# Resisting Resistance

## *Thinking Strategically about Antimicrobial Resistance*

Richard D. Smith and Joanna Coast

**Richard D. Smith** is Senior Lecturer in Health Economics at the School of Medicine, Health Policy and Practice at the University of East Anglia.

**Joanna Coast** is Senior Lecturer in Health Economics at the University of Bristol.

Not long ago, it appeared as if the great twentieth-century battle against infectious disease had been won by the "magic bullet" of antibiotics. Unfortunately, celebrations have proved premature, and we begin the twenty-first century in retreat, as our once powerful antibiotics appear to be no match for the ingenuity of infectious "superbugs."

It has been observed as a natural biological phenomenon that micro-organisms can develop resistance against the antibiotics used to treat them.[1] Although the development and spread of resistance is a complex process that depends on many factors, genetic transformation of micro-organisms into resistant strains is accelerated by the use of antibiotics.[2]

These superbugs now present an ever greater challenge to public health. Diseases, ranging from mild ear-infection and strep throat to malaria and tuberculosis, are all increasingly demonstrating resistance to the antibiotics used against them.[3] For example, in 1991 almost half of the 4,000 tuberculosis patients arriving at New York hospitals were suffering from resistant strains, and one such strain proved resistant to eleven different drug treatments.[4] By 1993, physicians were regularly trying six or more drugs in attempts to treat tuberculosis.[5] Doctors in New York have even died from drug-resistant tuberculosis; a situation that is being replicated in cities across

the United States, other Western countries, and especially in the developing world.[6]

Resistance creates serious health and economic repercussions. Patients infected with a particularly resistant strain are less likely to recover after the first antibiotic treatment. Such patients may require further examinations and treatments, and for some, a cascade of other drugs will be tried before the infection is eradicated. This generally means longer hospital stays, longer absences from work, and undoubtedly higher medical costs than for non-resistant infections.[7] In the mid-1990s, estimates suggested that the health care costs associated with the treatment of antimicrobial resistance (AMR) in the Unites States were approximately $4-7 billion annually, or approximately 0.5-1% of total U.S. health care costs.[8] Beyond increased health costs, patients with extreme cases of resistant infection face a greater likelihood of premature death.[9]

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This is understandably causing professional, government, and public concern. Indeed, the United States considers the potentially destabilizing economic and social effects of antimicrobial resistance, as well as its potential in biological warfare (especially in light of recent anthrax scares), sufficient to classify antibiotic resistance as a national security risk.[10]

There are a variety of strategies that may be used to tackle resistance, such as reducing the use of antimicrobials, developing new agents, and isolating resistant patients in hospitals. In general, the purpose of these strategies is to either (1) prevent the *emergence* of resistance or (2) contain the *transmission* of resistance once it has emerged. Presently, too much emphasis is being placed on tackling the transmission of resistant infection and too little is devoted to preventing its emergence. This current emphasis on transmission addresses a short-term problem, but does not do enough to address medium and long-term problems. However, it should be noted that the goal is not to eradicate resistance altogether. Such a goal would require a significant—if not total—reduction in the use of antibiotics, and would imply incurring significant mortality and morbidity. Instead, the aim is to use available strategies to optimise the balance between the use of antimicrobials and strategies to help prevent the emergence of resistance to these treatments.[11]

Cooperation on a global level is also required to achieve this optimization of antibiotic use. Since AMR produced in one country soon finds its way to others, resistance has become a global problem affecting both developing and developed countries.[12] Thus, strategies at a national level may be compromised by other nations' lack of action, implying that an international, as well as a national response to AMR is essential.[13]

The following sections outline the difference between the emergence and transmission of resistant infection; various strategies that may be used to address resistance; why strategies aimed at con-

taining the transmission of resistance appear to take precedence over those designed to prevent its emergence; the importance of global collective action; and how this problem may be addressed from the global perspective.

**Emergence vs. Transmission.** Resistance to antibiotics develops over time along a sigmoid distribution or "S" curve. Initially, there is a lag phase where the treatment is highly effective. Soon resistance begins to develop, and the proportion of resistant organisms increases rapidly. After a period of time, resistance stabilizes and reaches an equilibrium level.[14] For example, resistance to penicillin in hospital settings lagged during the 1940s with resistance skyrocketing from about 1947 to 1960, and stabilizing thereafter. The equilibrium level of resistance may range anywhere from 10% to 90%, and is determined by a number of factors, including the relative fitness of resistant strains, the genetic basis and stability of resistance, and the magnitude of the selection pressure.[15]

The importance of resistance's development pattern is that it is possible to affect both the rate of growth and the final equilibrium level of resistance by preventing its emergence in the lag period. However, once an equilibrium level has been reached, antibiotic activity will be severely compromised, and only strategies that reduce the transmission of already-resistant organisms will be possible. Although in some cases resistance may fall once the use of antibiotics stops, in many cases it appears that once resistance is developed, it remains genetically encoded. The significance is that once resistance to a specific antibiotic emerges, that drug may never regain its previous therapeutic powers.

It may seem obvious then that strategies focused on preventing the emergence of resistance offer greater long-term benefits than those responding to the transmission of already-resistant infections. Paradoxically, it appears that strategies to contain the transmission of resistant infection are more popular among policymakers than those to prevent its emergence.

**Strategies Affecting Emergence and Transmission.** Strategies intended to prevent the emergence of resistance include regulations and restrictions on the total usage of antibiotics, as well as an emphasis on provider and patient education. Ensuring the optimal use of existing agents by focusing on drug administration, the magnitude and duration of dose, and improving patient adherence is another technique aimed at minimizing the emergence of resistance. Additionally, the development of vaccines and alternative therapies increases the range of available agents and decreases the requirement for antimicrobials.[16]

Once resistant organisms have developed, they may be acquired through contact with food, animals, inanimate objects, or people. Typical strategies to reduce the transmission of already resistant organisms include hand-washing by medical staff, isolation of patients infected with resistant organisms, and decontamination practices for hospitals. These techniques rely on early recognition of resistant organisms to decrease opportunities for transmission, and could be as extreme as limiting international travel to reduce the spread of resistance. In practice, not only is transmission extremely difficult to control, but such strategies logically mean that at

least some people will suffer from resistant organisms. For this reason, approaches that target transmission are likely to be inferior to those designed to control the emergence of resistance.[17]

A focus on strategies to contain the transmission of resistance will lead to sub-optimal mid- and long-term outcomes since resistance may continue to emerge for all known therapies. At that point, there will be few, if any, effective agents to treat infections. However, in a recent systematic review of the literature, the body of published evidence indicates that most studies have been concerned with strategies to contain the transmission of resistance, rather than to prevent its emergence.[18]

## Why Transmission is Targeted.

Strategies to tackle transmission are easy to evaluate, and generate quick returns; therefore, they are very attractive to politicians and professionals. It is far easier to identify the current incidence of a resistant infection in a population and the impact that this infection has on their health than it is to predict how prevention strategies will change rates of future resistance. The essential difficulty in evaluating strategies aimed at preventing emergence is the uncertainty that comes from predicting the future of a disease.

Second, reducing the transmission of currently resistant infections will have quicker returns on health and cost of care than reducing the future emergence of resistance, where the effect may be uncertain and many years away. Thus, even large absolute health or cost effects occurring in the future are considered less significant than those occurring in the present—a phenomenon termed "discounting" in economics. Strategies that tangibly reduce the transmission of already resistant organisms are therefore preferred to policies that affect the selection pressure for the development of resistance, the impacts of which may not be seen until the distant future.

These two qualities of transmission-reducing strategies make them popular not only to policymakers, but also to professionals, as both groups increasingly favor evidence-based medicine (EBM) and evidence-based policy (EBP). Under EBM and EBP, strategies are accorded more weight the more rigorous the methods used to evaluate them and the stronger the outcomes of those strategies. Thus, strategies evaluated using rigorous experimental methods and showing statistically significant effects on health are prioritized above those with non-experimental design and outcomes that are less statistically significant.

Unfortunately, this can be a self-perpetuating cycle. Strategies focused on containing the transmission of existing resistance are easier to evaluate than those preventing its emergence, and likely to show higher immediate gains. These gains result in observable data, which facilitates subsequent evaluations and creates even more evidence of their success, eventually leading to full implementation of transmission containment strategies. In contrast, strategies aimed at preventing the emergence of resistance will not generate immediate, observable data, and evaluations will be based on the modeling of future resistance. These softer evaluation techniques and the initial lack of hard data limit the ability of emergence-oriented strategies to gain the early research funding that is necessary prior to full implementation.

The implication is that over time, the focus on containing the transmission of resistance rather than its emergence

causes levels of resistance to increase rapidly to their equilibrium level. At this point, containing the transmission of resistance will be futile, if not impossible, as the majority of infectious disease will be resistant. Furthermore, the resulting impact on morbidity and mortality is likely to be catastrophic.

**Global Collective Action.** Most strategies to prevent the emergence, or contain the transmission, of resistance may be provided at the national level. However, the increasing trend of globalization means that the level of resistance in any one nation is critically influenced by that in others, and not merely its closest neighbors.

However, contrary to expectation, this promotes inaction for two reasons. First, the prisoners' dilemma suggests that a nation ought not invest in preventing the emergence and containing the transmission of resistance when it may be undermined by the importation of resistance from other, less vigilant nations. Second, if other nations are taking action to prevent and contain resistance, the incentive is again for a nation to free-ride by doing little or nothing, since it can rely largely on the level of control generated by others. Both reasons create sub-optimal international situations for attacking resistance, and they present the need to secure global collective action in three specific areas.

First, cooperation is needed in the surveillance of resistance, which provides the fundamental data required to locate a resistance problem, monitor its growth, transmission, and direction of travel, and to determine the impact of interventions intended to contain it.[19] The establishment and maintenance of a global resistance database, which nations would both contribute to and have access to, could be extremely valuable in planning to deal with AMR.[20] The World Health Organization (WHO) has already attempted, though with limited success, to establish such a global surveillance database with WHONET.[21] Global action is required here because: (1) the barriers to establishing surveillance systems are high, particularly for poorer nations; (2) surveillance produces benefits for other countries which an individual nation does not account for in deciding whether to invest in a surveillance system; and (3) a global system requires comparable data of adequate quality.[22]

Second, mechanisms to encourage research and development (R&D) of new antibiotic and alternative treatments should be promoted. R&D is often expensive and time-consuming to conduct, yet its results are relatively cheap to disseminate. Thus, international agencies could encourage, coordinate, and standardize international research networks that would be able to undertake trials among geographically diverse patient groups and report strategy outcomes to all nations. Although there has been little progress in this respect, efforts are being made. For example, the WHO, in partnership with the WHO Collaborating Centre for Electronic Disease Surveillance in Paris, has recently established the Antimicrobial Resistance Information Bank (AR InfoBank) to provide access for policymakers and health care workers to quality information about drug resistance and resistance networks.[23]

Third, measures to ensure the appropriate and rational use of existing antibiotics must be adopted. Developed coun-

tries should concentrate on constraining the overuse of therapies by regulating the administration of treatments for certain conditions, whereas developing nations should focus on gaining access to the latest, least resistant therapies, which are often unaffordable.[24] In order to ensure that therapies are widely available to developing nations, international cooperation will be required to reform international patent laws.

more, resistance is a global problem requiring a global response. Global cooperation in surveillance, the development of new antibiotics and alternative therapies, and the rational use of both existing and new antibiotics will be the most effective route.

In achieving these, we advocate that international bodies—and indeed national governments of lead countries: (1) engage in raising the global awareness

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The focus of this paper has been predominantly on antimicrobial use and resistance in humans. However, there is considerable concern over the threat to human health from the use of antimicrobials in animals. Therapeutic doses to treat infection and sub-therapeutic dosages used as growth promoters lead to the development of antimicrobial resistance in animals that may be transferred to humans.[25] This fact has significant implications for the development, containment, and prevention of resistance in humans, but these considerations and other more specific issues, such as the implications of intensive production techniques and economic incentives to agriculture, are beyond the focus of this paper.[26]

Resistance is a growing problem that threatens to return us to the pre-antibiotic era, yet we are focusing on winning current battles as opposed to the overall war. Targeting the transmission of resistant infections is laudable, but it should not be at the expense of strategies aimed at preventing its emergence. Furthermore, resistance is a global problem requiring a global response. Global cooperation in surveillance, the development of new antibiotics and alternative therapies, and the rational use of both existing and new antibiotics will be the most effective route.

In achieving these, we advocate that international bodies—and indeed national governments of lead countries: (1) engage in raising the global awareness of resistance prevention and the interdependence of nations in achieving it; (2) support the creation, monitoring, and enforcement of national legislation and regulation mechanisms to ensure the production of prevention strategies; (3) facilitate the production and dissemination of information within and across nations; (4) advocate international funding structures to assist in the implementation of strategies, since without financial ability, the cooperation and effective participation of developing nations will be undermined; (5) provide an agenda, funding, and coordination for research in the area of resistance to address knowledge gaps and improve areas of uncertainty.

There are few naturally occurring incentives for this type of action where immediate gains are not realized. Therefore, active policy development by international bodies and national governments is required to prevent the emergence of resistance and to ensure that antibiotics will still be effective in combating diseases for future generations.

NOTES

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