

The Challenge of Antimicrobial Resistance: Lessons from the Past for the Present and the Future

Global Perspectives Series: Paper 2

CORMAC Ó GRÁDA

April 2015

SUMMARY POINTS

- The challenge of anti-microbial resistance (AMR) needs to be set in historical context: though real, it is unlikely to mean a return to 'the dark ages of medicine'.
- With the virtual eradication of most infectious diseases, life expectancy in the UK and other high-income countries has doubled in the last century (the gains in poor countries have been smaller, but still significant). Most of the increase in life expectancy preceded the antibiotics revolution.
- Public health measures in particular have been essential to controlling infectious diseases. Even if AMR increases, the effect of these and new public health measures will limit the negative consequences.
- The challenge of tackling AMR itself requires a focus on both supply of antimicrobials (the 'pipeline') and the demand for them (consumption).
- There is considerable scope for reducing consumption and thereby the spread of resistance. Public health initiatives and health education can usefully reinforce measures to restrain consumption.
- Equally the pipeline is not as dry as usually claimed. As of December 2014, in the US there were thirty-seven new antibiotic drugs listed as being under development. Though not all of these drugs will be successful, as one example, in 2014 alone four new drugs were approved for tackling MRSA.

ABOUT THE SERIES

This is the second briefing paper in the Global Perspectives series - a new collaboration between the Social Market Foundation (SMF) and Warwick's Centre on Competitive Advantage in the Global Economy (CAGE). The first paper by Dr Mirko Draca was published by the SMF in October 2014 and is titled *Institutional Corruption? The revolving door in American and British politics*.

ABOUT THE AUTHOR

Cormac Ó Gráda is Professor of Economics at University College Dublin; he is also a research associate of CAGE. His research is on the economic history of populations, famines, and well being. His books include *Ireland: A New Economic History* (Oxford University Press, 1994), *Jewish Ireland in the Age of Joyce: A Socioeconomic History* (Princeton, 2006), *Famine: A Short History* (Princeton, 2009), and *Eating People is Wrong* (Princeton University Press, 2015). He is a former co-editor of the European Review of Economic History. In 2010 he was awarded the Gold Medal of the Royal Irish Academy.

ABOUT CAGE

Established in January 2010, CAGE is a research centre in the Department of Economics at the University of Warwick. CAGE is carrying out a 10 year programme of innovative research. The centre's research programme is focused on how countries succeed in achieving key economic objectives such as improving living standards, raising productivity, and maintaining international competitiveness, which are central to the economic wellbeing of their citizens. Our research analyses the reasons for economic outcomes both in developed economies like the UK and emerging economies such as China and India. We aim to develop a better understanding of how to promote institutions and policies which are conducive to successful economic performance and endeavour to draw lessons for policy makers from economic history as well as the contemporary world. Research at CAGE examines how and why different countries achieve economic success. CAGE defines 'success' in terms of well-being as well as productivity. The research uses economic analysis to address real-world policy issues. The centre is distinctive in providing a perspective that draws on economic history as well as economic theory and is applied to countries at various different stages of economic development. www.warwick.ac.uk/cage

ABOUT THE SOCIAL MARKET FOUNDATION

The Social Market Foundation is a leading cross-party think tank, developing innovative ideas across a range of economic and social policy. The SMF's current research themes are: Productivity and Growth; Cost of Living; and, Public Service Reform. We champion policy ideas which marry markets with social justice and take a pro-market rather than free-market approach. Our work is characterised by the belief that governments have an important role to play in correcting market failures and that a sustainable market economy rests on social and political foundations that are widely regarded as fair. www.smf.co.uk

THE CHALLENGE OF ANTIMICROBIAL RESISTANCE

Concerns about the threat posed by antimicrobial resistance (AMR) are rising.¹ There have been warnings of a retreat to ‘a health system not dissimilar to the early 19th century’ and of ‘a bleak post-antibiotic future, in which infectious diseases once again reign supreme’.

These concerns stem from the combination of [a] accumulating evidence of first line of defence drugs - such as beta-lactam antibiotics (against infections caused by both Gram-negative and Gram-positive bacteria) and *artemisinin* (against malaria) - losing their effectiveness in certain contexts, and [b] fears that the pipeline of replacement drugs is running dry. So are we in imminent danger of losing the precious gains achieved in past campaigns against a long list of infectious diseases to superbugs? How big are those gains and losses? I argue here that economic history offers some insights into the costs and likelihood of a descent ‘into the dark ages of medicine’.²

1. THE HEALTH TRANSITION

The huge increase in life expectancy over the past century is one of mankind’s greatest achievements. Thanks mainly to a virtual end to deaths from a range of infectious diseases, those living in today’s high-income countries can expect to live almost twice as long as they did a century ago. In those same countries nowadays, the great majority succumb instead to chronic conditions such as cancer or heart disease. Life expectancy in the poorest of low-income countries, where infectious diseases still loom large, is nevertheless higher than it was anywhere before the revolutions in public health and medical technology that followed the work of Pasteur and Koch.

Infectious diseases remain a major policy concern though, for two main reasons. The first is their impact on mortality and morbidity in low-income countries, where such diseases are in retreat but still account for nearly half of all deaths. The second is evidence of increasing antimicrobial resistance (AMR). Although AMR is extremely unlikely to undo all the demographic gains just described, a careful analysis of the role of medical science in the conquest of once-lethal diseases can offer a timely reminder of potential progress undone by AMR.

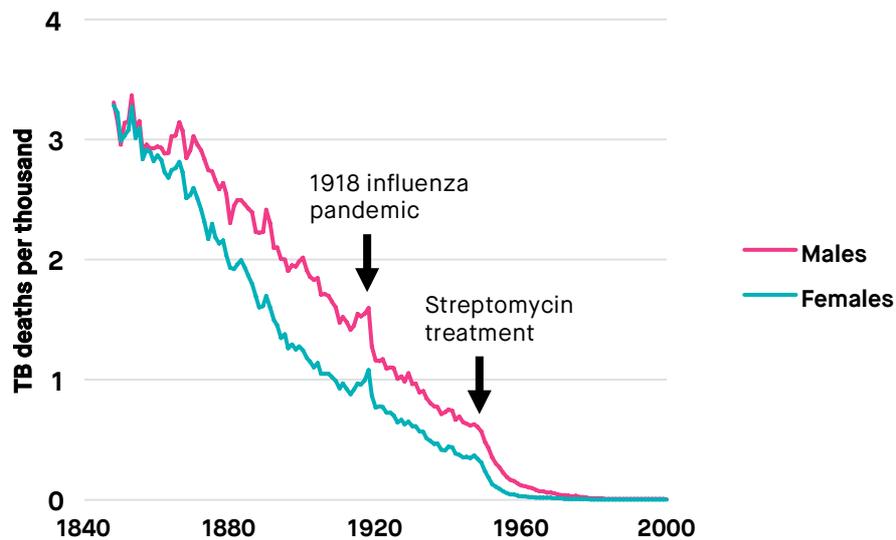
Surprisingly perhaps, history suggests that antimicrobials broadly conceived made relatively little contribution to the enormous falls in mortality over the twentieth century except in the case of malaria control.

Although nowadays the rise in the human life span seems almost limitless to some, by historical standards it is a recent phenomenon. In England the mortality decline has been continuous from the 1870s, but very limited before then. The heavy burden of infectious diseases began to lift decisively only in the mid-18th century with reductions in urban mortality. In developing countries the process of infectious disease control, so drawn out in England, was compressed into the twentieth century and enormously accelerated post-1950 by the availability of medical and public health technologies and knowledge.

In England and Wales infectious diseases accounted for 40 per cent of all deaths in 1860–69 and 32 per cent in 1900, but only 12 per cent by 1945. Today they account for 6 per cent of deaths, mostly attributable to respiratory infections in late adulthood. Much of the reduction in infectious

disease mortality before 1950 was due to falls in tuberculosis mortality. While penicillin decisively eliminated tuberculosis as a major cause of death after 1945 most of the enormous reductions in mortality from tuberculosis had already occurred then, as shown in Figure 1. Other major contributors to the falls in mortality before World War II were declines in scarlet fever, whooping cough, and croup (from the 1870s), diphtheria (from the 1890s), infantile diarrhoea (from 1900), measles (from 1910) and perinatal mortality (from the mid-1930s).

Figure 1: Tuberculosis mortality in England and Wales, age-standardised to the U.K. population in 2000



Source: Davenport, Hickson, and Ó Gráda (2014)

Given current concerns about AMR, it is important to place the role of antibiotics in the mortality decline in perspective. Note that with the exception of neonatal mortality (where the fall coincided with the introduction of sulfa drugs, the first antibiotics) most of the gains in infectious disease control in England were achieved earlier. Further gains after 1945 included specific effects of antimicrobials on tuberculosis, pneumonia and wound infections including puerperal fever. However much of that further improvement can be attributed to a combination of factors: the proliferation of immunisation therapies (including vaccines against measles, pneumococcal infections, influenza and tuberculosis), as well as continuations of the trends of increasing resistance and reduced exposure to infection that drove earlier declines.

In Britain the foundation for this achievement had been established in the mid-nineteenth century when improvements in sanitation, hygiene, nutrition, and living conditions in general began to take place. By the early twentieth century gastrointestinal infections, such as cholera, enteric fever and dysentery were under control, and deaths from 'diseases of infancy' such as scarlet fever, measles-rubella-mumps and whooping cough were on the wane. Polio, measles, mumps and rubella were virtually eliminated during the second half of the twentieth century, when the necessary vaccines were discovered. The infant mortality rate dropped in tandem, from 150 per thousand in the 1890s to 50 per thousand in 1941-45 and 19 per thousand in 1965. Immunisation played a major part in the virtual disappearance of diphtheria from the 1940s, whereas deaths from whooping cough had already fallen dramatically before widespread immunisation, which began in the 1950s, effectively put an end to them.

2. WELFARE COSTS

History suggests that AMR will not entail a return to an era in which infectious diseases reign supreme again. Nevertheless the economic and welfare gains associated with the decline of mortality from infectious diseases lend a useful resonance to the debate about AMR.³

RAND and KPMG have recently produced alternative estimates of the global impact of AMR in terms of GDP foregone in 2050 (RAND 2014; KPMG 2014; compare Smith and Coast 2012, 2013). Here our focus is on welfare rather than GDP, since GDP is an inadequate measure of the value that we place on health. Economists have developed a battery of alternative measures that focus on estimating the welfare or utility benefits from better health; here we look at two of them. Moreover, instead of speculating about the future, we invoke the past.

The United Nations-sponsored Human Development Index (HDI) is the geometric mean of measures of GDP per capita, education, and health relative to a maximum. This measure has its critics, but development economists and economic historians often invoke it as an improvement on GDP per capita.⁴ Applying HDI to British data for the years 1870, 1913, 1950, and 2013 produces some interesting insights (Table 1).

First, while GDP per capita grew more than six-fold between 1870 and 2013, HDI moved much closer to its ‘maximum’ value of 1. Second, and most noteworthy, the contribution of health—mainly the reduced incidence of infectious disease—to the rise in HDI dwarfed that of literacy and income between 1870 and 1950, while GDP per capita contributed most thereafter. Third, given its low life expectancy in 1870, mainly due to the role of infectious diseases, Britain’s HDI value in that year would place it well behind, say, Ghana or Zambia today.

Table 1: HDI and GDP per capita in Britain, 1870-2013

Year	HDI	GDP per head	Period	Relative contribution (percentage of total)		
				Y	H	L
1870	0.476	3,190				
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; the Maddison Project [<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).

Historical studies using the estimates derived from ‘the value of a statistical life’ (VSL), a measure of people’s willingness to pay for reductions in fatal risks from accidents, work-related illnesses, or infectious diseases are few.⁵ Here the results of applying this measure to a few historical contexts in order to obtain rough orders of magnitude for the gains from reduced prevalence or eradication of infectious diseases are summarised. This entails applying estimates of VSL in high-income countries to much poorer countries in an earlier era, which involves making an assumption about the appropriate income elasticity, i.e. what is the proportionate change in VSL resulting from a change in income. The estimates described here, which are intended to be illustrative, work on the assumption of $\eta=1$.

THE CHALLENGE OF ANTIMICROBIAL RESISTANCE

We begin with the disappearance of plague in London in the seventeenth century and the gradual elimination of smallpox in England in the eighteenth and early nineteenth centuries. Between 1560 and 1665 plague was responsible for about 15 per cent of all London deaths. What were the welfare gains for London from the disappearance of plague? VSL's answer to this question entails making assumptions about the crude death before and after the disappearance of plague and incomes in London in the 1660s relative to, say, the U.S.A. today, and choosing between estimates of VSL today. The details are given elsewhere: our 'first cut' answer is that the gain was worth a huge 140 per cent of London's GDP.

Turning to smallpox, assuming rather conservatively that it was responsible for one death in twenty in the period just before inoculation became widespread would mean an annual total of about 7,500 deaths circa 1750. Given GDP and population at the time, we estimate that the welfare benefit in terms of VSL of eliminating smallpox at nearly two-fifths of GDP. Again, this would represent an enormous gain, especially relative to the slow economic growth rates typical of the pre-industrial era.

We turn now to the malaria eradication campaigns in India and in China during the 1950s, which led to huge and quite sudden reductions in mortality.

Malaria killed more people in India in 1947 than it kills worldwide today; between then and 1965 the number of deaths fell from 0.8 million to virtually zero. Applying the same calculation as before to estimates of Indian population and GDP circa 1950 yields an estimate of the welfare gain of nearly one-half of GDP. Malaria killed even more people in China than in India in the early 1950s. 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. We reckon China's welfare gain at 56 per cent of 1950 GDP. Applying the same approach to Ceylon (Sri Lanka), where a vigorous eradication campaign reduced the number of malaria deaths from an average of 7,500 annually in 1936-45 to 1,500 in the early 1950s, yields a welfare gain, using 1945 GDP as denominator, of about 20 per cent of GDP.

These estimates of the welfare gains from eradicating three infectious diseases—plague, smallpox, and malaria—are preliminary, but rough as they are, they point to the significance of the welfare gains associated with three well-known historical examples. Those gains could be seen as a measure of what would be lost in the event of a return to an era where plague and smallpox were still a threat in England and malaria still killed millions in India and China. But history tells us that such a bleak scenario is very much an upper-bound estimate of the potential cost of AMR.

2.1. LEARNING FROM TB

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. 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.

How much? Kerry Hickson (2014) has produced three estimates of the loss for the UK. Her upper-bound estimate 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 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. 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*) and certain other infections, public health interventions, vaccination, 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.

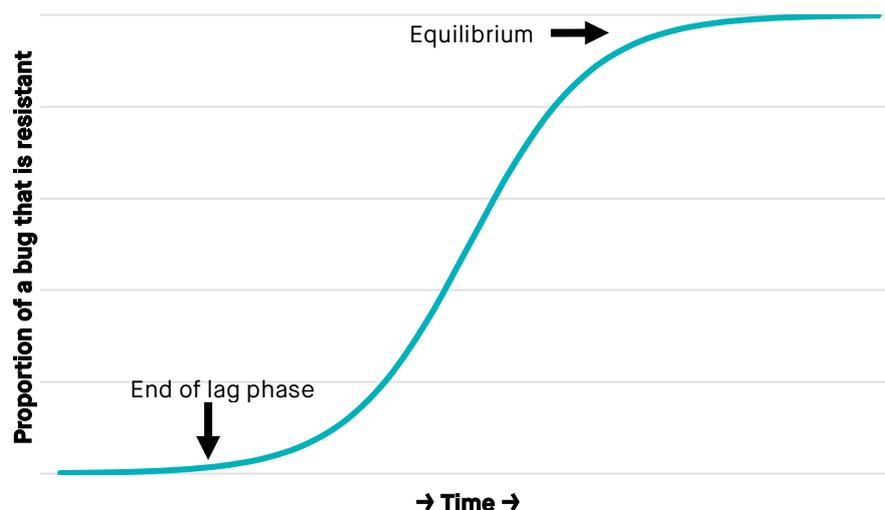
Hickson's lower bound estimate involves comparing the current situation with the most likely MDR-TB scenarios, which allow for a higher morbidity burden only, given that MDR-TB tends to be resolved in longer treatment times and not mortality. The estimated loss is calculated by applying a VSL function to the number of life years burdened with MDR-TB in 2013; this yields an estimate of \$1.9 billion.

Box 1: The development of antimicrobial resistance over time

The relationship between time and the proportion of any particular microorganism that is resistant tends to follow a sigmoid distribution, shown in Figure 2. There is a lag phase before resistance begins to appear, followed by a relatively rapid increase in the proportion of organisms that are found to be resistant, and a third phase in which the proportion of resistant strains has reached equilibrium. The equilibrium proportion varies considerably between different organisms, and is determined by a number of factors including the relative fitness of resistant and sensitive strains of an organism, and the selection pressure.

The sigmoid distribution also highlights the need for intervention before the lag phase is complete. During the lag phase, policies aimed at controlling resistance will help to curtail AMR. Once equilibrium resistance has been reached, only policies which reduce transmission of the organism will (generally) be effective in reducing the impact of resistance on health.

Figure 2: The sigmoid curve



Source: Smith and Coast (2013)

Note that this third estimate refers only to the early (current) phase of AMR. However, the time-path of any particular resistant microorganism tends to have a sigmoid shape (Figure 2). 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.

3. DEMAND ALSO MATTERS

Media discussion of AMR highlights the supply problem—‘the pipeline’. But just as current discussion on AMR pays insufficient attention to the role of public health and prevention in reducing the death rate from infectious diseases in the past, today we tend to discount the role of public policy in reducing the demand for antibiotics (compare Laxminarayan 2014).

Take, for example, the very large between-country and within-country variation in the consumption of antimicrobials. In 2013 Belgians consumed nearly three times as many antibiotics as their Dutch neighbours. 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 counties Roscommon and Meath would cut aggregate consumption by two-fifths, while reducing U.S. consumption to levels found in the six lowest consuming U.S. states would cut the aggregate by over a quarter. These variations are worth further study, because a more intelligent approach towards antibiotics usage could increase the shelf life of individual treatments and reduce the incidence of AMR.

The variation in resistance rates across Europe supports the presumption of a correlation between usage and AMR. The data seem to support this. But reduced usage requires conscious improvements in hospital hygiene and deliberate strategies to reduce dissemination of infections; and such improvements are more easily implemented 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. So the trade-offs involved here, while well established, require more statistical precision, articulation and publicity.

Measures to curb the use of antimicrobials in agriculture would help too, but face opposition from pharmaceutical companies who rely on big sales after discovery in order to recoup substantial R&D costs, and from producers. Recently, UK Chief Medical Officer Dame Sally Davies singled out the US where four times as many antibiotics 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. This highlights both the need for and the difficulty of reaching a global solution to a problem where vested interests loom large.

There is evidence that health education through nudging can help to reduce demand. A good example is the national campaign in France 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 (Sabuncu *et al.* 2009). Recent randomized control trials of the effect of campaigns directed at outpatients in Sweden and in Los Angeles 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 nudging campaign in the 2000s—proved lasting, however. In sum, there is something to be said for nudge campaigns, but if they are to be effective they cannot be once-off measures.

Table 2: Reducing demand

Concept	Target	Observations
Phages	Selectively kill bacteria containing AMR genes	Ongoing; informed by CRISPR biology
Research on genetic composition of E. coli bacteria	E. coli vaccine	Ongoing
Genetically engineering livestock against infections	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'	Clostridium difficile	Heralded as important breakthrough in late 2014

Source: Ó Gráda (2015)

Other developments that may help to reduce demand for antibiotics (Table 2) include:

- **Personalised medicine:** if this takes off, it should be possible to specify which antibiotics are appropriate to any given person, and thereby reduce usage;
- **Faecal microbiota transplantation (FMT):** with *clostridium difficile* bacteria becoming increasingly drug-resistant, faecal transplants—or 'crapsules'⁶—emerged in 2014 as a promising alternative therapy for resolving CDI;
- Vaccines such as NDV-3 (against MRSA) and RTS,S (against malaria) are at an advanced stage, also offer an alternative to antibiotics.
- More controversially, using CRISPR (clustered regularly interspaced short palindromic repeats) biology could create mosquitoes or livestock with parasite-blocking genes, and thereby prevent malaria or reduce drug usage.

4. THE PIPELINE

Most accounts of the state of the pipeline are unremittingly bleak. 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. 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. Similarly, as streptomycin resistance in the treatment of tuberculosis became a problem from the late 1940s, more effective

antibiotics replaced streptomycin in the initial treatment of that disease. The same holds for dozens of other drugs. So resistance is natural and inevitable: it becomes an issue only if the antimicrobial artillery is not being consistently updated.

The problem—so we are repeatedly warned—is that the artillery has not been updated. 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 the end of the millennium, is a bit of a mystery. There is a pervasive impression today that the supply problem is worse now than it was a decade ago. This techno-pessimism, which is not new, 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’.

Table 3: Light at the end of the pipeline?

<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	E. coli, cUTI	Cubist
teixobactin	2015	Early stages	MRSA, Mycobacterium tuberculosis	Academic/Big Pharma collaboration
KAE 609	2014	Phase IIb	Malaria	STI/Novartis
tafenoquine	2014	Phase III	Malaria	GKN
ceftazidime-avibactam (CAZ-AVI)	2014	Restrictive FDA approval	Complicated IAIs and UTIs	AstraZeneca/Forest Laboratories

Note: For further details see Ó Gráda (2015)

A closer look at the supply of new antibiotics suggests that technology is not at a standstill, even though the lack of certain kinds of new effective antibiotic is worrisome. As of December 2014, the U.S. FDA’s register listed thirty-seven new antibiotic drugs under development. 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 we stand in early 2015 is appropriate (Table 3).

4.1. MRSA

Not all antibiotic resistances are equally serious: for reasons stated earlier, in high-income countries MRSA is often seen as the gravest threat. But it is simply incorrect to say none of the drugs currently available offers a defense against *Staph. aureus* or that the pipeline for new drugs targeting *Staphs. aureus* is dry. In 2014 the FDA approved three such drugs under the 2012 Generating Antibiotic Incentives Now (GAIN) Act. The first two were developed by relatively small

biotech companies, but acquired by bigger fish in the wake of FDA approval. The third, originally developed by Eli Lilly, 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.

The race between these new drugs is now on. For what such numbers are worth, market analysts predict sales of \$204 million for Dalvance, \$309 million for Orbactiv and \$216 million for Sivextro by 2020. A fourth new antibiotic Zerbaxa also won FDA approval in 2014, although it does not claim efficacy against *Staph. A*. Four new approvals targeting AMR in a year compares favourably with five in the previous decade.

Teixobactin, the outcome of a public-private partnership between academic researchers and a privately owned biotech company based in Cambridge, Mass., captured some of the headlines in early 2015. 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.

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. Antibiotics can 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 the countries at risk, but their data should be regarded as part of what is in effect an early warning system.

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 they aim to have 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, which should be ready for use before the end of 2015. While an imperfect substitute for antibiotics, such a vaccine can help by reducing the demand for antibiotics.

4.3. MDR-TB

The supply-side outlook for MDR-TB is also mildly encouraging. 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.

4.4. CRGNB

If the outlook on malaria and MRSA is mildly ‘encouraging’, the big worry now is ‘nightmare’ carbapenem-resistant gram-negative bacteria (CRGNB), against which few therapeutic options exist. Fosfomycin, tigecycline, polymyxin B, and colistin are the last-line-of-defense therapies against CRGNB, but all either have limited effect or entail serious risks. Where such infections are

a threat, clearly rapid screening, detection, and isolation are crucial. Down the road, carbapenem-resistant bacteria may require more drastic public health interventions.

The highly restrictive—and controversial—nature of the FDA’s approval for CAZ-AVI (ceftazidime-avibactam) in late 2014 is an indication of 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’. The CRGNB danger suggests the need for a pipeline strategy that focuses not on resistance in general, but on where it presents the greatest threat.

5. CONCLUSION

AMR poses a major challenge to both policy-makers and to scientists. History suggests that the welfare costs of worst-case scenarios such as those broadcast in the media are very high indeed, and these should not be treated lightly. At the same time, history also shows that some of the more apocalyptic scenarios being aired are unlikely, partly because, as in the past, preventive medicine and public health measures can play a major role, partly because the threat should result in the reduced use of antimicrobials, and partly because the commercial opportunities that threats such as AMR offer to inventors and manufacturers.

Warnings about antibacterial resistance are not new: Alexander Fleming cautioned in his Nobel Lecture in 1945 that misuse would result in microbes becoming resistant. Warnings reached a new level in the 1990s and a crescendo during the last few years. The dreadful prospect of a post-antimicrobial world where, 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 then the point of the war against microbes 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? Perhaps not, for a range of reasons.

First, awareness of the problem is much greater. That explains the timing of institutional responses such as the GAIN Act, greatly increased U.S. federal funding, the Harrison Prize, the UK Five Year Antimicrobial Resistance Strategy (with due focus on conservation and stewardship), Jim O’Neill’s review of the economic incentives for drug discovery and the joint research initiative announced by the UK Science Minister in July 2014 in the wake of the Prime Minister’s warnings. By extending by five years the patent life of new antibiotics that treat serious or life-threatening infections, the U.S. GAIN Act addresses one regulatory uncertainty complained of by Big Pharma (although this entails welfare costs too). 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 two years ago the prospect of a 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 March 2015 four promising vaccines had been developed. Increasing public awareness of the AMR problem is also beginning to constrain corporate behavior.

Second, the big reductions in MRSA resistance in Ireland and the UK over the past decade are evidence of what can be done to arrest resistance in hospital settings at national level. 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 CRGNBs.

This suggests the need for a narrower policy focus on where the threat is greatest, rather than on new antibiotics 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. Yet although the challenge posed by AMR in certain areas is very real and while there is no room for complacency, warnings of 'AMR apocalypse now' are overdrawn.

BIBLIOGRAPHY

- Acemoglu, Daron and Simon Johnson. 2007. 'Disease and development: the effect of life expectancy on economic growth', *Journal of Political Economy*, 115[6]: 925-85.
- Crafts, N. F. R. 2002. 'The Human Development Index, 1870-1999: some revised estimates.' *European Review of Economic History* 6: 395-405.
- Crafts, Nicholas and Markus Haacker. 2003. 'Welfare implications of HIV/AIDS', IMF Working Paper 03/118.
- Davenport, Romola J., Kerry Hickson, and C. Ó Gráda. 2014. Health, wellbeing, and antimicrobial resistance: insights from the past for the present', unpublished.
- KPMG. 2014. The Global Economic Impact of Anti-microbial Resistance. London: KPMG.
- Laxminarayan, Ramanan. 2014. Antibiotic resistance: balancing conservation against innovation, *Science*, 345: 1299, 12 September.
- Ó Gráda, Cormac. 2015. "Cast back into the dark ages of resistance? The challenge of antimicrobial resistance", public lecture, University of Warwick, 28 April 2015.
- Prados de la Escosura, Leandro. 2014. 'Human development as positive freedom: a world view since 1870', The CAGE-Chatham House Series Number 12, February.
- President's Council of Advisors on Science and Technology. 2014. *Report to the President on Combatting Antibiotic Resistance*.
- Sachs, Jeffrey and Pia Malaney. 2002. 'The economic and social burden of malaria'. *Nature* 415: 680-65, 7 February.
- RAND Corporation. 2014. Estimating the Economic Cost of Antimicrobial Resistance. Santa Monica: RAND Corporation.
- Smith, Richard and Joanna Coast. 2012. *The economic burden of antimicrobial resistance: Why it is more serious than current studies suggest*. Technical Report. London School of Hygiene & Tropical Medicine, London.
- Smith, Richard and Joanna Coast. 2013. 'The true cost of antimicrobial resistance'. *British Medical Journal*. 346: f1493.
- WHO. 2014. *Antimicrobial Resistance: Global Report on Surveillance 2014* [<http://www.who.int/drugresistance/documents/surveillancereport/en/>].

ENDNOTES

¹ This paper draws heavily on joint work with Romola Davenport and Kerry Hickson (2014), but they are not responsible for the views expressed here.

² The words used by British Prime Minister David Cameron, warning of spreading anti-microbial resistance on 2 July 2014 [<http://www.bbc.co.uk/news/health-28098838>].

³ Some economists highlight how infectious diseases hinder economic growth, while others deny any link between health improvements and GDP growth in the past, arguing that the negative economic impact of resultant population growth trumped any direct health benefits (Sachs and Malaney 2002; Acemoglu and Johnson 2007; Weil 2014). But few countries today have yet to embark on the fertility transition, and indeed economic growth tends to reduce fertility. When this endogenous decline in fertility is factored in, the long-run outcome is a clear improvement in GDP per capita.

⁴ Compare Prados de la Escosura 2014.

⁵ See, however, Crafts 2002; Crafts and Haacker 2003.

⁶ *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>].