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**'Cast back into the Dark Ages of Medicine'?
The Challenge of Antimicrobial Resistance**

Cormac Ó Gráda, University College Dublin

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‘CAST BACK INTO THE DARK AGES OF MEDICINE’?
THE CHALLENGE OF ANTIMICROBIAL RESISTANCE ¹

Cormac Ó Gráda

University College Dublin and CAGE, University of Warwick

ABSTRACT

Antimicrobial resistance (AMR) is currently the focus of much media attention and policy discussion. A historical perspective on AMR suggests that although the challenge of AMR is real, the doomsday tone of most commentary is unwarranted. That is partly because most of the gains in life expectancy now deemed under threat preceded the antibiotics revolution. A combination of public health measures, rising living standards, and new medical knowledge all played their part in this. Even if AMR increases, the continuing effect of these factors and of new public health measures can limit the negative consequences. Moreover, recent developments suggest that the supply pipeline of new drugs is not quite as dry as usually claimed. The problem for now is not MRSA or malaria but carbapenem-resistant gram-negative bacteria, which pose an urgent threat and on which public funding for research on effective new therapies should concentrate.

Keywords: infectious disease, health, antimicrobial resistance, economic history

JEL codes: I, N

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1. Introduction

Today people in high-income countries can expect to live about twice as long as their forebears a century ago. This huge increase in life expectancy is due in large part to the eradication or near-eradication of a whole range of potentially fatal infectious diseases. In the UK c. 1900 one such disease, tuberculosis, was responsible for one death in ten; it cut short the lives of Emily Brontë (1848, aged 30), Aubrey Beardsley (1898, aged 26), D. H. Lawrence (1930, aged 45), George Orwell (1950, aged 46), and myriad others. Measles, scarlet fever, diphtheria, and whooping cough accounted for another 6.5 per cent of British deaths, and diarrhoea and typhus carried off another 5 per cent.² Today those diseases kill virtually no one in high-income countries.

The share of all deaths in England and Wales due to infectious diseases dropped from nearly half in 1850 to one-third in 1900, whereas today they account for about 7 per cent, mainly elderly people succumbing to pneumonia or acute bronchitis. In high-income countries like the UK most of us can expect to succumb, not to infectious diseases, but to cancer, heart disease, and other non-contagious causes and illnesses.³

Low-income countries, where infectious diseases still account for nearly half of all deaths, still have a long way to go. But they have been doing better too. Take Niger, perhaps the poorest place in the world today⁴, where the share of infectious diseases has dropped from 68 to 50 per cent between 2000 and 2012; or neighbouring Mali, where the drop was from 48 to 37 per cent.⁵ Indeed, life expectancy today even in the poorest of low-income countries is higher than anywhere before the revolutions in public health and medical technology that followed the work of Louis Pasteur (1822-95) and his rival Robert Koch (1843-1910) (Table 1).

[Table 1 about here]

In demographic terms, these gains are unprecedented. And not only do we live longer: the quality of life has risen in tandem with the quantity of life. In terms of human wellbeing, as discussed below, the gains are enormous. What if those gains were lost in part due to increasing antimicrobial resistance (AMR), i.e. the ability of microorganisms to resist the antimicrobial agent once capable of killing or inhibiting the growth of these self same microbes? The question is by no means a new one, but in the last few years it has taken on a new urgency, with the World Health Organisation warning of ‘a post-antibiotic era, in which many common infections will no longer have a cure and, once again, kill unabated’⁶ and, closer to home, the UK’s Chief Medical Officer, Dame Sally Davies, recently cautioning of the danger of ‘finding ourselves in a health system not dissimilar to the early 19th century at some point’.

There is no denying that resistance to several key antimicrobial drugs is increasing. Although Methicillin-Resistant *Staphylococcus aureus* (MRSA), a hospital acquired infection, has hogged the headlines, more and more microbes are becoming resistant to more and more antibiotics. The greatest worry now is the spread of carbapenem-resistant *Enterobacteriaceae* (CREs) such as *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., and *Acinetobacter baumannii*. Those are the pathogens; an added worry is enzymes such as New Delhi metallo-beta-lactamase (NDM) that confer resistance to carbapenems.⁷ Initially the concern was that bacteria were acquiring resistance to antibiotics, but other pathogenic microbes such as viruses, protozoa, and fungi are also developing resistance to the compounds being used to treat them, reducing the therapeutic options available to the medical

professionals. But does this justify Prime Minister David Cameron's claiming last July that AMR could 'cast the world back into the dark ages of medicine'?⁸ Could infectious diseases again assume the sinister role they played in the past?

2. *What History Says*

History and economics have an important part to play in telling us how far we have come and how much we risk losing. Let us begin with two key historical points. First, most of the gains in life expectancy due to the eradication of infectious diseases preceded the antibiotic revolution linked to sulfa drugs, penicillin, and streptomycin by centuries. The story begins with the disappearance of plague, which in England is usually dated back to 1665. The first attack of plague in the mid-fourteenth century cut England's population by half, and subsequent epidemics kept numbers down for a century or more. Then gradually the ravages of the Black Death diminished. Nevertheless, between the 1560s and the 1660s it was responsible for about one death in every five in London. Why did it then disappear? We are still not quite sure, but Paul Slack's case for effective quarantining, both at home and further afield, is the most persuasive.⁹

We know more about smallpox, which preventive medicine in the form of variolation (introduced to the west by Lady Mary Montagu in the early eighteenth century) and vaccination (Edward Jenner, 1798), reduced from being the single biggest killer in eighteenth-century Britain to a minor cause of death by the mid-nineteenth century.

And one could continue at some length describing Britain's victories over a litany of infectious diseases—cholera, typhoid fever, measles, diphtheria, and

tuberculosis—all due to a combination of public action (particularly in the provision of clean water and better sewage disposal), better living conditions, and preventive medicine (see Figure 3). This was all in an era before any antibiotics.

Second, the gains in life expectancy in the pre-antibiotics era far outweighed those that followed. This is important: although hailed as wonder drugs, the direct impact of antimicrobial technologies on historical trends in mortality was surprisingly slight. In England infectious diseases were already under control to a great extent by 1940 using methods that prevented transmission or increased resistance (rather than *cured* infections, as antibiotics do).

[Table 2 about here]

In Britain, public health measures such as isolation and improved sanitation were mainly responsible for the victories over cholera and typhoid fever. These older methods of disease control were further enhanced in the second half of the twentieth century by new vaccines against a range of infectious diseases (Table 2). Vaccines alone were responsible for the eradication of poliomyelitis and the near-eradication of measles. The BCG vaccine against tuberculosis was developed in the 1920s, but only brought into routine use in Britain in 1953. BCG immunisation was discontinued in Britain in 2005 but remains routine across most of the globe¹⁰, and has been reintroduced in high-risk areas of London, with a shift in the very recent past towards universal BCG immunisation for infants.¹¹

In sum, history tells us that many factors contributed to reducing the mortality from infectious diseases in developed countries, including better sanitation, better nutrition and vaccination strategies. Therefore losing several antibiotics all of a

sudden would not hurl us back into the medical dark ages; nor would it force us all the way back to the mid-twentieth century, when the age of antibiotics began. That is because factors which helped reduce infectious disease before antibiotics—medical, institutional, and economic—are likely to be much more powerful now than they were then.

But this is not to deny that the *huge dependence* of many modern medical technologies on prophylactic or curative antibiotics for their success. Before c. 1950 surgery remained a dangerous procedure, despite significant developments in sterile procedures and wound treatment. Many of the gains in survival from heart disease and cancers in the last half-century depended and continue to depend on surgical interventions that would have involved substantial risk before the advent of penicillin. Chemotherapy also relies on antibiotics in the event of opportunistic infections, as does organ transplant technology. Hip and knee joint replacements, of which there are now about 160,000 annually in the UK, would become much riskier without antibiotics and blood anticoagulants. Today infection rates are very low, and the infections can be successfully treated. But without antibiotics, they would be much higher and a significant proportion of those infected would not survive.¹² Given the odds presumably many, if not most sufferers would be forced to live with the pain.

2.1. The Global Surge in Life Expectancy Since c. 1950

While the health gap between rich and poor nations remains very wide, it has narrowed considerably over the last century, as has the gap in life expectancies (Figure 1).¹³ Figure 2 compares trends in the log values of income per head and life expectancy at birth (a common proxy for a community's health) in India, representing low-income

countries, and Sweden, representing high-income countries, since 1900. Note that while the proportionate gap in income per head is wider now than a century ago, the gap in life expectancy has narrowed significantly. That narrowing of the health gap has been mainly due to the radical reduction in India of deaths from famine, bubonic plague and smallpox.¹⁴ This narrowing also explains why measures of human wellbeing that incorporate health imply less inequality than those relying on income alone.

In developing countries the process of infectious disease control, so drawn out in England, was compressed into the twentieth century and enormously accelerated by the availability of medical and public health technologies. Unfortunately we have relatively little insight into mortality trends in most countries before the 1950s at the earliest. However, it is clear from the very rapid rates of population growth already evident by the mid-twentieth century that there must have been significant falls in mortality before 1950.

Mortality declines from the mid-twentieth century (when the U.N. began to publish systematic country-level data) are much better documented. Gains were particularly rapid almost everywhere in the 1950s and 1960s. Several factors played a role, including improved food supplies, the spread of immunisation programmes especially against smallpox, typhoid and yellow fever, control of plague, improved sanitation, and the advent of DDT in insect control. Rising educational levels and changes in the status of women also mattered.¹⁵ The result was a rapid increase in life expectancy globally, and a sharp convergence in life expectancies¹⁶ (Figure 2).

[Figures 1, 2 about here]

In low-income countries, however, lower respiratory infections (especially pneumonia) and acute diarrhoeal infections are still leading causes of death. Deaths from these diseases were substantially reduced in affluent populations well before antibiotics. Their persistence in poorer populations indicates both poor nutritional status and living conditions and the incomplete penetration of antibiotics to treat them, despite the relatively high and increasing per capita consumption of antibiotics in many developing countries. The contribution of antimicrobial drugs is most evident in the success of anti-malarial treatments and more recently anti-retroviral therapy (ART) in reducing HIV transmission and mortality. By the end of 2013, thanks to a combination of competition, technological progress, and activism, 13 million people, mostly in Africa, were receiving ART at a fraction of its original cost in the 1990s¹⁷. But the persistent importance of diseases eminently treatable by antibiotics indicates the continuing scope for better-targeted access to antibiotics, especially in reducing child mortality.

3. Welfare Implications

A proper understanding of the likely costs of AMR underlines the need to find a solution to it. Two recent estimates by RAND and KPMG offer bleak scenarios in terms of future mortality and GDP, proposing estimates of the global impact of AMR in terms of GDP foregone in 2050.¹⁸ Here I focus instead on what history can tell us about the welfare implications of increasing AMR.

Because GDP does not take account of how we value our health, economists have proposed several alternative measures. The best known of them, the Human

Development Index (HDI), includes health (proxied by life expectancy) as one of three elements contributing to ‘human development’; the others are income and education. Since 2010 the measure, which owes its origin to a request to Amartya Sen to produce a measure of human wellbeing that ‘captures in one number an extremely complex story’¹⁹, has been estimated as the geometric mean of measures of income, education, and health relative to a maximum. Its theoretical underpinnings have often been criticized²⁰ but it has endured, and has been invoked, sometimes in modified form, by economic historians²¹ as an improvement on GDP per capita.²²

[Table 3 about here]

Table 3 compares estimates of British HDI and real GDP per capita in 1870, 1913, 1950, and 2013. While GDP per capita grew more than six-fold between 1870 and 2013, HDI moved proportionally much closer to its ‘maximum’ value of 1. What is most noteworthy is that the contribution of health, as proxied by life expectancy, to the rise in HDI dwarfed that of literacy and income between 1870 and 1950, while GDP per capita contributed most thereafter. In other words, most of the gains preceded the antibiotics revolution. Another point worth noting is that Britain’s HDI value in 1870 would place it well behind, say, Ghana or Zambia today.²³

A second widely used measure of the welfare gains to increased life expectancy is the value of a statistical life (VSL), or what an individual is prepared to pay to save a life. This value is measured indirectly, through surveys or through observing how people insure themselves against being killed. The approach was developed initially with high-income contexts in mind; the application of estimates of VSL in high-income countries to much poorer countries, perhaps in an earlier era, entails an

assumption about which income elasticity to use, i.e. what is the proportionate change in VSL resulting from a change in income.²⁴ A meta-meta-analysis based mainly on studies in advanced economies by Doucouliagos *et al.* (2014) finds that the elasticity, η , is ‘clearly and robustly inelastic’. There is a presumption that η falls as countries get richer, however, and the higher η , the more poor economies discount VSL. Estimates of welfare gains are quite sensitive to the elasticity used.²⁵

Below I report ‘first cut’ estimates of the welfare gains from eradicating plague in London, smallpox in England, and malaria in India and China using the VSL approach, and more careful estimates of the welfare losses ensuing from bacteria becoming resistant to anti-tuberculosis drugs.²⁶

3.1. *Plague in London and Smallpox in England*

London’s (and England’s) last plague epidemic was in 1665; in the space of a few months it was responsible for the deaths of about one hundred thousand people, or one-fifth of the city’s population. Between 1560 and 1665 plague was responsible for about 15 per cent of all London deaths (Slack 1985; Cummins, Kelly, and Ó Gráda 2014).

What were the welfare gains for London of the disappearance of plague? The VSL methodology offers one way of answering this question. The population of London in 1666 was about 0.5 million. Before the plague’s disappearance a crude death rate of 30-32 per thousand implies that epidemics were responsible for an average of 2,500 deaths annually over the previous century. Let us suppose output per head in London was 50 per cent higher than the English average, so about \$1,300²⁷, versus \$30,490 for the U.S. in 2010. Assuming a U.S. VSL of \$9 million yields a VSL of

about \$380,000 for London c. 1665 when $\eta=1$. The gain as a percentage of London's GDP was $[(2,500)*380,000]*100/(1,300*500,000)$, or over 140 per cent of London's GDP. Naturally this huge percentage leaves out of account other economic and demographic impacts of the plague's disappearance. Assuming an elasticity of $\eta=1.2$ would yield 76 per cent, $\eta=1.4$ a still whopping 41 per cent.

Already endemic in Europe by the sixteenth century, smallpox was a deadly scourge in the seventeenth and eighteenth centuries. Assuming, conservatively, that it was responsible for 5 per cent of deaths in England before inoculation became widespread would mean that it killed about 7,500 people annually. A first-cut estimate of VSL c. 1700²⁸ for $\eta=1$ yields an estimated welfare gain of 39 per cent of GDP; assuming $\eta=1.4$ returns still significant 12 per cent.

3.2. *Malaria in India and China: A Case Study*

Samuel Pepys contracted it; Oliver Cromwell died of it; and Daniel Defoe described the fate of 'young lasses from the hilly country' who on moving into the marshes of Kent and East Anglia to marry 'presently changed their complexion, got an ague or two, and seldom held it above half a year, or a year at most' before succumbing. It is not *that* long ago since malaria—'ague' or 'marsh fever'—was endemic in those parts of England, so much so that their infant mortality rates rivalled those of London.²⁹ Those with no immunity, like Defoe's 'lasses', were particularly at risk. A combination of drainage and an increase in the livestock population, increased immunity, and improving nutrition reduced the mosquito population in the fens and the prevalence of ague, but it took quinine to rid England of fatal cases.³⁰

During the 1950s India's National Malaria Eradication Programme reduced the

number of deaths from malaria by nearly half. Between independence (1947) and 1965 the number of deaths fell from 0.8 million to virtually zero. In other words, malaria killed far more people in India in 1947 than it kills worldwide today. How did the benefits from virtually eliminating deaths from malaria compare to the eradication of smallpox in England? Skipping the arithmetic, the welfare gain from eliminating 0.8 million deaths from malaria as a percentage of GDP for $\eta=1$ was 47 per cent of GDP.

Malaria killed even more people in China than in India in the early 1950s. But beginning in the early 1950s the Chinese authorities employed a series of preventive measures—filling water holes, draining marshes, sprays and bed nets, barefoot doctors—with the result that by 1990 the disease was virtually eliminated. The same calculation applied to China with $\eta=1$ yields a welfare gain of 56 per cent of 1950 GDP.

The rough-and-ready character of these estimates of the welfare gains from eradicating malaria is clear. In particular, the choice of $\eta=1$ is controversial: choosing $\eta=1.2$ instead of $\eta=1$ would reduce the estimated welfare gains from eradicating malaria from India in the 1950s from 47 per cent to a still significant 26 per cent of GDP. Rough as they are, these estimates still point to the significance of the welfare gains associated with four well-known historical examples (Table 4).

[Table 4 about here]

3.2. A Closer Look at Tuberculosis

As noted earlier, tuberculosis was once *the* major killer disease in England. Although mortality from TB began to decline long before the arrival of an effective antibiotic remedy, it took a combination of antibiotics and BCG to eliminate it (Figure 3). TB remains a major killer in low-income countries today, and as multidrug

resistant tuberculosis (MDR-TB) becomes more commonplace some of the welfare gains associated with its eradication in high-income populations such as the UK will be lost unless an alternative remedy is found.

[Figure 3 about here]

How much? Kerry Hickson (2014) has produced upper and lower bounds of the loss for the UK. The former puts a value on the gains from the reductions in TB between 1950 and 2000. Note that this excludes the big gains made in the era before antibiotics. Still, the number is big: \$35 billion. But it is very unlikely to be incurred, since not all the gains from eradicating the disease would be lost. For one thing, housing and nutrition—improvements in which reduced the incidence of TB before 1950—have greatly improved since then. Then BCG, which was introduced in 1953, offers a strong second line of defence against TB. BCG is totally effective with children and current estimates of its efficacy against respiratory tuberculosis (the main adult form) range from 50 to 78 per cent.³¹ Taking these factors into account reduces the upper bound estimate to a more realistic \$9 billion.

This represents a pertinent historical example for the wider issue of AMR. As in the case of MRSA (Methicillin-resistant *Staphylococcus aureus*), for many infections public health interventions, or less efficacious or safe second line antimicrobials, may mitigate the impact of AMR. The real worry is about the small number of cases where this may not be so.

Hickson's lower bound estimate involves comparing the current situation with the most likely MDR-TB scenarios, which allow for a higher morbidity burden only,

given that MDR-TB tends to be resolved in longer treatment times and not mortality. The estimated loss is calculated by applying a VSL function to the number of life years burdened with MDR-TB in 2013; this yields an estimate of \$1.9 billion.

Note that this refers only to the early (current) phase of AMR. However, the time-path of any particular resistant microorganism tends to have a sigmoid shape. It is virtually flat before resistance begins to appear, but then takes off with the rapid increase in the proportion of resistant organisms, before levelling off as the proportion of resistant strains has reached equilibrium. Worse case scenarios involve moving closer to the upper bound estimate of \$9 billion as the proportion of drug-resistant cases increases. The sigmoidal evolution of antimicrobial resistance also highlights the need for policy before the lag phase is complete.

4. Supply: the Pipeline

Economics is about supply and demand, but current strategies to combat AMR focus much more on supply—the pipeline—than on demand. Here I will focus on both in turn, beginning with supply.

Because the history of antibiotics is also a history of antibiotic resistance, maintaining a supply of replacement drugs is essential. Methicillin, developed by Beecham in 1959, followed penicillin in the 1960s as a treatment against *Staphylococcus aureus*, but the first case of MRSA was diagnosed within a few years (in 1968), and newer drugs replaced methicillin. Similarly, as streptomycin resistance in the treatment of tuberculosis became a problem from the late 1940s on, more effective antibiotics replaced streptomycin in the initial treatment of that disease.

Artemisinin, the product of a massive research effort on the part of the Chinese

in the late 1960s and 1970s, followed the increasingly malaria-resistant drug chloroquine. In 2014 Sanofi announced the delivery of its first batches of semi-synthetic artemisinin to African countries where malaria is endemic. But meanwhile in recent years artemisinin has been meeting some resistance in Southeast Asia. The same holds for tetracyclines, gentamicin, fluoroquinolones, and, very recently, daptomycin. So resistance is natural and inevitable: it becomes an issue only if the antimicrobial artillery is not being consistently updated. The more you use an antimicrobial agent the shorter its shelf life. Microbes adapt and evolve quickly and are quite promiscuous with genetic material that acquires resistance.

The problem—so we are repeatedly warned—is that the artillery has not been updated. Warnings like ‘Today’s dearth in the antibacterial research and development pipeline will take decades to reverse...’ or ‘The antibiotic pipeline problem may change the practice of medicine as we know it’ are commonplace.³² Why the supply of new antibiotics seemed ample to cope with resistant bacterial strains in the 1950s and 1960s, and then practically dried up between then and century’s end, is a bit of a mystery. Again and again, the answers given are [a] the sheer difficulty of developing new broad-spectrum antibiotics and [b] the lesser commercial appeal of drugs with specific targets (and therefore lower returns on investment). Zyvox (linezolid) created quite a fanfare when approved by the U.S. FDA in 2000, and it continues to be an effective treatment for Gram-positive bacteria resistant to several other antibiotics. But there is a pervasive impression today that the supply of new antimicrobials has virtually dried up in the new millennium.

This techno-pessimism, which is not new³³, is based on a sense that all the ‘easy’ discoveries have already been made, and that major pharmaceutical

corporations have lost interest because the rewards for generating new drugs are low. The major pharmaceutical companies blame ‘a range of scientific, regulatory, and financial factors’³⁴. Certainly, there is a tension between the WHO’s perception of the threat posed by AMR, on the one hand, and the lack of activity on the part of Big Pharma, on the other.

Economics is somewhat agnostic about the future of technological change in general. Some economists, like Tyler Cowen and Robert Gordon, hold that all the low hanging fruit has been plucked; others, like economic historian Joel Mokyr, invoke the past to paint a much more cheerful picture of future prospects. For Mokyr institutional blockages, not the lack of new knowledge, are the greatest barriers to continued technological progress in the struggles against bad bacteria and other areas of concern, such as global warming.³⁵ In support, remember that when the first antibiotics emerged, little was known about cellular and molecular genetics, bacteriology, or virology. Science has advanced by leaps and bounds since, which should make it easier to develop far more effective weapons against microbes.³⁶ And there are early signs of this. Linking the use of bacteriophages (or phages) as therapeutic agents to what is being learnt about CRISPR (clustered regularly interspaced short palindromic repeats) biology is a promising case in point; using CRISPR to create mosquitoes with a parasite-blocking gene in order to prevent malaria is another.³⁷ Mokyr also reminds us that the ICT revolution should prove a boon to future R&D, not least in medicine.³⁸

The public good character of finding solutions to AMR implies that market forces alone will not generate an adequate supply of the appropriate technologies. Public investment in the ‘blue sky’ research necessary to produce new remedies has

long acknowledged this. Such investment should target the universities that stand to gain little from their discoveries, and the smaller biotech companies who take the biggest risks but lack the funds to sustain the later phases of R&D.³⁹ Thus comparative advantage may explain the emerging pattern of larger pharmaceutical companies foregoing basic research but buying up successful smaller fry and backing likely winners, i.e. focusing on the 'D' in R&D.⁴⁰

A closer look at the supply of new antibiotics suggests that although the lack of new effective substitutes is worrisome, technology is not at a standstill. As of December 2014, the U.S. Food and Drugs Administration's register listed thirty-seven new antibiotic drugs under development.⁴¹ Some, to be sure, are bound to fail and some are only in the early stages of development. But if even half a dozen of these drugs succeed, they would go some way towards alleviating fears of some forms of AMR for a while. A brief review of where things stand in early 2015 is appropriate (Table 5).

Table 5 about here

4.1. MRSA

Not all antimicrobial-resistant bugs are equally serious, nor is their pecking order unchanging over time. In Britain, for example, the threats posed by MRSA and *C. diff.* have decreased markedly in recent years: The number of *C. diff.* related deaths in England and Wales fell from 8,324 to 1,646 between 2007 and 2012, and over the same period the number of death notices mentioning MRSA or *Staph. aureus* plummeted from 3,645 to 849. Meanwhile the US Center for Disease Control considers the threat posed by MRSA today to be 'serious' rather than 'urgent', a

category it reserves for CRGNBs, *C. diff.*, and *Neisseria gonorrhoeae*.⁴² The credit for reducing the threat from MRSA goes to factors described below.

At the same time, drugs such as vancomycin, daptomycin, and linezolid are still pretty effective against *Staph. aureus*, and it is also simply incorrect to say that the pipeline for new drugs targeting *Staph. aureus* is dry. I am not referring here to the unpleasant ninth-century concoction ('garlic and onions or leeks as well as wine and the bile from a cow's stomach... boiled in a brass vessel, then strained and left for nine days') recently recreated by scientists at the University of Nottingham.⁴³ In 2014 the FDA approved three new drugs targeting *S. aureus* under the 2012 Generating Antibiotic Incentives Now (GAIN) Act. The first two were developed by relatively small biotech companies (Cubist Pharmaceuticals and Durata), which were acquired by bigger fish—MSD and Actavis, respectively—in the wake of FDA approval. The third, Orbactiv, has a longer history. Originally developed by Eli Lilly, it failed to gain FDA approval in 2008. In 2009 it was acquired by The Medicines Company, which carried out further trials and whose application to the FDA was successful. In January 2015 the European Medicines Agency (EMA) also granted market authorization for Orbactiv and Sivextro.

The race between these new drugs is now on. For what such numbers are worth, market analysts predict sales of \$204 million for Dalvance, of \$309 million for Orbactiv, and of \$216 million for Sivextro by 2020.⁴⁴ A fourth new antibiotic Zerbaxa also won FDA approval in 2014, although it does not claim efficacy against *S. aureus*. Four new approvals targeting AMR in a year compares favourably with five in the previous decade.

There has been much more hype about Teixobactin, a new antibiotic which has proven effective in mice against both *Staph. aureus* and *Mycobacterium tuberculosis*. The outcome of a public-private partnership between academic researchers and a privately owned biotech company based in Cambridge, Mass., and described as ‘the first new class of antibiotics to be discovered in 30 years’, Teixobactin claims to be resistant to resistance. But it has some way to go, clinical trials on humans being a few years away.⁴⁵

4.2. Malaria

The estimated number of deaths from malaria worldwide dropped from 875,000 in 2002 to 584,000 in 2013. In 2002 malaria still accounted for 1.8 per cent of all deaths worldwide; a decade later the percentage had fallen to 1 per cent.⁴⁶ Antimicrobial agents claim some of the credit for this, but now there are signs in parts of Southeast Asia of parasite resistance to the main antimicrobial treatment, artemisinin, when used as a stand-alone drug against one type of parasite (*Plasmodium falciparum*). So far, WHO data reveal no significant increase in reported deaths in any of the five countries at risk, but their data should be regarded as part of what is in effect an early warning system.⁴⁷

Here too there are some hopeful signs on the supply front. In July 2014 Novartis described as ‘encouraging’ the results of phase II trials on their anti-malarial drug KAE 609, which rapidly cleared patients in Thailand of the plasmodial parasites *P. falciparum* and *P. vivax*. Novartis are currently planning Phase IIb trials, which focus on the efficacy of particular dosage levels, for KAE609 and hope to have it on the market by 2018. In addition in April 2014 GKN announced Phase III plans for its anti-

malarial drug, tafenoquine, which, although designated a ‘breakthrough therapy’ by the FDA, has so far received no approval from any drug agency. Meanwhile, PATH and GlaxoSmithKline, with help from the Bill and Melinda Gates Foundation, have developed a rather promising vaccine for malaria (RTS,S), which should be ready for use before the end of 2015. While an imperfect substitute for antimicrobials, such a vaccine can help by reducing the demand for antibiotics.⁴⁸

4.3. *MDR-TB*

The supply-side outlook for MDR-TB is also mildly encouraging.⁴⁹ The FDA (in December 2012) and the European Commission (March 2014) have granted conditional approval to Sirturo (bedaquiline) as a treatment for MDR-TB in adult patients. This is the first TB drug to gain FDA approval since the 1960s. Approval is conditional because the drug is highly toxic, and so use is restricted to when there is no effective alternative. Research now focuses on reducing bedaquiline’s toxicity.⁵⁰

4.4. *CRGNB*

If the outlook on malaria and MRSA is mildly ‘encouraging’, the threat posed by the ‘nightmare’ carbapenem-resistant gram-negative bacteria (CRGNB) mentioned earlier, against which few therapeutic options exist, is indeed worrisome. Fosfomycin, tigecycline, polymyxin B, and colistin are the last-line-of-defense therapies against CRGNBs, but some bacteria are resistant to fosfomycin; polymyxin B has limited therapeutic scope; some carbapenem-resistant bacteria are also intrinsically resistant to colistin; and there have been reports recently of tigecycline-related and polymyxin B-related deaths.⁵¹ Where such infections are a threat, clearly early detection and rapid

screening are crucial.⁵² Down the road, carbapenem-resistant bacteria may require more drastic public health interventions.

The highly restrictive—and controversial⁵³—nature of the FDA’s approval for the drug Avycaz (ceftazidime-avibactam) in February 2015 is an indication of the gravity of the CRGNB problem. A recent useful appraisal by one industry insider concludes that while ‘novel drugs for bad bugs are emerging’ all ‘have some holes in their spectrums against MDR gram-negative pathogens’.⁵⁴ The dangers posed by CRGNBs suggest the need for a pipeline strategy that focuses not on resistance in general, but on where it presents the greatest threat (as with Ebola).

5. Demand Also Matters

Policy has a role to play in reducing the demand for antibiotics, but what may seem straightforward in principle is not so easy in practice.⁵⁵ Take, for example, the very large between-country and within-country variation in the consumption of antimicrobials. In 2013 antibiotics consumption per capita was three times as high in Belgium as in the Netherlands next door.⁵⁶ Reducing average consumption elsewhere in Europe to the Dutch level would cut the consumption of antibiotics on the continent by almost half. Reducing use in Ireland as a whole today to the rates found in the counties of Roscommon and Meath would cut aggregate consumption by two-fifths, while reducing U.S. consumption to levels found in the six lowest consuming states would cut the aggregate by over a quarter (Figure 4).⁵⁷

[Figure 4 about here]

A more intelligent approach towards antibiotics usage could thus increase the shelf life of individual treatments and thereby reduce the incidence of AMR. However, usage is also a function of hospital hygiene, which is more easily improved in some environments than in others. For example, between 2010 and 2014 the MRSA rate per thousand used bed days in two of Dublin's private hospitals, Vincent's and the Mater, was zero, while in the eponymous adjoining public hospitals the rate averaged 0.85 over the same period. The variation in resistance rates across Europe supports the presumption of a correlation between usage and AMR⁵⁸, but how much of this variation in consumption is due to socioeconomic context, and how much to human agency? Again, there are choices to be made between infection control policies. The trade-offs involved here require more statistical precision and contextualization—and publicity..⁵⁹

Forceful measures to curb the use of antimicrobials in agriculture would help too: ideally, one would like to see their use restricted to the treatment of infections. But such measures face opposition from pharmaceutical companies and from producers. Recently, Chief Medical Officer Dame Sally Davies singled out the US where four times as many antimicrobials are used on animals as on humans and where the authorities are content 'to work with industry' and to have veterinarians (hardly disinterested parties) supervise drug use, but this ignores the difficulty that the consumption of antibiotics by livestock in some European countries rivals that in the U.S., and also the role of China, where antimicrobial consumption in livestock production (23 per cent of the global total) currently far exceeds that in the US (13 per cent). Moreover, China's share is set to reach 30 per cent of a much higher aggregate by 2030.⁶⁰ This highlights both the need for and the difficulty of reaching a global

solution to a problem where vested interests loom large. An alternative or complementary solution—to genetically engineer livestock against infections—seems within reach. What is very controversial today may seem the only way out some years from now.⁶¹

Health education also has a role to play in reducing demand. A good example is the French public health campaign based on the slogan '*Les antibiotiques c'est pas automatique*', which, it is claimed, led to a reduction of over a quarter in the number of antibiotic prescriptions per head over a five-year period.⁶² Recent randomized control trials of the effect of reminders directed at outpatients in Stockholm and in Los Angeles both found that they had a substantial negative effect on usage. However, neither the drop in antibiotics consumption in France nor the improvement in hand hygiene in Belgium—focus of another campaign in the 2000s—proved lasting. In sum, there is something to be said for information campaigns, but if they are to be effective they cannot be once-off measures.⁶³

One more related thought: a recent US study⁶⁴ reveals that the likelihood of a clinician prescribing an antibiotic for an acute respiratory infection (ARI) increases significantly over the course of clinic sessions, implying that the temptation to prescribe inappropriately increases with decision fatigue (see Figure 5). This suggests the need for mandatory breaks and shorter sessions and for ways of nudging clinicians (as opposed to patients).

[Figure 5 about here]

Finally, other developments may also help to reduce demand for antibiotics. First, in institutional settings there is the prospect of technologies that will reduce the spread of multidrug resistant organisms: examples include more effective hand hygiene; antibiotic coatings that hinder the spread of bacteria or kill them; and the prevention of duodenoscope infections. Second, if personalized medicine ‘takes off’ it should be possible to specify which antibiotics are appropriate to any given person, and thereby reduce usage.⁶⁵ Third, a new study in *PLoS Biology* raises the intriguing possibility that alternating combination therapies may offer some respite against bacteria.⁶⁶ Fourth, the same goes for what the *New Yorker* dubbed the excrement experiment⁶⁷, i.e. treating *C. diff.* infections with faecal transplants or ‘crapsules’. Is it too much to hope that this relatively simple and apparently safe therapy can relieve what the U.S. Center for Disease Control categorizes ‘an urgent threat’?⁶⁸

[Table 6 about here]

6. Concluding Remarks

This lecture has sought to put our present concerns about AMR in economic historical perspective. It began by stressing the major welfare gains from reduced mortality due to infectious diseases, while at the same time giving due credit to public health reforms that preceded the widespread use of antibiotics. Warnings about antimicrobial resistance are not new: Alexander Fleming cautioned in his Nobel Lecture in 1945 that misuse would result in microbes becoming resistant.⁶⁹ Warnings reached a new level in the 1990s and a crescendo during the last few years. The dreadful prospect of an ‘antimicrobial apocalypse’ when, in the words of Dame Sally

Davies, ‘routine operations like hip replacements or organ transplants could be deadly because of the risk of infection’ has finally sunk in. But she was referring to MRSA, whereas the people most at risk today from AMR are not those requiring surgery but patients, especially elderly patients, at the mercy of carbapenem-resistant bacteria.

The war against microbes is a war against Darwinian evolution: the point is not to win it but to stay ahead. Is the situation regarding AMR more serious now than it was five or ten years ago? Despite the alarm bells, I would argue perhaps not, for several reasons. First, awareness of the problem is much greater. That explains the timing of institutional responses such as the GAIN Act⁷⁰, greatly increased U.S. federal funding⁷¹, the Harrison Prize, the UK Five Year Antimicrobial Resistance Strategy (with due focus on conservation and stewardship), and the joint research initiative announced by the UK Science Minister in July 2014 in the wake of the Prime Minister’s warnings. A really serious outbreak of some infectious disease would prompt a bigger response from governments. One has only to consider the example of Ebola where ‘trials, which would normally take years and decades, are being fast-tracked on a timescale of weeks and months’.⁷² Two years ago the prospect of an Ebola vaccine being developed seemed remote. Yet in late October 2014 the WHO announced plans to begin testing two experimental Ebola vaccines in areas at risk from Ebola by January 2015 and applying a blood serum treatment available for use in Liberia ‘within two weeks’⁷³. By March 2015 four promising vaccines had been developed. Increasing public awareness of the AMR problem is also beginning to constrain corporate behavior.⁷⁴

Second, the big reductions in MRSA resistance and in the number of deaths attributable to *Staph. aureus* and *C. diff.* in the UK over the past decade are evidence

of what can be done to arrest resistance in hospital settings at national level (Figure 4). Increased biosecurity and higher hygiene standards in health care settings and institutions can reduce the possibility of infection further, and thereby the use antimicrobial agents. Quicker and more effective diagnoses of antibiotic needs are also vital, as recognized by the EU Commission's recent announcement of the Horizon Prize.⁷⁵ But conservation and sustainability also require global action on aspects such as use in livestock production, surveillance, infection control, and sales promotion.

Third, the new drugs pipeline is finally beginning to show more signs of activity than at any point since the 1960s. Three new anti-MRSA drugs have recently appeared on the market; the real worries now are those carbapenem-resistant gram-negative bacilli (CRGNB) (see too Table 6). This suggests the need for a narrower policy focus on where the threat is greatest, rather than on new drugs generally. Past experience urges caution about what new antibiotics will emerge from current efforts, how effective they will be, and how long it will be before they too encounter resistance. In the end, the challenge posed by AMR is very real and there is no room for complacency: meeting that challenge requires not just keeping a close watch on the pipeline but paying much more attention to demand and conservation. The situation is challenging but by no means hopeless.

Causes	England and Wales 1850	England and Wales 1900	England and Wales 1939	High-income countries 2012	Low-income countries 2012
Infectious diseases	44.7	35.8	14.5	6.0	38.6
Infectious (not respiratory)	26.2	18.2	3.7	2.6	28.2
Respiratory infections	18.5	17.6	10.8	3.4	10.4
Maternal conditions	0.9	0.8	0.4	0.02	1.7
Neonatal conditions	6.0	3.7	3.7	0.34	9.3
Non-communicable	44.8	56.1	76.5	87.3	40.3
Injuries	3.6	3.6	4.9	6.4	10.1
Total deaths	368,995	587,830	498,968	1,167,361	5,696,969
Life expectancy	43	46	64	79	62

Sources: Davenport, 2007; ONS, 2003; WHO Global Health Observatory; Human Mortality Database.
Notes: the infectious diseases category excludes infectious causes of maternal and neonatal mortality; the non-communicable diseases category includes deaths due to nutritional deficiencies. High (Gross National Income per capita \geq \$12,476) and low-income (\leq \$1,025) groups are as defined by the World Bank in 2012.

Year	[1] HDI	[2] GDP per head	Period	Relative Contribution (percentage of total)		
				<i>Y</i>	<i>H</i>	<i>L</i>
1870	0.476	3,190		<i>Y</i>	<i>H</i>	<i>L</i>
1913	0.628	4,921	1870-1913	14.2	54.1	31.7
1950	0.762	6,939	1913-1950	14.6	63.3	22.1
2013	0.923	23,500	1950-2013	44.0	39.5	16.5

Source: Crafts 2002: 396-7; Maddison website [<http://www.ggdc.net/maddison/oriindex.htm>]
Note: GDP per head is measured using 1990 international Geary-Khamis dollars; education component estimated using years schooling as a proportion of 15 years (assumed to be 3 years in 1870).

Disease	$\eta=1$	$\eta=1.2$	$\eta=1.4$
Plague in London	140	76	41
Smallpox in England	39	22	12
Malaria in India	47	26	15
Malaria in China	56	24	10

Table 2. Major diseases and their prevention and treatment				
Disease	Prevention	Date	Treatment	Date
<i>Diseases reduced or eliminated before 1750</i>				
Bubonic plague	Quarantine, isolation	From c15 in Europe	Antibiotics	1946 (streptomycin)
<i>Diseases reduced or eliminated 1750 - 1870</i>				
typhus	Quarantine, isolation, hygiene, DDT to kill lice Vaccine	C18 reductions 1943 (not currently in production)	Antibiotics	1948 (chloramphenicol)
Smallpox	Quarantine, isolation Inoculation Vaccination	C17[?], C18 C18 1798	None	
Cholera	Water purification, notification and isolation of cases	Last epidemic in Britain 1866 (1890s in continental Europe). Still endemic in south Asia	Oral rehydration	1968
Typhoid	Water purification, isolation of cases Vaccine	Reduced in importance over course of C19 in England 1897	Antibiotics, oral rehydration	1948 (chloramphenicol); 1968 (ORT)
Malaria	Reduction in mosquito host populations (drainage, DDT) and prevention of bites (bednets, insecticide)	Eliminated in England by early C20th. Very large global reductions through DDT use 1940s+	quinine, chloroquine, artemisinin and combination therapies	quinine used in Bolivia and Peru at least since C15
<i>Diseases reduced or eliminated 1870-1940</i>				
Yellow Fever	Reduction in mosquito host populations (drainage, DDT) and prevention of bites (bednets, insecticides) Vaccination	Early C20, used successfully during Panama canal construction 1936, used by US army WWII	None	
Tuberculosis	BCG vaccination	1921 (routine use in England 1953)	Antibiotics	1946 (streptomycin)
Measles	Vaccination	1963	None	

Scarlet fever		Apparent decline in virulence 1870+	Antibiotics	1942 (penicillin)
Whooping cough	Vaccine	1947	Antibiotics	1946 (streptomycin)
Diphtheria	Vaccination (with 'anti-toxin')	1890, but used widely only from 1940s	Antitoxin and antibiotics (latter largely to prevent transmission)	
<i>Diseases reduced or eliminated after 1940</i>				
Poliomyelitis	Vaccination	1954, 1957	None	
Pneumonia	Vaccination	1975	Sulphonamide, penicillin	1937, 1944
Chickenpox	Vaccine	1975	None	
MRSA	Hygiene	Reductions in hospital-acquired infections from 1880s due to aseptic and antiseptic surgical techniques and improvements in wound treatment	Antibiotics	Sulfa drugs (1930s) penicillin (1942). Rapid evolution of resistance

<i>Drug</i>	<i>Year</i>	<i>Status</i>	<i>Target</i>	<i>Other</i>
Zyvox (linezolid)	2000	Available	Gram-positive bacteria, MRSA	Pharmacia/Upjohn
Sivextro (tedizolid)	2014	Available	MRSA	Trius/Cubist
Dalvance (dalbavancin)	2014	Available	MRSA	Pfizer/Durata
Orbactiv (oritavancin)	2014	Ready	MRSA	Eli Lilly/The Medicines Company
Zerbaxa (ceftolozane/tazobactam)	2014	Available	<i>E. coli</i> , cUTI	Cubist
teixobactin	2015	Early stages	MRSA, <i>Mycobacterium tuberculosis</i>	Academic/Big Pharma collaboration
KAE 609	2014	Phase IIb	Malaria	STI/Novartis
tafenoquine	2014	Phase III	Malaria	GKN
ceftazidime-avibactam (Avycaz)	2015	Restrictive FDA approval	Complicated CIAIs and UTIs	AstraZeneca/Forest Laboratories/Actavis

<i>Concept</i>	<i>Target</i>	<i>Observations</i>
Phages	Selectively kill bacteria containing AMR genes	Ongoing, informed by CRISPR biology
Research on genetic composition of <i>E. coli</i> bacteria	<i>E. coli</i> vaccine	Ongoing, but <i>E. coli</i> are attracted to animals and the environment as well as to humans.
Genetically engineering carriers against parasite genes	Malaria, resistance generally	Feasible, but politically contentious
NDV-3 vaccine (NovaDigm Therapeutics)	Fungal and bacterial infections	Phase I 'strong antibody and T-cell immune responses in healthy adults' [Dec. 2012]
Nanosponge vaccine	MRSA	Developed at UCSD 2013
RTS,S	Anti-malaria vaccine	Path/GSN/Gates, likely launch 2015
'Crapsules'	<i>Clostridium difficile</i>	Heralded as important breakthrough in late 2014

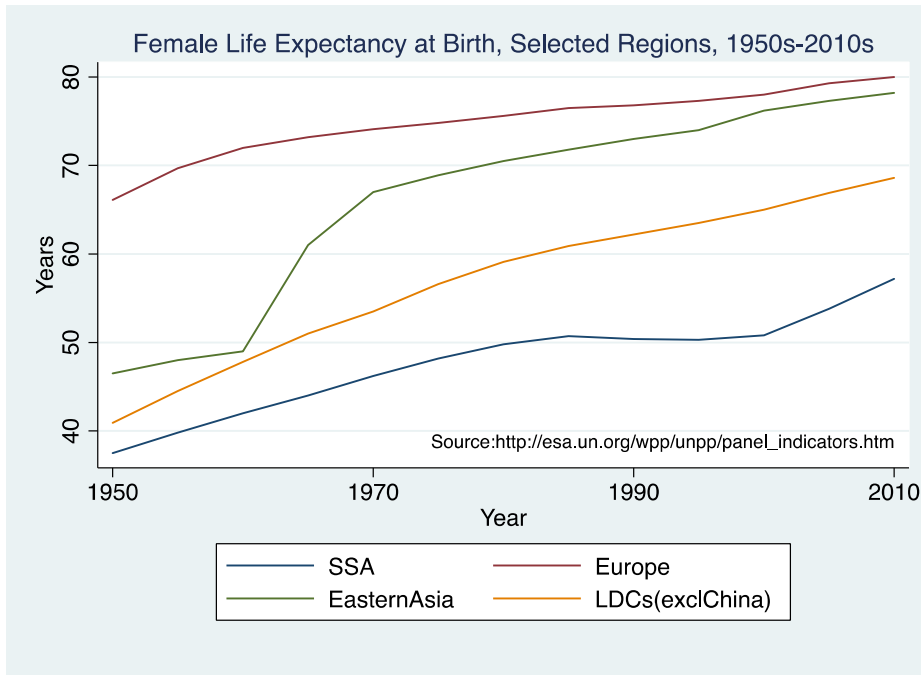


Figure 1. Global convergence in life expectancy at birth, 1950 – 2000

Source: World Bank

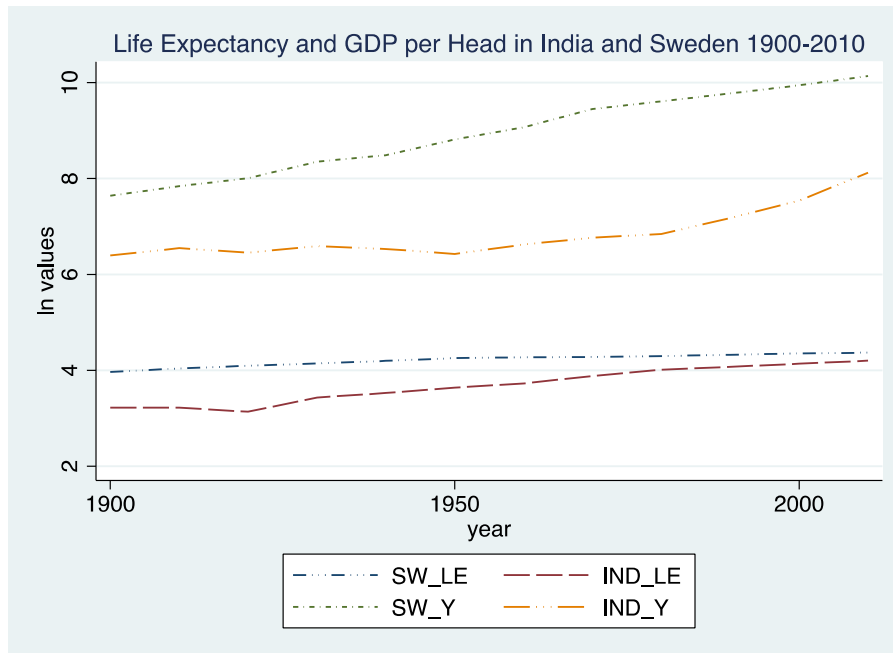


Figure 2. Income per capita and life expectancy at birth, India and Sweden

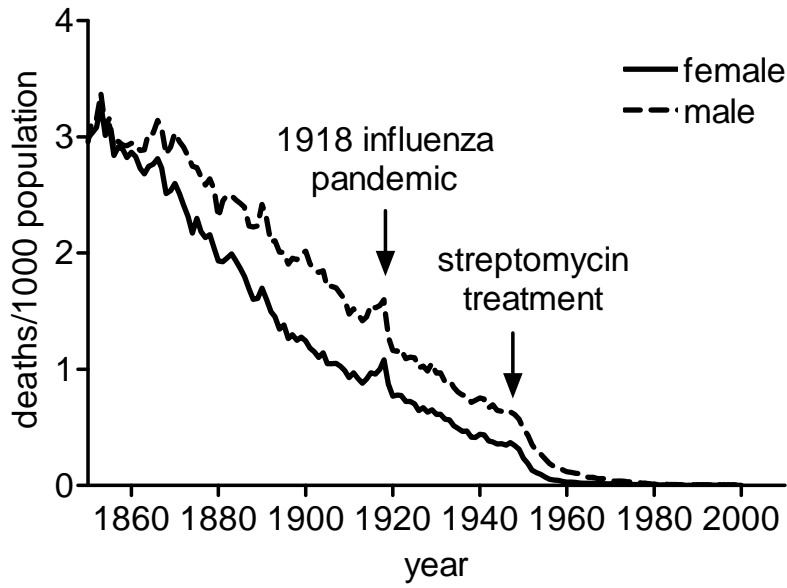


Figure 3. Tuberculosis mortality in England and Wales, age-standardised to the U.K. population in 2000.

Sources: Davenport, 2007; Office of National Statistics, 2006.

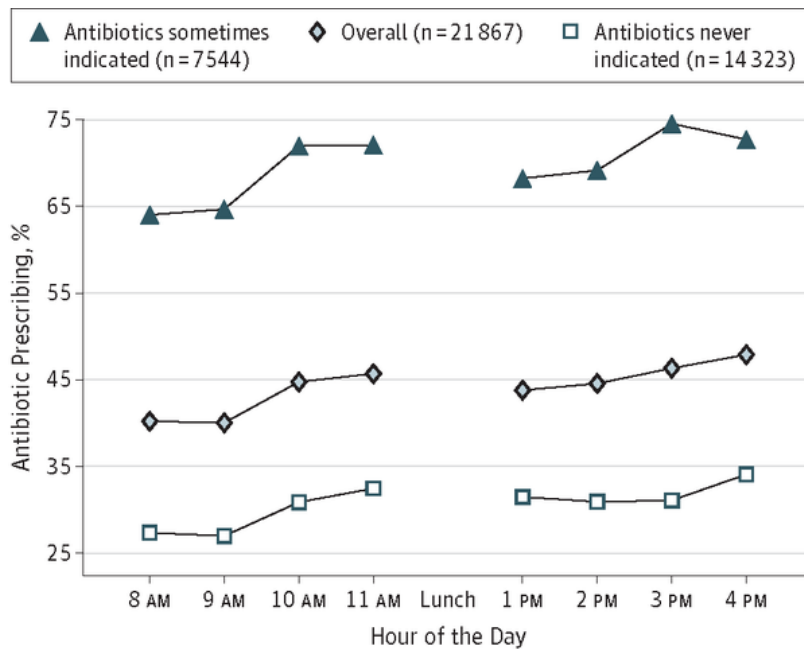


Figure 3. Antibiotic Prescribing and the Time of Day

Sources: Linder et al. 2014

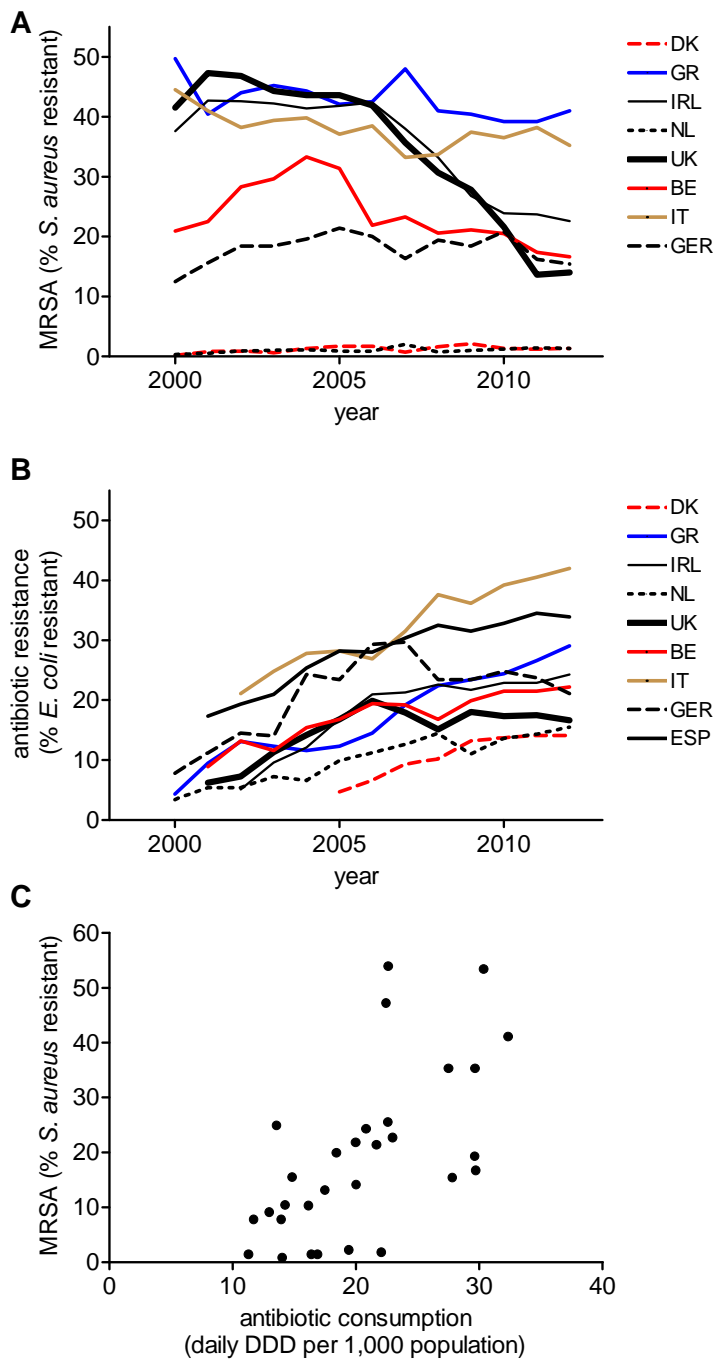


Fig. 4. Antibiotic resistance in *Staphylococcus aureus* (A) and *E. coli* (B) in Denmark (DK), Greece (GR), Ireland (IRL), Netherlands (NR), U.K., Belgium (BE), Italy (IT) and Germany (GER) 2000–2012, and antibiotic resistance according to antibiotic consumption by country in 2012 (C).

Source: ECD

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ENDNOTES:

¹ Text with footnotes of a public lecture delivered at the University of Warwick, 28 April 2015. The comments of Sean Boyle, Kevin Denny, Alun Evans, Mark Harrison, David Madden, Joel Mokyr, Rafique Mottiar, Laurent Poirel, Patrick Wall, and Brendan Walsh on earlier drafts is gratefully acknowledged. Thanks also to Rachel Zetts (Pew Research) for data. Parts of the lecture draw heavily on joint work at CAGE with Romola Davenport and Kerry Hickson, but they are not responsible for the opinions expressed here.

² Woods 2000: 350-1.

³ Compare Cutler, Deaton, and Lleras-Muney 2006.

⁴ UNDP. *Human Development Report 2014*. 'The Human Development Index and its Components' [<http://hdr.undp.org/en/content/table-1-human-development-index-and-its-components>].

⁵ Global Health Repository [available at: <http://apps.who.int/gho/data/node.main.12?lang=eng>]

⁶ From statement by WHO director-general Margaret Chan on World Health Day 2011 [http://www.who.int/mediacentre/news/statements/2011/whd_20110407/en/]. Compare James Gallagher, 'Analysis: Antibiotic apocalypse', BBC News, 11 March 2013 [<http://www.bbc.com/news/health-21702647>]; Arjun Srinivasan, "We've reached 'The end of antibiotics, period' ", *PBS Frontline*, 22 October 2013 [<http://www.pbs.org/wgbh/pages/frontline/health-science-technology/hunting-the-nightmare-bacteria/dr-arjun-srinivasan-weve-reached-the-end-of-antibiotics-period/>]. Srinivasan is associate director of the U.S. Center for Disease Control.

⁷ Poirel and Nordmann 2006; Nordmann *et al.* 2012; Ryan *et al.* 2011; Johnson and Woodford 2013.

⁸ Sarah Boseley, "New wave of superbugs poses dire threat", says chief medical officer", *Guardian*, 11 March 2013; Peter Dominiczak, "Superbugs could 'cast the world back into the dark ages', David Cameron says", *Daily Telegraph*, 1 July 2014.

⁹ Slack 1985.

¹⁰ See *The BCG World Atlas: a Database of Global BCG Vaccination Policies and Practices* [<http://www.bcgatlas.org/index.php>].

¹¹ Mangtani *et al.*, 2014.

¹² On the basis of data on amputations in the era before antibiotics, Smith and Coast (2013) reckon that without antibiotics the infection rate could hit 40-50 per cent and that 30 per cent of those infected would not survive.

¹³ The coefficient of variation of life expectancy at birth across the globe has fallen by almost half since the 1950s.

¹⁴ Dyson and Das Gupta (2001) have attributed these improvements, which date from the 1920s, to colonial policies that improved food distribution, monitored plague outbreaks and increased smallpox vaccination coverage.

¹⁵ Livi-Bacci, 2001; Riley 2001; Caldwell, 1986.

¹⁶ For data on life expectancy see <http://www.gapminder.org/data/documentation/gdoo04/>.

¹⁷ For data on prices see <http://www.avert.org/antiretroviral-drug-prices.htm>; WHO, *Transaction Prices for Antiretroviral Medicines from 2010 to 2013: Global Price Reporting Mechanism* [http://apps.who.int/iris/bitstream/10665/104451/1/9789241506755_eng.pdf?ua=1].

¹⁸ RAND 2014; KPMG 2014; compare Smith and Coast 2012, 2013.

¹⁹ Cited in e.g. Jon Gertner, 'The rise and fall of the GDP,' *New York Times*, 30 May 2010.

²⁰ E.g. Kelley 1991; Srinivasan 1994; Ravallion 1997, 2012. For a review of critiques of HDI see Kovacevic 2010.

²¹ E.g. Costa and Steckel 1997; Crafts 2002; Prados de la Escosura 2013.

²² The health component has always been proxied by the gap between actual and maximum achievable life expectancy at birth. The income index uses the gap between the log values of actual income and a maximum currently capped at \$75,000. The education index originally combined information both on literacy and school attendance, but in recent years uses data on actual attendance rates relative to anticipated future attendance rates.

²³ It might be added that one criticism made of HDI is the relatively low value it implicitly places on gains to life expectancy.

²⁴ An estimate of the value of a statistical life in Country *C* in year *t* may be obtained by calculating (OECD 2012):

$$VSL_{C,t} = [VSL_{US,2010}][Y_{C,t}/Y_{US,2010}]^\eta$$

where *Y* is GDP, $VSL_{US,2010}$ and $Y_{US,2010}$ refer to present-day US values and η is the income elasticity of demand for staying alive. PPP-adjusted US\$ estimates

of $Y_{C,t}$ may be obtained from the Penn World tables or (for the pre-1950 period) Angus Maddison's historical national accounts estimates.

²⁵ Hammitt and Robinson 2011: 21; Leon and Miguel 2013; but see too Wang and He 2010. Miller (2000) recommends $\eta=1$ as the 'best estimate' and a recent OECD report (2012) recommends $\eta=0.8$, while Hammitt and Robinson (2011) advise analysts not to rely on a single value but to report outcomes using a range of estimates of η .

²⁶ These results are fully explained in Davenport *et al.* 2014.

²⁷ GDP per head in GB (including Ireland) in 1650 was \$925 (1990 international GK dollars): Maddison Project database.

²⁸ Using the formula in fn24.

²⁹ William Farr noted the lower mortality from cholera in those who lived on higher ground. He was well aware that water does not flow uphill but dismissed the role of water in favour of those who live higher up being fitter! I am grateful to Alun Evans for this point.

³⁰ Dobson 1997: 358-59.

³¹ For a detailed account see Davenport *et al.* (2014: fn15).

³² These quotes are taken from So *et al.* 2010; Infectious Diseases Society of America 2013. See also Ezekiel Emanuel, 'How to develop new antibiotics', *New York Times*, 24 February 2015.

³³ See e.g. Travis 1994; Hancock 1997; Spellberg *et al.* 2004; Spellberg *et al.* 2008.

³⁴ International Federation of Pharmaceutical Manufacturers and Associations, 'IFPMA Position on Antimicrobial Resistance', 7 April 2011 [http://www.ifpma.org/fileadmin/content/Innovation/Anti-Microbical%20Resistance/IFPMA_Position_on_Antimicrobial_Resistance_New_Logo2013.pdf]. See too Association of the British Pharmaceutical Industry [ABPI], *AMR: An Urgent Need for Economic Incentives in a New Economic Model: Principles to Consider*; and Office of Health Economics [OHE], 'New Business Models for Antibiotics. What Can We Learn from Other Industries?', 7 April 2015 [<https://www.ohe.org/news/new-business-models-antibiotics-what-can-we-learn-other-industries>]. OHE is an affiliate of ABPI.

³⁵ E.g. Mokyr 2013, 2014. Compare Vijg 2011.

³⁶ I owe this point to Joel Mokyr.

³⁷ 'Battling superbugs: two new technologies could enable novel strategies for combating drug-resistant bacteria', *MIT News*, 21 September 2014

[<http://newsoffice.mit.edu/2014/fighting-drug-resistant-bacteria-0921>]; Michael Eyre, 'Novel antibiotic class created', *BBC News Health*, 24 September 2014 [<http://www.bbc.com/news/health-29306807>]; Balcazar 2014; Wiedenheft 2013; *The Economist*, 'Strange medicine: a way to treat bacterial infections with artificial viruses', 28 February 2015; Jenny Rood, 'CRISPR chain reaction: a powerful new CRISPR/Cas9 tool can be used to produce homozygous mutations within a generation, but scientists call for caution', *The Scientist*, March 19, 2015.

³⁸ Mokyř 2014.

³⁹ Mazzucato and Dosi 2006; Mazzucato 2013. Compare Brogan and Mossialos 2013; NIH Directors Blog, 'New strategies in battle against antibiotic resistance', 18 September 2014 [<http://directorsblog.nih.gov/2014/09/18/new-strategies-in-battle-against-antibiotic-resistance/>].

⁴⁰ *The Economist*, 'Invent it, swap it or buy it: why constant dealmaking among drugmakers is inevitable', 15 November 2014; *The Economist*, 'Drug research: all together now, charities help Big Pharma', 21 April 2012. Examples include Amgen's purchase of Onyx (which had developed a promising cancer drug) in August 2013; Actavis's acquisition of Durata, October 2014; Merck's acquisition of Cubist, December 2014; Sanofi-Aventis's licensing of the semi-synthetic artemisinin developed by Amyris Technologies in 2008. According a source cited by the *Wall Street Journal* ('Drugmakers tiptoe back into antibiotics R&D', 23 January 2014) 'small and medium-size companies are now responsible for 73% of antibiotics in development'.

⁴¹ Pew Charitable Trusts, 'Antibiotics Currently in Clinical Development December 31, 2014' [<http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development>]; Center Watch, 'FDA approved drugs' [<http://www.centerwatch.com/drug-information/fda-approved-drugs/year/2015>].

⁴² CDC: http://www.cdc.gov/drugresistance/biggest_threats.html, 16 September 2013.

⁴³ BBC News, '1,000-year-old onion and garlic eye remedy kills MRSA', 30 March 2015 [<http://www.bbc.com/news/uk-england-nottinghamshire-32117815>]; Jonathan Owen, 'A new (old) cure for MRSA? Revolting recipe from the Dark Ages may be key to defeat infection', *The Independent*, 31 March 2015.

⁴⁴ E.P. Vantage, 'Upcoming events: Dalvance data and US decisions for Lynparza and Zerbaxa', 12 December 2014 [<http://www.epvantage.com/Universal/View.aspx?type=Story&id=547144&isEPVantage=yes>]. The drugs are expensive [see: <http://www.podiatrytoday.com/blogged/key-considerations-costs-and-use-dalbavancin-and-oritavancin>].

⁴⁵ Ling *et al.* 2015; Judy Stone, 'Teixobactin And iChip Promise Hope Against Antibiotic Resistance', *Forbes*, 8 January 2015 [<http://www.forbes.com/sites/judystone/2015/01/08/teixobactin-and-ichip-promise-hope-against-antibiotic-resistance/>]; Ed Yong, 'A New Antibiotic That Resists Resistance', *National Geographic*, 7 January 2015 [<http://phenomena.nationalgeographic.com/2015/01/07/antibiotic-resistance-teixobactin/>].

⁴⁶ Derived from data in WHO Global Health Observatory Data Repository.

⁴⁷ Compare Tun *et al.* 2015. The number of reported cases is given only from 2000 on, since the data for the 1990s seem very suspect. Given the sigmoid shape of the resistance time-path, it would be foolhardy to base policy on such data.

⁴⁸ Path Malaria Vaccine Initiative [<http://www.MalariaVaccine.org/>]; RTS,S Clinical Trials Partnership 2015.

⁴⁹ WHO 2013; WHO 2015 ('Frequently asked questions on bedaquiline': <http://www.who.int/tb/challenges/mdr/bedaquilinefaqs/en/>).

⁵⁰ 'Bedaquiline for multidrug-resistant tuberculosis'. *Drug and Therapeutics Bulletin* 2014, 52[11]: 129-132 [<http://dtb.bmj.com/content/52/11/129.full.pdf+html>]; 'Verapamil increases anti-tuberculosis activity of bedaquiline', *Pharmaceutical Journal*, 17 January 2015, 294[7845].

⁵¹ Crusio *et al.* 2014; Dubrovskaya *et al.* 2013; Qureshi *et al.* 2015. Crusio *et al.* (2014) find that mortality linked to carbapenem-resistant Gram-negative bacteria (CRGNB) affects the elderly is related to age, severity of medical condition, and extent of previous antibiotic exposure. Paul *et al.* (2014) question the effectiveness of carbapenem-colistin combination therapies. Colistin is ineffective against *Proteus* and *Serratia* spp., and increasingly so against *Acinobacter baumannii*.

Compare Tängdén 2014; Di *et al.* 2015.

⁵² Dortet *et al.* 2014.

⁵³ 'National Center for Health Research, 'Letter to FDA Commissioner Hamburg on New Antibiotic Product (CAZ-AVI)', 19 December 2014 [<http://center4research.org/public-policy/letters-to-government-officials/letter-to-fda-commissioner-hamburg-on-new-antibiotic-product-caz-avi/>]; FDA, 'FDA approves new antibacterial drug Avycaz', 25 February 2015 [<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.htm>].

⁵⁴ Presentation by Joyce Sutcliffe of Tetrphase Pharmaceuticals [http://www.tufts.edu/med/apua/practitioners/resources_23_2817980013.pdf].

⁵⁵ 'More must be done to cut unnecessary antibiotic prescriptions, say experts', *The Guardian*, 5 August 2014. Compare Blommaert *et al.* 2013; Plachouras *et al.* 2008.

⁵⁶ ECDC: *Quality indicators for antibiotic consumption in the community (primary care sector) in Europe 2012* (http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/quality-indicators-primary-care.aspx).

⁵⁷ Data in Sabuncu *et al.* (2009: 4) imply that reducing consumption in the rest of France to levels found in the lowest quartile of regions would cut the aggregate intake by 15-20 per cent.

⁵⁸ Figure 3a reports trends in MRSA in a cross-section of European countries since 2000. Note the very low rates of MRSA in the Netherlands and very high rates in Greece and Italy, and the significant drop in resistance rates in Ireland and the UK, in particular. Figure 3b describes the trends in *E. coli* resistance to fluoroquinolones in the same set of countries; again Greece and Italy perform rather poorly relative to others. Figure 3c plots the relationship between consumption and MRSA in 2012 (compare Blommaert *et al.* 2013, Table 3).

⁵⁹ Compare Sadsad *et al.* 'Effectiveness of hospital-wide Methicillin-Resistant *Staphylococcus aureus* (MRSA) infection control policies'.

⁶⁰ Dame Sally Davies, cited in Anne Gulland, 'Antimicrobial resistance will surge unless use of antibiotics in animal feed is reduced', *BMJ*, 347, 7 October 2013; FDA, 'FDA's Strategy on Antimicrobial Resistance', 28 March 2014 [<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm216939.htm>]; Van Boeckel *et al.* 2015. In 2011 in the US 3.29 million kilograms of drugs were sold for human consumption, whereas 13.77 million kilograms of antibiotics were approved for use in food-producing animals. Between 2009 and 2012 the total for animal use rose from 12.8 million kilograms to 14.7 million kilograms. The figure for human consumption excludes what was administered directly [United States Food and Drug Administration, <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm261160.htm>; <http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm042896.htm>].

⁶¹ BBC News Science and Environment, 'Scientists produce disease-resistant cows', 3 March 2015 [<http://www.bbc.com/news/science-environment-31709107>].

⁶² Sabuncu *et al.* 2009.

⁶³ Sabuncu *et al.* 2009; Meeker *et al.* 2014; Wickström Östervall 2014; Goosens *et al.* 2008.

⁶⁴ Linder *et al.*, 'Time of Day and the Decision to Prescribe Antibiotics'.

⁶⁵ Compare Smitha Mundasad, 'Rapid blood test to cut antibiotic use', BBC News health, 19 March 2015 [<http://www.bbc.com/news/health-31941538>].

⁶⁶ Richardson, 'Alternating antibiotics'.

⁶⁷ *New Yorker*, 'The excrement experiment: treating disease with fecal transplants', 1 December 2014; *BBC News Magazine*, 'The brave new world of DIY faecal transplant', 26 May 2014 [<http://www.bbc.com/news/magazine-27503660>].

⁶⁸ Resistant bacteria against which, so far, no replacement drug has been announced or promised include *Enterotoxigenic E. coli* (*ETEC*). In this case resistance rates have risen from near zero at the turn of the century to 10-15 per cent across Europe today (and much higher in Italy). Although *ETEC* infections are rarely life threatening, the lack of replacement antibiotics makes it imperative to focus on any second-best solutions available. It has been suggested that recent findings on the genetic composition of *E. coli* bacteria could open the way for vaccines capable of preventing infection globally. See 'Large-scale study raises hopes for development of *E. coli* vaccine', 10 November 2014 [<http://www.sanger.ac.uk/about/press/2014/141110.html>]. But given that *E. coli* is a commensal organism widespread in humans, animals, and the environment, it is not clear how a vaccine could combat such a pathogen.

⁶⁹ Alexander Fleming, 'Penicillin' [http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf].

⁷⁰ By extending the patent life of antibiotics that treat serious or life-threatening infections, the U.S. GAIN Act seeks to energize Big Pharma (although this entails welfare costs too).

⁷¹ *PBS Frontline*, 'Obama Budget Would Double Federal Spending to Fight Superbugs', 27 January 2015 [<http://www.pbs.org/wgbh/pages/frontline/health-science-technology/hunting-the-nightmare-bacteria/obama-budget-would-double-federal-spending-to-fight-superbugs/>].

⁷² BBC News Health, 'Ebola: the race for drugs and vaccines', 24 February 2015 [<http://www.bbc.com/news/health-28663217>].

⁷³ 'WHO aims for Ebola serum in weeks and vaccine tests in Africa by January', *Guardian*, 22 October 2014.

⁷⁴ As with Perdue Chicken and McDonalds in the US, for example.

⁷⁵ EU Commission Research and Innovation, 'European Commission launches €1m prize for a diagnostic test to combat antibiotic resistance', 25 February 2015 [<http://ec.europa.eu/research/index.cfm?pg=newsalert&year=2015&na=na-260215>].

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