

NewStatesman



Antimicrobial drug resistance

The end of modern medicine?

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Plagued progress

Modern antimicrobial medicines have transformed our lives. No longer does injury, infection or disease spell automatic death. Drugs that terminate or inhibit the growth of harmful micro-organisms have facilitated surgery, disinfection and the treatment of devastating bacteria, parasites and viruses.

But these “miracle drugs” have not come without side effects. Their widespread availability and general low cost has caused resistant microbes to proliferate. Medicines that once saved lives are now inert. The scientific community is in agreement that without immediate, co-ordinated action to stem resistance, these

bugs will get the better of us.

This follow-up report to a recent round table, hosted by the *New Statesman* in partnership with the Wellcome Trust, captures the themes that emerged from an impassioned debate on the role of politicians, scientists, business and public in addressing this crisis before it's too late. |

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What next, when the drugs won't work?

The government has made progress on the urgent crisis of antimicrobial resistance, but sustained public pressure is still needed, says **Zac Goldsmith**

On accepting his part of the Nobel Prize for the discovery and isolation of penicillin, Alexander Fleming warned: "There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." From the moment these miracle drugs became available, there has never been any doubt about the link between misuse of antibiotics and resistance to them. But despite that, we have spectacularly failed to heed Fleming's warning, and as a consequence we now face the prospect of losing modern medicine as we know it.

Dame Sally Davies, chief medical officer for England, has described an "apocalyptic scenario". She has warned of a return within 20 years to a "19th-century environment", in which routine operations carry a deadly risk. The World Health Organisation has said that we are hurtling towards a "post-antibiotic era".

In 2006 there were just five cases where patients failed to respond to even so-called last-resort antibiotics, but last year that number was 600. Clearly we must hope new antibiotics are developed, but there is no escaping that the principal cause of this crisis is our industrial-scale misuse of the antibiotics we already have. Even in this age of irresponsibility, it is hard to imagine anything more reckless.

Now that the medical establishment has sounded the alarm, you'd expect this, perhaps the greatest single threat to our health, to top the political agenda and dominate the tabloid news. If only.

In fairness, the Department of Health has issued stronger guidance to GPs and hospitals. But very little is being done to limit misuse of antibiotics in agriculture.

In many nations globally, the use of antibiotics for animals exceeds the amount used for human medicine. A 2012 report produced by the Soil Association suggests that the overall use of antibiotics per animal on UK farms increased by 18 per cent between 2000 and 2010. The problem is even worse in the US, where non-government studies have estimated that upwards of 70 per cent of antibiotics are used on farms.

At the same time, we are fast losing our traditional antibiotics to resistance: penicillin for staphylococcal wound infections, ampicillin for infections of the urinary tract and ciprofloxacin for treating gonorrhoea. We are increasingly having to use reserve antibiotics and, worryingly, seeing the spread of resistance to them as well.

You'd expect the greatest health threat to top the political agenda. If only

The link between misuse and resistance is not disputed, and so we have to ask why emergency action isn't being taken. There is no philosophical or ideological reason why any of the mainstream parties should be reluctant to engage. After all, the solutions involve responsible use of what drugs we have, and the promotion of science.

So why aren't the newspapers hounding ministers for action? Why aren't MPs being bombarded by angry letters? In short, what makes this crisis different, and less important to policymakers than the Aids crisis of the 1980s, which successfully galvanised drug companies and the authorities?

One answer perhaps is that there is less focus – there is no single infection to

fight, no single drug to be found. But more significant, I believe, is the influence of vested interests. If intensive farms have grown dependent on antibiotics, then their removal would require significant changes. Not surprisingly, the resistance put up by agribusiness lobby groups is immense, and I believe that explains a lack of urgency in the Department for Environment, Food and Rural Affairs (Defra).

It would be wrong to suggest there has been no progress. Last year I initiated a debate in parliament on the matter and, in response, a UK health minister told me: "Routine prophylactic use of antibiotics in both humans and animals is not acceptable practice. I am writing to Defra to ensure that existing veterinary guidance makes that very clear."

Then last year, the Cabinet Office confirmed it would look at resistance as a national security issue. The government subsequently announced a "Five-Year Antimicrobial Resistance Strategy", which was published by the Department of Health and Defra. The Prime Minister has also openly described the issue as "an extremely serious problem".

However, we still lag far behind many other countries in terms of concrete steps. The Netherlands, for instance, has endorsed a 50 per cent reduction in livestock antibiotic sales from 2009 levels by 2014.

The bottom line is that governments here and elsewhere must prioritise human health over short-term vested interests, and that, I believe, will be achieved only with sustained and intense public pressure. That will happen, but we must hope it does so before a crisis sets in. |

Zac Goldsmith is the MP for Richmond Park (Conservative)

The greatest public health threat of our time

A world without antimicrobials would be a world without modern medicine, so why is there not more urgency in addressing the global rise of drug resistance? *The New Statesman* brought leading health experts together to discuss the problem. By **Charlotte Simmonds**

Introduction

Imagine a world without antibiotics: hip replacements, cancer therapies, C-sections and most routine surgery would no longer be possible without greatly increased risks. A visit to hospital would become rife with danger. Hundreds of thousands of people would die of diseases such as tuberculosis, pneumonia and gonorrhoea that we once, perhaps arrogantly, thought we had beaten.

This nightmare is not as far off as you might think. Already, bacteria and parasites are developing resistance to front-line antimicrobials that are overprescribed and under-regulated. Each year about 25,000 people in Europe die of infections that doctors were unable to treat with the drugs available to them. That's about the same number as die in road-traffic accidents. In south-east Asia the situation is even worse: every five minutes a child dies as a result of a drug-resistant bug.

The threat of antimicrobial resistance is on a major scale, opening us up to the possibility of global pandemics and undermining the foundations of modern medicine. We are running out of antimicrobial drugs, and we are not developing enough new ones.

This is the greatest public health threat of our time, but as things stand there is a limited

sense of urgency. Dame Sally Davies, the chief medical officer for England, has shown commendable leadership in highlighting the issue, but antimicrobial resistance can't be addressed by any single country. The problem is global. In an increasingly interconnected world, an infection that emerges in Delhi today will have an impact in London tomorrow.

We can do more on a scientific level to develop new antibiotics and improve diagnostics, but science alone will not solve the problem. We need a greater political will to affect policy, we need to incentivise the pharmaceutical industry to develop new antimicrobials, and we need to look at social and behavioural issues to tackle the misuse of those drugs we do have. A commitment by the agricultural industry, which uses the majority of all antibiotics in many countries worldwide, is also key.

We need global leadership to tackle antimicrobial resistance; current institutions, which were set up in the 1940s, are not fit for purpose. Waiting until children and young people in the western world are dying of the same diseases as the Victorians is a mistake we can't afford to make. ●

Dr Jeremy Farrar is the director of the Wellcome Trust

peak of more than 2,000. Hot spots of antimalarial-resistant parasites are springing up in south-east Asia, and cases of extreme drug-resistant tuberculosis (TB) in South Africa and other parts of the African continent are among the many examples that illustrate the urgent nature of this health problem.

In order to assess the causes of and possible solutions to antimicrobial resistance, the *New Statesman*, in partnership with the Wellcome Trust, gathered leading figures from science, pharmacology, politics and agriculture for a round-table discussion. Delegates were tasked with assessing the UK's position in antimicrobial strategy domestically and internationally; how to improve development pathways for drugs; how to incentivise political and public engagement; and the role of the agricultural industry and wider governance structures in curtailing antibiotic misuse.

The issues at hand are ones that span human beings, animals and the environment, said Dame Sally Davies, chief medical officer for England, in her opening remarks. She made note of the British government's Five-Year Antimicrobial Resistance Strategy, led by the Department of Health under the One Health Agenda. However, there is still far to go.

"This is the start of a journey," she said. "We have a beefed-up government strategy and the National Health Service is starting to take things seriously. But in the UK thousands die annually of drug-resistant septicaemia. One child every five minutes dies in south-east Asia as a result of an antibiotic-resistant infection. Worldwide, this is having a massive impact on health, mobility and happiness for people and their families."

The discovery during the course of the 20th century of antimicrobial drugs, a class of medicines that includes antivirals, antimalarials and antibiotics such as penicillin, is among the greatest medical breakthroughs of our time.

Yet according to the World Health Organisation the reality of a "post-antibiotic era", in which even the most minor infections caused by bacteria could spell death, is fast becoming a possibility. Experts agree that misuse, overprescription and

poor diagnostics have driven an environment that favours the proliferation of resistant strains of bacteria, rendering once-vital medicines obsolete.

The "honeymoon period" in recent decades, of cheaply available, widely effective antimicrobial compounds, has driven a rise in resistance levels across the globe. For example, deaths in England and Wales related to MRSA, a bacterial infection resistant to a number of popular antibiotics, rose steadily from 1993 onwards to a 2007



Putting up resistance: delegates agreed on the need for better diagnostics, more accessible data and stronger leadership in order to fight back

Picking up on Davies's comments, Jeremy Farrar, director of the Wellcome Trust, emphasised that the scale of the problem was "global in every way".

"This is geographically global in that it harms all of us," he said. "It is also global in the sense that there is a pressing need to talk about regulation and the way we mitigate drug resistance worldwide. It is global in its scope of impact; the long-term consequences will stretch across medicine. Surgery would be impossible, as would oncology [cancer treatments]. Even childbirth would become a risk."

While Farrar said that there was a "pressing need" to discuss regulation and surveillance of antimicrobial usage, he stressed that the spectrum for solutions must be more wide-ranging. "We cannot pretend surveillance alone will solve the problem," he said.

"Unless we take in all the social drivers of drug resistance – including human and animal health, and the economic incentives for governments and industry to invest in doing something – then we won't address this properly."

For Professor Christopher Whitty, chief scientific adviser and director of research with the Department for International Development (DfID), it was important to bear in mind that this "global scale" mustn't overlook critical country differences. "In the developed world, infections

"The impact would stretch across surgery, cancer and even childbirth"

in the elderly are repeatedly treated with antibiotics, while in the developing world they are used for a different set of people, such as children and pregnant women. Restricting antibiotic use in poor countries, where access to health care is extremely limited, is a very difficult tension. There is a danger of turning a global issue into 'one problem' when in fact it's a series of problems in varying populations. That means different drivers and different drugs."

Another of these "drivers" is poor diagnostic techniques, many around the table

agreed. An inability to identify a patient's infection quickly and cost-effectively, or indeed whether antimicrobials are needed at all, is a root cause of "blanket" drug usage around the world.

To Sir John Savill, chief executive of the Medical Research Council (MRC), the issue of poor diagnostics was as prevalent in the UK as anywhere in the developing world. "Even in the very best hospitals here we rely on techniques for the diagnosis of bacterial infections that [Robert] Koch and [Louis] Pasteur would recognise," he said, referring to the two giants of early germ theory. "We are a high-resource country with 19th-century diagnostics; elsewhere in the world the capacity to diagnose is even more limited."

Nicholas White, professor of tropical medicine at Mahidol and Oxford Universities, was more optimistic, saying progress had been made in the past few years and that soon there could be "an hour's turnaround" in the identification of microbial-resistant genes: "Ninety per cent of the variants in TB treatment can now be explained by known resistant genes. If we +

➔ can make these techniques quick, affordable and applicable in other areas than I think there is a real possibility for hope.” As Dr Paul Cosford, medical director for Public Health England, summarised it, the conversation on diagnostics was all about getting “the right antibiotics to the right people at the right time”.

While improved diagnostics increase the effectiveness of antimicrobials already in use, the need to develop more sophisticated drugs that can keep pace with the dynamic evolution of resistance is critical. A new, distinct class of antibiotics has not been discovered since 1987.

For Davies, the lack of investment in health-care research is connected to the dwindling of industry, and results in a “bare pipeline” for new drugs. “I think we’re pussyfooting around the issue,” she asserted. “We’ve lost microbiology in hospitals, we’ve lost clinical microbiologists, and funding from the NIHR [National Institute for Health Research] isn’t much. The lack of pull from the health services has signalled that this issue doesn’t matter, and industry has deinvested. [Yet] we know that if you put more money in, then the better brains come.”

The consensus around the table was that if new drugs are to be brought through the pipeline, pharmaceutical companies must be part of the equation. Yet the number of companies engaged in significant antimicrobial research has declined. Moreover, the structure of antibiotic usage needs to shift from blanket distribution to more bespoke, patient-specific drugs with a limited range. Taking all of this into account, where is the economic incentive for pharma to foot the bill?

With senior research and development figures from AstraZeneca and GlaxoSmithKline (GSK) present at the table, discussion on this topic was lengthy. Patrick Vallance, president of pharmaceutical R&D at GSK, stated plainly that from a business perspective, pharmaceuticals are wary of funding a “billion-pound pill” with limited scope for use afterwards.

“The number of companies engaged in this kind of research has fallen since the 1980s to just a handful,” he said. “Today, the right thing for society is to use new drugs in an extremely restricted way, but that’s a horrible economic model. Nor can we introduce a targeted antimicrobial and sell it for the price of a cancer drug, because you’re entering a market where people are

used to getting antibiotics for peanuts. It’s simply impossible.”

Manos Perros, who serves as the global head of infection and site head of AstraZeneca’s R&D facility in Boston, agreed wholeheartedly with Vallance. “Pharmas and biotechs are all businesses,” he said, “and the way to engage with business is to provide incentives.”

Many of the incentive hold-ups, he said, lay in the fact that the old drugs still worked. “Much of the plan across pharma is traditional antibiotics,” he said. “This year there will probably be three new MRSA project groups, but we are going to reserve them because well-known drugs still work, and if one of them doesn’t there is always a back-up that will.”

Vallance backed Perros on this, noting that the incentive is twofold. First, there is a need to reduce the cost of making drugs and holding clinical trials. Second, we need to delink R&D payoff from bulk sales.

“Quicker, more affordable diagnostics offer a possibility for real hope”

On the first point, reducing the cost of clinical trials requires mixing “investment in the basic antimicrobial science” with introducing novel, more flexible clinical trial projects of the sort being advanced by the Innovative Medicines Initiative (IMI) across Europe.

Referring to the R&D question, Vallance said that refocusing attention away from large-scale distribution could be achieved using a model similar to the one applied to vaccines, in which the pre-purchasing of new antimicrobial drugs for a set number of years is agreed at late clinical stage. “Pre-purchase agreements would mean that the health-care system becomes responsible for things like proper usage and surveillance, and would put a stop to the perverse commercial incentives,” he said. “It worked for vaccines, and it could work for antimicrobials.”

While rousing support from the pharmaceutical industry will no doubt form an elemental part of long-term strategy, it was also time to start talking about how to create incentives for engagement with an even wider stakeholder group – the public.

Delegates agreed that, generally, public apathy toward the risk of a post-antibiotic

era remained high, and that this bled into other areas of society, including the media and government, where rallying around the issue was perceived to be lacklustre. Tom Feilden, a science correspondent for the BBC’s *Today* programme, revealed that newsroom editors were “a bit bored by the story” and said that the scientific community needed to give them something new to report. “I think it’s beholden on people like me to win the argument within newsroom discussions and say that we should be talking about this more,” he said. “But it also reflects a sentiment from the public; that they’ve heard all this before. There is a willingness to report, but we need something new to say.”

The picture isn’t all bleak. The very week this report went to press, the public voted to focus the new £10m Longitude Prize on antibiotics. The money will go to whoever can develop a rapid bacterial infection diagnosis test within five years. Many at the round table had mentioned the prize as a promising opportunity, but agreed that a continued lack of solutions lay at the root of apathy. As Professor Ian Boyd, the UK government’s chief scientific adviser on food and environment, put it: “I think there’s a commonality with a lot of environmental issues I have to deal with. The public don’t want to be continually bombarded with bad news if we aren’t going to give answers. That means getting more sophisticated in our messaging – we need to show the public how we are marching towards a larger objective.”

At this point, the conversation turned to a natural comparison with the HIV/Aids crisis of the 1980s and the “convergence of forces”, as Farrar put it, which eventually put Aids at the top of the health agenda.

“Why haven’t we got that same level of attention in relation to antimicrobial resistance?” Cosford asked. “One factor that influenced the Aids crisis was the absolute sense of public urgency on the issue.”

Vallance offered further insight, reiterating the importance of strong diagnostics and the availability of clinical trials. “It was possible to tackle HIV in a relatively short period of time because the virus was relatively well understood.

“Patients could be diagnosed with accuracy, and there was a great willingness in the coalition of clinical investigators to do clinical trials. Plus [when it came to drug development], there was an economic return at the end of it.”

For Professor Jackie Hunter, chief executive of the Biotechnology and Biological Sciences Research Council (BBSRC), it was important to remember that the science base alone didn't solve everything. "We cannot forget the vociferous public lobbying that took place in the US and made the issue political. That's where we've got to go. We're deluding ourselves if we think investing in basic research is going to solve this quickly. It isn't."

Hunter also stressed that making firm, clear data on the issue more widely available is essential to prompting both public and political action. "We need to get much better at having the basic facts," she said. "There's plenty of data out there, but there has got to be a better way of articulating it."

White wholly agreed, and added that this data must disseminate the quality, quantity and the global pathways of antimicrobial drugs in use: "You cannot go on to Google right now and find out exactly how much doxycycline or erythromycin is being manufactured in China, or what the pathways are for that drug. Nor can you find the pathways for the vast quantities of veterinary antimicrobials. These are incredibly vulnerable situations – we don't treat these drugs like radioactive material, but they are that dangerous. So why can't we find out about them? If there's one simple thing that would help politicians it would be high-quality, real-time, easily digestible information."

Despite the consensus on the need to survey and regulate antimicrobial usage, adhering to such measures is easier said than done. As Mark Woolhouse, professor of infectious disease epidemiology at the University of Edinburgh reminded the group, an EU-wide ban on the use of antibiotics as growth promoters in animal feed, an effort to curtail the spread of resistance, has been in effect since 2006. "It was probably the single biggest effort to reduce antimicrobial usage," he said, "and it's failed. Completely. There is no net reduction in antimicrobial controls across Europe – just a few pockets where drug use is going down matched by other pockets where it's going up."

Woolhouse concluded that if blanket bans made no impact, it was time to look at "alternatives". "We need to find other ways to produce animals that are healthy, that have high standards of welfare and are productive."



Davies called for discussion at Ungass 2016

Zac Goldsmith MP, the sole politician at the table, said that the UK's Department for Food, Environment and Rural Affairs (Defra), and its worldwide equivalents, were held back by the interests of agricultural lobbyists, whose voices were often heard by government above those of clinicians and scientists. "If there was a debate in parliament on this issue next week I wouldn't hear from the scientific base, but I would hear from business," he said. "Unfortunately, I think that's led to a perversion of policy."

Boyd, who advises Defra, countered that it "takes this issue very seriously", but warned that antimicrobials could not be eradicated quickly. "You cannot expect

“Public lobbying made the Aids crisis political. That's what we need”

to ban them overnight without dangerous outcomes. We have to make sure we put in proportionate measures.”

Representing the lobby perspective, Catherine McLaughlin – adviser on animal health and welfare policy to the National Farmers' Union – offered to correct some of the “outdated” misperceptions of the agricultural industry. She said that the sector is actively seeking fact-based solutions and is happy to work with governments on the issue.

“A good lobbyist doesn't spin facts,” she continued. “While the Danish ‘yellow card’ system [which alerts the government when producers purchase over their set limits of antibiotics] restricts usage, we are also starting to see more post-slaughter

evidence of disease. So the debate is complicated, and one of the most unfortunate things is that it has also become polarised. We spend too much time blaming one sector for the problems.”

In an effort to pursue the discussion down the route of solutions, Mike Barrett, the chair of the round table, who is also a professor of parasitology at the University of Glasgow, raised a recent proposal put forward jointly by Farrar and Woolhouse in *Nature* magazine: it called for the creation of an organisation similar to the Inter-governmental Panel on Climate Change to “marshal evidence” and “catalyse policy” on antimicrobials.

Did others think a cross-governmental action group was needed?

“Leadership isn't strong enough within our current structures,” said Farrar, clarifying his argument. “Such bodies, I believe, are timid in the way that they approach this issue. Is the WHO fit for purpose to deliver change at the scale and in the multidimensional way that is required? As we've seen, this issue is not only about human health but animal health, regulation and ensuring that industry links up in a positive way.”

Davies welcomed the proposal, but stated that the form was “not quite right yet”. She advocated, first, a dedicated day at the UN General Assembly in 2016. “At the end of such a day we would indeed need to reach some form of international treaty,” she said. “The question isn't *should* we have something, but rather what would it look like?”

“We must remember that it will be subject to international negotiations and that we cannot impose anything. We must also be very careful not to become the north doing it to the south.”

A concluding current of the conversation was that of “consortiums” and the desire to link academia, pharma and science to maximise what each could offer. The UK has ready expertise in the science base, many participants agreed; now is the time to bring the moving pieces together.

“We have world-class chemists, fantastic biologists and synthetic biologists, environmental researchers and economists,” Savill said. “But are enough of them engaged in this issue? No. We need to move on from centres of excellence towards networks of excellence.” |

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