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Global Responses to the Growing Threat of Antimicrobial Resistance

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1. INTRODUCTION

"We are further away from mastering infectious diseases than we were 25 years ago" (The Times, 4th April 1995).

We begin the 21st Century in a position of retreat against infectious disease, with the latter half of the 20th Century in danger of being consigned to the history books as the time when a valuable new resource in this battle was both discovered and squandered.

'Superbugs', micro-organisms which have become resistant to the major therapies used to treat them, present a major threat to current and future medical advances (Neu 1992, Tomasz 1994, Murray 1994, Fox 1996, ACSP 1996, Liss & Batchelor 1987, Cannon, 1995). The potential impact of this increasing antimicrobial resistance on health care expenditure and population morbidity and mortality is causing professional, government and public concern (House of Lords Select Committee on Science and Technology 1998, Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance 1998, US Congress 1995, American Society for Microbiology 1995, World Health Organisation, 2001, Garrett 1995, Hunt 1996). Indeed, the US considers the potentially destabilising economic and social effects of antimicrobial resistance, as well as its potential in biological warfare, sufficient to classify antimicrobial resistance as a national security risk (CIA, 1999; Kaldec et al, 1997; World Bank, 2001).

As with infectious disease more generally, antimicrobial resistance is not something isolated to any one country, but is a truly global problem. Increased globalisation has further increased the vulnerability of countries to the diseases of others, with infectious disease able to travel faster and further than ever before (Yach & Bettcher, 1998; Gellert et al, 1989; Fidler 1997). Since the 1970s, for example, over twenty diseases have re-emerged or spread globally, many in a drug-resistant form (WHO 2000c). It is becoming clear that as each country's health affects, and is affected by, events and processes outside its own borders, securing our own health may often require securing the health of others (Folland et al, 1997).

That no single country can orchestrate a response sufficient to protect the health of its population against the effects of antimicrobial resistance means that international collective action is essential. However, although international collective action is required to deal with the global problem of antimicrobial resistance, responsibility for health is still predominantly national: controlled by national government and legislation (Fidler, 1998). This generates the potential for a significant mismatch between the problems generated by (and solutions required to contain) antimicrobial resistance, and the *current* institutions and mechanisms available to deal with them (Jamison et al, 1998). It is this global problem of antimicrobial resistance, the adequacy of current national and international institutions and mechanisms to respond to antimicrobial resistance, and the potential that the 'global public goods' concept has as a framework for informing collective action at the international level, that this paper considers.

Following this introduction, section 2 provides a description of what antimicrobial resistance is, and its health and economic impact. Section 3 explores briefly the economic conceptualisation of resistance, including global public good aspects.

Section 4 considers strategies to contain antimicrobial resistance, focusing on the co-ordinated activities of countries at a global level. Section 5 then reviews existing national and international responses to the challenge and assesses the adequacy of these arrangements, with section 6 considering the actions that international bodies may take to address the problems highlighted in section 5. Section 7 concludes by suggesting how securing collective international action to contain antimicrobial resistance may be progressed.

2. WHAT IS ANTIMICROBIAL RESISTANCE?

2.1. The nature of antimicrobial resistance

Micro-organisms, as part of the natural biological process of defence against attack, evolve to develop resistance (immunity) to the effects of antimicrobials (Ashley & Brindle 1960). Although resistance may be acquired from the environment, other micro-organisms or through random mutation, the emergence of resistance is essentially a reaction to the use of antimicrobial treatments[1].

In general, the development of resistance over time appears to follow a sigmoid (or epidemic) distribution, illustrated in the figure, with a lag phase before resistance appears (time x), then a relatively rapid increase in the proportion of resistant organisms, followed by a third phase (time x+n) in which this proportion reaches an equilibrium (Austin & Anderson 1999). This equilibrium level is determined by the relative 'fitness' of resistant and sensitive strains, the genetic basis and stability of resistance and the magnitude of the selection pressure. At this level, the proportion of resistant organisms may range from 10% to 90% (Anderson 1999).

FIGURE ABOUT HERE

Importantly, although a few studies have suggested that micro-organisms may lose their resistance levels over time once drug exposure has been removed, in general resistance is slow to reverse, and often appears to be irreversible (Rice et al, 1990; Seppala, 1997). This suggests that it is vital to act early to prevent *emergence* of resistance (that is, during the 'lag phase') rather than wait until resistance has already begun to emerge, and then seek to reduce its *transmission*.

However, although true in general, for any specific antimicrobial the correlation between its consumption and the development of resistance to it is complicated and uncertain (Magee et al, 1999). In particular, there is uncertainty resulting from poor knowledge about basic scientific, clinical and epidemiological factors relating the development of resistance to health outcomes, with further uncertainties about the costs and benefits associated with treatment (Coast et al, 1996). Further, the direct development of resistance within an individual can happen when individuals take antimicrobials to treat one particular micro-organism, but resistance is also encouraged in other organisms within the body at the same time. Alternatively

[1] Although the process of natural selection encourages micro-organisms to adapt to environmental pressures, the use of antimicrobial therapies accelerates this natural process, whereby those micro-organisms which are sensitive (i.e. effected by) therapies are soon eliminated by the resistant ones.

individuals may acquire resistant organisms from food, animals[2], inanimate objects or through contact with other individuals (Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance, 1998).

Notwithstanding this uncertainty, there is a growing body of evidence showing high rates of resistance, and growth in resistance, for many disease/drug combinations. For example, *Staphylcoccus aureus* is the commonest cause of post-surgical wound infection and one of the commoner causes of very serious septicaemia (blood infection), also causing toxic shock syndrome, skin infections, abscesses, and food poisoning. However, isolates resistant to the primary treatment (Methicillin Resistant *Staphylcoccus aureus,* or MRSA), as a percentage of all isolates, is approximately 70% in Japan and Korea, 40% in Belgium, 30% in the UK and 28% in the USA, from rates of close to zero just 10 or 15 years ago (Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance, 1998). Similarly, in the late 1980's and early 1990's, rates of resistance to *Streptococcus pneumoniae* (the commonest cause of community-acquired pneumonia, and one of the most serious forms, also causing various other upper respiratory infections, septicaemia and meningitis) were less than 2% in Italy, Belgium and Finland, but 7% in Germany, 9.5% in Iceland, 25% in Romania, 44% in Spain and 58% in Hungary (Appelbaum, 1992).

Further, resistance is not a localised problem. Once resistant micro-organisms have developed, their spread is exacerbated by a number of aspects of modern society including increasing international travel, ecosystem disturbances, war, the rapid growth of large cities and the increasing numbers of individuals with immunocompromise (Coast et al, 1996). For example, during the 1990's a resistant pneumococcus first identified in Spain was rapidly identified in the USA, Mexico, Columbia, Brazil, Argentina, Uruguay, Chile, South Africa, Thailand, Malaysia, Taiwan, South Korea and the Philippines (WHO, 2000c).

2.2 The health and economic impact of antimicrobial resistance

The consequence of the development of resistance is that antimicrobials become ineffective in treating infections (Coast et al, 1996). Thus, patients infected with resistant micro-organisms are less likely than those infected with a sensitive micro-organism to recover from infection with the first antimicrobial used in their treatment. They may require additional investigations and additional treatments (often more toxic and more expensive antimicrobials). For some patients a cascade of antimicrobial drugs may be used before one is found to be successful in eradicating the infection. Patients may require longer hospital stays and longer periods of time away from work. Most serious is the increased likelihood of premature death. The evidence for these outcomes is found in a number of case-control studies. A review of such studies found that, in almost every case, patients with resistant organisms had

[2] In this paper we are concerned predominately with antimicrobial use, and resistance, in humans. However, there is considerable concern over the threat to human health from the use of antimicrobials in animals: principally that use of therapeutic does to treat infection, but particularly sub-therapeutic dosages as growth promoters, leads to the development of antimicrobial resistance that may then be transferred to humans (WHO, 1997a; 1998; Witte, 1997). The global use of such products, and the global travel of produce and antimicrobial resistance in animals, means that many of the issues discussed in this paper apply here, although there are some more specific issues, such as the implications of intensive production techniques, economic incentives to agriculture, particularly in developing countries, which we are unable to cover explicitly in this paper.

poorer health and economic outcomes than those patients with sensitive organisms. For example, in outbreaks of resistant Salmonella the mortality rate was 3.4% compared with a mortality of 0.2% for those with sensitive Salmonella strains (Holmberg, Solomon, & Blake 1987).

Assessments of the economic and health costs have tended to be crude and are focused on the developed rather than the developing world. As well as being rudimentary, the sorts of cost estimates that have been produced almost certainly underestimate the total current costs of resistance, as they are limited to costs incurred by the health care system. Further, none of these cost estimates includes any estimate of the costs that will be incurred by future generations – costs which will almost certainly be larger than those being currently experienced (Coast et al, 2001).

Notwithstanding this caveat, some estimates are available. For example, in 1995 the American Society for Microbiology estimated annual health care costs associated with treatment of resistant infections in the USA at over $4 billion (American Society for Microbiology 1995). More recent estimates have put this figure at more that $7 billion, with up to $4 billion used for the treatment of nosocomial infections due to antimicrobial resistant bacteria (John & Fishman 1997). Other estimates from the USA have suggested that effective nosocomial control programs would save approximately 30 000 lives each year (Haley *et al* 1985). In France it has been suggested that there would be large cost savings if those costs associated with the 500,000 patients who acquire nosocomial infections each year could be avoided (Astagneau *et al* 1999). In 1995, the cost of containing an MRSA outbreak in a district general hospital in the UK was estimated to be greater than £400,000 (Cox *et al* 1995).

It could be expected that these sorts of estimates would be higher for the developing world than for the developed world. The economic, health and infra-structure systems of these countries (for example, irregular drug supply and availability of drugs from unofficial sources (Munishi 1991, Hogerzeil *et al* 1993, Salako 1991)) lead to the inappropriate use of antimicrobials (Guyon *et al* 1994, Bojalil & Calva 1994, Nizami *et al* 1996, Paredes *et al* 1996, Hui *et al* 1997, Reyes *et al* 1997, Rodolfo *et al* 1997) resulting in nosocomial infections from strains that are far more drug resistant that those currently encountered (Wolff 1993).

Developing countries, as well as experiencing problems related to diseases more commonly associated with them than the developed world (e.g. highly drug-resistant shigella, malaria, cholera and typhoid), are also more susceptible to resistant forms of global diseases. For example, the use of antiretrovirals in developed countries has contributed to growing resistance to them, causing great concern to those affected. However, with over 95% of HIV/AIDS occurring in the developing world, this growing resistance to current HIV treatments could be catastrophic. There are, however, to our knowledge, no specific estimates of the economic or health costs associated with antimicrobial resistance in the developing world[3].

[3] Although there has been some attempt at modelling the impact of resistance in malaria (Good man et al, 2001), and tuberculosis (Wilton et al, 2001), in developing countries such analysis is very limited.

3. THE ECONOMIC CONCEPTUALISATION OF ANTIMICROBIAL RESISTANCE

3.1. Antimicrobial resistance as an externality

Although the economic analysis of antimicrobial resistance remains limited, economists have tended to conceptualise antimicrobial resistance as *a negative externality* associated with the consumption of antimicrobials (Phelps 1989). That is, the positive personal benefit from the consumption of antimicrobials (i.e. cure of an infection) generates a cost external to that individual of a reduced likelihood of that drug working as effectively against that infection in another person (or indeed the same person) in the future. Recognition of this indicates that the benefit derived from antimicrobial consumption is more complex than cure rates traded against side-effects. This complexity is illustrated by the equation, reproduced below, developed by Coast et al (1998).

The net benefit which might be expected to result from antimicrobial usage in any period would be:

$$NB^{A}_{t} = f(B_t, E^{P}_{t+1}, C_t, S_t, D_t, E^{R}_{t+1}, A_t, X^{i}_{t})$$

where NB^{A}_{t} is the net benefit resulting from antimicrobial usage in time *t,* B_t is the direct benefit to the patient of taking the antimicrobial, E^{P}_{t+1} is the positive externality arising from reduced transmission of infection in the next period, C_t is the drug plus administration cost, S_t is the cost associated with side-effects, D_t represents problems caused by difficulties in diagnosis, E^{R}_{t+1} is the negative externality associated with increased resistance in the next period, A_t is the quantity of antimicrobials consumed in time t and X^{i}_{t} is a vector of exogenous factors which might influence the levels of the positive and negative externalities. It is important to note that this general relationship, although framed in the context of an individual patient, will apply equally at the national, regional and global level, with NB^{A}_{t} representing the national, regional or global benefit from antimicrobials, and the other variables correspondingly relating to national, regional and global factors.

This conceptualisation suggests that the net benefit resulting from antimicrobial usage in time *t* would be a function of the direct benefit to the patient of taking the antimicrobial, the cost of the drug plus administration costs, the costs associated with side effects, problems caused by difficulties in diagnosis, the negative externality associated with the development of resistance, the positive externality associated with limiting the current spread of infection, the quantity of antimicrobials consumed and a vector of other factors determining resistance within the community.

There are two important implications of this from a policy perspective. First, any individual does not face the true cost of antimicrobial use, as they do not necessarily incur the external costs associated with resistance. This means that an individual is unlikely, expect by chance, to consume antimicrobials to either the clinically or socially optimal degree. That is, they will either over-use or under-use antimicrobials. This is true both of over- and under-use, defined according to the clinically optimal regimen, and over- and under-use according to the economically defined balance of the value of the current and future benefits of consumption. Of course, there is no

reason that the clinically optimal level of use will be equivalent to the socially optimal level, as clinical regimens do not take account of the wider social costs and benefits of use.

As a generalisation, in the developed world the wide availability and affordability of antimicrobial therapies means that it is typically over-use that is of concern, where therapies are taken that have little or no clinical benefit[4]. Conversely, it is under-use that is of concern for the developing world, where clinically sub-optimal doses of therapies are taken, typically through ignorance or poverty, compounded through the use of counterfeit or poor quality drugs, where the therapeutic content is ineffective in treatment and therefore contributes to antimicrobial resistance. This is important to bear in mind when considering the implementation of strategies to contain resistance at the global level. However, in each case, leaving consumption decisions to the 'market' unrestricted is likely to produce a sub-optimal consumption of antimicrobials, and a depletion of their effectiveness.

The second implication is that the 'eradication' of resistance is neither a realistic nor a desirable goal: to eradicate resistance entirely would require significant, if not total, reduction in the use of antimicrobial agents. The aim must therefore be (as illustrated in the equation) to use strategies to *optimise the balance* between the use of effective antimicrobials to treat infection now (thus reducing morbidity and mortality), and the emergence and spread of resistance to these antimicrobials (in turn leading to increased future morbidity and mortality). Such optimisation is here referred to as the '*containment of antimicrobial resistance'* and it can be helpful to think about this containment in terms of a dynamic model, with a number of interactions. There are people taking antimicrobials leading to the development of resistance, and at the same time there are 'strategies' in operation either to stop this taking of antimicrobials, to ameliorate the resistance-inducing effects of taking antimicrobials or to ameliorate the transmission of resistance at any one time. A 'contained' pool of resistance is one for which the strategies have reduced the effects of the further development of resistance (which itself arises through additional consumption of antimicrobials).

3.2. Containment of antimicrobial resistance as a 'global public good': the need for collective action

It has been noted above that economists conceptualise the 'production' of antimicrobial resistance as a negative externality resulting from private consumption decisions to take antimicrobials in the treatment of disease. Yet, although the *production* of resistance is a result of *private* consumption, the *containment* of resistance can be thought of as a *public* good, as it is neither possible to exclude people from benefiting from the containment of antimicrobial resistance nor is the containment of resistance *per se* rival in consumption (Smith & Coast, 2002). The non-rival nature of the containment of resistance means that, even if it is *feasible* to exclude someone, or some nation, from its consumption, it is not *desirable* on efficiency grounds, as long as the benefit from that consumption is positive

[4] This is akin to the common concept of the 'tragedy of the commons', in which a common resource is quickly exhausted by consumption based on short-term gains rather than long term sustainable benefits. Globally, this essentially refers to the unsustainable exploitation of antimicrobials by any particular nation having effects on others, in a fashion similar to the use of carbon-based fuels, and the reduction of rainforests, and their impact on global warming.

(Woodward & Smith, 2002). Further, the containment of antimicrobial resistance is a *global* public good because of the significant cross-border (as well as intergenerational) effects.

Although it is possible to conceive of such public goods being provided in private markets, in general this will result in the provision of a sub-optimal quantity of the good, thus justifying the need for *collective action* (Woodward & Smith, 2002). However, here a difficulty is that there is no obvious global body that can either improve the efficiency of provision in private markets nor provide these global public goods on a public basis. In this respect, an added difficulty is the difference between the final policy goal of containment of resistance, and the intermediate means to achieve this goal. That is, although it can be helpful, conceptually, to classify the policy goal of containment of antimicrobial resistance as a global public good to emphasise the importance of collective action strategies, it is of little direct help in determining the most efficient methods for reaching this goal. This is because, although the final output is undoubtedly a global public good, the strategies through which such containment may be provided vary along a spectrum from pure private goods which are best provided locally, to strategies which might best be referred to themselves as global public goods. A more detailed discussion of the importance of the distinction between final and intermediate global public goods can be found in Woodward & Smith (2002), and discussion in relation to antimicrobial resistance in Smith & Coast (2002).

4. STRATEGIES FOR THE CONTAINMENT OF ANTIMICROBIAL RESISTANCE: THE ROLE OF INTERNATIONAL COLLECTIVE ACTION

There are many strategies for containing antimicrobial resistance, some of which may be best pursued at the international level, and others of which will be pursued at more micro-levels (regional, national or local), whilst still conferring benefits on other countries and to future generations. However, a critical distinction between strategies is whether they aim to avoid the *emergence* of new resistance or the *transmission* of existing resistance. Inevitably, transmission can only occur once resistance has emerged, and thus avoiding the *emergence* of resistance may be seen as the primary goal in the development of strategies to contain antimicrobial resistance overall.

A further strategy, *technically* relating neither to the emergence nor transmission of antibiotic resistance, is the development and production of wholly new antimicrobial treatments. However, although in a sense this strategy is an 'avoidance' of existing resistance, resistance to these new compounds will inevitably develop. As such, this is likely to be only a short-term solution unless these new therapies are well managed, and thus themselves subject to strategies within the other two categories of emergence and transmission.

4.1. Strategies for containing the emergence of resistance

Strategies for avoiding the *emergence* of resistance can essentially be divided into four categories (Smith et al, 2001). The first is to reduce the opportunity for resistance emerging by *optimal* use (not necessarily *reduction* in use, as identified

above) of existing antimicrobial agents. Policies with this aim include choosing the optimal agent, dose and dosage frequency for different infections, ensuring compliance and using antibiotic combinations. The second, third and fourth strategies all involve *reducing* the usage of antimicrobials. The second involves using alternative treatment options, for example, antiseptics, probiotics and cranberry juice (the latter for urinary tract infections). The third involves reducing the need for antimicrobials by increasing immunity, such as through vaccination, improved nutrition and minimising the time for which a patient is immunocompromised. The fourth method of reducing emergence involves reducing the use of antimicrobials in humans and agriculture without providing an alternative form of treatment. A number of means are available, including education of professionals and patients, antibiotic policies and regulations restricting availability, and financial incentives/disincentives.

4.2. Strategies for containing the transmission of resistance

Strategies aimed at reducing *transmission* of antimicrobial resistance can, again, be divided into four categories (Smith et al, 2001). The first requires early recognition of resistant organisms via methods such as more rapid diagnostic techniques, surveillance systems and screening of patients or staff. The second requires the reduction of infectivity by (somewhat ironically) using antimicrobials. The third aims to reduce the possibility of transmission by methods such as isolation, improvements in general hygiene and handwashing, and improvements of the spacing of beds in hospitals. The fourth aims to reduce susceptibility to infection among the population by increasing immunity and improving nutrition.

Complete descriptions of all these strategies can be found in Smith et al (2001), and further discussion of the relative importance of such strategies in *national* contexts is provided by the WHO Global Strategy for the Containment of Antimicrobial Resistance (WHO, 2001).

4.3. The geographic level of strategies: local, national, regional or global?

The table[5] shows the authors' views about the geographic level (local, national, regional or global) at which an intervention will be most effective for each of the different strategies available for containing the emergence and transmission of resistance. Where a strategy is felt to be inappropriate at a particular level, the cell in the table is blocked out. Where an intervention is felt to be primarily a local or national level intervention, but where the authors' views are that international aid may be needed in order to provide that intervention in some countries, the regional and international cells are lightly shaded and the aid that may be required is noted.

TABLE ABOUT HERE

It is clear from the table that the interventions available for dealing with resistance are both many and varied, and may operate at a number of different levels. Many of these interventions are best provided at the national, or even local, level, given the very different national contexts in which policies must operate and, at least as important for

[5] Note that the list of strategies provided in the table is not meant to be exhaustive, but rather illustrative of the range of strategies that may be pursued in the containment of resistance.

this particular issue, the great variation in infective agents even across relatively small areas and across time.

It is also clear, however, that there are a number of interventions where collective action may lead to greater efficiency than action (or non-action) by individual nations in achieving a solution to the problems of containing resistance. In some respects, the issue of whether international collective action is required mirrors discussions of the appropriateness of provision by private or public means at a national level. Notions of public and private goods can be helpful here in noting the likelihood of underinvestment in public goods and thus the desire for collective action at the international level, but other aspects of economics can also be helpful.

Preker *et al* (2000), for example, draw on institutional economics and organisational theory to develop a framework to determine whether goods are best provided privately or publicly. This framework draws on notions of the extent of contestability (whether there are barriers to entry and exit from the market) and the extent of measurability of the good. Goods and services with low contestability (that is, high barriers to entry and exit) and low measurability are those most likely to be efficiently provided on a public basis. This sort of framework, as well as the notions of the public or private nature of the good according to neoclassical economics, can be helpful in determining, *a priori*, the basis for international collective action.

5. INTERNATIONAL COLLECTIVE ACTION: CURRENT EVIDENCE AND POTENTIAL PROBLEMS

The dominant (although not exclusive) strategies to contain antimicrobial resistance on the national, regional and importantly global level, have, to date, been: (i) surveillance of antimicrobial resistance, as well as tracking use of antimicrobial therapies; (ii) mechanisms to encourage research and development of new antimicrobial therapies and alternatives for treatment of infectious disease where antimicrobial resistance is a significant problem; and (iii) measures to ensure the 'appropriate' and 'rational'[6] use of antimicrobial drugs (WHO, 2001).

Each of these three strategies is reviewed in more detail in this section, with reference both to current evidence of action at the international level, and problems in achieving international collective action in these areas. Importantly, a defining characteristic of 'public goods' is, in fact, the existence of a *collective action problem* in securing their provision. That is, the incentive for collective action to produce the good is weakened by the potential for 'free-riding' (benefiting from the actions of others without reciprocation) and the 'prisoners dilemma' (lack of communication and information about each participant's actions, and lack of enforcement mechanisms, impeding co-operation) (Woodward & Smith, 2002). In the discussion in this section specific reference will be made where appropriate to these problems.

[6] There is often some confusion over what 'appropriate' and 'rational' refer to, particularly between the medical and economic disciplines. In this paper, we are using the term 'appropriate' to refer to treatment which has some identifiable and quantifiable clinical therapeutic effect. This does not mean that the treatment *should* be used however, and so we use the term 'rational' to refer to the treatment being optimal in terms of the balance of costs and benefits as identified in equation 1.

5.1. Surveillance

Surveillance is the fundamental stage in the containment of resistance, as it provides the information required to establish, for example, the location of an antimicrobial resistance problem, its growth, transmission and direction of travel, and the impact of interventions to contain it[7]. Surveillance may therefore be considered a necessary prerequisite to any other strategy highlighted in this paper.

The ideal would be to have an accurate *global* surveillance system because of the very different, and quickly changing, patterns of resistance in different areas. However, at the global level, although there have been some in-roads into such surveillance (e.g. MDR-TB surveillance (WHO, 2000a)), it is currently undertaken in a rather piecemeal fashion, with few countries having well-established national networks. Importantly, surveillance faces high barriers to entry because of the large investment costs that must be made initially and which would be unlikely to be recouped were the surveillance system to be sold. These large investment costs will put the development of surveillance systems beyond the reach of many poorer nations.

Surveillance is therefore susceptible to the classic problems of public good provision. Current piecemeal collection and use of resistance data means that there is a lack of sharing of information, with no current international regulations enforcing comparable collection, classification and reporting of data. The key underpinning an effective international surveillance system is, of course, the legal duty to report specific information. Without this, the incentive is for countries to obtain and use information generated by, and for, other countries, without the cost of reciprocating (that is, to free-ride). Paradoxically, a lack of co-ordinated information gathering may, on the other hand, invoke a prisoners dilemma, with nations unaware of potentially useful information collected by neighbouring countries, and thus unable to pursue an optimal strategy for their region.

Existing laws, at the international and national level, generally require the reporting of a small number of specific disease outbreaks. Internationally, for example, the International Health Regulations require member states to inform the WHO of outbreaks of plague, cholera and yellow-fever (WHO, 1983). Although none of these laws *currently* requires the reporting of antimicrobial resistance, the WHO has proposed that antimicrobial resistance be incorporated in a revised International Health Regulations (WHO, 1997; see also: O'Brien & Stelling, 1996). However, creation of a legal duty does not ensure compliance with the policy; as has been identified with the current International Health Regulations (Fidler, 1996; 1997a). Compliance depends upon having adequate resources to fulfil the legal duty of surveillance. These are often lacking in many of the poorer nations, or subject to more extreme opportunity costs in terms of benefits forgone from alternative uses of these resources in directly tackling health problems. The need for international co-operation in financing to ensure compliance is dealt with in more detail in section 6.

[7] Linked with surveillance, although not explicitly incorporated in the table, is the production of research which would eliminate many of the uncertainties associated with the development and containment of resistance. This includes basic scientific and epidemiological research as well as clinical and economic studies of the costs and effectiveness of alternative interventions and strategies.

In developed countries too there are significant problems in collective action due, for example, to different interpretations at the national level of privacy requirements. There exist tensions currently between the need to maintain individual privacy and the good of the community in terms of HIV/AIDS. It is likely that this tension will be further evidenced in the realm of antimicrobial resistance surveillance, such as in sexually transmitted disease and MDR-TB. A key concern here is the different mechanisms that countries adopt in their interpretation and enforcement of privacy. In the EU, for example, the processing of individual health data is only permitted with express permission of the individual (European Union, 1995). In contrast, in the US there is a lack of legislation to protect privacy, with much freer movement and use of such data (Schwartz, 1995). There are further issues here with respect to private industry utilising such information, and the conduct and sale of surveillance commercially by private firms, as currently occurs within the pharmaceutical industry, such as through Intercontinental Medical Statistics (IMS) International.

Historically there has been little invested in surveillance of antimicrobial resistance. In the US, for example, with a well-developed infectious disease network and facilities, only US$50,000 was spent on antimicrobial resistance surveillance in 1992 (American Society for Microbiology, 1995). However, it is extraordinarily difficult to generate an estimate of the costs that would need to be associated with an adequate global surveillance system, for a number of reasons. First, each individual country already has a certain level of infrastructure in place: this will determine the *additional* costs of adding to this infrastructure. Second, each country already has particular procedures for testing patients in place: again, there will be costs associated with changing practice. For example, in the UK, patients receiving antimicrobial therapies for some conditions may not be tested for the presence or absence of bacteria unless the initial therapy fails. Third, there will be costs associated with transport of samples, which again will depend upon the procedures already in place. Fourth, the unit cost of resources in individual countries will vary hugely.

It might therefore be suggested that early work on the feasibility of setting up surveillance systems across the globe uses the experience that has already been gained in surveillance in some countries as a basis for determining the level of resources required in surveillance, the extent to which these are already met in particular countries and the resources (and the cost of those resources) that would be required to set up surveillance systems at particular levels in different nations. Such work is a prerequisite to the development of any effective global system.

5.2. Research and development into new antimicrobial (and other) therapies

The second strategic element in the international fight against antimicrobial resistance is the development of new antimicrobial therapies and alternatives to antimicrobial use. Generally, of course, such R&D happens predominately in, or funded by, the pharmaceutical industry, with some public sector research body funding, although this occurs on the national level (e.g. Medical Research Council in the UK, National Health and Medical Research Council in Australia). However, there is precedent for international R&D support for diseases that pose significant international concern. For example, the Multilateral Initiative on Malaria is a multiagency programme to coordinate research on antimalarial products, supported by both the WHO and World

Bank (Bulter, 1997; Gallagher, 1997; Mons et al, 1998)[8]. However, it is still the private pharmaceutical industry that needs to be brought into the collective action situation to address antimicrobial resistance, which poses significant problems around, for example, international patent laws, licensing and regulatory approval.

Significant here is the issue of patent laws. Patenting is of critical interest to the industry, as it is this that largely determines profitability. Industry will not invest in the research and development of new products if it cannot be sure of an adequate return, where return is a function of expected market volume and price. Whilst the pharmaceutical *product* is itself a private good (excludable and rival), the *knowledge* upon which it is based is a public good: once in existence it is both non-excludable and non-rival in consumption. The problems of free-riding would ordinarily preclude research and development on these grounds, which led to the development of patent laws to artificially, and for a fixed period, create a private good out of the information generated, in order to provide the incentive required to pursue its research. Currently, industry therefore seeks to maximise volume and price during this patent period before a drug becomes susceptible to generic competition. The containment strategy of, essentially, reducing or restricting further pharmaceutical consumption thus threatens the profitability of new antimicrobial products and may require reform to patent laws if continued research and development is to be ensured. As countries have significantly different laws relating to intellectual property rights, international law is thus a critical element of the strategy to encourage development of new products.

Furthermore, industry faces different regulatory approval mechanisms for products, which could be streamlined for new antimicrobials, or toughened concerning dosing protocols for other countries. Conversely, patent protection in many developing countries is poor, allowing sale of generic drugs, and stimulating counterfeit drug production, resulting frequently in the inappropriate use of drugs.

Co-ordination of use of specific antimicrobials, as well as dissemination of appropriate dosing, for example, are also important in the reduction of the global emergence of resistance. Thus, development of international standard treatment guidelines could prove an important global public good, if accessible and adaptable for local circumstance and, crucially, backed up with access to requisite technologies and infrastructures (that is, have *access* to the information provided, as discussed in section 5.4). The WHO have moved forward in this area to some degree – for example, see the WHO antimicrobial resistance Surveillance Standards (WHO, 2000b), WHO Guidelines for treatment of MDR-TB (WHO, 1997b) and WHO protocols for detection of drug-resistant malaria (WHO, 1996).

5.3. Appropriate and rational use of antimicrobials

The 'appropriate' and 'rational' use of antimicrobial therapies is the key long-term intervention to contain antimicrobial resistance (WHO, 2001; Smith & Coast, 2002).

[8] There are other examples, such as the Sexually Transmitted Infections Diagnostic Group, International AIDS Vaccine Initiative and the Medicines for Malaria Venture, all of which involve multiagency partners from academia, international organisations (e.g. WHO, UNAIDS), NGOs, a variety of charitable organisations (e.g. Bill and Melinda Gates Foundation) and private industry, as explored by Buse and Walt (2000).

Although the development of antimicrobial resistance is a complex mix of epidemiological, microbiological and environmental factors, the misuse of antimicrobial drugs (that is, over- or under-use), for human and animal consumption, is widely regarded as the major cause of the development of antimicrobial resistance. For example, when Iceland removed its government subsidy for antimicrobial drugs, the level of resistance fell, whilst there was no change in neighbouring countries whose subsidy was maintained (Stephenson, 1996). Similarly, the international rates of MRSA (as indicated in section 2) are higher where drug access is more liberal, and lower where it is more stringent (Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance, 1998). It is therefore vital that the appropriate use of such treatments is ensured worldwide to lengthen the effective life of therapies.

There are a number of means by which this may be approached. For example, education of prescribers and consumers is a central tenet of the WHO Global Strategy (WHO, 2001), and the WHO has also recommended a code of practice for the use of antimicrobials in agriculture (WHO, 2000d). However, it is unlikely that education alone will work, and there is a vast literature on the limited long-term success of clinical guidelines and other educational packages. The limited success of developing countries, in particular, in regulating antimicrobial drug use is cause for concern, as often this is due to *existing* laws not being enforced, rather than a lack of legislation or regulation.

Internationally, there is little taking place to tackle drug usage. For example, there are current talks between the US, Japan and the EU concerning harmonisation of pharmaceutical regulatory systems, but this is obviously of limited participation, and it is not clear to what extent antimicrobial resistance specifically is being discussed. The potential for the use of financial incentives and disincentives at this level has received little consideration, as has the role of international legislation in enforcing strategies (covering, for example, intellectual property rights, the requirement for antimicrobial resistance data in pre-approval evaluation of drugs, use of sub-therapeutic doses as growth promoters in animals, labelling of drugs, or prescription requirements).

There is also potential for conflict with the pharmaceutical industry, and the possibility that regulation may, ironically, lead to a reduction in development of new antimicrobials and thus worsen the problem in the long run. In some areas regulation may lead to a fall in market volume, in others it may result in an increase in volume, but the impact on price is unclear (that is, will price be forced downward to increase use, or will use be expanded through price subsidy or other measure). Whatever strategy is pursued, the impact upon this sector will have to be considered if it is not to result in a worsening situation though reducing the incentive for industry to research and develop new therapies, or for it to engage in strategic gaming behaviour which may have other adverse effects (e.g. movement of manufacturing plants).

Such regulation could be implemented at either national or international level. The advantage of regulating at the national level is that the local context can be taken into account. The potential disadvantage is one of free-riding among nations – there may be little incentive to regulate against use of antimicrobials if their increased use is perceived to lead to higher profitability in an industry that tends to have strong lobbying powers. This highlights the need for a coordinated and integrated multi-

faceted strategy to avoid *ad hoc* adoption of strategies leading to an overall worsening of antimicrobial resistance. There needs to be consideration of how to ensure that development of new drugs is encouraged *simultaneously* with incentives for the more rational use of existing therapies, such as through limiting *new* antimicrobials by licensing them only for use under specific circumstances.

5.4. Importance of 'access goods'

A final area where international collaboration may be necessary is in the financing of strategies and, specifically, the provision of aid to countries to allow them to invest in the *private* goods required at the local or national level to achieve the global public good of containing resistance. The problem here, of course, is that under-investment in some areas is likely in less wealthy countries, in relation to, for example, the infrastructure required for rapid diagnosis, surveillance and vaccination, all of which are likely to be important in the attempt to contain resistance. The requirement for assistance with infrastructure may be classed as an 'access good'. For example, to benefit from the public good of clean water, a household has to be connected to the (excludable) infrastructure to access it. Similarly, to benefit from the information provided through surveillance, countries require a means to access and interpret that information.

Access goods are thus goods which, although not global public goods themselves, may be *treated as such* to the extent that international co-ordination of their finance and provision would lead to a more optimal outcome in the containment of antimicrobial resistance than if each nation acts independently (Sandler 1997). They may therefore be considered as important as the global public good itself, for without the goods to enable the mechanisms to be utilised, or to allow the benefits to be accessed, the global public good of containment of antimicrobial resistance will be difficult, if not impossible, to achieve.

Of specific importance here is the role of health systems as access goods. In many developing countries the health systems are weak, as would be expected with per capita expenditure on health running at well below US$100 per person per year, and often a small fraction of this amount (WHO, 2000). Disease surveillance and reporting is often non-existent, facilities are poorly staffed, and there is often a lack of basic public health and health service infrastructure. HIV/AIDS has also placed such a considerable burden on many country systems so as to make the resources available for other purposes almost non-existent.

One of the significant benefits of the global public goods concept is therefore in establishing the impact of non-concordance with the rest of the 'community of nations' to persuade these other nations of the rationality of ensuring that the country in question is assisted in finance and/or provision of the strategy in question. To this extent, international support to strengthen national health provider systems may be seen as an important input to the containment of antimicrobial resistance.

6. INTERNATIONAL COLLECTIVE ACTION: POSSIBLE SOLUTIONS

As highlighted in previous sections, in tackling the problem of antimicrobial resistance from the global perspective, there are three core considerations: (i) international surveillance; (ii) research and development for new therapies or alternatives to antimicrobials; and (iii) implementation of measures to encourage the rational use of drugs. Yet, as indicated in section 5, there is little being undertaken at the global level to contain antimicrobial resistance, and the action being undertaken is very piecemeal. For example, the EU has banned the use of four antimicrobial products which are important for human treatment but were used in animal feed (EU, 1997; 1998) – although this may be a fruitless exercise if their use is still adopted, or even increased, in other countries through drug company marketing pressure. In the USA, the Food and Drug Administration is reviewing its responsibility for ensuring that use of drugs in animals does not compromise use in humans (FDA, 2000a), and proposed new labelling for drugs to warn of antimicrobial resistance (FDA, 2000b). The Centre for Disease Control, in collaboration with other federal agencies, has issued a 'Public Health Plan to Combat Antimicrobial Resistance'[9], as have several other countries including the UK[10], Canada[11], France[12], Norway[13] and Sweden[14].

Perhaps the only concerted attempt to address the problem of antimicrobial resistance containment from a *global* perspective has been the development by the WHO of their 'Global Strategy' (WHO, 2001), which built upon the World Health Assembly Resolution of 1998 (WHA, 1998) urging Member States to develop *national* measures to encourage appropriate use of antimicrobials and to develop systems to detect resistant pathogens.

Problems relating to the undersupply of public goods by the market are usually 'solved' by the intervention of national government (Cornes and Sandler, 1996). The fundamental reason for the lack of a *global* response to achieve the global public good of antimicrobial resistance containment is essentially the lack of a 'global government' to ensure collective action at the international level. In this case, it is a useful starting point in considering how one might address this international collective action to consider what a 'government of the world' would do if there were one, and, therefore, in the absence of such a 'global government', how these activities are best pursued. This section seeks to address this issue, and focuses specifically on the role that international bodies might play in these activities.

6.1. What would a 'government of the world' do to contain antimicrobial resistance?

As identified, the authors' view is that a 'government of the world' would seek to secure internationally compatible surveillance systems, the development of new therapies and the more rational use of antimicrobial drugs, both in humans and

[9] http://www.cdc.gov/drugresistance/actionplan/index.htm
[10] http://www.doh.gov.uk/pointh.htm
[11] http://www.hcsc.gc.ca/hpb/lcdc/publicat/ccdr/97vol23/vol23s7/index.html
[12] http://www.invs.sante.fr/
[13] http://www.odin.dep.no/shd/norsk/publ/handlingsplaner/030005-990326/index-dok000-b-f-a.html
[14] http://www.sos.se/fulltext/0044-001/0000-044.htm

animals. In securing this collective action, however, there are two key inter-related dimensions that would need to be addressed: the economic and the legal.

At its most basic, successful collective action requires all participants to perceive a net benefit – often in economic terms – and to behave *strategically* to secure the best outcome for themselves (Hargreaves-Heap et al, 1992). Although simple, this realisation is often overlooked. For example, international reduction in CFCs was achieved relatively quickly and easily, whereas carbon emission reduction has been more troubled, with the US recently 'opting out' of the Kyoto agreement. The difference here is in the perceived benefits gained by the US from these actions. This realisation means that one must recognise that any vision of a government pursuing the containment of antimicrobial resistance simply for the good of humanity is unlikely, unless backed up by evidence of a more selfish nature.

However, there is another, perhaps more subtle, economic factor: the imbalance of wealth between nations[15]. Economically, the wealth imbalance between nations exacerbates the potential for 'free-riding' in two ways. First, low levels of resource mean that the marginal opportunity cost of using that resource is higher in poor than in wealthy nations, creating a disparity between national priorities, and the place of antimicrobial resistance containment within those. Second, even if countries could be persuaded to be involved in joint strategies, such as surveillance, many will simply lack the ability, through lack of direct financial, infrastructure or technical expertise. Any recommendations for surveillance, the appropriate use of antimicrobial therapies, and research and development, will therefore require consideration of their resourcing.

Generally, government policies to adjust the market are based on legal frameworks, from restrictions on advertising to pricing policies for privatised public utilities. Legally, the response to antimicrobial resistance on a global level may be achieved in two ways. First, through the harmonisation of individual national mechanisms, legislation and strategies, with non-binding recommendations being made and adopted to varying degrees by different nations. Second, through the construction of new international mechanisms, legislation and bodies. These are discussed further in this section.

To achieve an integrated strategy encompassing global surveillance, new research and development, and the more appropriate use of antimicrobial drugs, a 'global government' would thus have to: (i) establish the legal imperative to comply with these strategies; and (ii) develop structures to enable the transfer of resources from more wealthy to less wealthy nations to enable the practical compliance with these legal imperatives. Given that there is no 'global government', this section now turns to consider how international agencies, which undertake 'pseudo-global government' activities, may address these two elements (legal and economic) to help secure the global activities of surveillance, research and development and rational drug use.

[15] In 1991, the richest 20% of nations controlled 85% of the worlds income, with the poorest 20% receiving just 1.4% - this disparity increasing over the previous thirty years, where the richest 20% controlled 70% of income and the poorest 20% 2.3% (UNDP, 1992; 1994).

6.2. Role of international bodies in achieving these elements

The WHO, World Bank and United Nations are perhaps the obvious international institutions to take a major role in tackling some of the issues discussed above. The WHO in particular has begun to take a lead in the development of a 'Global Strategy' to contain antimicrobial resistance (WHO, 2001). This strategy covers, for example, issues and interventions relating to patients and the community, prescribers and dispensers, hospitals, agricultural use of drugs, drug development, pharmaceutical promotion and national health systems. Within each of these areas recommendations are provided and a process for prioritisation and implementation that national governments might take is suggested.

However, this strategy follows the historical preference of the WHO, as with many other international bodies, to operate through recommendations and guidelines to nation states, and to rely upon largely *ad hoc* harmonisation of individual national mechanisms, legislation and strategies, rather than formal international legislation. Unfortunately, evidence suggests that such an *ad hoc* strategy may well be inadequate in dealing with antimicrobial resistance in the long-run[16]. For example, WHO themselves suggest that a major reason for the development of multi-drug resistant tuberculosis (MDR-TB) has been that around 50% of countries have not adopted their recommendations for the use of DOTS (Directly Observed Therapy – Short-course) for treatment of tuberculosis (WHO, 1999). Fidler (1998; 1999) in particular questions the historical preference of the WHO for codes of practice and other non-legal routes in tackling international health problems, and suggests that these will be inadequate to deal with the coordinated international response to antimicrobial resistance that is required.

This is disappointing, as the WHO has the ability to lead on development of such international legal frameworks. For example, although the WHO has the ability to adopt a convention on the use of antimicrobial drugs, it has not (as yet) done so (Fidler, 1997a). Importantly, the WHO International Health Regulations in particular, which require member states to report outbreaks of international importance, might offer an ideal starting point for securing international surveillance of antimicrobial resistance. However, at present, although these *might* be seen to cover antimicrobial resistance outbreaks, surveillance of antimicrobial resistance is not explicit in their remit, and nor is it specifically covered under the proposed revisions (WHO, 2001a).

The other important element in achieving successful collective action is the economics of securing the strategies. For example, regulatory systems would have to cover drug licensing, monitor compliance, enforce penalties against violations and protect intellectual property rights, and be achieved with relative equality across diverse national boundaries. This may be feasible for regions such as the European Union and North America, but developing countries in particular, with limited national resources, are unlikely to be able to sustain such complex national systems.

[16] Interestingly, it appears that WHO may have considered this themselves with respect to tobacco control, through moves away from the recommendatory approach to the 'framework convention', creating binding legal rules under international law (Taylor & Bettcher, 2000; WHO, 2001b).

In this situation, the 'weakest link' in the net will allow a considerable hole for antimicrobial resistance to slip through[17].

It may, therefore, be more productive to appeal directly to international frameworks, with legally binding support from developed countries to assist the less wealthy, as well as technical assistance and support in specific areas, such as information technology. Such international legal frameworks could cover, for example, availability of specific drugs, informed by surveillance data, and labelling and licensing requirements. Ultimately, these international frameworks will be built on agreed international legislation. The global public goods concept may assist in the development of such international legal cooperation through demonstrating the potential pitfalls of non-cooperation (prisoners' dilemma, free-riding) and thus the necessity for international action: assistance for developing countries in meeting the goals set, for example in terms of surveillance, is in each country's self-interest. In the case of a global issue, such as antimicrobial resistance, it is unrealistic to expect unilateral action, since the level of antimicrobial resistance in one nation is ultimately at the mercy of antimicrobial resistance in others.

Funding is a critical element of securing international collaboration, made even more so by the lack of effective sanctions against transnational corporations who, for example, may threaten to relocate if economic and/or political changes are unfavourable. Financial and other support is therefore key in securing concordance with international decisions. Further, to avoid counterproductive incentives, compensation for the negative health or economic effects of such concordance may be required in some instances (this may also apply to households as well as governments if low-income households bear significant costs as a result of provision).

There is a considerable amount to be learnt here from environmental economics and law. Fidler (1999a; 2001), in particular, has made some important observations in this area. For example, as antimicrobial resistance is considered to be an externality, there are substantial similarities with the environmental sector. This is important in both consideration of economic incentive structures, such as pigovian taxes or permits (Smith & Coast, 1998), as well as the legal frameworks that are developed to deal with aspects of environmental pollution. In this regard, consideration of the literature on the economics of environmental control, and on international environmental law, provides a rich source of precedent and experience from which to draw in the consideration of strategies for the global containment of antimicrobial resistance.

For example, environmental economics has developed thinking about the internalisation of pollution externalities, through tax systems or, more recently, tradable emission permits, which have been considered in relation to global carbon emissions. Here the upper limit on the level of carbon emissions is fixed, and then the 'right' to pollute up to this limit is specified in 'permits' which are available on the

[17] The 'weakest link' is recognised as a significant issue in economic game-theory. Here the 'weakest link' player is the one with the least to gain, is the least able to collaborate or has to contribute the least amount, yet their behaviour can determine the overall success of the collaborative venture, and as such their contribution in the game is vital to its success (Hargreaves-Heap, 1992). In the case of containing antimicrobial resistance, the weakest link could be the small and/or poor nation who does not wish, or is unable, to be involved in a global strategy, yet whose resistance levels will undermine the efforts of the rest of the community of nations.

open market. Those who can reduce pollution at less expense than the cost of the permits will face the incentive to do so, those who cannot can purchase the permit (Tietenberg, 1974). The application of this has already been considered in relation to antimicrobial resistance (Smith & Coast, 1998). Another development has been in the establishment of the 'Global Environment Facility', a collaborative project of the World Bank, United Nations Development Programme and United Nations Environment Programme, created in 1991 to administer a fund to developing nations for compliance with international environmental agreements. This fund, contributed by developed countries, constitutes approximately US$250 million per year for a restricted group of situations in which environmental expenditure by the developing nation would not be cost-effective for the nation itself, but would benefit the broader global community of nations [REF OTHER WG2 paper]. It is not hard to imagine that a similar system could be established to assist in the support for international endeavours by poorer countries.

In terms of environmental law, Fidler (2001) points out that the UN Convention on Biodiversity (UN, 1992) specifies the financial and technical assistance required from developed countries to assist developing countries in reducing unsustainable development, and establishes the institutional machinery to oversee implementation of the Convention. A similar 'bargain' between countries, whereby developed nations provide financial and technical assistance to developing nations (or they are subject to differential 'duties'), is found within the framework-protocols relating to ozone depletion and global warming (e.g. Montreal and Kyoto Protocols). This could well be envisaged for the global strategies for containment of resistance considered in this paper, such as international surveillance systems and appropriate use of drugs.

Nevertheless, there are problems here as well, with the 'inverse pyramid' effect associated with international agreements. That is, the less demanding the international agreement is, the more countries are willing to collaborate, and vice-versa once conditions become stringent. The obvious example of this is in respect of strategies to tackle climate change. Here, many nations signed the Vienna Convention on Climate Change, which was not specifically demanding, but far fewer have joined the Kyoto Protocol, which demanded specific reductions in carbon emissions by specific dates (United Nations, 1992; 1997). Such difficulties provide lessons about the difficulty of ensuring the, essentially, voluntary nature of participation in such agreements unless countries can be fully convinced of the importance to themselves of taking part.

7. CONCLUSION: A GLOBAL AGENDA FOR CONTAINMENT

Antimicrobial resistance is a global problem. No single nation, however effective it is at containing resistance within its national borders, can protect itself from the effects of resistance through travel and trade. The health of future generations too is in the hands of the current generation, and will depend heavily upon how well the current generation manages its consumption of antimicrobials and its development of new antimicrobial agents.

This global nature of resistance clearly calls for a global response, and three specific areas were highlighted in this paper: surveillance, development of new antimicrobials

and alternative therapies, and the rational use of existing (and new) antimicrobials. Current activities in these areas were discussed, and suggestions made as to how they may be improved. It was suggested that, although economic theory (in terms of excludability, rivalry, contestability and measurability) suggests that the majority of strategies for containing resistance are best operated at a local or regional level (the main exception being surveillance), this does not obviate the need for collective action in terms of the allocation of resources in order to ensure that the global public good of containment of resistance is achieved.

The need for financial and other assistance for developing countries cannot be overemphasised here. The lessons of other areas, in health but particularly so in environmental pollution, are that 'soft law', such as recommendations, framework conventions and agreements, will only work if countries are both willing and *able* to comply. For many developing countries their ability to participate may not match the will, even if it were present. For example, surveillance will require established procedures for collecting samples, transport of samples to laboratory facilities, the existence of such laboratory facilities, the ability to report findings and the monitoring of procedures and findings across different settings.

Rational drug use requires public health infrastructure and finance to enable purchase and dissemination of good quality drugs, as well as to combat infectious disease through other means, such as vaccination and the provision of education. The research and development of new drugs is expensive and, for pharmaceutical companies to undertake such activities, they have to see the potential for profitability. Where profitable markets for particular drugs do not exist, for example in relation to drugs specifically relevant to the developing world, partnerships between the public and private sectors or the use of economic incentives may be required to ensure such research and development takes place.

From the discussion presented in this paper, we suggest three key activities that international bodies could undertake to encourage and promote global collaboration to address antimicrobial resistance: (i) raising the profile, and thus priority, of antimicrobial resistance on national agendas; (ii) development of an international surveillance database; and (iii) promoting standardisation of research methods and coordinating research activities.

First, to secure *international* cooperation requires *national* recognition of the problem that antimicrobial resistance presents, the interdependency of nations, and the impact and responsibility that each nation has in relation to global health. This is a prerequisite to effective collective action. It is not necessarily the case that national agendas will match global agendas. Indeed, it is arguably far more likely that each national agenda will *not* give equal priority to control of the same communicable diseases, or to control of communicable disease *per se* versus other priorities. The more divergent are national agendas, the greater is the potential for free-riding and the prisoners dilemma to compromise the provision of communicable disease control.

Perhaps a first, and fundamental, role for international organisations is therefore to raise the awareness of the importance of antimicrobial resistance, and the interdependency of nations in this respect. An important role for international bodies is therefore identifying, and quantifying, the input required from agencies that might

be involved in the production/supply of these strategies (which will vary according to the type of strategy). This information will enable the strengthening of agencies or networks as required, and the prevention of potential losers (politically or economically) blocking provision of the good or limiting effectiveness through non-concordance[18]. It may be that, in some cases, new 'institutions' and/or legislative frameworks will be required to achieve this. Here, international bodies can provide advice and assist in the co-ordination of multi-national support for nations in pursuing reform (Sandler, 1997).

Second, the establishment and maintenance of a global database of antimicrobial resistance surveillance data to which nations contribute, and from which they have access to information and alert mechanisms, would be extremely valuable to each nation in planning how to deal with antimicrobial resistance. A major challenge in achieving this, however, is the multiplicity of laboratory susceptibility testing techniques across the world. An important step in this area will therefore be in the specification and co-ordination of international standards in laboratory susceptibility testing techniques.

Third, the research and development of new drugs and vaccines, and evaluation of strategies to contain antimicrobial resistance, is often expensive and time-consuming, yet the results are relatively cheap to disseminate. Thus, international agencies can encourage and co-ordinate international research networks, utilising a core set of standard methods, to undertake epidemiologically-sound clinical studies in different patient groups and geographical regions, and to report the outcome of strategies where implemented. They could also act as a repository for information from nations about current research projects, and implementation and evaluation of strategies to tackle antimicrobial resistance.

This information also has to be communicated to be of any use. International agencies, through activities such as those mentioned, could therefore also assist in maintaining communication channels to reduce the potential for the 'prisoners dilemma' problem arising in cross-nation communication[19]. Similarly, educational material (e.g. medical education, information to pharmacists and citizens), although often costly to develop, may be repeatedly used at a low marginal cost. Thus, the provision and/or coordination of the collection of, and access to, such material, and its translation, could be undertaken by international bodies (e.g. WHO 2000).

The containment of antimicrobial resistance is a complex process that requires action at all levels from local to global. This paper has concentrated on the international collective action strategies that might be used to provide the necessary coordination at the global level. As with global warming, one of the great challenges of containing resistance, is its intergenerational nature: the greatest problems associated with resistance are, undoubtedly, still to be seen. Thus one of the greatest impediments to dealing effectively with the problem is that of persuading those at both the national and international levels of its importance *now* relative to the other pressing health and

[18] Although unlikely, it may be that there will be some gainers as a side-effect of strategies who may be able to 'compensate' the losers.

[19] It has to be acknowledged that communication of information is, in this respect, a 'necessary but not sufficient' condition to prevent the 'prisoners dilemma' problem arising, since communication of information itself does not ensure the mechanisms to enable it to be acted upon.

non-health priorities that these institutions face. Only if the relevant collective action strategies are put in place early in this new century will the vast potential for high future morbidity and mortality across all nations be ameliorated.

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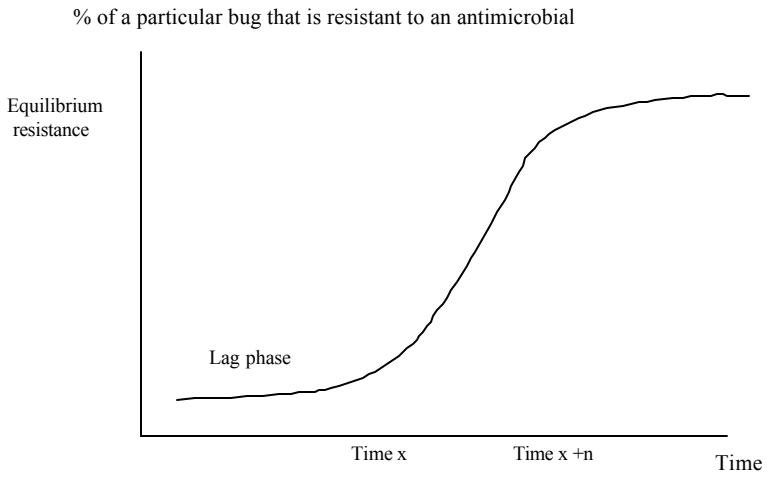

Figure: Development of AMR over time.

Table. Characteristics of the strategies for containing the emergence and transmission of resistance

	Level of intervention			
	Local	**National**	**Regional**	**Global**
General strategies applicable to containing both the emergence and transmission of resistance				
1. Surveillance	Required at all levels to obtain an accurate picture of emerging resistances and the rate of transmission of new resistances, and to identify the impact of interventions designed to contain antimicrobial resistance in particular contexts.			
2. Financial (dis)incentives	Could be used at all levels in conjunction with many other policies as a mechanism for improving the uptake of/compliance with any intervention. Would include such mechanisms as financial benefits, "environmental" taxes and the use of "permit" systems.			
Strategies for containing the emergence of resistance				
1. Education of professionals on appropriate clinical indications	On specific problematic micro-organisms in the local area	On issues most relevant to general national conditions	On general principles, through regional organisations and using the internet	On general principles, through global organisations and using the internet
2. Patient education both regarding inappropriate use and the importance of compliance with instructions on taking antimicrobials	Local campaigns, as well as education on an *ad hoc* basis by health professionals at the time of patient consultation	By providing national information campaigns as, for example, recently conducted in women's magazines the UK	On general principles, through regional organisations and using the internet	On general principles, through global organisations and using the internet
3. Rapid diagnosis of bacterials	By improving local facilities	By providing the infrastructure for improved local facilities	Through provision of aid to countries whose infrastructure is lacking	Through provision of aid to countries whose infrastructure is lacking
4. Control of sensitivity data related to prescribers	From local facilities	By providing the infrastructure for improved local facilities		
5. Antimicrobial policies	Developed by local facilities, taking into account specific local conditions	Developed by national medical associations taking into account general national conditions		
6. Restriction of drug availability	Taking into account specific local issues BUT may potentially be considered unacceptable on grounds of geographical equity	Developed by national policy makers taking into account general national conditions		

7. Antimicrobial cycling	Carried out at the local level taking into account prevailing local conditions			
8. Regulation on the use of antimicrobials in agriculture		Developed by national policy makers taking into account general national conditions	Through regional agreements, for example through the European Union	Through international agreements, for example through the WHO
9. Choosing the optimal agent, dose and dosage frequency for different infections	Carried out at the patient level taking into account prevailing local conditions and the particular patient characteristics			
10. Removal of potential septic foci/prostheses	Carried out at the patient level			
11. Use of drug combinations	At the local/patient level taking into account prevailing local conditions as well as the particular patient characteristics.			
12. Using antiseptics as an alternative to antimicrobials	At the patient level taking into account prevailing local conditions and the particular patient characteristics	Guidelines suggesting use of alternative agents could be produced at national level		
13. Using cranberry juice as an alternative to antibiotics for urinary tract infection	At the patient level taking into account prevailing local conditions and the particular patient characteristics	Guidelines suggesting use of alternative agents could be produced at national level		
14. Using probiotics as an alternative to antimicrobials	At the patient level taking into account prevailing local conditions and the particular patient characteristics	Guidelines suggesting use of alternative agents could be produced at national level		
15. Increasing vaccination to increase immune competence	Operation of national policies at local level	National policy development concerning vaccination, including both guidance and financial incentives	Through provision of aid to improve vaccination levels in countries that cannot afford vaccination programmes	Through provision of aid to improve vaccination levels in countries that cannot afford vaccination programmes
16. Improving nutrition to increase immune competence	Local policy development focusing on particular communities	National policy development	Through provision of aid to countries with poor nutrition	Through provision of aid to countries with poor nutrition

17. Minimise time patient is immunocompromised	At the patient level			
Strategies for containing the transmission of resistance				
1. More rapid diagnostic techniques	By improving local facilities	By providing the infrastructure for improved local facilities	Through provision of aid to countries whose infrastructure is lacking	Through provision of aid to countries whose infrastructure is lacking
2. Screening of patients/staff	For example, on admission to hospital	Guidelines regarding screening could be produced at national level		
3. Use of antimicrobials to reduce infectivity	In particular patients			
4. Isolation	Of particular patients	Guidelines regarding isolation could be produced at national level		
5. Handwashing	In particular institutional settings	Guidelines regarding handwashing could be produced at national level		
6. Improvements in bed spacing	In particular institutional settings	Guidelines regarding bed spacing could be produced at national level		
7. Improving immunity by vaccination to reduce susceptibility to infection	Operation of national policies at local level	National policy development concerning vaccination, including both guidance and financial incentives	Through provision of aid to improve vaccination levels in countries that cannot afford vaccination programmes	Through provision of aid to improve vaccination levels in countries that cannot afford vaccination programmes
8. Improving nutrition to reduce susceptibility to infection	Local policy development focusing on particular communities	National policy development	Through provision of aid to countries with poor nutrition	Through provision of aid to countries with poor nutrition