Antimicrobial resistance: are we doing enough?

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UK government initiatives and new research seek to tackle the problem of antimicrobial resistance, but are these strategies enough to have an impact on this looming global catastrophe?

The thunderous, foreboding music and swirling mists of a Hollywood movie trailer seem the perfect frame for the world’s fast-accelerating collision course with the “antibiotic apocalypse”. The Chief Medical Officer, Dame Professor Sally Davies, is unlikely to appear as an Arnold Schwarzenegger Terminator-style figure but her dire warnings are anything but movie taglines.

The public statements are doom-laden but the danger is clear and present: an estimated 10 million deaths globally every year by 2050 and a cost of £66 trillion in lost productivity to the global economy.1 The overprescribing of antibiotics for minor ailments, principally in primary care, their widespread use in agriculture and the lack of new therapies from the pharmaceutical industry – no new class of antibiotics have been discovered since the 1980s – are neutering the impact of a class of drugs once hailed a ‘miracle’.

A postantibiotic era?

A report by the WHO in 20142 was blunt: “Antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, co-ordinated action, the world is heading towards a postantibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill.”

The sobering prediction is that superbugs could kill more people than cancer by 2050 and the final report of Lord Jim O’Neill’s Review on Antimicrobial Resistance, which is due in May, is unlikely to make pleasant reading.

Ten countries have already recorded the failure of third-generation cephalosporins, the drugs of last resort, for gonorrhoea, according to a report from the WHO.2 Resistance of common intestinal
bacteria to carbapenem antibiotics is spreading around the world, drug-resistant tuberculosis now affects 630,000 people and drug effectiveness is declining for serious diseases like malaria, HIV and flu, it added.

Another report published by Public Health England last November crystallised concern: antibiotic-resistant infections are rising, with the rate of of E. coli and Klebsiella pneumoniae bloodstream infections up by 13.5 per cent and 17.2 per cent, respectively, from 2010 to 2014. A 6.5 per cent rise in overall consumption of antibiotics through GP surgeries was recorded between 2011 and 2014, although the number of prescriptions is falling, it added.

Globally, the overuse of antibiotics is profligate—some national health schemes even incentivise prescription in inappropriate settings—and a worst-case estimate from NICE recently suggested that 10 million of the 42 million antibiotic prescriptions doled out in the UK each year are needless. There is a broad acceptance that prescribing habits must change and infection prevention and control—everything from antimicrobial stewardship (see Table 1) to hand decontamination—needs to be a priority, as outlined in the 2014 NICE quality standard.

The role of GPs

Dame Sally has just promised written warnings every year to GPs who are in the top 20 per cent of antibiotic prescribing rates in their areas, after a pilot study showed the scheme to be successful at reducing the number of prescriptions. In the UK, 74 per cent of antibiotics are prescribed by GPs—18 per cent in hospital settings—who are often cast conveniently in the ‘baddy’ role; prescribing with gusto, oblivious to the consequences. But the full picture, and therefore any solution, is multifaceted. Curbing alleged GP “excess” (see Table 2 for a summary of antibiotic consumption in general practice) will not work unless it is woven into a global approach that encourages industry to develop new therapies, removes incentives for prescribing in some countries and checks the use of antibiotics as a “mass medication” in farming.

Alongside the raft of restrictions and controls, there needs to be a huge behaviour change from the UK public who see antibiotics as a right, a panacea for everything from the cold to cancer, and a social justification that their GP visit was necessary. NICE is currently piecing together a campaign aimed at jolting the public into a more realistic acceptance that antibiotics do nothing to cure common viruses and that being denied them is a sign of medical expertise not negligence.

Its last guidance, in September, warned of the rise of antimicrobial resistance, with Professor Gillian Leng, deputy chief executive and health and social care director at NICE, stating: “The overuse of antibiotics in the last 30 years has led to microbial resistance, and with so few new antibiotics being developed, this could result in once-treatable infections becoming fatal in years to come.”

The public campaign needs to be a blockbuster says Dr Tim Ballard, vice chair of the Royal College of General Practitioners (RCGP), who believes it should match the AIDS awareness push of the 1980s, if it is to resonate with the public and make a difference. “At the moment there is a misalignment of the message coming from the top of the medical establishment—Dame Sally ranking it up there with climate change as a global danger—and what the system is doing to support GPs and help the public understand the role of antibiotics in minor illness.

“The majority of antibiotic prescribing on the NHS happens in general practice, where there are 370 million patient con...
tacts a year, so we do have a huge role
to play but it is not just down to GPs and
we all have to work together to get the
message out. We need to address patient
expectation – some believe that not get-
ting antibiotics is somehow about cost
controls and GPs denying them treatment,
which couldn’t be further from the truth.”

Pressure to prescribe
GPs, of course, shouldn’t crumble in the
face of pushy patients, but Dr Ballard
emphasises that growing surgery lists and
diminishing resources have created a fer-
tile landscape for antibiotic prescription.
“If I see someone with a bacterial infection
where antibiotics have a high probability
of working then it is a quick consultation
with an effective treatment and people are
grateful,” he adds. “It takes a lot longer to
explain why antibiotics are not appropri-
ate and might even make them more ill.
The layers of pressure on top of this are
lack of time and the impact of a complaint
from someone who feels they have been
denied a treatment. It involves costs and
a huge amount of stress for GPs who are
already overstressed.”

A study by the British Journal of
General Practice last year found that anti-
biotic prescribing volume was a signifi-
cant factor in patients’ satisfaction with
their GP and that a 25 per cent reduction
of antibiotics would lead to lower patient
d scores and a drop of three to six centile
points in national satisfaction ranking.8
Its conclusion was: “Patients were less
satisfied in practices with frugal antibi-
otic prescribing. A cautious approach to
antibiotic prescription is somehow about cost
controls and GPs denying them treatment,
which couldn’t be further from the truth.”

The position of the 18,000 locum
GPs across the UK is a prime area for consider-
ation. They take 80 million appointments annually and work in an average of 30 different surgeries a year with an estimated 50 per cent of GPs in London being locums, according to the National Association of Sessional GPs (NASGPs). “Research has shown that GP locums are the most profes-
sionally isolated section of the NHS workforce. In GP practice, the norm is for locums to use a generic computer log-in so nobody has a clue who wrote that pre-
scription,” says Dr Richard Fieldhouse,
NASGP chairman and a locum doctor on
the south coast for 20 years.

He is part of a group of 100 locums
working across 800 practices in the
south who arrange their posts via a
barristers’ chambers-style process with
managers insisting each has a named
log-in when they arrive at a surgery. “As a
locum it is so easy to have this collusion
of anonymity. You can be an anonymous
prescriber and you can prescribe atro-
ciously, but if you are very exposed you
are going to prescribe carefully,” adds Dr
Fieldhouse.

Easy access
Tightening up on procedure will help
but there is a global aspect out of GPs’
control. Dr Fieldhouse recently treated a
patient with a UTI and, on the advice of
a consultant microbiologist, prescribed a
powerful third-line antibiotic that is rarely
used. “The consultant almost whispered
that it was one they were holding back
and could only be used on a named-
patient basis,” he says. “I told the patient
and she produced the antibiotic from her
handbag, saying she had bought it over
the counter at a chemist’s in Spain.
“This is a problem that needs the Prime Minister, President Obama and heads of state to get on top of it. I cannot understand why the government appears to be making GPs scapegoats for this. It is really quite sinister and undermines GPs.”

Sourcing antibiotics over the internet without a consultation is simple. Research by Prescriber found a range of drugs ready to be shipped with either no questions asked or a rudimentary online questionnaire. The proposition from one internet pharmacy is obvious from its tagline “Pills online without prescription”. It observes: “The world is running out of antibiotics and we can help”. It supplies a full “no prescription required” range of drugs with worldwide shipping for 60 x 500mg tetracycline tablets, which are used to treat urinary tract and sexually transmitted infections, at £28.44 and 30 x 500mg cephalexin tablets, used for conditions such as upper respiratory tract infections and ear infections, with the promise that the pills will “arrive in discreet unmarked parcels”. The service is one of many with supplies – real and counterfeit – criss-crossing the globe daily.

That such a pure scientific discovery could descend into a wild west frontier of medicine in under 90 years can be viewed as a betrayal of Sir Alexander Fleming’s discovery of penicillin in his laboratory at St Mary’s Hospital, in 1928. It was a dark time, when pneumococcal pneumonia had a mortality rate approaching 85 per cent and almost 90 per cent of children with bacterial meningitis died. He won a Nobel Prize, alongside Oxford University’s Howard Florey and Ernst Chain, who took antibiotics to the therapeutic mainstream, but even back then he warned about the potential danger from overexposing patients to treatments.

It was a concern drowned out by the astonishing advantages antibiotics provided when they came into widespread use in the 1940s and were hailed for their role in treating the 40,000 troops injured in the D-Day Normandy Invasion in 1944. But association with the symbolism of winning a war was misplaced as bacteria mutate and evolve, changing their genetic coding to ensure they survive antibiotic attack; an attribute they pass on freely, by transferring genetic material in a process known as conjugation.

Agricultural use
As medicine basked in the glory of taming the scourge, the surviving bacteria limped away, rebuilt their defences and have gradually gathered strength to fight again. This resurgence has become supercharged by the dissolving national borders that have encouraged population movement and trade without geographic boundaries. Intensive farming is now a norm with refrigerated produce consumed across the other side of the world.

Farm animals account for almost 66 per cent of all antibiotics used in 26 European countries and more than 50 per cent worldwide, according to the
Alliance to Save Our Antibiotics (ASOA), a pressure group dedicated to reducing their agricultural use. Antimicrobial resistance built up in animals is transmitted to humans by a number of pathways (see Figure 1) with strains of Salmonella, E. coli and Campylobacter now resistant to antibiotics that once rendered them harmless, ASOA states. Its figures record that agricultural antibiotic use in the UK rose from 384 tonnes in 2008 to 420 tonnes in 2013. ASOA wants to see the end of the mass medication of healthy animals as a purely prophylactic measure and is targeting a 50 per cent reduction in farming antibiotics by 2020, rising to 80 per cent by 2025.

“Around 90 per cent of antibiotic use in farming is mass medication, particularly common in pig and poultry sectors where animals are farmed intensively,” says Emma Rose, its campaigns manager. “It contributes to E. coli, Salmonella and Campylobacter outbreaks and the link between animals and humans has been acknowledged by experts all over the world.”

An important step to reduce farming use was taken by the European Parliament environment committee last month with a 60-2 vote in favour of restrictions. But the case must go through the agriculture committee before reaching a binding council vote. Hope is also rising from efforts by the Medical Research Council (MRC), which is partnering with the Department of Health and the Department for Environment, Food and Rural Affairs to form an “AMR War Cabinet” to explore innovative ways to combat institutionalised antibiotic prescribing routines.

**A global issue**

“Antimicrobial resistance is a huge and complex problem that spans agriculture, the interplay between animals and people, and the environment, which is why it needs a multipronged approach,” says Dr Jonathan Pearce, head of infections and immunity for the MRC, which is investing £30 million into a project to identify bacterial resistance routes and to promote diagnostic tools to help sharpen prescription practice. “Antibiotics are absolutely critical for prophylactic use in Caesarean sections, chemotherapy and transplant surgery, among many things. If we lose the ability to fight bacteria, it is not just a cold that’s going to get you, it is the lack of ability to intervene in many other areas of healthcare that will be a problem.

“Antimicrobial resistance is responsible for 25,000 deaths in Europe and 700,000 worldwide so, unless we get on top of this issue, it could outstrip cancer as the major killer. A century ago, 25 per cent of deaths were due to bacterial infection and we do not want to go back to those days. We are dealing with a global environment where resistance in one place can, and will, travel. Galvanising effort across the globe is important and the UK has taken a leading role, working with partners in China and India. Using our knowledge and expertise to help them will benefit us in the long term.”

The MRC underscores the need for a “one-world” approach by revealing some private clinics in Malaysia are financially rewarded for prescribing antibiotics to women with menstrual pain and that, in China, a large proportion of hospital revenue is derived from drug sales. India has only just made a declaration that second to fourth-line antibiotics for tuberculosis can only be given with a prescription, ending a dangerous free-for-all.

The research war chest is growing with a €24 million EU fund linking academia and industry, while the Newton and Fleming funds are also cranking up the antimicrobial resistance fight, says Dr Pearce. “It is not impossible to fight this,” he adds. “We have some strong opportunities and can bring together expertise, research and behavioural designs to look at the reactions between doctor and patients in clinic.”

He points to the Antimicrobial Resistance Collaborative at Imperial College NHS Trust in London, led by Professor Alison Holmes, which has developed a decision-support app that provides patient information and infection data along with current and historical local patterns. At St George’s Hospital in London, another tech device is being developed to pinpoint strains of gonorrhoea in 30 minutes so that an appropriate antibiotic can be administered, rather than a broad-spectrum antibiotic, while waiting for traditional test results to return. “I don’t think there is one knock-out blow, so success will be about gains from many angles. Antimicrobial stewardship of what we have now and what emerges will always be critical,” he remarks.

**New hope**

The pipeline from the pharmaceutical industry may not be as dry as feared and a collaboration between Allergan and AstraZeneca, announced in January, to develop and commercialise ATM-AVI, an investigational, fixed-dose antibiotic combining aztreonam and avibactam to treat serious infections, offers hope. The two companies are also part of the Biomedical Advanced Research and Development Authority, established to develop a portfolio of drug candidates over the next five years. “The rate of antibiotic resistance continues to increase worldwide, representing a truly global threat that requires collaboration and sustained commitment from industry and government to develop solutions,” says David Nicholson, executive vice president, global brands research and development, Allergan.

More than 80 leading international companies and professional bodies signed a Declaration on Combating Antimicrobial Resistance at the World Economic Forum in Davos, Switzerland in January, calling for government support for drug and diagnostics development. New pricing models should also be introduced to incentivise pharmaceutical companies to develop antibiotics, as the current volume-based structure restricts their potential earnings, says Professor Jane Lawrence, chief scientist at the Royal Pharmaceutical Society. “We should be very worried and something needs to be done soon because, in some parts of the world, we now have bacteria resistant to common drugs,” she says. “People may have heard talk of this before but we must be clear that this is not a scare. Each and every one of us can play a part in antimicrobial stewardship, making sure we have good hygiene and effective hand washing and that patients don’t automatically ask for antibiotics so doctors feel less pressurised.”
Advanced scientific approaches such as new vaccines, administering infection-fighting white blood cells and bacteriophages that land a destructive payload virus into a bacteria are as vital as the more mechanical aspects of building awareness and changing habits, she points out. Professor Lawrence adds: “We are never going to win the war because bacteria are smart and evolve. But we have to stay ahead and we have to work together.” It is a view echoed by Dr Pearce: “I don’t think any of us want to go back to an era where 25 per cent of us die younger from infectious diseases,” he says. “Bacteria naturally evolve against what we do, so will this ever be finished? No. Should we be vigilant? Yes. Is it hopeless? Absolutely not.”

References

Declaration of interests
See http://www.mjauk.org/author/bucklandd/

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POEMS

DECAF score provides accurate prognosis for patients with acute exacerbation of COPD

Clinical question:
Does the DECAF score accurately predict mortality in hospitalised patients with an acute exacerbation of COPD?

Bottom line:
The cleverly named Dyspnoea, Eosinopenia, Consolidation, Acidemia and atrial Fibrillation (DECAF) score accurately identifies patients with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) as being at low, moderate, or high risk of mortality. The DECAF score can serve as a check on a physician’s judgment about a patient and can help identify which patients may be safe for discharge and which patients may require closer monitoring or intensive care. (LOE = 1b)

Reference:

Study design: Decision rule (validation).


Synopsis:
The DECAF score was developed to predict mortality in hospitalised patients with AECOPD. In this study, the authors attempted to validate this score both internally in the two hospitals where the DECAF score was originally developed (n=880 patients), and externally in four additional hospitals (n=845 patients). Eligible patients had an AECOPD, were 35 years or older, with at least 10 pack-years of tobacco use and evidence of airflow obstruction on admission. Dyspnoea was assigned 1 point if too breathless to leave the house unassisted but not needing assistance with washing or dressing, 2 points if assistance was needed with washing or dressing, and 0 points if not too breathless to leave the house. All of the other factors received 1 point if present and none if absent. Eosinopenia was defined as less than 0.05×10⁹ per litre, consol-