HEALTH, WELLBEING, AND ANTIMICROBIAL RESISTANCE:

INSIGHTS FROM THE PAST FOR THE PRESENT[1]

A RESEARCH AGENDA

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[1] NOTE: a much longer and more technical version of this paper (Davenport, Hickson, and Ó Gráda 2014), with a full list of citations, is available.

Non-technical summary

The development of resistance by organisms to antimicrobials is a natural phenomenon. There is evidence of resistance to most antimicrobials within years of their discovery. The problem in the twenty-first century is that this resistance is coinciding with the reduction in new therapies to replace ineffective ones. Antimicrobials are used widely across the healthcare service: from treating specific infections, to prophylactic applications in surgery, radiotherapy, and cancer chemotherapy. As a result some maintain that many modern advances in medicine could be lost. Our research highlights a more optimistic scenario. Although antimicrobial resistance is likely to pose some serious problems, history highlights that there are numerous strategies that governments can employ to maintain the health of the population. For example, preventative measures such as vaccination, hand washing, appropriate family practice prescribing, effective infectious disease control procedures in hospitals, and surveillance will go a long way to curtailing the extent and consequences of microbial resistance. This is reflected in the history of numerous diseases, from the plague to tuberculosis to methicillin-resistant *Staphylococcus aureus* (MRSA). These experiences all highlight that with good governance that delivers sound public health policies it will be possible to substantially reduce the impact of antimicrobial resistance. A key next area of research is therefore to consider the most efficient public health policies to stem the spread of antimicrobial resistance.

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EXECUTIVE SUMMARY

Antimicrobials have played a key part in the large reductions in deaths and illness caused by infectious diseases in high-income economies since the 1940s. Today infectious diseases remain a major policy concern for two main reasons: for their impact on mortality and morbidity in low-income countries, and also as a result of evidence of increasing levels of resistance of certain pathogens to antimicrobials in both the developed and developing world. Antimicrobial resistance (AMR) is a serious and growing concern. The World Health Organisation claims that 'resistance to common bacteria has reached alarming levels in many parts of the world and … in some settings, few, if any, of the available treatments options remain effective for common infections' (WHO 2014a), while H.M. chief medical officer recently predicted that 'we will find ourselves in a health system not dissimilar to the early 19th century at some point', while prime minister David Cameron has warned that antimicrobial resistance could 'cast the world back into the dark ages of medicine'.[2]

Although current levels of antimicrobial resistance are low and as a result the economic or welfare losses are minor, much of the concern pertains to future predictions and to the greater urgency of managing antimicrobial resistance now. Antimicrobial resistance is analogous to global warming in the sense that there is widespread agreement about the potentially disastrous consequences of both, but because those consequences are not immediate, little is done about them.

AMR is a natural phenomenon: in time, micro-organisms evolve strategies to evade the drugs designed to destroy them. The problem today is that ineffective drugs are not being replaced by effective substitutes: the pharmaceutical pipeline seems in danger of drying up. This is the source of the fear that many of the gains linked to modern advances in medicine could be lost.

[2] 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.

With this in mind, a better historical appreciation of what health gains are now in danger of being lost and what alternative solutions could be resurrected is needed. Here it is argued that although antimicrobial resistance is extremely unlikely to undo all the gains achieved in eradicating and reducing the prevalence of infectious disease, 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. This report accordingly identifies that part of the health transition associated with the gradual reduction in deaths from infectious diseases, and the factors associated with it. It also discusses the economic and welfare gains associated with the resultant improvement in health and life expectancy.

A worst case, apocalyptic, scenario recently put forward by Richard Smith and Joanna Coast postulates a situation in which most, if not all, antimicrobials become ineffective, with the resultant loss of many advances in medical care that antimicrobials have enabled. The list is vast and ranges from advances in surgical procedure to cancer chemotherapy in addition to the more obvious infectious diseases. Hence, some claim that antimicrobial resistance will jeopardise the entire health care system.

Our historical account generates more sanguine conclusions about future health associated with antimicrobial resistance. Although the timing and magnitude of resistance is difficult to predict, we use historical evidence associated with some key diseases in order to highlight that there are numerous coping strategies. In fact, in developed economies significant falls in mortality from infectious diseases had already occurred before antibiotics were invented. A constellation of other factors—public health measures, personal hygiene, better nutrition, and later vaccination programmes—were responsible for these earlier declines. Much of the decline in tuberculosis occurred before the introduction of efficacious therapy (streptomycin) in the middle of the twentieth century. More recently the dramatic decline in methicillin-resistant *Staphylococcus aureus* (MRSA) transmission in the decade following the UK Government's introduction of mandatory reporting highlights the

range of alternative measures that can be employed to tackle antimicrobial resistance. Hence, with good governance that delivers public health policies to curtail the spread of resistant antimicrobials, coupled with increased public awareness of the risks and benefits, we can go a long way to solving the problem of 'super bugs'. As such, an increase in antimicrobial resistance, even to apocalyptic levels, will not see a return to the pre antimicrobial world.

That said, there is little room for complacency. The sigmoid distribution and timing of antimicrobial resistance highlights that there is also a role for government to act promptly to limit the increase of antimicrobial resistance. For example, policies related to responsible prescribing, improved hygiene and sanitation, immunization and surveillance can curb usage and, thereby, resistance. Given the public good character of protection against AMR, public policy also has a role to play in encouraging the supply of replacement drugs.

The need for good governance - in both developed and developing economies - is underlined by the value of health to the economy. Economic analysis indicates that health gains made a major contribution to increases in living standards during the 20th century and provided a significant contribution to twentieth century growth rates in developed economies.

Introduction

Antimicrobial drugs are compounds that treat infection by destroying or preventing the growth of pathogenic microbes. Most antimicrobials are targeted against bacteria (these are often termed 'antibiotics'), but some target viruses (key examples include Tamiflu-type drugs and anti-retroviral therapies) as well as other unicellular pathogens such as fungi and malarial parasites. The evolution of antimicrobial resistance (AMR) is inevitable: resistance to the first key antibiotic, penicillin, emerged within three years of its commercial use (Bergstrom & Feldgarden 2008). However concern about AMR has become acute in the face of evidence of [a] progressive loss of effectiveness of front-line drugs against especially *Staphylococcus*, tuberculosis and malaria and [b] a slowing of the rate of discovery of new antimicrobials. References to a retreat to 'a health system not dissimilar to the early 19th century' and to 'a bleak post-antibiotic future, in which infectious diseases once again reign supreme' pose an apocalyptic future without antimicrobials. However almost all antimicrobials have come into use since the late 1930s and therefore made at best a late and minor contribution to the enormous declines in infectious disease mortality that occurred in high income countries over the last two centuries. An historical perspective is therefore essential to any evaluation of the likely consequences of AMR. Moreover historical analyses can help to identify key factors other than antimicrobial technologies that have underpinned the effective control of infectious diseases.

1.1. The Health Transition

The huge and global increase in life expectancy over the past century is one of humanity's greatest achievements. Global life expectancy is now over 70 years, compared with perhaps 30 years in 1900. Most of this profound shift in longevity has been driven by reductions in infectious diseases. Infectious diseases accounted for around half of all deaths in most high-income countries two centuries ago, but only roughly 6 per cent today. Even in the poorest group of low-income countries, where

infectious diseases still loom large, infections still account for less than half of deaths and life expectancy is higher than it was anywhere in the world before 1850 (WHO 2014d; Riley 2001, Table 1).

Table 1. Distribution of causes of death, 1850 – 2012 (%)

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	1,1671,361	5,696,969
Life expectancy	43	46	64	79	62

Sources: Davenport, 2007; ONS, 2006; 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 ≥ $12,476) and low-income ≤ $1,025) groups are as defined by the World Bank in 2012.

While most of the enormous gains in life expectancy in low income countries were achieved after 1950, the control of infectious diseases in European societies dates its origin to at least the fifteenth century. The devastating impact of bubonic plague in Europe, where the Black Death of 1348-52 probably halved the population, was followed by a prolonged evolution of quarantine and surveillance methods that resulted in the progressive contraction of plague to urban areas and finally in the

eradication of plague first from Scotland (1648), then England (1665), and eventually from western Europe (in the 1720s) (see section 1.2). In contrast plague remained a major problem in its old areas of endemicity until the early twentieth century.

In England the disappearance of plague was accompanied by the disappearance of infectious disease epidemics associated with food shortages. Before the twentieth century most famine-related deaths were caused by infectious diseases rather than starvation: it was the rigorous control of epidemic diseases in the last century that made starvation per se such a prominent phenomenon of modern famines (Ó Gráda 2009). England was the first country decisively to escape famine, as a consequence of market integration facilitated by internal peace and free trade, and the development of an effective welfare system (the Poor Laws). Ironically the decisive reduction in mortality crises caused by plague and famine was not accompanied by a rise in life expectancy. On the contrary the precocious escape from famine was accompanied by an epidemiological integration that increased the circulation of diseases (Figure 1). Smallpox in particular became a major cause of death in seventeenth and eighteenth century England, and was particularly lethal in towns. This period was characterised by very high urban death rates and cities functioned as 'urban graveyards' requiring high levels of rural in-migration just to sustain their populations. Under these conditions modern levels of urbanisation were impossible without population decline. However the heavy burden of infectious disease began to lift in the late eighteenth century as a consequence of a range of preventative health measures the most important of which was vaccination against smallpox. Thus urban death rates fell decisively during the key period of British industrialisation and made possible modern rates of urbanisation and economic growth.

In Britain the demographic transition from high mortality and fertility to low mortality and fertility began in the late eighteenth century. While the falls in mortality in the period 1750-1820 remain poorly understood it appears that the greatest improvements occurred in death rates from those diseases that were most lethal but also most easily prevented by practices that broke relatively tenuous chains of transmission. These practices included improved personal hygiene and local and state policies regarding quarantine, isolation and immunisation. Smallpox was reduced to a

minor cause of death by public vaccination campaigns. Typhus, the great scourge of armies, gaols, ships and slums, declined in parallel with increased efforts to isolate sufferers and inate contacts as well as improvements in clothing and personal hygiene. Malaria was controlled by drainage schemes that reduced mosquito populations. Cholera, which swept through Europe in five pandemics between 1831 and 1896, was ultimately controlled by improvements in water supplies and faecal disposal, by the tracing and isolation of victims and by quarantine of shipping to prevent introduction, strategies which protected England but not continental Europe from the fifth pandemic in 1881-96. Progressive control of the more lethal infectious diseases after 1750 reduced overall mortality and made especially cities much safer. Acute infectious diseases became confined largely to childhood (measles, whooping cough, scarlet fever, diphtheria) and to the extremes of life (diarrhoeal and respiratory infections in infancy and old age). These diseases were in the main less lethal but also more infectious and therefore harder to prevent than the major killers of earlier periods. Respiratory tuberculosis, a chronic infectious disease, remained the main cause of death of young adults. In England at least it appears that wealth provided little survival advantage before the nineteenth century and this probably reflects the ability of very lethal infections to overwhelm any advantages of host nutritional status, compared with the more discriminating diseases that came to the fore after 1800.

Despite rising incomes life expectancy stagnated between 1830 and 1870, however this stagnation should be viewed as a remarkable achievement given the enormous redistribution of the population from rural to insalubrious urban centres in this period, and probably masks considerable improvements in mortality in most areas.

The modern secular decline of mortality began in the 1870s in Britain and was reflected initially in falls in both scarlet fever (a major killer of children that apparently became spontaneously less virulent) and respiratory tuberculosis. Falls in childhood infectious diseases and diarrhoeal mortality from 1900 raised life expectancy fastest at youngest ages but survival improved at all ages except those above 80+ as a consequence of falls in tuberculosis but also respiratory infections and cardiovascular diseases. While earlier mortality improvements were confined largely

to Britain and a few other north-west European populations (most notably Sweden and France), improvements after 1870 were very widespread in European and neo-European societies. These mortality declines coincided with improvements in both living standards (especially nutrition) and sanitation (drinking water and sewerage), making it hard to disentangle the impact of public health interventions from the 'invisible hand' of the market. Less widely acknowledged is the role of mass education and falling family sizes in promoting child health, although these factors loom large in explanations of mortality declines in less developed countries in the twentieth century (Woods 2000; Caldwell 1986). Although the breakthroughs in microbiology associated with Koch and Pasteur did not result in immediate breakthroughs in vaccine and antibiotic technologies the applications of antiseptic and aseptic techniques made surgery progressively safer from the 1870s onwards. The importance of hygiene and disease prevention is perhaps most obvious in military statistics. WWI was the first major war in which more deaths were caused by battle wounds than by epidemic diseases (particularly typhus, dysentery, smallpox and typhoid) (in fact the Japanese army is credited as the first *army* with this distinction, having vaccinated its troops against typhoid in its successful 1905 war against Russia) (McWeeney 1915). Inoculation and vaccination against smallpox (from the 1770s) and typhoid (from the 1900s) and improvements in personal hygiene and in the disposal of faeces conferred measurable advantages on modern armies and were widely adopted over the course of the nineteenth and early twentieth centuries. These developments were paralleled to some extent by developments in the rapid and hygienic treatment of battle wounds to reduce infection (Cooter et al. 1999).

By the late 1930s, when the first antimicrobial sulfa drugs came into widespread use, infectious diseases accounted for less than 15 per cent of all deaths in England, down from 36 per cent in 1900 and 45 per cent in 1850 (Table 1). This profound reduction in infectious disease mortality was achieved by a combination of preventative public health measures (surveillance, quarantine, isolation, vaccination, waste disposal and clean water supplies), preventative medical practice (in preventing infections of accidental and surgical wounds), education (resulting in better hygiene and childcare practices) and increased resistance to diseases as a consequence of

poverty reduction (especially improved nutrition and reduced crowding). *Treatments* for infectious diseases remained largely ineffective (or dangerous, as in the case of amputation) until the advent of antibiotics, and played relatively little role in the so-called 'epidemiological transition' in high-income countries. The most important contributions of antibiotics to mortality decline in this context were in the control of infections associated with wounds, operations and childbirth, in reductions in mortality from pneumonia, and in the elimination of tuberculosis as a major cause of death and morbidity (see section 2.2). The immediate impact of antibiotics was least in populations such as the U.K. and U.S.A. where very substantial declines in infectious disease mortality (especially tuberculosis) preceded the discovery of penicillin, and larger in populations with a higher infectious disease burden (such as Finland: Kannisto et al. 2011).

Since the 1940s infectious disease mortality has halved in Britain, and these gains reflect both the impact of antibiotics in controlling tuberculosis, pneumonia and diarrhoeal diseases, and the proliferation of vaccines against childhood and respiratory diseases (including pneumonia and influenza). However much of the impact of antibiotics is hidden in these statistics. A superficial reading of historical trends would suggest that the loss of all antimicrobial remedies would at most 'only' double infectious disease mortality. However this is over-simplistic for two main reasons. First, infectious disease rates have fallen for a variety of reasons since 1945, of which antibiotics is only one component. Death rates had been falling progressively for at least seventy years before 1945, and it is likely that these trends would have continued to some extent without antibiotics and especially given the profound effects of vaccines against childhood diseases, influenza and pneumonia developed after 1950. Second, the population of Britain today is much older than it was in 1950 and deaths are now concentrated overwhelmingly at advanced ages. This exaggerates the relative effect of infectious diseases today, because many of the deaths attributed especially to pneumonia occur as a sequalae of severe chronic diseases (ONS, 2010). However the impact of loss of antibiotics would be significantly higher because treatments for the main non-contagious diseases - cancers and cardiovascular diseases - that cause the vast majority of deaths today rely on the prophylactic use of antibiotics to prevent

opportunistic infections (Smith and Coast 2013). While some of these infections, including MRSA (methicillin-resistant *Staphylococcus aureus*), can be prevented to some extent by traditional preventative measures such as high standards of hygiene and wound care, much of the advantage of the enormous advances in medical technologies in the last sixty years would be jeopardised in the event of widespread antimicrobial resistance.

In less developed countries the impact of antimicrobial technologies has arguably been larger than in high-income countries, although very difficult to quantify. Even in many low-income countries very substantial falls in mortality occurred before the mid-twentieth century, resulting in the very high population growth rates evident in most developing country populations by 1950 (Davis 1956). These were achieved in part by preventative measures against plague, malaria, yellow fever and smallpox, and by the stabilisation of food supplies (Livi-Bacci 2001; Riley 1983; Preston 1980; Dyson 2010). Reductions in mortality seem to have been most profound in societies with relatively egalitarian access to food and basic health care, and with relatively high levels of female autonomy and education, indicating the importance of hygiene and childcare practices (Caldwell 1986; Riley 1983). However in most low income countries gains in life expectancy were most rapid in the period since 1945, and have dwarfed historic rates of improvement in high income populations (Figure 2).

While the rapidity of these gains is widely attributed foremost to health technologies (Davis 1956; Preston 1975; Easterlin 1998) it is very difficult to attribute gains to particular interventions in the absence of evidence of causes of death in many populations, or even of reliable all-cause death rates. More recent cross-sectional data also suffer from the difficulty of separating the contribution of particular interventions in a situation where many interventions are operating synergistically and in tandem with rapid social and economic change to reduce mortality. The importance of different interventions depends partly on the geographical distribution of diseases. Where malaria was endemic then control of mosquito populations using drainage and insecticides (especially DDT) has driven profound improvements in mortality. The area of the world at risk of malaria has halved since 1900 (Hay et al. 2004). In

surveying early changes in causes of death in a selection of poor countries between 1950 and 1980 Preston (1980) attributed the greatest gains to malaria reductions in malarial areas, and to declines in respiratory infections elsewhere. Although pneumonia is largely treatable with antibiotics Preston attributed most of the improvements in influenza and pneumonia mortality to improved resistance to infection as a consequence of gains in nutritional status. Large improvements in mortality from cardiovascular diseases (CVD) are also an almost ubiquitous feature of the early stages of mortality declines, and these may be largely a consequence of falls in infectious diseases that trigger or predispose sufferers to CVD (Preston, 1976). More recently reductions in smoking and medical innovations such as beta-blockers and statins have sustained falls in CVD mortality (Deaton 2013: 131-40)

Analyses of more recent mortality declines in developing countries have identified large geographical heterogeneities but consistently identify access to clean water as one of the most important factors in reducing mortality, together with maternal characteristics such as education or female autonomy (Fewtrell et al. 2005; Caldwell & McDonald 1982; Hobcraft 1993). Immunisation programmes are credited with profound reductions in especially childhood mortality since the 1980s and the expansion of access to vaccines and the development of new vaccines (especially against causative agents of pneumonia and most recently diarrhoea) have been identified as a major factor in the impressive reductions in child mortality under the Millennium Goals programme since 2000 (WHO 2014d, 2014e). Diarrhoeal mortality, which is largely due to causes untreatable by antimicrobials, has fallen dramatically in the last 40 years due both to the enormous impact of clean water provision and hand-washing campaigns, and also because of oral rehydration therapy, an inexpensive and lifesaving treatment for dehydration. Although per capita antibiotic consumption is relatively high and increasing in most developing countries (Col & O'Connor, 1987; van Boeckel *et al*., 2014), the persistence of pneumonia as one of the leading causes of death indicates both the widespread persistence of poor nutritional status and living conditions and the incomplete penetration of antibiotics. UNICEF estimates that currently only 29 per cent of children with pneumonia in developing countries are treated with antibiotics (UNICEF, 2012).

At present many key infections are targeted in a concerted manner by preventative and curative technologies, for example the combined use of vaccines and antibiotics against respiratory infections, or insecticides and artemisinin combination therapy against malaria. Since treatment can reduce transmission rates it is very difficult to separate the impact of specific technologies, and to estimate the costs of their loss. One virtue of historical studies is that evidence of progressive gains from the step-wise introduction of specific technologies can be used to estimate the independent contribution of each intervention.

To summarise, declines in infectious disease mortality have been the main cause of the profound improvements in global life expectancy since 1800. The elimination of individual diseases has been demonstrated clearly to reduce mortality and morbidity ((rather than simply raising deaths from other causes without improving life expectancy)). However the contribution of antimicrobial drugs to historical mortality declines is, at first inspection, surprisingly slight. The control of infectious diseases was achieved predominantly by relatively low technology methods. However these methods often required strong state intervention to enforce public health measures such as surveillance and quarantine and to promote vaccination, and so while these interventions were implemented progressively from the fifteenth century in England they remain incompletely implemented in low-income countries today. Although some of these interventions have been scaled back with the advent of antimicrobial treatments they remain key to disease control. For example antibiotics are now used prophylactically to prevent disease transmission in cases of bubonic plague outbreaks in preference to more traditional methods of surveillance and quarantine because the later are more expensive (although also more effective, and preferred by disease control experts: Dennis et al. 1999). However the advent of antimicrobial resistance may require implementation of older methods to prevent or halt disease outbreaks when 'fire-fighting' style responses fail. This has already happened in the case of MRSA, a major cause of hospital-acquired infections. In the U.K. the incidence of MRSA infections has fallen not because of new antibiotic treatments but because of enhanced application of longstanding rules regarding hygiene and prevention of transfer of infection (BBC 2012; Figure 3). Immunisation,

the twin of the antibiotics revolution, can reduce the need for antibiotic treatment and has already been demonstrated in some instances to reduce the incidence of antimicrobial resistance by reducing pathogen transmission (Andre et al. 2008). One advantage of immunisation over prophylactic use of antimicrobials is that immunisation does not impose any genetic selection for antimicrobial resistance. The very widespread prophylactic use of antibiotics in immune-compromised organ transplant and cancer chemotherapy patients and in routine surgery requires an urgent assessment of the consequences for these treatments of antimicrobial failures, and of alternative strategies to prevent infection.

1.2. Successful Interventions Before Drugs: Plague as a Case Study

Plague (*Yersinia pestis*) is the most fearsome of all infectious diseases. It caused the death of perhaps 50-60 per cent of the population of northern Europe in the late 1340s and reintroduction from Asia caused persistent violent epidemics that were sufficient to suppress population growth for up to two centuries after the Black Death. In England population did not recover to its pre-Black Death level until the 1620s.

Since the Black Death reduced labour inputs but not those of land or capital, it should have increased wages and output per head. And, indeed, in Western Europe workers gained while landlords lost. It is sometimes claimed that the rise in wages may have spurred labour-saving innovations such as the printing press and firearms, though this remains speculative. Plague, unlike, say, malaria or HIV/AIDS today, did not lead to increases in health expenditures or morbidity-induced declines in labour productivity and life expectancy. The economic impact of other killer diseases is more complex because they increase both mortality and morbidity.

Although initially a very widespread phenomenon plague outbreaks were gradually confined to urban centres. London endured five serious plague epidemics between 1563 and 1665. Cross-section evidence on mortality from London c. 1560-1670 suggests that rich and poor suffered similarly at the outset, but by 1665 the poor were much more at risk than the rich, partly because the rich were better placed to leave

the city (Champion 1995; Cummins et al. 2014).

The disappearance of plague from the western world in the early modern era owed nothing to curative medicine. Nor were increasing incomes responsible, since wages were already declining when the Black Death was retreating. Increasing immunity may have played a role, although this is controversial. The most comprehensive analyses of the disappearance of plague from Europe suggest that a combination of routine surveillance (such as urban Bills of Mortality, instigated to give early warning of plague outbreaks) and quarantine of shipping and to a lesser extent infected individuals and their contacts was sufficient to break the fairly tenuous chain of transmission between infected ships and European populations. Northern Italian cities devised an elaborate system of *cordon sanitaire* (including naval blockade of affected ports), economic sanctions and espionage in a partially successful attempt to prevent transmission, but their functions as European *entrepots* for Asian trade, and mistrust between the city states, meant that plague was not completely excluded from southern Europe until the 1720s. Britain's position on the edge of Europe made surveillance and quarantine more viable and plague disappeared from Scotland after 1647 and from England after the Great Plague of 1665.

A third plague pandemic spread globally in the 1890s, killing an estimated twelve million in China and India and spreading via shipping as far as Africa and America. That pandemic was also very uneven in its impact across classes: in Bombay in 1897-1900 it killed 9 per cent of the ordinary and low-caste Hindu population, 6.1 per cent of upper-caste Brahmins, 2.7 per cent of Jews and Parsis, but only 0.5 per cent of Europeans. In this case early warning systems and quarantine did not prevent long-distance transmission but where rigorously implemented was sufficient to prevent local epidemics (for example 535 died in Australia, mostly in Sydney, and 113 in San Francisco).

Plague continued to be a major public health issue until the 1940s, and plague infection is still present in wildlife rodent reservoirs in parts of Asia, Africa, and the western U.S. But whereas between 1898 and 1918 plague killed over ten million in India, in the recent past rare localized outbreaks have been contained using the

antibiotic tetracycline as a chemo-prophylactic agent. Although plague is nowadays treatable with antibiotics, deaths still occasionally occur.

2. Economic Impacts

Clearly, AMR will not entail a return to a Year Zero in which infectious diseases reign supreme once again. Nevertheless it is useful to consider what the past can tell us about the economic and welfare gains associated with the decline of mortality from infectious diseases. The nature/prevalence of the disease in question matters. Some diseases kill but have little impact on the health of the few victims who survive (e.g. plague); others don't usually kill but debilitate those who contract them (e.g. hookworm); while others both kill and scar (e.g. smallpox, malaria). And some diseases also scar those who don't necessarily contract them but are unfortunate enough to have been born or very young during an epidemic (e.g. malaria, influenza). Nevertheless how improvements in health affect economic performance is controversial.

Some economists highlight how infectious disease hinder economic growth (e.g Sachs and Melaney 2002), while others deny any link between health improvements and GDP growth in the past, arguing that the negative economic impact of the population growth that ensued trumped any direct health benefits (Acemoglu and Johnson 2007). This point is teased out further by Cervellati and Sunde (2011), who find the impact of health (proxied by life expectancy) on growth depends on whether a country has been through the demographic transition or not. However, mortality decline is generally regarded as a pre-requisite for fertility decline, and economic growth tends to reduce fertility (Cleland and Wilson 1987; Guinnane 2011). When the impact of reduced mortality on fertility is factored in, the long-run outcome is a clear improvement in GDP per capita. Most have identified this in cross-country data using life expectancy as a proxy for health (e.g. Bloom, Canning and Fink 2013; Weil 2014); Audibert *et al.* (2012), using a different set of proxies, find that morbidity exerts a strong negative impact on GDP growth.

Estimates of the economic impact of malaria eradication are of particular interest, because out of all diseases in the parasitic class, malaria is arguably the most significant, in terms of mortality, morbidity, and socioeconomic burden. Malaria is a life-threatening disease caused by parasites that are transmitted to mammals via infected female mosquitoes. In 2012, the WHO reckons that there were over two hundred million cases of malaria and 0.6 million deaths – mostly among children living in Africa.

Humanity's long campaign against malaria has ranged from attempting to reduce mosquito populations through drainage in eighteenth century England and the Netherlands and with DDT and other insecticides from the 1940s on, to the treatment of affected individuals with the anti-malarial drug artemisinin and the subsequent evolution of Artemisinin Combination Therapy (ACT) since the 1980s. The environmental consequences of large-scale insecticidal spraying led to the current three-pronged strategy of reducing exposure via insecticidal bed nets and indoor spraying, and treatment of infected individuals with ACTs. However genetic approaches focused on control of infected insect populations via introduction of genetically manipulated organisms are a key focus of research on malaria and other insect-borne diseases such as dengue fever and yellow fever. Evidence of developing resistance to artemisinins in south-east Asia lend the case of malaria a particular resonance.

Estimates of the impact of malaria on productivity and income vary rather widely. In much-cited studies using cross-country data, Jeffrey Sachs and various co-authors have calculated that malaria imposed a substantial annual cost in terms of GDP growth foregone on heavily infected countries (Gallup and Sachs 2001; Sachs and Melaney 2002). A commonly noted problem with Sachs's approach is that results may be biased if the geography linked to the prevalence of malaria is also independently associated with lower economic growth. Attempts to control for this find that malaria still helps to account for the variation in per capita GDPs, though less than originally claimed (Bhattacharyya 2009; McCord and Sachs 2013; Depetris-Chauvin and Weil 2014).

Country-level studies also report a link between the prevalence of malaria and productivity. These include studies of India's anti-malarial campaign in the 1950s, and of eradication campaigns in Sri Lanka, in Latin America, and in the U.S. South (Cutler et al. 2010; Bleakley 2010; Barreca 2010). The economic benefits of getting rid of malaria are reflected in increases in school attendance and per capita expenditure, and reductions in literacy. Studies of eradication campaigns on four continents all reported that the eradication of childhood exposure to malaria had beneficial consequences, ranging from increases in per capita expenditure of 1.5 to 6.8 percentage points from a ten percentage point reduction in incidence to the narrowing of the income gaps between the US North and South c. 1900 by 7 to 13 per cent and between a group of Latin American economies and the US c. 1950 by 10 to 16 per cent (Bleakley 2010).

2.1. Welfare Costs

GDP is an inadequate measure of human wellbeing. If we shift the focus to measures of what better health and longer lives are worth to people, the gains turn out to be much more significant. Economists have developed a battery of alternative measures; here we briefly review how two of them can inform assessments of the gains from the health transition described above.

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[3], but development economists and economic historians often invoke it as an improvement on GDP per capita. Applying HDI to British data for the years 1870, 1913, 1950, and 2013 produces some interesting insights (Table 2). 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,

[3] For more see Davenport, Hickson, and Ó Gráda (2014).

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 2. HDI and GDP per capita in Britain, 1870-2013

Year	[1] HDI	[2] GDP per head	Period	Relative Contribution (percentage of total)		
1870	0.476	3,190		*Y*	*H*	*L*
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: *Y*, *H*, and *L* are the HDI indices for income, health, and literacy. GDP per head is measured using 1990 international Geary-Khamis dollars; *L* is estimated using years schooling as a proportion of 15 years (assumed to be 3 years in 1870).

Other measures that seek to incorporate health, proxied by longevity, include variants of the 'real' national income measure first proposed by Canadian economist Dan Usher (1973; see too see too Nordhaus 1999; Becker *et al*. 2003); *DALY*s (Disability Adjusted Life Years) associated with the World Health Organisation; QALYs (Quality Adjusted Life Years); and 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. While all are improvements on GDP per capita, they are also subject to several caveats not discussed here. Historical studies using the VSL approach are few: here the potential of this method is illustrated with respect to tuberculosis.[4]

[4] For more examples see Davenport, Hickson, and Ó Gráda (2014).

2.2. Learning from Tuberculosis

Tuberculosis is a chronic infectious disease that is very lethal in childhood but which also affects particularly young adults. In mid-nineteenth century England the disease known as the 'white plague' accounted for half of female mortality between ages 15-39 with knock-on effects on the survival chances of children who lost parents to the disease. While mortality from tuberculosis declined very substantially in England well before effective antibiotic therapy (Figure 4) the disease was only decisively eliminated in England by a combination of antibiotic treatment and universal vaccination of infants with BCG (the Bacillus Calmette-Guérin vaccine). Tuberculosis remains a major cause of mortality in many low-income countries today (WHO 2014e), and recent gains are threatened by the emergence of several strains of multi-drug resistant tuberculosis (MDR-TB). As MDR-TB becomes more commonplace some of the gains associated with the virtual eradication of tuberculosis from high-income populations in the twentieth century will be lost. Estimating this loss with any precision is very difficult, not least because of the need for epidemiological forecasts about the outlook for MDR-TB.

Hickson (2006, 2014) has estimated upper and lower bounds of the potential costs associated with MDR-TB in the United Kingdom. The former puts the welfare value of the reductions in mortality and morbidity from tuberculosis between 1950 and 2000 at $35 billion. This sum can be interpreted as an upper bound 'apocalyptic' estimate, since it assumes the loss of virtually all the gains from virtually eradicating tuberculosis between 1950 and 2000. History suggests that such a scenario would be unrealistic. In the case of tuberculosis, significant improvements in the disease burden were seen before the discovery of drugs, due mainly to a combination of improving living conditions and possibly isolation of sufferers that reduced transmission, and improvements in nutritional status that increased resistance to infection. Subsequent improvements in population health probably mean that levels of resistance are generally higher now than in 1950. BCG inoculation was introduced into the U.K. in 1953 and although universal vaccination was stopped in 2005 BCG vaccination of neonates is currently recommended in high-risk areas of London (NHS 2013). Current estimates about the efficacy of BCG against respiratory tuberculosis (the main adult

form) range from 50 to 78 percent.[5] As such, a more realistic upper bound estimate would be in the region of $9 billion, an estimate that takes into account the use of BCG as a potential weapon against MDR-TB[6]. This represents a pertinent historical example for the wider AMR issue. As with MRSA for many infections there are likely to be public health interventions, or less efficacious or safe second line antimicrobials, that will mitigate the impact of antimicrobial resistance.

Hickson's lower bound estimate involves comparing the current situation with the most likely MDR-TB scenarios. Here she allows for a higher morbidity burden only, given that MDR-TB tends to be resolved in longer treatment times and not mortality. The proportion of MDR-TB cases was 1.6 per cent in the UK in 2012. Currently and for the foreseeable future in the case of MDR-TB, the key issue seems to be one of increased morbidity rather than 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.

[5] Colditz, G. *et al.* (1994) provide a recent survey of 1264 studies about the BCG vaccination and 70 articles were reviewed in depth and used to construct outcome measures. They use a random-effects model to estimate that BGC provided a protective effect of between 50 and 71 per cent. In a recent meta-review of a number of BCG studies (Mangtani et al., 2013) the authors found that all of the variation in reported efficacy of BCG against TB was explained by age at vaccination, stringency of testing for prior TB infection, and latitude. BCG vaccination of adolescents or adults provided 70-80 % protection against respiratory TB (the main adult form) at latitudes above 40 degrees, and less at lower latitudes. However vaccination of infants with no prior TB exposure provided up to 90% protection against the main childhood forms of TB (military and meningeal TB), regardless of latitude. Few studies have followed vaccinated individuals for long enough, but those studies that have show significant levels of protection against respiratory TB in adulthood for those vaccinated with BCG in infancy.

[6] This is calculated by reducing the number of life years lost due to tuberculosis between 1950 and 2000 by 71%, which represents a mid estimate of BCG efficacy.

The scenarios described by Hickson are highly pertinent for AMR-related policies. During the lag phase, policies aimed at controlling drug resistance will help to curtail costs. Thereafter, only policies that reduce transmission of the organism will (generally) be valuable as a means of reducing the impact of drug resistance on health. Policies directed at reducing antimicrobial usage will at this point have a limited impact. This biological reality frustrates the results of economic impact studies. During the lag phase the estimated costs of AMR are relatively low, and do not motivate expensive policy interventions. However if we wait for costs to become significant, in the exponential phase of AMR development, then the window of opportunity for intervening to prevent AMR is effectively already closed. Strengthening health systems to prevent disease transmission can contribute to reductions in AMR by preventing the spread of resistance, and will become even more important if AMR becomes widespread.

3. Back to the Future? The Looming Threat of AMR

Expressions of concern and deliberations about the dangers posed by antimicrobial resistance (AMR) are not new. Now, however, the issue is making the headlines, with gloomy warnings from G8 science ministers (2013), the WHO, the UK prime minister, and others. The WHO's first global report on AMR offers evidence of increasing resistance by an increasing range of bacteria to antibiotic treatments for intestinal and urinary tract infections, gonorrhea, and MRSA (Methicillin-resistant *Staphylococcus aureus*) infection. With growing antibiotic usage in humans and animals, the accumulation of manufactured antibiotics in the environment has expedited this process. Such is the threat, according to a senior WHO official, that 'the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill'.

Still, AMR has received less attention than many other health-related issues: witness the two decades of inaction between early warnings from specialists[7] about AMR and the WHO report. One of the main reasons for this inaction is that both policymakers and pharmaceutical companies tend to focus on the present or the short-term future, i.e. on the first phase of the sigmoidal time-path described above. Because the threat of a 'post-antibiotic era', albeit real, is not imminent, it is not a priority. This highlights the issue of incentives for policymakers arising out of evidence-based policy making, which requires the burden of AMR to be high *now* in order to justify more measure to be taken *now*. As in the case of global warming, where projected costs also assume a sigmoidal function, the potentially disastrous consequences are increasingly acknowledged, but because they are not immediate, little is done about them.

Another reason why AMR has received less attention than many other issues in health economics is because studies about the imminent burden of AMR generate results that are substantially lower than estimates about the economic burden from other (modern) diseases. For example, Murphy and Topel (2002) calculate that eliminating deaths from either cancer or heart disease in the US would generate gains in life expectancy worth $47 trillion. They show that even a modest reduction in the cancer mortality rate of 1 per cent would have an economic value of $500 billion. Estimates of the burden of AMR, evaluated on the same incremental cost basis are much lower, but, as Smith and Coast (2013) stress, this masks the most critical economic burden, which is a potential scenario of AMR leading to the loss of many advances in medical care that antimicrobials have enabled: the list is vast and ranges from advances in surgical procedure to cancer chemotherapy. According to Smith and Coast (2013) none of the studies consider the bigger picture, where AMR jeopardises the entire health care system. Estimates of the importance of antimicrobials to non-contagious disease treatments, and the costs associated with the partial failure of these treatments, should be a priority.

[7] E.g. Nobel laureate Joshua Lederberg warned in 1994 that 'we are running out of bullets for dealing with a number of infections. Patients are dying because we no longer in many cases have antibiotics that work.'

3.1. Learning from the Past

A multidimensional approach to research on the AMR threat is needed. Scientists can increase our understanding of resistance and speed up the development of new therapies, while medical practitioners have a major role to play in influencing usage and behaviour in institutional settings within their control. What can a better understanding of economic, medical and demographic history contribute?

3.1.1. Welfare and Growth

First, a historical perspective can be used to estimate the contributions of specific technological and public health interventions, and thus to calculate the welfare costs of scenarios in which these advances are lost. The stepwise introduction of most interventions, and differences in the timing of introduction in different populations, makes it possible using longitudinal historical data to estimate the disease-specific gains from each intervention. Focusing on the total welfare and output losses associated with counterfactual worlds in which antimicrobial resistance is partial or endemic yields sobering estimates of the potential costs of AMR. Such estimates, informed by history and the present, need to be refined and debated. Even the most careful of them will be indicative rather than precise. But the gap between the modest costs associated with the initial loss of resistance and the significant costs associated with a scenario in which drugs lose all their effectiveness needs highlighting. Its message is that complacency based on the currently low rates of AMR (e.g. malaria in Southeast Asia or tuberculosis in the United Kingdom) is not warranted; if we wait until the evidence-based numbers are really big it will be too late.

3.1.2 Healthy Populations and Strong Health Systems

A very brief consideration of the history of infectious disease control raises a number of key policy issues. Most importantly, successful control of some of the most

lethal diseases was achieved through fairly rudimentary techniques of surveillance quarantine, isolation, hygiene and vaccination implemented by an effective state. These very old strategies have been developed to very high levels of sophistication and efficacy in the last sixty years and remain key to the identification and control of epidemics, especially in cases where no treatment exists. A very recent example is the success of Nigeria in containing the 2014 Ebola outbreak, thanks in part to the presence of epidemiological experts and surveillance technologies associated with the global polio eradication campaign (WHO 2014c). While AMR itself must be combated by a combination of reductions in antimicrobial usage[8] and development of new drugs, health systems also need to be strengthened to reduce disease transmission and to provide early warning of disease outbreaks. Reductions in transmission reduce the need for antimicrobials, and thus can contribute to preventing both the development and the spread of AMR. Stronger health care and disease surveillance systems will also be essential in mitigating the impact of AMR.

3.1.3. The Pipeline

Most accounts of the state of the 'pipeline' of new drug development are unremittingly bleak. And they are persuasive for two reasons. One is that drug companies have little incentive to invest in new drugs for which demand is limited. The second is that, as noted, the science involved is inherently difficult. The major pharmaceutical companies blame 'a range of scientific, regulatory, and financial factors' for the unhealthy state of the pipeline, but others too (e.g. Smith and Cost 2012) insist that the once prolific pipeline bringing new antimicrobials into clinical practice is faltering. This could mean that we at a pivotal stage in the history of infectious disease, where the window of opportunity afforded by antimicrobial therapies over recent decades is rapidly closing. While the situation may not be quite as bleak as drug companies insist, both in Europe and the US current apprehensions have focused policy-makers' attention on incentives for the inventors of new microbe-

[8] In Europe today, by and large, countries with the lowest consumption of antibiotics have the lowest levels of AMR.

resistant drugs, and rightly so. The classic public good character of protection against AMR or a malaria epidemic argues for public subsidies of attempts at achieving that goal.

Medical history provides insights into incentives and research environments that led to significant medical breakthroughs. In an environment where commercial incentives for antimicrobial discovery may be insufficient an understanding of the factors driving historical innovation can help in the design of incentives for basic and state-funded research.

Consideration of the long history of disease control also provides precedents for effective use and development of new treatments. Many interventions failed in their desired effect because of popular opposition (for instance to smallpox or polio inoculation). These examples can provide important lessons regarding policy implementation.

3.4. Concluding Remarks

AMR poses a major challenge both to policy-makers and to scientists. This report has sought to place the issue of AMR in historical context and to suggest ways in which an historical perspective can inform the current discussion. Its main points may be summarized as follows. First, history suggests that the welfare costs of worst-case scenarios such as those being broadcast in the media are very high indeed, and should not be treated lightly. Much more precise estimates of those costs are needed. Second, history also shows that some of the more apocalyptic scenarios being aired in media are unlikely, partly because, as in the past, preventive medicine (including vaccination) and public health measures play a dominant role in disease control. Third, analyses of historical trends in infectious disease mortality and control are key to making informed estimates of the welfare and economic costs associated with AMR. Fourth, such analyses can also identify the full range of interventions that remain available, and the advantages accruing to the enhanced implementation of these interventions. In sum, it will not be possible to estimate properly the costs of AMR nor to identify the most effective alternatives to antimicrobial therapies without

historically informed research. Even in populations where infectious diseases still predominate the disease environment has been altered so fundamentally by public health interventions and social change over the last century that nowhere today approximates the disease environments of the pre-antibiotic era. Careful analyses of historical evidence must play a key role in developing an understanding of the full range of possible epidemiological scenarios and in evaluating their likelihood.

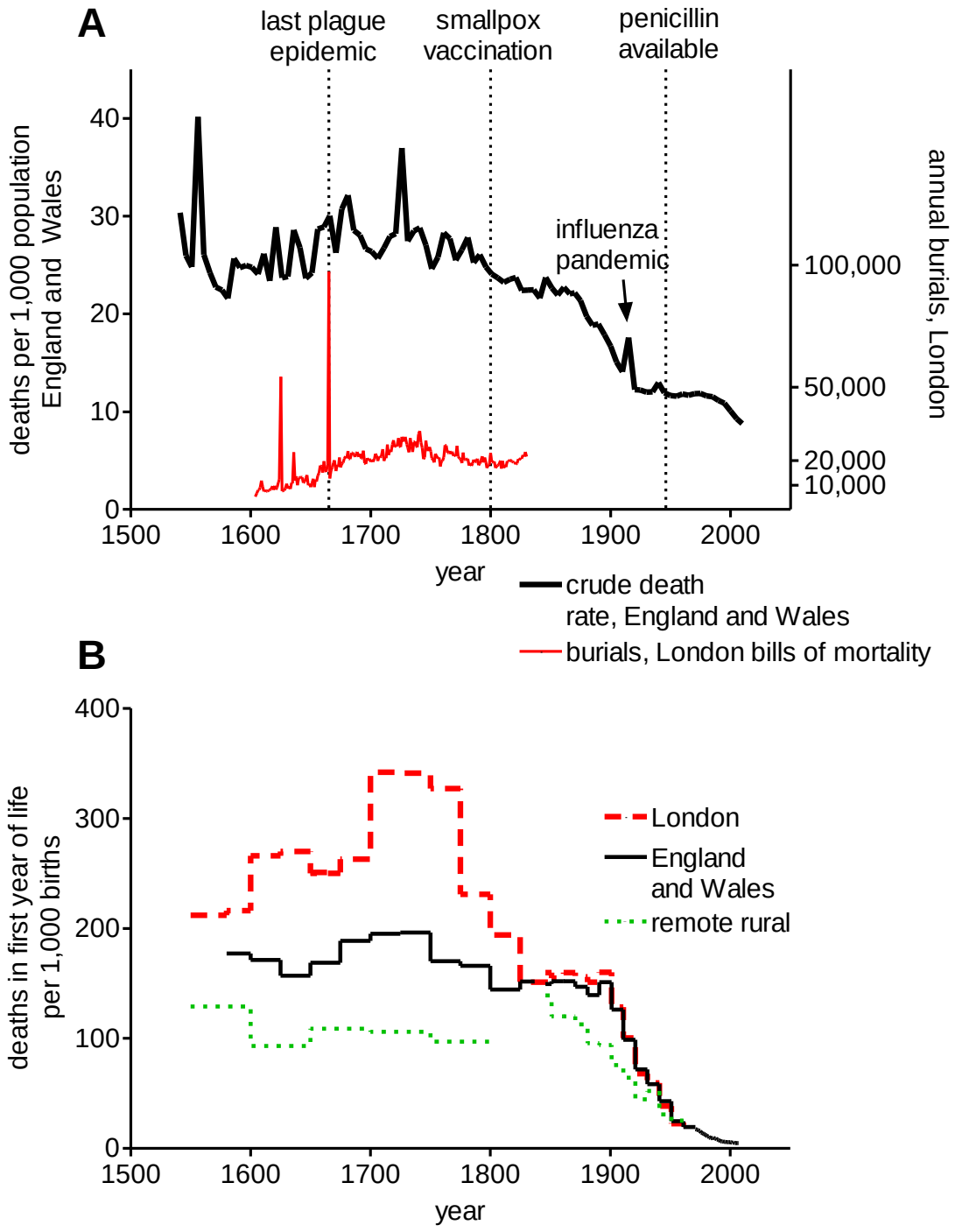

Figure 1. Long-run trends in crude death rates (A) and infant mortality (B) in England.

Sources: Wrigley et al. 1997: 614-15; Landers 1993; Smith, 1988; Creighton 1894.

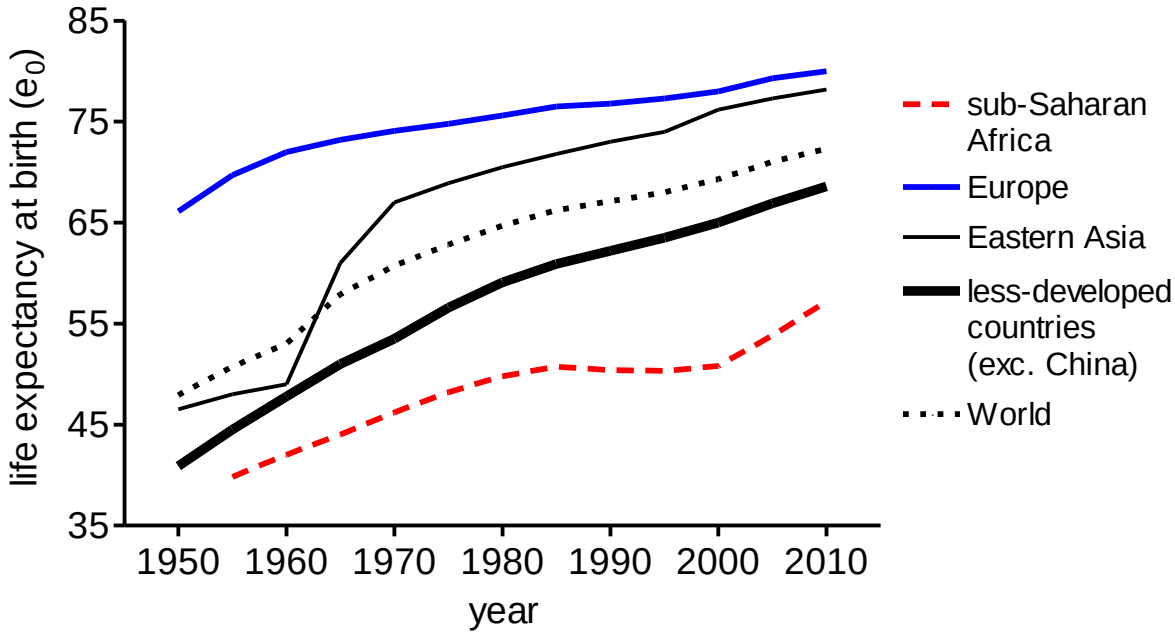

Figure 2. Global convergence in life expectancy at birth, 1950 – 2000

Source: World Bank

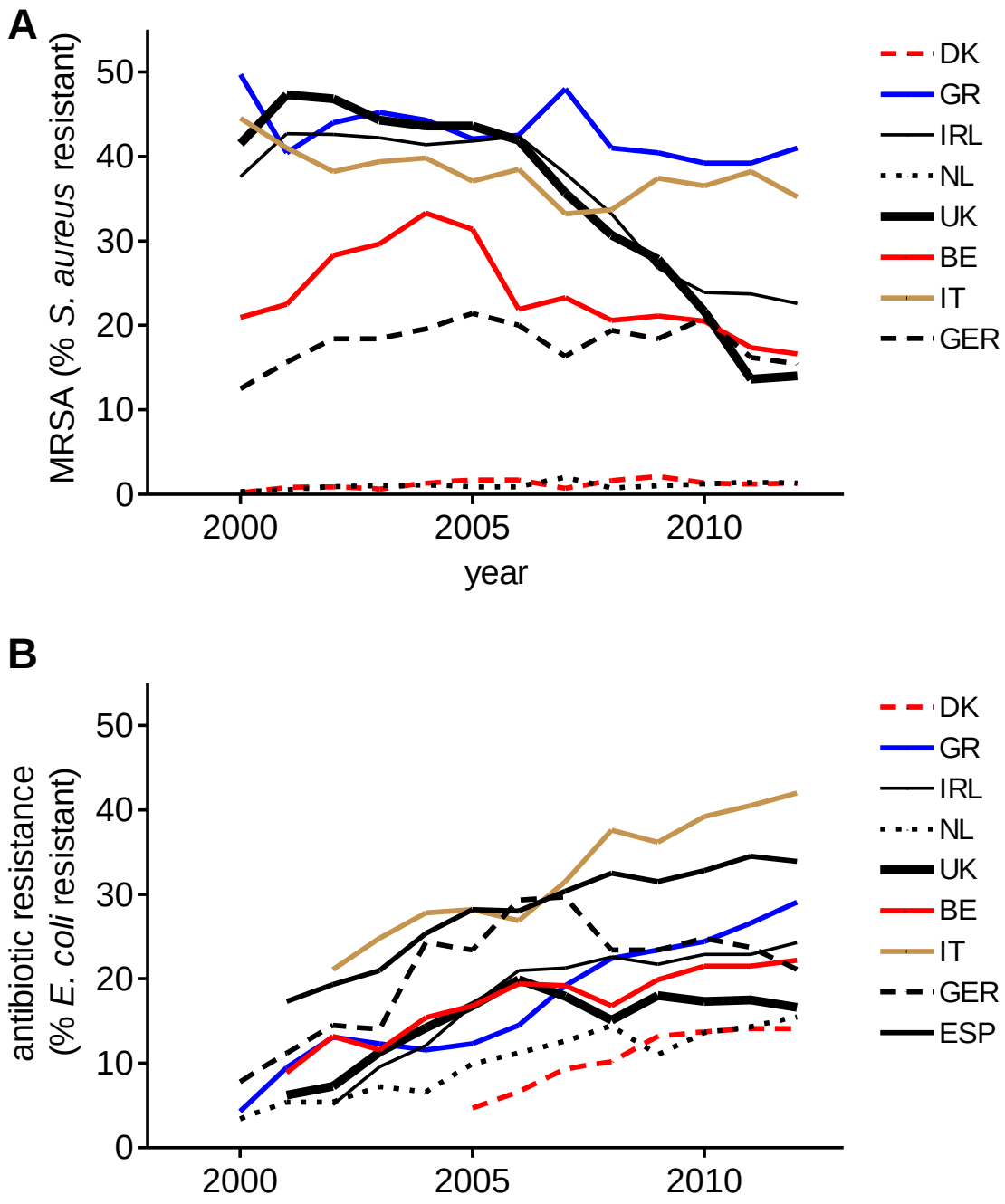

Fig. 3. Antibiotic resistance in *Staphyloccocus aureus* (A) and *E. coli* (B) in Denmark (DK), Greece (GR), Ireland (IRL), Netherlands (NR), U.K., Belgium (BE), Italy (IT) and Germany (GER) 2000 – 2012.

Source: ECDC

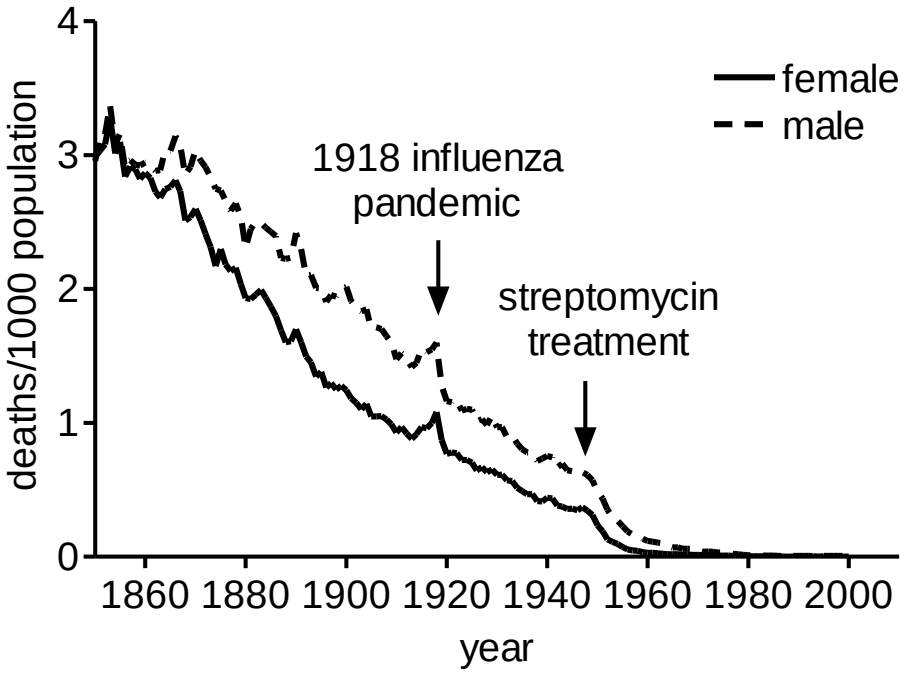

Figure 4. Tuberculosis mortality in England and Wales, age-standardised to the U.K. population in 2000.

Sources: Davenport, 2007; Office of National Statistics, 2006; Human Mortality Database (accessed Oct 10 2014).