

## Analysis

### Meeting the challenge of antibiotic resistance

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A concerted global response is needed to tackle rising rates of antibiotic resistance, say **Otto Cars** and colleagues

Antibiotics changed the world. Since their discovery almost eight decades ago, they have revolutionised the treatment of infections, transforming once deadly diseases into manageable health problems. The growing phenomenon of bacterial resistance, caused by the use and abuse of antibiotics and the simultaneous decline in research and development of new medicines, is now threatening to take us back to a pre-antibiotic era. Without effective treatment and prevention of bacterial infections, we also risk rolling back important achievements of modern medicine such as major surgery, organ transplantation, and cancer chemotherapy.

Data from low income and middle income countries indicate that, because of the development of resistance to first line antibiotics, 70% of hospital acquired neonatal infections could not be successfully treated by using WHO's recommended regimen.<sup>1</sup> A recently published study of Tanzanian children confirmed that ineffective treatment of bloodstream infections due to antibiotic resistance predicts fatal outcome independently of underlying diseases.<sup>2</sup> In that hospital based study, mortality from bloodstream infections caused by Gram negative bacteria was more than double the mortality from malaria.

Antibiotic resistance is becoming important in high income countries. In England and Wales, for example, the number of registered deaths in which meticillin resistant *Staphylococcus aureus* (MRSA) is mentioned increased from less than 50 in 1993 to more than 1600 in 2006. In 2007 there was a slight decrease.<sup>3</sup> The European Centre for Disease Prevention and Control, in its first epidemiological report on communicable diseases in Europe, states that the most important disease threat in Europe is from micro-organisms that have become resistant to antibiotics.<sup>4 5</sup>

The emergence of antibiotic resistance is further complicated by the fact that bacteria and their resistance genes are travelling faster and further.<sup>6 7</sup> We are facing not only epidemics but pandemics of antibiotic resistance.<sup>8</sup> Airlines now carry more than two billion passengers annually, vastly increasing the opportunities for rapid spread of infectious agents, including antibiotic resistant bacteria, internationally.<sup>9</sup> The spread of resistance is also facilitated by worldwide distribution of food.<sup>10</sup> Another important factor is poor hygiene in hospitals as well as in the community, augmenting the rapid spread of antibiotic resistant bacteria in vulnerable populations.

## **Unblocking collective action**

Although the essential components of control of antibiotic resistance have long been well known, success has been limited in changing policies and efficiently responding to the problem.<sup>11 12</sup> The relative lack of data on the morbidity and mortality attributable to antibiotic resistance, including the economic impact on individuals as well as on health care and societies, may explain the weak reaction from politicians, public health workers, and consumers to this threat to public health.

Individual stakeholders might well recognise the problem, but because it is complex, antibiotic resistance often becomes no one's responsibility, which blocks collective action. Action is urgently needed in three key areas: leadership on international and national levels, change in the behaviour of consumers and providers, and the development of antibacterial agents to match current public health needs.

## **International and national leadership**

### *International organisations*

In 1998, the World Health Assembly adopted a resolution urging member states to take action on the problem of antimicrobial resistance.<sup>13</sup> In 2000, the World Health Organization requested a massive effort to prevent the "health care catastrophe of tomorrow,"<sup>7</sup> and shortly thereafter presented a global strategy for the containment of antimicrobial resistance, calling for a multidisciplinary and coordinated approach.<sup>14</sup> However, sufficient financial and human resources to implement the strategy were never provided. Member states recognised this lack of leadership and initiated a new resolution, adopted by the World Health Assembly in 2005, requesting the director general to strengthen WHO's leadership role in containing antimicrobial resistance and to provide more technical support.<sup>15</sup>

Little has taken place to implement the resolution. The difficulties of enforcing these recommendations on a global level are evident, and the links between the well formulated strategies at the level of global society and the acceptance level by national policymakers are weak. WHO, international professional organisations, and other international stakeholders must provide coordination and resources for generating up to date information on the burden and the magnitude of antibiotic resistance at regional and subregional levels. Evidence is needed on effective interventions for prevention and control of antibiotic resistance at national and local levels, and more emphasis on prevention of infectious diseases is needed. Solving basic problems such as lack of safe drinking water, poor nutrition, and dysfunctional sanitation will go a long way toward curbing the needless use of antibiotics as quick-fix solutions to avoidable diseases.<sup>7</sup>

### *At national level*

Strategies for containing antibiotic resistance in low income countries are still blocked by patients' poverty and weak health systems,<sup>16</sup> and many high income countries with well developed

regulations and policies lack coordinated strategies against antibiotic resistance. Although the European Union has responded to the resistance problem, antibiotics are still sold over the counter without a prescription in some EU countries, violating existing laws and regulations, and in all countries self medication with leftover medicines occurs.<sup>17</sup> The root causes of certain behaviours need to be tackled, and the ultimate responsibility for coordinating the work lies with the government.

National mandated multidisciplinary programmes can move from recommendations to implementation and audits.<sup>18</sup> For example, in Sweden the government is funding Strama, a nationwide multidisciplinary and multifaceted action programme against antibiotic resistance. Antibiotic sales have been reduced without measurable negative consequences, and resistance remains low.<sup>19</sup> In Chile, after a mass media campaign, regulatory measures were implemented to make antibiotics available by prescription only, resulting in an initial decrease of 35% in antibiotic sales.<sup>20</sup>

### **Behavioural change**

Social constraints and cultural views of infectious conditions influence the use of antibiotics.<sup>21</sup> Although the public's demand for antibiotics often is perceived as high even for conditions without a clinical indication for antibiotic treatment,<sup>22 23</sup> studies have shown that this demand is overestimated by the prescriber,<sup>24</sup> and antibiotics could therefore successfully be replaced by better information and follow-up.

The role of the patients as consumers is growing stronger. They need access to information and knowledge to reduce their expectations of antibiotics in self limiting infections, and doctors need new tools to help them justify their treatment decisions.<sup>25</sup> It could be unrealistic to expect people to restrict their antibiotic use in favour of a common good to prevent resistance—but if the arguments for restricting the use of antibiotics can be made sufficiently convincing, reduced demand from the consumer may be the strongest force driving change. Studies increasingly emphasise the risk for the individual when taking an antibiotic, including the risks of becoming a long term carrier of antibiotic resistant bacteria,<sup>26 27</sup> which might confer a greater risk in a subsequent severe infection. Reliable information on the adverse effects of antibiotics on the microbiological flora might provide a stronger incentive for not using antibiotics unnecessarily than would more general messages about risks for society through the development of resistance. For prescribers and other drug providers, multifaceted interventions including so called academic detailing are effective to increase adherence to recommendations in both high income settings and low income settings.<sup>28 29</sup>

### **Developing new antibacterials**

For many years, needs for antibacterial drugs were met by the pharmaceutical industry, and the apparent symbiosis between the interests of the community and those of the industry prevailed. Today we see a different scenario. Existing antibiotics are losing their effect at an alarming pace, but development of new antibiotics is declining. More than a dozen new classes of antibiotics were developed in the 1930s through the 1960s, but only two new classes have been developed since then.<sup>30</sup> Nor does the trend of declining innovation seem to be reversing. In a study of the top 15 pharmaceutical companies, only 1.6% of drugs in development were antibiotics, none of which were from novel classes and leaving need unmet for multiresistant Gram negative infections.<sup>31</sup>

With existing incentives, current levels of innovation are clearly inadequate.<sup>32</sup> Proposals on how to break this trend have been put forward. Some have suggested arrangements that would increase the

anticipated revenue by lengthening the period of patent protection or exclusivity over data submitted for drug registration. However, antibiotics already have small markets and emergence of resistance may further reduce the expected return of investment, so these incentives are likely to do little to stimulate greater innovation for antibacterials.<sup>33</sup> There are also scientific challenges for development of new antibiotics.<sup>34</sup>

If today's market cannot deliver what the public needs, we must envisage other approaches that better engage both public and private sector resources.<sup>35</sup> One model is product development partnerships (PDPs), arrangements between public organisations and private companies to develop drugs when markets otherwise fail to meet public health priorities. This approach is now used for some drug projects targeting other neglected infectious diseases, such as malaria and tuberculosis.<sup>36</sup> Mechanisms creating supplements or replacing revenues in small and resource poor markets are another approach. Advanced market commitments (AMCs) create a fund that guarantees a certain price for drugs that meet therapeutic targets where there is a demand for the drug. A recent example is the pneumococcal vaccine AMC.<sup>37</sup>

A gap analysis of drugs currently under development in light of current resistance patterns and trends would give priority to the most urgently needed antibiotics and give incentives for developing antibacterials with new mechanisms of action. But no matter how innovation is accelerated, any public investment must be matched by public health accountability. The use of new antibiotics must be safeguarded by regulations and practices that ensure rational use, to avoid repeating the mistakes we have made by overusing the old ones.

Another lack is efficient and affordable diagnostics with high sensitivity and specificity to distinguish bacterial from viral diseases, and to identify resistance patterns in bacteria. Such diagnostics would reduce inappropriate use of antibiotics and minimise the delays of treatment, thereby saving lives.

### **Moving to concerted action**

A fundamentally changed view of antibiotics is needed. They must be looked on as a common good, where individuals must be aware that their choice to use an antibiotic will affect the possibility of effectively treating bacterial infections in other people. All antibiotic use, appropriate or not, "uses up" some of the effectiveness of that antibiotic, diminishing our ability to use it in the future.<sup>38</sup> ReAct—Action on Antibiotic Resistance believes that for current and future generations to have access to effective prevention and treatment of bacterial infections as part of their right to health, all of us need to act now. The window of opportunity is rapidly closing.

#### **Summary points**

- Antibiotics are a prerequisite for many of the advanced technologies in today's healthcare
- Although antibacterial resistance is growing, development of new antibiotics has declined
- A new paradigm in which antibiotics are considered as a non-renewable resource is needed
- The know-do gap in control of bacterial resistance to antibiotics must be tackled on international, national, and individual levels

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