements for local and global response. The regional and national forums may also take up normative action on enforcing strategies covering, for example, intellectual property rights, the requirement for AMR data in the pre-approval evaluation of drugs, the use of subtherapeutic doses as growth promoters in animals, the labelling of drugs, and prescription requirements.

There is an additional benefit of collective norm-setting as envisaged above. The collective forum norm-setting at regional and national levels would also enable dissemination of information and appropriate communication aimed at national and regional settings. This would give the process an advantage of being “owned” by the constituents, resulting in better compliance mechanisms for AMR containment. The collective forums at national and regional levels may also develop management mechanisms for antimicrobials, as distinct from drugs used for other purposes. The creation of a separate set of mechanisms at all levels dealing with antibiotics: research, production, marketing, communication and advertisement, and health systems handling, etc. would enable an effective response to AMR.

References and bibliography


