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SUPERBUGS II: HOW SHOULD ECONOMIC EVALUATION BE CONDUCTED FOR INTERVENTIONS WHICH AIM TO REDUCE ANTIMICROBIAL RESISTANCE ?

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ABSTRACT

An earlier paper by the authors questioned whether increases in antimicrobial resistance, a negative externality associated with treatment with antimicrobials, should be included as a cost in economic evaluations comparing management strategies for infectious diseases. This earlier paper questioned whether any of four factors (small costs associated with resistance, discounting for time preference, discounting for uncertainty and the difficulty of assessing costs) could explain the fact that resistance is seldom, if ever, incorporated as a cost in such evaluations. The paper concluded that, whilst theoretically desirable, the difficulty of identifying and measuring these costs means that it would be unlikely to happen for individual drug evaluations. Clearly, however, these difficulties do not mean that there is no need to assess the costs associated with resistance. The importance of such assessment is equally acute when considering studies which aim to evaluate empirically the efficiency of alternative strategies *specifically* aimed at reducing resistance (for example, handwashing, educational strategies, isolation policies). This paper examines issues in conducting evaluations of interventions and policies aimed directly at addressing resistance in broadly the same four areas used in the earlier paper: problems associated with the diffusion of costs (apparent 'smallness'); problems associated with future costs; problems associated with the uncertainty of costs; and problems associated with difficulties in measurement. Each of these is examined in relation to the theoretical and conceptual literature and by using examples from the small number of studies that have been conducted in this area.

INTRODUCTION

There is evidence that resistance to antimicrobials is increasing rapidly.[1-3] The problems associated with rising resistance among microorganisms to the drugs used to treat them, have become an increasingly important topic across the medical and academic literature,[4-13] among governments and international agencies,[14-17] and in the media.[18-23] Although economic analysis of antimicrobial resistance remains limited, economists have begun to define the problem in economic terminology,[24-28] and to consider appropriate policy responses.[27-29] Antimicrobial resistance is conceptualised by economists as a negative externality: an impact that can occur as the by-product of a decision made by the patient (or on their behalf by the doctor, or through the interaction of the doctor and patient), that the patient should receive an antimicrobial as a means of treating or avoiding (in cases where the treatment is prophylactic) illness.

Only one paper, Superbugs 1, has considered in depth the issue of antimicrobial resistance in relation to the economic evaluation of alternative health care treatment strategies, programmes or policies.[27] This paper questioned whether increases in antimicrobial resistance, a negative externality, should be included as a cost in economic evaluations which aimed to compare management strategies for infectious diseases. Four factors were considered in arriving at an answer to this question. First, the size of the current cost associated with antimicrobial resistance was examined to determine whether this cost was so small as to conclude that incorporating the cost within economic evaluations of alternative treatment strategies was unnecessary. This was not, however, shown to be the case. Second, the paper questioned whether the costs were so small in terms of their present value (that is, after discounting) as to be irrelevant. Again this was found not to be the case. Third, the paper discussed the issue of uncertainty, examining whether implicit discounting (on the basis of a risk premium) could explain the omission of this cost from empirical work. As before, the evidence did not support this basis for excluding these costs. A final section considered the practical problems associated with assessing these costs, and suggested that the difficulties in estimating the costs of resistance were too great to deal with adequately given the time and resource constraints of most economic evaluations of treatment strategies.

The paper, further, identified other difficulties with using economic evaluation as a basis for an effective policy response to the problem of antimicrobial resistance. The externality of resistance is diffuse by nature and partial evaluations would be unlikely to sum to an adequate policy response. There is also the important issue of who makes decisions in health care and the viewpoint from which they make these decisions. The analysis concluded that those making decisions about treatment strategies in health care have little incentive to take account of the societal perspective in their decisions about whether an antimicrobial treatment is the treatment of choice[27] (and, indeed, evidence to

this effect was recently found in a qualitative study of perceptions surrounding antibiotic prescribing for patients with sore throat, where it was noted that "possible patient benefit outweighed theoretical community risk from resistant bacteria" (Butler et al,[30] p.637)).

Although there has been a tendency to use Superbugs 1 to support non-inclusion of the costs of resistance in individual evaluations of treatment strategies,[31; 32] the difficulties outlined above do not lead to the conclusion that there is no need to assess the costs associated with resistance nor that these difficulties do not have to be tackled. A further reason for considering these issues is that there are some programmes and policies where antimicrobial resistance is not an external by-product of treatment for a particular illness, but where its reduction is the focus of the policy itself. In studies which aim to evaluate empirically the efficiency of alternative strategies specifically aimed at reducing resistance, these costs need to be identified and measured.

This paper, therefore, examines issues associated with attempting to assess the cost and impact of policies aimed at reducing resistance. The paper draws on three broad areas of the economic literature. The environmental literature is typically concerned with the evaluation of negative external effects. Here the issue tends to be one of trading goods and services now for poor effects on the environment and, in some cases, health at a later date – frequently for future generations. This literature also deals with the uncertainty problems which are found with antimicrobial resistance – uncertainty about the physical mechanisms which result in the negative externality of interest. The natural resources literature is concerned with the evaluation of policies to ensure that use of natural resources (such as forests, fish stocks, oil, coal) is optimal, particularly where resources are not easily renewable: essentially the question concerns the trading of resources now for resources in the future, with comparisons across generations being pertinent.[33] Where this literature has similarities to resistance is in the idea that there is a set stock of the resource that is available, but once used, the resource cannot easily be renewed. The health economics literature is concerned with the evaluation of alternative treatments which provide health. In many cases it is concerned with alternative means of improving health for one individual, but policy questions are also concerned with trading health for one individual with health for another. This literature does not, however, generally have to deal with questions of the intergenerational use of resources nor with the extreme uncertainty associated with resistance.

It should, here, be noted that in Superbugs 1 changes in antimicrobial resistance were conceptualised as a negative external cost associated with antimicrobial treatment.[27] The paper was concerned with interventions in which resistance was a by-product of a decision about treatment of an illness. In the current paper the focus is more on the more straightforward economic evaluation where the intervention is designed to tackle resistance. Here, the focus is still on changes in antimicrobial resistance but in this case

the change in antimicrobial resistance is the outcome of interest. The paper raises similar issues to those described in Superbugs 1, but the focus of these issues is very different. Four areas, broadly similar to those examined in Superbugs 1, are used to consider the particular difficulties which studies evaluating policies aimed at reducing resistance are likely to face: problems associated with the identification of diffuse impacts (the apparent 'smallness' noted in the original paper); problems associated with comparing current and future impacts; problems associated with uncertainty; and problems associated with difficulties in measurement. Each of these is examined in relation to the theoretical and conceptual literature and by using examples from the small number of studies that have been conducted in this area. The paper begins, however, by examining the nature of policy responses to antimicrobial resistance.

WHAT POLICIES ARE AVAILABLE TO DEAL WITH RESISTANCE?

The development and spread of resistance is a complex process dependent on many factors which are not yet fully understood. At one level there is the process of the development of resistance within an organism to consider. At a second level there is the process of the acquisition of resistant organisms by an individual. Each of these is discussed below in relation to the sorts of policies that may, given the known factors which influence resistance, be able to deal with the problem of resistance. It is worth noting at this point, however, that there are essentially two ways of distinguishing between strategies to decrease the prevalence of resistant organisms. The first is in terms of their purpose – whether the strategy aims to control the selection pressure to prevent or reduce emergence of resistance, or whether it aims to decrease the transmission or spread of resistance between organisms, individuals and the environment. The second is in terms of the level at which the policy is focused – whether the policy focuses on the 'micro' level of an individual institution, for example a 'closed' environment such as a hospital, or whether it is a 'macro' policy focused at the broader community level.

The development of resistance within an organism

There are five main mechanisms by which resistance may come about: enzymatic destruction, alterations of the cell wall to prevent entry, increased efflux, chemical modification of the antimicrobial and modification of the site or metabolic pathway targeted by the antimicrobial. Resistance may be acquired by previously sensitive

isolates from the environment, from other organisms, from bacteriophages or through random mutation. Resistance can also develop more gradually, as shown by rises in the minimum concentration of antimicrobial required to inhibit the growth of an organism. Using antimicrobials exerts a selection pressure favouring the emergence of resistance, but for any specific antimicrobial the correlation between consumption and resistance is complicated by factors such as the relative fitness of resistant and sensitive strains and linked multiple resistances – so that a package of genes coding for resistance to several different antibiotics can be selected by use of any one agent.[34]

It is possible that reducing usage of antimicrobials, once resistance has developed, will result in a fall in the amount of resistance. This depends, however, on the extent to which resistance is a problem for the organism (so called "genetic cost"). For some organisms, resistance appears not to incur these costs and so they maintain their resistance pattern even once the selection pressure is removed.[35] The policy implication is that measures to reduce usage of antimicrobials (as a means of reducing the selection pressure) may only be valuable for those antimicrobials to which there is not yet significant resistance. This will, however, depend on the extent of the "genetic cost" associated with resistance to each particular antimicrobial, a factor which is largely unknown.

Policies where the aim is to reduce usage of antimicrobials could include education policies such as the recent initiative by the UK Government,[36] the regulation of antimicrobials in countries where their use is currently unregulated, and the use of taxation or permit systems.[28 29]

The acquisition of resistant organisms by an individual

Individuals may acquire resistant organisms directly (that is, by the development of resistance in an organism within the body) or indirectly from food,[14] animals, inanimate objects or through contact with other individuals.

The direct development of resistance within an individual can happen when individuals take antimicrobials to treat one particular pathogen, but selection pressure is exerted on other organisms within the body at the same time. Factors which influence the success of antimicrobial therapy, such as the choice of agent, its method of administration, the magnitude of the dose, the frequency of administration, the duration of therapy, the use of combinations and patient adherence, will also influence the development of resistance. The emergence of resistance is particularly likely in the hospital setting where there is widespread use of antimicrobials for both treatment and prophylaxis, as well as large numbers of vulnerable patients. Policies which are concerned with these

sorts of issues, for example, the cycling of antimicrobials may all help to avoid, or control, the direct development of resistance within individuals.

The transmission of resistant organisms tends to be exacerbated by cohorting of vulnerable individuals, as in the hospital setting, but also in some areas of the community such as day care for the under fives, and residential and nursing homes for older people. Transmission by hand and through equipment can occur, as well as between patients and health care workers. Policies which have reduced transmission as their main aim include hand washing, isolation, decontamination and surveillance.

Designing and assessing policies

Gaps in knowledge about the development and transmission of resistance make the design and assessment of policies to reduce resistance particularly difficult. A recent contribution to the literature on the increasing prevalence of resistant bacteria suggests that important policies include hospital control of infections, prescribing policies and the need for substitute treatments, both antimicrobial drugs and vaccines[1]. It is clear from the above discussion that, at a number of levels, many very different types of action may come under the umbrella of policies aimed at dealing with resistance. Thus this paper may be concerned at one level with the impacts of policies such as hand washing or cohorting of patients or using treatment to reduce the length of time for which an infection is present,[37] or even limiting international travel as a means of limiting transmission of resistant organisms and, at another, with policies which aim to limit the emergence of resistance. Policies in the latter area will include those which aim to use antimicrobial therapy optimally, both through appropriate use (such as completing the full course of antibiotics so that the infection is removed), the development of substitutes such as vaccinations, educational interventions, and economic measures such as financial incentives, taxes or permits.

The purpose to which the economic evaluation will be put is also of relevance in determining the issues which face those carrying out research studies. Is the concern a technical issue related to a particular outbreak of a resistant organism in a particular closed system such as a hospital? Or is it to know how to allocate scarce resources between alternative means of approaching the problem of resistance at a national or even global level? Some of these evaluations will be considerably easier to carry out than others. Unfortunately those that are easiest to conduct, as this paper will show, are also those likely to be least useful in relation to long term policy. Indeed there is a danger of focusing on particular policies purely because they are the easiest to evaluate.

MEASURING THE IMPACT OF RESISTANCE FOR ECONOMIC EVALUATIONS

Diffuse impacts: how should the impact of policies on resistance be identified?

It was indicated in Superbugs 1 that "[a]ttributing the costs of an increase in antimicrobial resistance to any one treatment intervention will be difficult, maybe impossible." (Coast et al,[27] p.222). Similarly, one of the major problems which will be associated with assessing the value of different policy responses to antimicrobial resistance will be in identifying the influence of a particular policy on resistance. Unlike many other evaluations, it is the indirect impact upon individuals not directly targeted by the policy that is likely to be the greatest area of benefit in an evaluation. It has already been noted that the mechanisms by which resistant organisms may emerge in individuals are through direct acquisition (i.e. the individual is hosting an organism which becomes resistant) or through some form of transmission, such as through food or by contact with an infected person. It will be easier to identify the impact of policies aimed at reducing transmission (at least in the initial case) than those aimed at stopping the emergence of resistance. Similarly, it will be easier to identify the impact of policies in a closed environment such as a hospital or day care centre for young children.

It is notable that much of the literature that currently exists in this area, is strongly focused on the closed hospital system and tends to concentrate upon the effects of policies aimed at reducing transmission, for example decontamination strategies (see, Verwaest et al[38], Quinio et al[39]), handwashing (see Larson,[40] Hedin and Hambraeus[41]), surveillance (see, Haley et al[42]) and isolation policies (see, Chaix et al[43], Rao et al[44]). In these studies it appears to be relatively easy to identify the impact of a particular policy. For example, the study by Chaix et al examined hospital control policies for endemic methicillin-resistant *Staphylococcus aureus* (MRSA) including selective screening of potential carriers and isolation of patients found to have MRSA (see for example the study by Chaix et al[43]). Here the authors were able to identify those suffering from the condition with and without the control policy and to link directly the control policy (or lack of) with the cases identified. Yet even for studies such as these the impact of not operating the policy may go further than researchers are able easily to identify. As Chaix et al note, another important benefit of control relates to reducing the opportunity for further development of resistance: "… limitations of vancomycin usage in hospitals is an important objective in the context of increasing resistance in enterococci and emerging resistance in staphylococci." (Chaix et al,[43] pp.1750-1751)

The other main focus of the current literature is on educational interventions or the introduction of guidelines intended to reduce prescribing of antimicrobials.[45-47] Here the concern *is* with both a community level intervention and with a policy aimed at reducing emergence of resistance, but unfortunately the impact tends to be measured in terms of changes in antibiotic prescribing as a proxy for impact on resistance. In practice, there are only limited data which evaluate the impact of reducing prescribing on resistance rates.[47] Indeed the impact of prescribing changes on resistance will depend very much on the extent to which resistance has already developed for a particular microorganism, and the importance of "genetic cost" in determining whether selection pressures remain important once resistance is established. The impact of policies which aim to reduce the selection pressures on antimicrobials (which will include not only educational interventions but forms of economic incentive such as pigovian taxes and permits) will therefore differ significantly depending upon both the particular microorganism and the context in which that microorganism is present. Further identifying the extent of such impacts will be extremely difficult as it will be a function of both the development of the resistance and its subsequent transmission.

In terms of assessing the best way forward in an allocative sense there is a distinct problem in that, with one type of policy (policies aimed at reducing transmission) it is more likely that the research will be able to identify some impact relatively easily (although possibly not the entire effect) than for the other type of policy (policies aimed at reducing the selection pressure for resistance). This is particularly true at the current time, where policies aimed at reducing transmission are mainly confined to the relatively closed hospital system, and often even the intensive care unit. As resistance becomes more important at the community level, however, identifying the impact of policies intended to reduce transmission is also likely to become more difficult.

Dealing with current and future impacts

Any evaluation of policies to deal with resistance inevitably has to deal with issues of time preference and intergenerational equality. Discounting of costs and benefits which occur in the future is standard practice in economic evaluation and, as was noted in Superbugs 1, even large absolute costs (or effects) occurring far into the future would potentially be insignificant after taking into account time preference.[27] It was, however, also noted that individual time preference is not universally accepted as a basis for discounting, and that there may be moral reasons for not using a positive discount rate.[48] Indeed, Broome covering a variety of arguments in favour of discounting, argues for a zero discount rate in relation to the environmental problem of global warming.[49] He argues that future generations are not fully accounted for by the use of consumer interest rates and thus that this method is useless for long-term projects

such as global warming. Later, starting from a presumption in favour of the impartiality associated with utilitarianism, he dismisses a variety of arguments in favour of a pure discount rate, including: that discounting may protect the environment; that there is always some small risk of extinction which means that future generations should be discounted; and that maximising an impartial value function could lead to excessive sacrifices for the present generation. Broome concludes that current generations are not justified in applying a positive discount rate to major harms imposed on future generations.[49]

This argument could also be applied to the issue of antimicrobial resistance because of the major harms which will be imposed on future generations as resistance increases. The apparent irreversability of resistance might also be used as an argument for a zero discount rate. The implications of positive discount rates may be particularly problematic for antimicrobial resistance, given the particular nature of its development. The development of resistance for antimicrobials is shown in a stylised form in figure 1.

Figure 1: The development of antimicrobial resistance over time

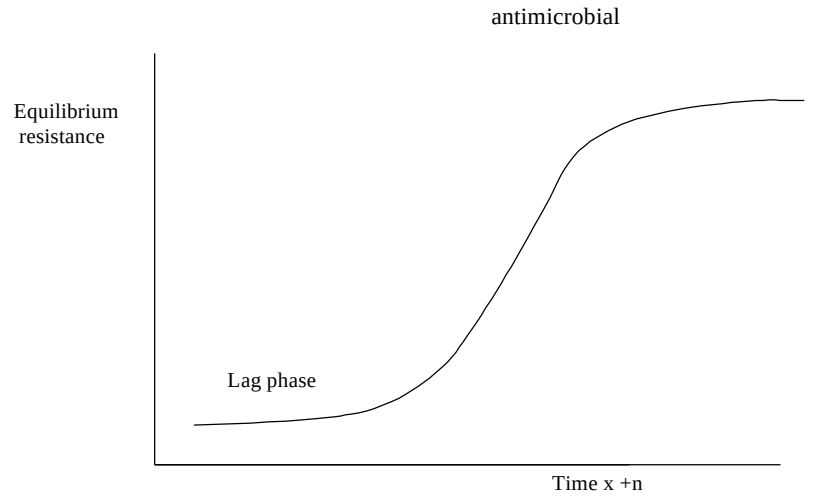

Figure 1 indicates how antimicrobial resistance develops over time. The relationship between time and the proportion of any particular microorganism that is resistant tends to follow a sigmoid distribution,[37] with a lag phase before resistance begins to appear, followed by a relatively rapid increase in the proportion of organisms that are found to

be resistant, followed by a third phase in which the proportion of resistant strains has reached an equilibrium – although this equilibrium proportion varies considerably between different organisms, and is determined by a number of factors including the relative fitness of resistant and sensitive strains of an organism and the selection pressure. Taking the case of resistance to penicillin in the hospital setting as one of the first examples of resistance that was noted, the lag phase would have occurred during the 1940s, with time x, the time at which the rise in resistance began to occur, taking place in the late 1940s from around 1947.[50] Time x+n, at which the equilibrium point had been reached would have been after about 1960. Once time x+n has been reached, only policies which reduce transmission of the organism will (generally) be valuable as a means of reducing the impact of resistance on health. Prior to this point, and particularly when in the lag period, it is possible to affect both the rise towards resistance and the final level of equilibrium by altering the selection pressure, that is, by reducing usage of antimicrobials.

It is important to note the influence that discounting may have on the choice between policies that affect transmission and those that affect the selection pressure for the development of resistance. Where there are limited resources available to deal with the problems of antimicrobial resistance and where discounting at a positive rate is undertaken, policies that reduce transmission of already resistant organisms – for which the benefits can be seen today – may seem to be more efficient than policies which affect the selection pressure for the development of resistance – the impacts of which may not be seen until the distant future (particularly when the issue of multiply resistant organisms is taken into account). Yet in terms of the health impact on future generations the benefit of reducing the pressure towards greater selection of resistance is likely, in absolute terms, to be much greater. This is obvious when considering figure 1: policies to reduce transmission will never avoid all the ill health associated with a resistant organism (and this may be particularly true in community environments), whereas policies which avoid the emergence of resistance could avoid all the additional ill health associated with the resistant organism. Discounting at a positive rate may, therefore, lead to major harms being imposed on future generations. Indeed, when considering figure 1, the current generation might well wish that early use of antimicrobials had been more cautious – and that the future had not, apparently, been discounted so heavily.

Dealing with uncertainty

Numerous variables related to the evaluation of policies for dealing with antimicrobial resistance are shrouded in uncertainty.[28] Here only the uncertainty associated with the future development of new antimicrobials and the uncertainty associated with the nature

of the sigmoid curve for any specific antimicrobial in any particular context are considered. The uncertainty related to the development of new antimicrobials was discussed in the original superbugs paper.[27] In this paper it was noted that no new classes of antimicrobials had been developed since the 1960s,[51] and the same situation exists today.[4] The prospects for development of new classes of antimicrobials are extremely uncertain. The sigmoid distribution for any antimicrobial in any particular context is also extremely uncertain: as indicated earlier, the epidemic curve will be the same, but the duration of the lag phase and the proportion of isolates resistant at the stabilisation phase will vary with the particular condition.

How should these uncertainties be dealt with? It may be that different sorts of uncertainties should be dealt with in different ways. The implication of uncertainty about the development of new antimicrobials is that we may incur costs now (in terms of morbidity and mortality) for future benefits (in terms of reduced morbidity and mortality) which may in fact not be needed if the development of new antimicrobials keeps pace with the emergence of resistance. This type of uncertainty could, theoretically, be dealt with by the inclusion of a risk premium[52] (added to the discount rate whether zero or positive) as, essentially, the probability of finding a new antimicrobial agent in each year. Evidence about recent development of antimicrobials would suggest that such a risk premium would probably be quite small.

The uncertainties concerning the likely impact of emerging resistance are much more difficult to deal with. One option would be to model many different options to obtain an idea of the expected benefits of policies under different scenarios. Another option is to be more cautious about use of antimicrobials (and therefore pressure for selection), given uncertainty, than one would be under a situation of certainty. This is because it is possible to learn from experience and increase antimicrobial usage later, but too much usage now may have irreversible effects (see Arrow and Fisher for detailed analysis in relation to non-renewable resources[53]). As Arrow and Fisher state "… the point is that the expected benefits of an irreversible decision should be adjusted to reflect the loss of options it entails." (Arrow and Fisher,[53] p.319) At its most extreme, this would imply viewing policies to reduce the emergence of resistance as a form of insurance (see Broome in relation to global warming[49]). These sorts of policies would reduce the risks of a scenario in which antimicrobials were useless in the fight against serious infectious diseases which could in turn lead to extensive morbidity and mortality. Hence there could be benefit, in terms of risk reduction, in acting to avoid the emergence of resistance, even if the uncertainty associated with both the sigmoid distribution and the possible development of new antimicrobials meant that the expected net benefit of such policies compared with those aiming to reduce transmission, would be large or small, positive or negative. An alternative way of conceptualising this issue is to think in terms of the natural regenerative capacity of susceptible antimicrobials – as Pearce and Turner

suggest "… if we wish to sustain renewable resources we must be careful to harvest them at a rate no greater than their natural regenerative capacity." (Pearce and Turner,[54]p.39). (One further issue not discussed here should also be acknowledged, however, which is that reducing antimicrobial usage now may impact on current morbidity and mortality.[28])

Of particular concern is that these uncertainties may be of much greater importance in one type of policy than the other. The impact of policies which aim to inhibit emergence of antimicrobials is likely to be much more subject to the influence of these uncertainties than policies to reduce transmission, the benefits of which are likely to be much more immediate and for which there is information about the sigmoid distribution, if not about the development of antimicrobials.

Difficulties in measurement (and valuation) of impacts

In addition to the problems of identifying where the impacts of policies to reduce resistance are likely to occur, is the problem of measuring the differential impact on health of resistant organisms compared with susceptible organisms. This is because resistance is an additional aspect of an infection, where infection itself causes deleterious effects. In order to determine the effectiveness or otherwise of a policy control groups are needed where infections that exist are not resistant. (For example, see the work by Holmberg et al, which showed that patients with resistant organisms generally had worse health and economic outcomes than patients with organisms susceptible to antimicrobials [55] and more recently, work by Carmeli et al[56]).

One way of bypassing this issue would be to value directly, using contingent valuation methods, preferences for maintaining the effects of antimicrobials. Such valuation would involve asking individuals about their willingness to pay to avoid the development of antimicrobial resistance in the future. Such valuation would be likely to be difficult if the complexities of antimicrobial resistance and its potential impact on health are difficult for respondents to understand. (This would be expected: the issue is more complex than the sorts of benefits often valued directly in the environmental literature which include the valuation of recreation sites and air quality improvements.)

The alternative is to develop what is referred to as a "dose-response relationship between pollution and some effect" (Pearce and Turner,[54] p.142). This would reduce the valuation problem to one much more common to health economics, in which there was some epidemiological assessment of the likely impact on health of avoiding the development of resistance, followed by asking individuals at this point to assess the willingness to pay for these different health impacts. One problem with this option, inevitably, is in understanding the dose-response relationships. Perhaps more

importantly, this latter form of evaluation would only provide valuations for one area of benefit resulting from policies to reduce resistance: the actual health impacts of the different policies. Missing from this latter valuation, importantly, would be any assessment of option value, which can occur when people anticipate purchasing a commodity at some time in the future, but never in fact purchase it but that as "economic men" consumers "… will be willing to pay something for the option to consume the commodity in the future" (Weisbrod,[57] p.472). Option value may be particularly important in relation to one form of policy response to antimicrobial resistance – that which concentrates on avoiding the emergence of resistance – and not to the other form of policy response – policies to avoid transmission. This is because people may value (and be willing to pay for) the existence of the option to use antimicrobials in the future, even if they do not in practice do so. Thus there may be a value attached to maintaining the option to benefit from antimicrobials in the future which would not be captured by valuations of the health impacts of different policies alone.

ECONOMIC EVALUATION OF ALTERNATIVE OPTIONS FOR DEALING WITH RESISTANCE: THE WAY FORWARD

The main issue arising from this examination of the problems of conducting economic evaluation in the area of policies to deal with antimicrobial resistance is the very real danger of focusing on short-term policy responses at the expense of long-term policies and of concentrating on small technical issues rather than the more challenging area of allocating resources for dealing with antimicrobial resistance optimally. It is clear that policies aimed at reducing transmission will be easier to evaluate for a number of reasons: the persons to whom the organism is transmitted are more easily identifiable, the issue of discounting is less challenging, the uncertainty associated with levels of resistance is much less and the problem of measuring option value does not have to be confronted. Conversely policies aimed at avoiding the emergence of resistance are subject to the very real difficulties of identifying an impact on resistance, of dealing in an acceptable way with issues of time preference and intergenerational equality, and of dealing with the considerable uncertainty about the extent to which resistance will develop in the presence and absence of intervention. The measurement of option value in this area poses another challenge.

Unfortunately, the policies which are likely to be easiest to evaluate are not likely to produce an optimal long-term outcome given the importance of remaining at lower points on the sigmoid curve because of the apparent irreversability of much resistance

and the potentially severe harm which could be imposed as a result. Yet, given the increasing importance of evidence-based medicine, policies which have been evaluated using experimental methods such as randomised controlled trials and well conducted economic evaluations may be prioritised above these policies which are much more difficult to evaluate.

Given this difficulty and the desirability of avoiding such a scenario, one way forward would be to combine the results obtained from empirical studies with epidemiological and economic modelling: Indeed there is already some work on starting to develop epidemiological models which consider the impact of particular policies.[37] Such a way forward would also help to deal with two other very real problems associated with resistance. First, difficulties with generalisation are likely to be faced because of the huge importance of context in the development of resistance and the desirability of tailoring policy responses to these different contexts using the available evidence as a basis. And second, evaluating single policy options in isolation may be inadequate given the potential for sets of policies being operated at any one time (for example policies put in place nationally, at the hospital level and at the GP level) which may, cumulatively, have a greater or lesser effect than would be expected by summing the effect of each individual policy response.

Issues for discussion during HESG session

We would appreciate further exploration and discussion of the following issues:

- The appropriate way to discount given the potential for intergenerational equity;
- Combined epidemiological/economic modelling;
- Contingent valuation studies and accessing information about option value;
- Superbugs 1 – do we need to revisit incorporating the resistance externality in evaluations of drug interventions?

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