The Global Threat of Antibiotic Resistance:

Moving towards Concerted Action

Summary report of a multidisciplinary meeting
The Dag Hammarskjöld Foundation, Uppsala, Sweden 5–7 May 2004

Introduction

Many of the bacteria that cause infectious disease are no longer responding to antibiotics. This threat to world health is escalating, and the consequences for rich and poor countries alike are potentially devastating. Yet, as the impact of antibiotic resistance continues to grow, we see a paradoxical downward trend in development of new antibiotics. Only limited progress has been made in countering the problem, which remains largely a 'faceless threat' as the consequences are hidden within different disease entities. Motivated by the urgency to deal with the 'ticking bomb' of antibiotic resistance, 25 participants from all continents met for a three-day meeting at the Dag Hammarskjöld Foundation, Uppsala, Sweden, on 5–7 May 2004. Participants represented a unique range of backgrounds including the health sector, international organisations, the research community, the pharmaceutical industry, drug regulatory authorities, non-government groups, consumers, the media and national authorities.[1]

The meeting considered not only the problem and status of resistance but, critically, why there has been limited action to address this global health issue. Discussion took place on various means by which awareness of the issue might be increased among donors, funders, the public, professionals and politicians, and a proposal to try and address these problems was formulated. The following report presents the seminar's understanding of the problem and the challenges that need to be tackled in a concerted way.[2]

[1] A list of participants is provided at the end of the document.

[2] The views incorporated in the Summary Report do not necessarily represent a consensus of all participants on every issue. They reflect, rather, the conceptual space covered by the discussion. It should furthermore be noted that participants expressed themselves in their personal capacities, that is, not on behalf of the organisations or governments to which they belong.

The Problem

Less than 10 years after penicillin was introduced, it was recognised that bacteria causing infections can develop resistance to antibiotics.[3] Since then, resistance has grown dramatically and involves most kinds of antibiotics and a wide range of bacteria causing disease. Yet, the scale of the problem may well be underestimated in many parts of the world, where most antibiotics are purchased without prescription and where there are few facilities for measuring resistance.

Participants expressed their deep concern that resistance may proceed to the point where it is disastrous for global health. They feared a return to the conditions of the pre-antibiotic era and, for example, that child mortality from respiratory tract infections such as pneumonia, already high in many developing countries, would substantially increase. Resistance would also jeopardise advanced medical procedures, such as cytostatic therapy for cancer, organ transplantations and implants of prostheses, where antibiotics are crucial to ensure patient safety and avoid complications. In essence, everyone is at risk as bacteria with multiple antibiotic resistance may accumulate in hospitals, making hospitalisation, even for less serious diseases, potentially life-threatening.

Resistance is a natural biological outcome of antibiotic use. The more we use these drugs, the more we increase the speed of emergence and selection of resistant bacteria. In human use, around 80 per cent of antibiotic consumption takes place in the community and at least half of this is considered based on incorrect indications, mostly viral infections. Some data indicate that once resistance to an antibiotic has developed in the community its presence may not be reversible, though adequate action may still prevent a further increase of resistant bacteria.

The problem is increasingly a global one, as a result of growing migration, trade and travel. Resistant bacteria are spreading rapidly from one population to another, and will not be contained unless tackled in all parts of the world: in this respect nations are truly interdependent. The maintenance of a pool of effective antibiotics has also been termed a 'Global Public Good for Health'.[4]

The failure to deal effectively with the problem

Although the threat of increasing resistance is well documented and recognised by experts in the field, effective action to contain it has been largely lacking. Despite the fact that the elements of a strategy are well known, the problem has not been regarded as a challenge deserving priority action at the political level, and donors have shown little interest in it. Though some countries have instituted national 'action plans', even these have failed to stem the advance of resistance, and there has been no concerted, multifaceted and worldwide action of the type that is needed.

There are several reasons why it has until now been hard to convince policy makers and others to act:

- Antibiotic resistance is not a problem relating to a disease entity such as AIDS or SARS, which pose an evident and acute threat, easily understandable to all.
- It is difficult to measure the burden that it imposes on the population (illness, death or economic loss) and equally difficult to measure in the short term the effects of efforts to counter it.
- Antibiotic resistance is a multifaceted problem and therefore not a matter that is the clear responsibility of a particular institution, authority or organisation.

The basic reasons for the escalation of the problem

Any use of antibiotics brings with it the risk that the bacteria being targeted as well as those in the normal bacterial flora within the body will eventually develop resistance to it. The risk of resistance has, however, not been a sufficient reason to avoid employing antibiotics in situations where they are not strictly needed. Perceived short-term advantages of antibiotic use usually outweigh concerns about future consequences. It is clear that resistance develops earlier and more rapidly in populations where antibiotics are heavily or inappropriately used, though the risk varies markedly with the antibiotic and the type of bacteria concerned. The harm that

[3] The term 'antibiotic' is used here in its widely used sense, referring to a substance that kills or prevents multiplication of bacteria. Thus, in this report, it includes synthetic antibacterial drugs.

[4] A Global Public Good for Health is defined as a good from which no-one can be effectively excluded and where one person's consumption of it does not affect the ability of another to consume it (reference: Woodward D, Smith R D, 'Global Public Goods for Health: concepts and issues', in Smith R D, Beaglehole R, Woodward D, Drager N (eds), Global Public Goods for Health: Health economic and public health perspectives, Oxford University Press, 2003, chapter 1: 3–29). Global Public Goods address issues that: (i) are deemed to be important to the international community; (ii) cannot, or will not, be adequately addressed by individual countries acting alone, and (iii) must therefore be addressed collectively on a multilateral basis, by both industrialised and developing countries.

may be caused by unnecessary use is unlikely to be immediately visible to the individual patient or his/her physician.

Among the many factors influencing the development of antibiotic resistance in the community are:

- Use of an antibiotic where none is needed, for example where no proven infection is present, where an infection is caused by a virus rather than bacteria, or where a minor bacterial infection is likely to be eliminated by the body's own defences.
- Situations in which prescribing is profitable for the prescriber (dispensing doctor, prescribing pharmacist).
- Heavy use of antibiotics in the veterinary field, livestock production and agriculture.
- Incorrect dosage: if an antibiotic is given in too low a dose or too briefly it may be incapable of curing the infection but sufficient to cause the bacteria to become resistant.
- The presence in many countries of sub-standard antibiotics, which are therapeutically ineffective but contribute to the development of resistant strains of bacteria.
- Heavy marketing by the pharmaceutical industry, targeting prescribers, pharmacists and consumers, as well as sales of antibiotics over the Internet.
- Sale of antibiotics to the public from pharmacies or other drug outlets without the need for a prescription, often referred to as 'over the counter' (OTC) sales.
- Spread of resistant bacteria facilitated by, for example, overcrowding, poor sanitation and hygiene.

Aggravation of the problem: the decline in innovation

For many years the growth of resistance to older antibiotics was countered by the continuous flow of newer compounds. This helped to solve the immediate problems, though prescribers were induced or tempted to move too rapidly from older antibiotics to newer and more potent ones, even when this was not necessary.

Innovative research to find new antibiotic classes subsided in the 1970s and, instead, the focus moved to modifying already existing products. Since these drugs basically use the same mechanism to attack bacteria, they may overcome existing resistance to a limited degree and for a short time, but do not constitute real long-term alternatives.

Declining innovation is in part due to the fact that fewer pharmaceutical companies are now involved in antibiotic research, either because of mergers or because of commercial decisions to abandon the field. The risks of failure in research are regarded as high, and if the rewards are smaller than in other therapeutic areas the pharmaceutical industry will regard investment in this field as unattractive.

Some research does indeed continue, notably directed towards treatments for serious hospital infections due to multiple drug resistance in industrialised countries. In other areas there are, however, worrying gaps in the development of new antibiotics, in particular those needed to treat resistant bacterial diseases in developing countries, including sexually transmitted infections, tuberculosis and intestinal infections; and those needed in all parts of the world to replace major antibiotics now encountering resistance. It is clear that the burden of infectious disease for which effective antibiotics are lacking today falls disproportionately on developing countries, and this is where the unmet need for new, high-quality antibacterial drugs will be greatest.

Participants emphasised that the slowdown in innovation is not final and inevitable; and that it must be possible to reverse it:

- The list of biochemical targets in the bacteria, which antibiotics should be able to tackle, is far from exhausted, but new approaches in the financing of research are needed.
- It may be possible to develop more specific antibiotics, which target a specific organism without harming the microbial environment more generally.
- Some promising research approaches appear to have been prematurely abandoned because of incorrect predictions of the risk of mutation and resistance and of the overall chance of success; these fields should be reconsidered in the light of present knowledge.
- In some therapeutic areas it may well be possible to develop other forms of innovation (new vaccines, non-pharmacological methods of treatment).

The Response: Roads Towards Concerted Action

The seminar devoted much attention to exploring constructive ways forward, both in terms of tackling longer-term challenges and in terms of immediate follow-up through the formation of an action-oriented network. Whilst there has been much work conducted by a variety of organisations and institutions, it was felt that these have focused on specific issues with respect to tackling resistance. This can mean that action is fragmented rather than co-ordinated. To achieve concerted global action the resources of these existing institutions need to be harnessed in a constructive way. Thus, the approach suggested here is one of complementarity with existing networks to facilitate bringing together existing resources, as well as seeking additional resources, so as to move action forward in a concerted manner.

A global network for concerted action

The global threat to humanity posed by the emergence of resistance to antibiotics is in many respects well documented. Participants agreed that building on these this documentation and existing activities it is now necessary to create a structured network of individuals, groups and institutions, who appreciate the need for action and involvement. The network must be organised so as to ensure a coordinated and well-managed approach to all that now needs to be done. The network must be global, consisting of partners, like-minded organisations in the fields of public health and the treatment of infectious disease, both at the international and national levels. It should also actively link up with movements and networks in other, related areas of relevance, such as the environmental movement. It must gain and retain credibility and independence.

The network will initially set out to raise broader awareness of the serious dangers of antibiotic resistance and will serve as a face of the hitherto 'faceless' threat, ensuring that it is more widely recognised and that support is mobilised both at the political and the popular levels. As a longer-term goal, the network will strive to promote the emergence of a broad movement to bring about real change.

The network will, in addition, actively seek to promote sustainable access to effective antibacterial treatment for all, to optimise use of existing antibiotics and to ensure that new antibiotics, as they emerge, are used with special care so that emergence of resistance is delayed.

The network will also develop initiatives favouring the development of new antibiotics as well as of alternatives to antibiotics for treatment and prevention.

The structured network will operate in three broad areas, as set out below.

1. Communicating the message

The network will develop a simple, generic message to generate an urge for action without creating panic.

The global message will be adapted to the interests and understanding of different audiences (e.g. politicians, professionals and consumers) across the world and disseminated widely. The message must be one with which everyone can identify.

The network should serve as a focal point of the issue.

Questions and requests for information from the media, politicians, professional organisations and others will be invited and should be handled promptly and with expertise.

The network will employ means of informing and influencing national policy makers in efforts to overcome the problem of antibiotic resistance.

Governments will be urged to adopt broad approaches to the antibiotics issue, working for cross-sectoral collaboration between various ministries, departments and agencies.

The network should prepare documentation on the extent of the health and economic consequences of the problem.

The network should invite and form strategic alliances with relevant parties, including governments, international organisations, civil society organisations and concerned individuals.

The network should identify potential key actors and allies and learn from examples where important but neglected issues, such as landmines and light weapons, have successfully been put on the highest political agenda as a result of concerted action.

Common communication and media strategies should be developed to introduce the issue of antibiotic resistance into the public debate and create public pressure.

Possibilities of recruiting media and communication strategy competence to the network should be explored. Successful examples of using a variety of media forms, including TV, internet, advertisement, comic books and written material should be drawn upon and harmonised in joint communication strategies.

2. Ensuring appropriate use

The network will document antibiotic use and misuse, as well as efforts to correct it.

There is a strong need to develop better methods of surveillance both of antibiotic resistance and use in the community. It will be necessary to identify national and local data sources, including existing but hitherto inaccessible data from the private domain. Cross-sectoral coordination will be developed to support corresponding improvements in related sectors, such as veterinary practice and agriculture.

Building on existing experience, ways will be sought to bring about real improvements in antibiotic use.

The network should aim for integration of existing international and national initiatives. An important role should be to support national activities in a manner befitting local needs and opportunities.

Knowledge transfer between countries on well-proven methods should be facilitated. The structured network should conduct reviews of existing studies and experiences to identify those approaches most likely to reduce inappropriate use of antibiotics and contain the development of resistance, and to work to integrate this knowledge into the curricula of health professionals.

The issue of 'over the counter' (OTC) sale of antibiotics will need to be examined critically.

There must be context-specific examination of the ways in which OTC may be regarded as tolerable in the present situation and a strategy to eliminate the practice in the longer term without restricting access to essential drugs.

Questionable promotional activities and financial incentives within the health sector must be exposed.

The network should expose and work to minimise the excessive promotional influence on prescribers and consumers.

Unsound economic incentives for prescribing doctors and pharmacists should be tackled.

3. Ensuring the supply of new antibiotics

The network will scrutinise the biological, technological and commercial reasons for the current lack of innovation, document the need for new antibiotics and explore means of ensuring their development.

It seems very unlikely that the technical possibilities of developing new antibiotics have been exhausted. It is also clear that many substances that appear promising in the research phase fail to be selected for full development, either for financial or other reasons. Innovative approaches must be sought to make available such 'shelved' substances for further development. Establishment of compound libraries accessible to all those willing to pursue research and development of antibacterials should be encouraged.

The supply of new, effective antibiotics is a global public good and the public sector must therefore take the lead. The possibility of the public sector taking a more decisive role in antibiotic innovation will be examined and relevant opportunities pursued.

The network should explore ways in which the public sector can constructively intervene in the industrial value chain of antibiotic development. Such interventions may range from taxation and strict regulations, via the provision of incentives, to full public financing and development. With greater public investment, products should better reflect public health priorities and be more affordable upon market entry.

Measures may draw on experience of the early development of antibiotics, when governments played a decisive role, but also from other relevant areas including the current discussions on global public goods for health.

All parties, including industry, share a moral responsibility to help ensure the supply of new antibiotics. Thus, industry should be encouraged to use a larger share of the revenues from the most profit-generating drugs for neglected and less profitable drugs. It may, however, also prove necessary to develop greater efficiency and improved financial incentives to promote antibiotic development by industry.

In selecting and setting reimbursement levels for drugs, health insurance agencies can reward the development of drugs meeting public health priorities. By accepting differential pricing arrangements, innovation in fields that

are otherwise unprofitable may be encouraged. Other forms of financial incentives that may be considered include selective tax breaks and possibly patent extension in the case of significant antibiotic innovations. It is important that incentives are put in place only after careful examination of their likely effects. Various models of public-private partnership, academic research consortia, and licensing of publicly funded R&D to generic drug firms deserve consideration.

Means of alleviating other possible obstacles to the development of new antibiotics, regulatory or other, will be identified, with the aim of encouraging constructive responses.

Views on the extent to which drug regulation has impeded the development of new drugs in general or antibiotics in particular vary markedly. There may well be a need for a special regulatory regime for antibiotics in situations where a great public health need exists, for instance in infections caused by multiresistant bacteria where little or no alternative treatment is available. Modified requirements already exist for certain other special groups of drugs, such as cancer treatment drugs; this approach should be also considered for antibiotics. Regulatory authorities should also encourage the development of appropriate fixed-dose drug combinations as a way to minimise resistance development for new antibiotics.

Participants committed themselves to act within their own areas to bring about the development of this network, seek potential financing and promote its rapid extension globally. Coordinators were designated for the three main areas of action and concrete short-term goals were decided on. An interim core group was formed to coordinate the work until the next meeting, which is planned to take place within nine to twelve months.

List of Participants

Dan Andersson (Sweden), Bo Aronsson (UK), Claude Carbon (France), Otto Cars (Sweden), Graham Dukes (Norway/The Netherlands), Eduardo Gotuzzo (Peru), Kathleen Holloway (UK), Niclas Hällström (Sweden), Richard Laing (Zimbabwe), John McConnell (UK), Dominique L. Monnet (Denmark), Olle Nordberg (Sweden), Per Nordberg (Sweden), Eva M.A. Ombaka (Tanzania), PehrOlov Pehrson (Sweden), Steven J. Projan (USA), Jérôme Sclafer (France), Richard Smith (UK), Anthony So (USA), Cecilia Stålsby Lundborg (Sweden), Göran Tomson (Sweden), John Turnidge (Australia), Krisantha Weerasuriya (Sri Lanka), Anthony R. White (UK).