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This week's poll asks: "Are the dangers of antibiotic resistance exaggerated?" Cast your vote on bmj.com
Editorial: Improving antimicrobial stewardship and surveillance: the Chennai Declaration (*BMJ* 2013;346:f591)
Research: Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care (*BMJ* 2012;344:d8173)

Antimicrobial resistance: the true cost

Richard Smith and **Joanna Coast** argue that current estimates of the cost of antibiotic resistance are misleading and may result in inadequate investment in tackling the problem

Almost as soon as antibiotics were discovered, we knew that bacteria were able to develop resistance to them.[1] This is not necessarily a problem, as long as there are other antimicrobials to take their place. During the latter half of the 20th century this was the predominant situation, but no longer.[2] A rapid decrease in the number of new drugs approved and numerous withdrawals on quality and safety grounds have left the well dry, and it is clear that "the existing classes of antibiotics are probably the best we will ever have."[3]

In light of this, there have been efforts to support interventions that encourage the more conservative and appropriate use of antibiotics in a bid to halt or slow the progress of resistance.[4] However, this action is often too little and may be too late.

Given that the dangers of resistance are widely acknowledged, why isn't more being done? One reason is that antibiotic resistance has fallen victim to evidence based policy making, which prioritises health problems by economic burden and cost effectiveness of interventions.[5] Health economists have been unable to show that antibiotic resistance costs enough to be a health priority.

Limitations of health economic research

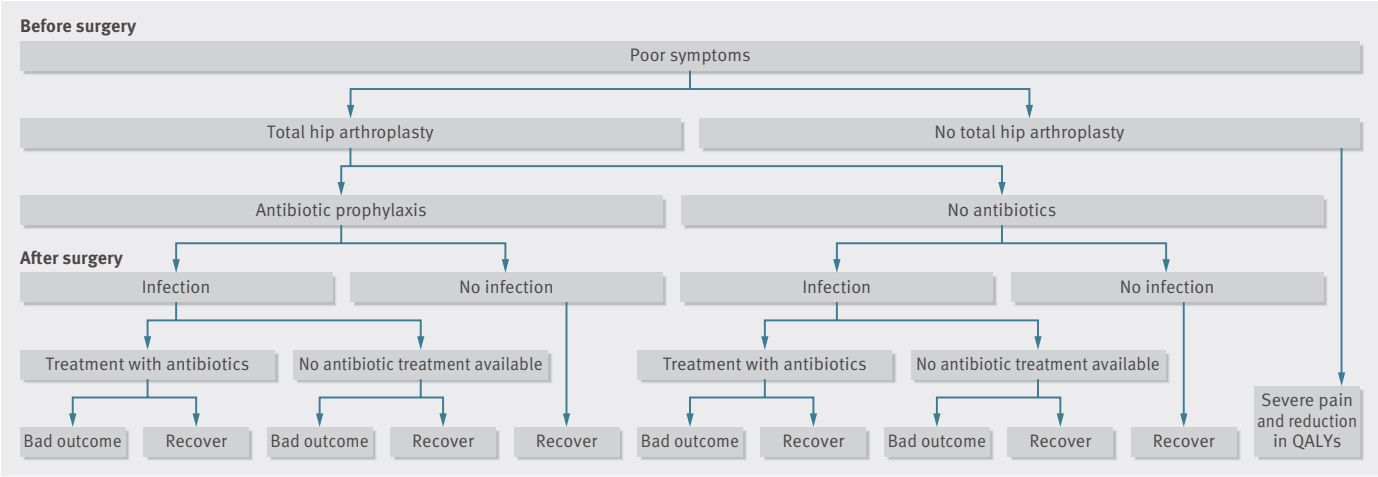
Ten years ago we published a systematic review on the economics of resistance.[6] We asked two questions: what is the cost of resistance and what is the cost effectiveness of interventions to reduce it? The lack of research meant we could investigate only the second question.[7] And even here we concluded that the evidence for the cost effectiveness of interventions for resistance was poor.

We have just performed a rapid review at the Department of Health's request to take into account newer information on the first question. The box summarises our methods and further details are available in the full report.[8] Estimates of additional cost varied from less than $5 (£3; €4) to more than $55 000 per patient episode. This might be explained by type of resistance and how productivity losses are dealt with.

Although there was little intrinsically wrong with these papers, we became concerned that their estimates of the actual economic impact may not be accurate because the research used to produce these estimates is limited in its scope. For example, economic estimates are based on the incremental costs and focus on a specific infectious disease or set of diseases: estimates are based on the cost of extra treatment of a resistant infection compared with susceptible infection, such as costs of additional investigations, more expensive drugs, side effects from extra treatments, longer hospital stay, and greater mortality.[9] Some may also include costs associated with surveillance and activities associated with trying to control resistance. Most studies were from the United States and based

KEY MESSAGES

- An increase in resistant organisms coupled with a big fall in the number of new antimicrobial drugs suggests an apocalyptic scenario may be looming
- Current estimates suggest antimicrobial resistance has a low economic impact
- Such estimates do not take into account that antimicrobials are integral to modern healthcare
- We may not ever be able to make an accurate forecast of the costs
- We should view greater investment in antibiotic resistance as an insurance policy



Care pathway for total hip arthroplasty with and without antimicrobials

in hospitals and included the costs related to additional hospital stay and treatment but not early mortality.

None of the studies considered the bigger picture—a world in which there are no effective antibiotics for situations where they are currently used routinely, such as in hip replacement or cancer patients. Our concern is that today's limited estimates will be used to project future costs. Will the current worst case scenario place antibiotics high enough up on the health agenda to ensure adequate action?

Current worst case scenario is still an underestimate

We took the study that found the highest cost of antimicrobial resistance, of $55bn ($20bn in health service costs and $35bn in lost productivity) per year overall to the US, and compared it with economic burden figures for other health problems in the US. These burden figures are taken from a variety of studies, and the dates range considerably, but it is clear that resistance rates fairly low down (table).

However, the costs of resistance could be much higher than these estimates suggest. As an example we estimated the consequences of having no antibiotics for patients having a total hip replacement. Because antibiotics have been used as prophylaxis and treatment for hospital acquired infection since hip replacements were first performed we looked at information relating to limb amputation as a proxy for what infection rates might have been with and without antimicrobials.

The figure shows the care pathway for patients requiring hip replacement. Currently, prophylaxis is standard practice, and infection rates are about 0.5-2%, so most patients recover without infection, and those who get an infection have it successfully treated. We estimate that without antimicrobials, the rate of postoperative infection is 40-50% and about 30% of those with an infection will die.[w14-w17] Thus, removal of antibiotics would increase postoperative infection by 1-50% and deaths by 0-30%. Of course, at such rates it is likely that the rates of hip replacement would fall, which would increase the burden of morbidity from hip pain.

We recognise that this is a simplistic analysis, with many of the data obtained from literature relating to amputation as a proxy for hip replacement. However, we use it as an example to illustrate and provoke, to emphasise the point that infection rates and their consequences in terms of health service costs and human health may be unimaginable. As we struggle to imagine the clinical consequences, it is easy to see why the economic burden is at present inestimable.

A world without antibiotics

Modern healthcare was built over the past century on the basis that infections can be prevented or treated using antimicrobials (exemplified by the US surgeon general famously proclaiming in 1968 that "the war against diseases has been won").[10]

Resistance is said to present a risk that we will fall back into the pre-antibiotic era.[11] However, this is perhaps optimistic. Our health system is now designed to treat more chronic conditions. Healthcare has become increasingly technological and invasive, improving mortality and morbidity significantly, and antimicrobials have become integrated in many aspects of such care. For example, antimicrobials are given as standard to prevent iatrogenic infection in surgical care,[11] to women

Annual cost of illness for selected conditions in US

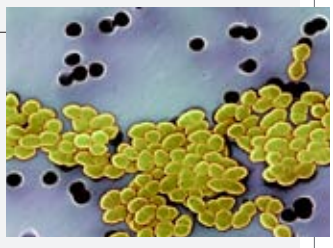
Health problem	Societal cost ($bn, 2004)
Cardiovascular disease[w1]	380
Musculoskeletal conditions[w2]	300
Motor vehicle accidents[w3]	270
Occupational injury and illness[w4]	266
Mental disorders[w5]	260
Substance abuse[w6]	195
Cancer (all)[w7]	185
Diabetes[w8]	145
Alzheimer's disease[w9]	70
Antimicrobial resistance[w10]	55
Skin disease[w11]	48
Urinary incontinence[w12]	23
Asthma[w13]	16

Box 1 | Methods used in the review[8]

We searched for the combinations of terms relating to resistance, antimicrobial and costs. Some papers did not refer to antimicrobial resistance generally but only to particular drugs or micro-organisms. We extended the search terms to focus on meticillin resistant *Staphylococcus aureus* and vancomycin resistant enterococci, two of the most studied and potentially serious current resistant infections.

We included English language studies (empirical or modelling) with data on costs associated with resistance, since 2000. For empirical studies, we selected studies that included a control group with a susceptible infection because the aim was to focus on costs of resistance, rather than costs of infection.

Data extracted included: study design; sample size/modelling approach; relevant micro-organism and drug; cost perspective, year, currency, time frame, discounting approach; resource use included; valuation methods; summary of results. We identified 192 possible papers, from which 24 were eventually included in our analyses.



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Vancomycin resistant enterococci

delivering by caesarean section,[12] and to those having cancer treatment.[13] From cradle to grave, antimicrobials have become pivotal in safeguarding the overall health of human societies.

When viewed in this broader way, the costs of resistance are not limited to those associated with additional treatment for a primary infection , such as a "strep throat." Rather, they must encompass the costs that might relate to the loss of modern healthcare. In the same way that health systems need adequate and effective health workers to function, they also require effective antimicrobials. Resistance is not just an infectious disease issue; it is a surgical issue, a cancer issue, a health system issue.

To calculate the true economic burden of resistance we therefore have to consider the burden associated with not having any effective antimicrobial drugs. And, as witnessed when there are outbreaks of hospital acquired infection, the system can very quickly come to a standstill.[14] In the future we may need to rethink how the health system is developed—for instance, redesigning many facilities or reintroducing sanatoriums if effective antibiotic treatments are no longer available.

Planning for an uncertain future

Although we now have more empirical information on the economic burden of resistance than was available a decade ago, it is unlikely to help us plan for the future. Even the highest current estimates of the costs of resistance provide false reassurance and this may mean that inadequate attention and resources are devoted to resolving the problem. Our illustrative example for hip replacement without antibiotics shows how difficult it is to forecast the likely economic burden of resistance. And we have explained how resistance has the potential to undermine modern health systems.

Full health systems analyses seem a more appropriate means to assess the potential impact of resistance and evaluate measures to stem it. Although this approach is complex, understanding the threat to the health system overall, not just for specific diseases, could be the single most important step in better understanding the economic burden that resistance presents. Analysing outbreaks of resistant infections and the cost of disruption to the healthcare system may help produce future estimates.[15]

A change in culture and action is needed to plan for a future with more antibiotic resistance. Considerable inertia remains regarding radical change in our stewardship of antimicrobials, precisely because there is a focus on current economic burden. The same is true with climate change and, to a degree, the financial system. A major driver of this inertia is likely to be collective uncertainty about the clinical and financial implications of increasing resistance. But there is a tried and trusted way to deal with such uncertainty—insurance. Waiting for the burden to become substantial before taking action may mean waiting until it is too late. Rather than see expenditure on antimicrobial policies as a cost, we should think of it as an insurance policy against a catastrophe; albeit one which we hope will never happen.[9]

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BMJ BLOG **Elizabeth Loder**

How can journals help stop disease mongering?

How can medical journals address their role in selling sickness and disease mongering? I suggested two possible strategies at the 2013 Selling Sickness conference held in Washington last month.

First, why not quarantine apparently groundbreaking studies about new treatments or interventions in a special journal until the findings are replicated and long term consequences explored? Print copies of the journal would arrive in plain brown wrappers that, undone, would show the journal's cover logo of a skull and crossbones. During quarantine, any news stories or summaries of research from this journal would travel with a sternly worded disclaimer, along the lines of those that accompany investment company advertisements. Something like the following would do nicely:

"Warning! Taking any action on the basis of this research could result in injury or death. The results described in this study have not been replicated and the long term effects of this treatment are unknown. Past performance is no guarantee of future results. When subjected to further investigation, most published research findings turn out to be false."

To fill the void, medical journals deprived of these sensational research studies could instead devote themselves to the promotion and prioritisation of the less glamorous medical research that really matters: replication studies, comparative effectiveness trials, and long term pharmacosurveillance and safety studies.

My second suggestion was that several parts of a typical research paper are too important to be written by the researchers or anyone else with a vested interest in the outcome of the research. These include the portions where "spin" is mostly likely to enter into the paper—namely, the title, abstract, results, and conclusion sections, and any summary or "what this study adds" statements that authors are now sometimes asked to supply. These portions of research papers should instead be written by disinterested parties with subject matter expertise.

I have no illusion that these things will come to pass, but I can dream, can't I?

Elizabeth Loder is US research editor, *BMJ*

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