HEALTH, WELLBEING, AND ANTIMICROBIAL RESISTANCE: INSIGHTS FROM THE PAST FOR THE PRESENT

29 November 2014

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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 prophylaxis, to treating specific infections, to surgery, radiotherapy, and cancer chemotherapy. As a result some maintain that many modern advances in medicine could be lost.

Our research highlights a less pessimistic 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 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.

CONTENTS

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.

Joshua Lederberg, 1994

Introduction:

Infectious diseases have accounted for a very high proportion of deaths in most historical populations. A century ago, even in today's high-income countries life expectancy was only half what it is now, and infectious diseases were mainly responsible for this. Their reduction to accounting for only a minority of deaths in such countries represents one of the most profound developments of the last century. In high-income countries the great majority of people nowadays succumb instead to cancer, heart disease, and other non-contagious causes. In low-income countries, where children are particularly vulnerable to infectious diseases, such diseases still account for nearly half of all deaths. But life expectancy in even the poorest group of low-income countries is higher than it anywhere was before the revolutions in public health and medical technology that followed the work of Pasteur and Koch (Table 1).[1]

Today infectious diseases remain a major policy concern, for two main reasons. The first is their impact on mortality and morbidity in low-income countries. How to enable available medical technologies to reduce that impact is one of the great challenges currently facing humanity. The second reason why infectious diseases are so important is evidence of increasing antimicrobial resistance (AMR), i.e. the ability of microorganisms to resist antibiotics. AMR is a serious and growing concern of the World Health Organisation: 'resistance [in] 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).

Some accounts depict the threat in very sombre terms indeed: 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

[1] Yet there is considerable variation within high- and low-income countries. Compare Nigeria (real GDP per capita $2,100 in 2010, infant mortality rate (IMR) 60 per thousand in 2013) and Rwanda ($1,135 and 37 per thousand) or the U.S. ($42,300 and 6 per thousand) and Sweden ($35,000 and 2 per thousand). See: http://data.worldbank.org/indicator/SP.DYN.IMRT.IN.

Cameron has warned that AMR could 'cast the world back into the dark ages of medicine'.[2] Does this imply that infectious diseases could be restored to the sinister role they played in the past?

Although AMR 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 describes that part of the health transition associated with the gradual reduction in deaths from infectious diseases, and the factors underpinning this change. It also discusses the economic and welfare gains associated with the resultant improvement in health and life expectancy.

1. A Brief History of Infectious Diseases

Section I provides a brief overview of the global history of infectious diseases with particular reference to England, the first national population for which we have relatively long-run data (from the 1540s). The mortality transition was a very drawn-out process in the English population and infectious disease mortality was very substantially reduced by preventative public health measures and rising living standards before the medical advances of the twentieth century (including antibiotics, insecticides and most vaccines). However in most developing country populations mortality decline was compressed into the twentieth century and has been enormously accelerated by the implementation of modern preventative measures and medical advances. We divide the discussion into four periods: (1) c.1300 to 1750, when plague devastated European populations and then receded; (2) 1750-1870 when some of the most lethal infectious diseases including smallpox, typhus, malaria and cholera were brought under control in the English population; (3) 1870 – 1940, when an impressive range of improvements in sanitation and hygiene, preventative medicine and living standards profoundly reduced mortality from childhood diseases and tuberculosis in European and neo-European populations, and (4) the antibiotic era post-1940, when medical technologies including antibiotics and a range of vaccines acted in synergy with older strategies to confine infectious disease mortality largely to the oldest ages in developed countries. We conclude with a comparison of the mortality transition in developed and developing countries.

[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.

1.1. Infectious diseases before 1750

Before the twentieth century infectious diseases were responsible for perhaps half or more of all deaths in most settled societies, and were the direct cause of most deaths associated with famines and wars. It is a peculiar triumph of modern societies that a high proportion of famine victims now die of starvation not disease and that the main cause of military deaths is now battle wounds instead of typhus or cholera. However although epidemics regularly accompanied subsistence crises and social dislocation, most demographic historians concur that variations in food supplies and living standards were not the main determinants of variations in infectious disease mortality in the European past. A Malthusian connection between food prices and short-run fluctuations in mortality is evident in most studies of medieval and early modern Europe (c. 1000 – 1750 A.D.), but it also appears that, with some notable exceptions such as the Great Famine of 1315-16 and the Irish Famine of the 1840s, these fluctuations generally had little influence on population growth rates, and much of the high mortality and mortality crises evident in historical populations were determined largely by variations in the intensity of infectious disease *exposure* (Livi-Baci 1989; Walter & Schofield 1989).

The apparent autonomy of infectious disease mortality with respect to living standards and food supplies is clearest in the plague period in Europe, 1347 – 1730. The Great Famine of 1315-19 may have destroyed ten per cent of the European population and suggests that the population was dangerously close to a medieval 'carrying capacity' at that point. However the explosive introduction of bubonic plague into Europe (the 'Black Death' 1347-53), as a consequence of long-distance trade within Eurasia, resulted in the loss of perhaps 50-60 per cent of the European population (on which see Section 2.4). It is widely agreed amongst historians that recurrent outbreaks of plague were sufficient to suppress population growth in continental Europe for a full century after the Black Death, establishing a very favourable ratio of resources to population amongst survivors and raising living standards especially amongst the poor (Livi-Bacci, 2001).

However the impact of plague diminished from the mid-fifteenth century, and plague disappeared from Scotland after 1647, from England after 1665, and from western Europe after the 1720s. The progressive reduction of plague mortality was accompanied by the recovery of population to pre-Black Death levels in most of Europe. The demographic history of England is uniquely well characterised from c.1540 and surprisingly indicates that as population rose to its previous medieval maximum of c. 5 - 6 million (by the mid-seventeenth century) famine did not intensify but instead disappeared, with the last nationwide subsistence crisis in the 1590s

(Wrigley and Schofield, 1989). England was extremely precocious in this early escape from famine, as a consequence of a unique combination of free trade, agricultural specialisation and a social safety net that afforded access to grain markets for the poor. However famine also receded gradually in continental Europe, although very major crises persisted on the fringes of Europe well into the nineteenth century, most famously in Ireland (1845-50) but also in Finland (1866-68).

The disappearance of both famine and plague in the seventeenth century produced a very marked stabilisation of mortality in England (Figure 1A). Wrigley and Schofield estimated that mortality 'crises' accounted for only 5 per cent of deaths in the period 1600 - 1750 and had very little influence on population growth. However these remarkable achievements in the control of food supply and disease transmission (see sections 2.1 and 2.4) were *not* accompanied by a rise in life expectancy. On the contrary there was a rise in 'background' mortality in the period 1600-1750 that fell most heavily on infants and children (Figure 1B). The most plausible explanation for this pattern is that the economic integration of the English population that together with welfare transfers drove the precocious escape from famine was accompanied by an epidemiological integration that increased the circulation of contagious diseases (Walter & Schofield, 1989; Wrigley *et al*., 1997; Smith & Oeppen, 2006). As an increasing proportion of the population was drawn into a national system of disease circulation those diseases such as smallpox in particular, measles, whooping cough, and scarlet fever that conferred lifelong immunity gradually became diseases of childhood.

[Figure 1 about here]

The apparently *negative* association between living standards and life expectancy identified in the English population in the period 1347 – 1750 is borne out by the lack of evidence for any gradient in survival by wealth. Most studies of mortality by socioeconomic status in European populations before the mid-nineteenth century indicate little protective effect of wealth, contrary to the strong and ubiquitous differentials in life expectancy by social class in contemporary populations (Bengtsson & van Poppel, 2001; Kelly & Ó Gráda, 2014). English peers had lower life expectancy in adulthood than the general population until the mid-nineteenth century, and never surpassed those living in poor and remote but healthy rural areas (Smith & Oeppen, 2006). Mortality was highest in urban populations despite the higher incomes and greater food security associated with towns. Instead regional variations in life expectancy were dictated to a large extent by the degree of

urbanisation and breastfeeding habits, and mortality was lowest in those remote rural communities where prolonged maternal breastfeeding was the norm (Knodel, 1987; Wrigley & Schofield, 1989, Wrigley et al., 1997).

The apparent autonomy of the death rate from living standards narrowly conceived was at least partially a consequence of the types of diseases that dominated mortality in this period. Plague, typhus, smallpox, cholera and typhoid were sufficiently lethal that host nutritional status appears to have provided little protection. Although outbreaks were often triggered by over-crowding and subsistence migration, the close proximity of the rich and poor in early modern towns meant that even epidemics that arose as a consequence of the influx of desperate rural migrants spread indiscriminately to rich and poor families (Weir, 1989). Where epidemic mortality did show a strong economic gradient this usually reflected the superior ability of the wealthy to flee or otherwise avoid exposure (e.g. Champion, 1995).

Towns were always dangerous disease environments as a consequence of the inevitable concentration of human waste and opportunities for disease transmission in large dense populations, together with their function as hubs within networks of trade and migration of both pathogens and people. Jan de Vries (1984) has argued that the high mortality inevitably associated with urban populations imposed a limit to urban growth such that national populations could not sustain an urban population of greater than c. 40 per cent without suffering population decline. Under this scenario modern economic growth was impossible without accompanying improvements in urban survival rates. However urban mortality rates probably varied very substantially depending on cultural habits and prevailing pathogens. Plague and later smallpox seem to have rendered English towns particularly lethal in the period 1350-1750, (Figures 1 and 2). Moreover where rural populations remained only partially absorbed into an urban disease network then rural migrants to towns would have lacked immunity to many urban diseases and so young adult migrants as well as children were at particular risk in urban disease environments (McNeill, 1980; Landers, 1992).

In London 35 – 40 per cent of infants died within a year of birth in the early eighteenth century (Figure 1B), a level of mortality that required a constant influx of migrants simply to sustain the metropolitan population, in addition to the mass migration required to fuel London's rapid growth in this period. These levels were probably exceptional in the history of English urban centres, but were matched in non-breastfeeding areas of *rural* Germany in the nineteenth century (Knodel, 1987), and compare favourably with major Indian cities in the late nineteenth century, where estimates ranged from c. 30 per cent in Madras to an astonishing 55 per cent of infants dying within a year of birth in Bombay (Dyson, 1997: 127). The exceptional lethality of London in the period 1650-1750 appears to have been due to the practices of wet-

nursing and artificial feeding of infants especially amongst the wealthier half of the metropolitan population, and to smallpox (Landers, 1993; Davenport, 2014). While smallpox accounted for only 6 – 10 per cent of burials in London and Stockholm in the late eighteenth century because other causes of death were so prolific especially in infancy, in northern English towns smallpox accounted for 10 – 20 per cent of all burials, and for 8 - 15 per cent of all burials in Sweden as a whole (Figure 2).

[Figure 2 about here]

England was precocious in the elimination of extreme mortality crises after the 1720s (the 1918-19 influenza pandemic being the only notable exception), and experienced a very prolonged process of infectious disease control dating at least from the elimination of plague by 1666. Elsewhere both famines and extreme epidemic events remained features of some more isolated European populations until the mid-nineteenth century, and of many developing country populations until well into the twentieth century. Nonetheless the economic and epidemiological processes driving mortality trends in England c.1300-1750 were writ large at the global level. The progressive globalisation of migration and trade since 1000 C.E. gradually produced what Le Roy Ladurie (1973) termed the '*unification microbienne du monde*', the trans- and inter-continental fusion of pathogens into a single global disease pool. The most obvious of these exchanges include the three global pandemics of plague (541-750, 1345-1840, 1866-1959); the so-called 'Columbian exchange' that introduced smallpox and a host of so-called 'childhood diseases' to immunologically naive New World societies with devastating consequences (Crosby, 1972; McNeill, 1976) and syphilis into Europe and beyond (Harper *et al*. 2011); the rise in infectious disease mortality in Japan following the opening to global trade from the 1860s (Jannetta, 1987), and in the twentieth century the dramatic reversals of mortality declines associated with the global influenza pandemic of 1918-19 (Tatem et al. 2006) and the HIV pandemic that continues to depress life expectancies in most sub-Saharan African countries.

1.2 The control of infectious diseases in north-western Europe 1750 - 1870

The heavy burden of infectious diseases in the English population only began to lift decisively in the mid-eighteenth century with reductions in urban mortality (Figure 1). Recent accounts of what Easterlin termed the 'Mortality Revolution' of the last century situate the origins of this revolution in the nineteenth century and associate it with the breakthroughs in medical knowledge and technologies achieved

in European and neo-European societies in that period (Easterlin, 1998; Deaton, 2013). However while secular improvements in life expectancy date from the mid-nineteenth century at the earliest the apparent stability of life expectancy estimates before this date (Figure 1) conceals profound changes in the structure of mortality at least in north-west European populations that were crucial to the subsequent precocious rise of life expectancy in these populations. Profound improvements in urban mortality, although masked by the relatively small urban proportion of the total population, made possible the rapid urbanisation associated with the Industrial Revolution.

These remarkable improvements in urban mortality occurred in England well before the classic period of Victorian sanitary reforms (from the 1860s) and before any sustained rise in real wages. In London infant mortality fell from 35 – 40 per cent in the first year of life in 1750 to the national average of 16 per cent by 1850 (Figure 1B). By the mid-nineteenth century even the most notorious Victorian mortality blackspot, Liverpool, reported infant mortality rates no higher than those prevailing in minor market towns such as Banbury and Gainsborough a century earlier (c. 20 per cent; Davenport, 2014). Although the historical demography of urban populations is very under-developed what evidence there is indicates that human agency rather than evolutionary or environmental factors was key to these improvements (Landers, 1997; Davenport, 2014). Infant and child mortality fell decisively as a consequence of increases in maternal breastfeeding of infants and of immunisation against smallpox (via inoculation from the 1760s and more importantly vaccination from c.1800).[3] The control of smallpox by vaccination from 1798 onwards made a major contribution in reducing especially urban mortality throughout north-western Europe (Mercer, 1990; Figure 2). Smallpox was exceptionally lethal and accounted for 20-40 per cent of deaths of children aged under ten in large towns. Thus, as in the case of plague, control of a single pathogen probably caused a very significant shift in patterns of mortality.

The extent to which smallpox inoculation and vaccination effected similar reductions in mortality in non-European populations before the vaccination campaigns of the twentieth century remains unclear. Lee et al. (1994) documented a very substantial decrease in child mortality amongst the Qing imperial lineage between 1700 and 1840 and suggested that this was driven mainly by the progressive implementation of compulsory smallpox inoculation for lineage children. Inoculation and vaccination were propagated very rapidly in Japan from 1849 with decisive effects on smallpox rates (Jannetta, 2001). Banthia and Dyson (1999) concluded that smallpox was a major cause of death in most of colonial India (with the exception of Bengal

[3] Smallpox inoculation involved infection with a small dose of possibly attenuated smallpox through a cut in the skin (or sometimes via nasal inhalation, in China). Smallpox vaccination involved infection with Vaccinia virus which produced a mild infection and conferred cross-immunity to smallpox. Whereas inoculation carried the risk of contagion, vaccination did not.

where there was a long tradition of inoculation) before the extension of vaccination programmes between the 1860s and 1880s substantially reduced smallpox infection rates. Compulsory vaccination was introduced in colonial Jamaica in 1865 and although the impact on smallpox incidence and death rates is unknown, there few cases or deaths from smallpox by the late nineteenth century (Riley 2005: 50). Smallpox vaccination campaigns were only initiated in the twentieth century in African colonies.

In England there is also evidence for substantial reductions in mortality from a number of other infectious diseases after 1750 that suggests wider changes beyond vaccination and infant feeding fashions. Typhus was a major and much-feared epidemic disease in the seventeenth and eighteenth centuries and is credited with the destruction of numerous armies (most notably Napoleon's *Grande Armée* during its disastrous invasion of Russia in 1812). It is spread by human lice and infects humans under conditions of close contact and poor hygiene. Typhus outbreaks were common where migrants or soldiers were crowded together as a consequence of dearth or war, and in gaols and ships (hence its synonyms 'ship fever' and 'gaol fever'). Although typhus outbreaks propagate in poor and crowded conditions the wealthy were not immune and the relationship between nutritional status and susceptibility to typhus remains unclear (Hardy, 1988). Over the course of the eighteenth century typhus epidemics in western Europe appear to have been confined increasingly to urban populations (Creighton, 1894; Hardy, 1988). There were widespread outbreaks associated with the end of the Napoleonic wars (1817-19) and in England nineteenth century epidemics were closely associated with waves of Irish immigration and associated overcrowding and poverty. However typhus accounted for a progressively declining proportion of deaths and the last significant outbreaks in Britain occurred in the 1860s and 1870s (Hardy, 1988).

Malaria was also endemic in England in the seventeenth and early eighteenth century and rendered many low-lying areas of Kent and East Anglia exceptionally lethal environments (Dobson, 1997). Infant mortality rates in rural fen and other marshy areas rivalled those of London in the mid-eighteenth century and as in towns recent migrants to malarial areas were at high risk compared with local adults who had acquired immunity through repeated exposure. However the disease receded from England from the late eighteenth century and was eliminated by the early twentieth century. Dobson credits drainage and water control as key factors in reducing the mosquito population and so preventing transmission (see also Riley, 1983: 122-29). The extent to which such measures reflected a general process of disease control is discussed in section 2.

These eighteenth century improvements in especially urban mortality, evident in much of north-western Europe, marked the true onset of the 'Mortality Revolution'

and the associated demographic transition. Although mortality showed continuous improvement in relatively rural Sweden from c.1750 in England and France improvements stagnated c.1820-70, apparently as a result of both an autonomous rise in streptococcal infections (esp. scarlet fever) and rapid urbanisation (Figure 3). This stasis should really be viewed as a remarkable achievement given the enormous redistribution of the population from rural to less healthy urban areas, and probably conceals considerable reductions in infectious disease rates within towns at least after 1850 (Woods, 2000).

While rising calorific intake was undoubtedly important to mortality declines after 1870, attempts to project these processes into the early modern period underestimate the profound differences in cause of death structures between the eighteenth and later nineteenth centuries (McKeown 1976; Floud et al. 2011). Fogel and colleagues for instance posit a constant mortality 'surface' across which the English population moved mainly as a consequence of changes in calorific intake between 1750 and 1870 (Floud et al. 2011, chapter 2). It is hard to reconcile such claims with the declines in real wages c.1790 – 1820 that coincided with the most rapid period of improvements in mortality. It is more likely on balance that mortality improvements in the period 1750 – 1820 were a function mainly of large reductions in causes of death that were fairly insensitive to nutritional status, including smallpox, typhus and malaria. The recession of these diseases brought to the fore in the nineteenth century milder infectious diseases (childhood infections and tuberculosis) that were much more sensitive to the health status of the host. This hypothesis is elaborated in section 2.1.

[Figure 3 about here]

1.3. Secular Improvements 1870 - 1940

Rapid and almost continuous mortality decline resumed in England from the 1870s and has continued to the present. In England and Wales infectious diseases accounted for 45 per cent of all deaths in 1850, 36 per cent in 1900, but only 15 per cent by 1939, before the widespread impact of penicillin (Table 1). In 2012 infectious diseases accounted for 6.5 per cent of deaths in England and Wales, most of these attributable to respiratory infections in late adulthood. Most of the decline in mortality between 1870 and 1940 was driven by declines in infection-related mortality with the most rapid improvements occurring in the period 1900-40. In contrast to the first stage of mortality decline described in section 1.2, which was confined to populations in north-western Europe (and may have been eclipsed at least in coastal

Mediterranean areas by the resurgence of malaria), mortality declines were widespread after 1870 in European and neo-European populations and extended to parts of Latin America including Mexico, Paraguay and Costa Rica (Riley, 2001).

[Table 1 about here]

In the English population scarlet fever and respiratory tuberculosis mortality began to decline from the 1870s and the age groups where these diseases were most critical (young children and young adults) benefitted earliest (Figures 4-6). The other major 'childhood' diseases (measles, diphtheria and whooping cough) all underwent very substantial and poorly understood declines in the period after 1900 (Figure 5). In the case of scarlet fever there is reason to think that the pathogen (*Streptoccocus pyogenes*) declined in virulence, but no similar arguments have been made for other infections in this period, with the partial exception of tuberculosis (Woods, 2000) and streptococcal puerperal fever (Loudon, 1992). These childhood diseases were not waterborne but transmitted person to person, and so cannot have improved as a consequence of public sanitation programmes. They are highly infectious (Table 2) and it appears that reductions in mortality resulted from declines in case-fatality rates rather than in incidence of infection. In the case of measles Aaby and colleagues have made a strong case for the importance of crowding and dosage of infection to mortality from measles (Aaby et al., 1988), and much of the mortality associated with measles is the outcome of subsequent respiratory infections preventable by protection from exposure and good nursing (Hardy, 1993). Improvements in nutrition associated with rising incomes doubtless acted to increase host resistance. In addition, improvements in housing conditions and the progressive and substantial declines in fertility and family size from the 1870s would also have acted to reduce infection dosage and exposure to opportunistic infections (Reves, 1985). The same constellation of factors probably contributed substantially to improvements in mortality from tuberculosis (Figure 6), although in this case the extent to which incidence of infection was also reduced via preventative measures such as confinement of sufferers to sanitoria remains unknown (Vynnycky & Fine, 1997).

[Figures 4 - 6 about here]

Diarrhoeal diseases remained high especially in urban areas until 1900 despite intensive efforts at sanitary reform, and infant mortality did improve until 1900 (Figure 4B). However from 1900 infant mortality showed rapid and continuous improvement throughout the twentieth century, declining from a national rate of around 15 per cent mortality in the first year of life to 0.5 per cent today. Between 1900 and the mid-1930s these improvements were a consequence of reductions in especially diarrhoeal diseases associated with weaning and in the key childhood infections affecting all ages under five (scarlet fever, measles, diphtheria and whooping cough). Mortality in the first month of life (neonatal mortality) did not improve at all between c. 1820 and 1937, and therefore accounted for an increasing proportion of all deaths in infancy (rising from 20 per cent in 1900 to 51 per cent by 1937). However neonatal mortality, particularly deaths in the first week of life, declined precipitously with the introduction of the early antibacterial sulfa drugs, in tandem with dramatic reductions in puerperal fever ('childbed fever') and late foetal (stillbirth) mortality (Figure 7). Although late foetal and neonatal mortality is usually considered largely of non-infectious origins and associated mainly with genetic and in utero conditions and maternal health, the apparent impact of sulfa drugs evident in figure 7 suggests a role for one of the narrow spectrum of infectious diseases sensitive to sulfa drugs (Løkke, 2012).

Children and young adults benefitted most from the dramatic reductions in tuberculosis and childhood infections between 1870 and 1940, however after c. 1900 older adults also benefitted substantially (with the exception of the oldest ages, 85 years and over, where substantial improvements occurred only in the second half of the twentieth century) (Figure 4). The main gains in life expectancy at ages 40+ from 1900 were a consequence of falls in deaths attributed to tuberculosis, other respiratory infections (especially pneumonia and influenza), cardiovascular diseases (strokes and heart disease) and 'other' causes (Figure 8) The latter category included mainly diseases related to the stomach, liver and kidneys and was supposed by Preston to contain a substantial cardiovascular component (Preston, 1976), but also included diseases of infectious origins (such as acute nephritis caused by streptococcal infection). The disastrous impact of cigarette smoking (a habit that was most intense in men born around 1900) reversed some of the early gains in cardiovascular mortality and raised cancer rates amongst men in the mid-twentieth century. As a consequence of sex differences in smoking habits the gap between male and female life expectancy widened from around three years in 1900 to six years by the 1950s before narrowing again to a three year female advantage by the close of the twentieth century.

Similar age-specific and cause-specific patterns of mortality decline have been observed in a variety of populations at different stages of economic development (Preston, 1976). Importantly, infectious diseases account for a large proportion of deaths not only in childhood but at all ages in both historical and poor contemporary

populations, and falls in infectious disease mortality are associated with large falls in mortality from non-communicable diseases. Preston (1976) demonstrated using long-run cause of death data for 42 countries that falls in cardiovascular disease made a major contribution to the early stages of mortality decline and he attributed this to both the tendency of respiratory infections in particular to trigger heart attacks and to the debility produced in survivors by certain infections.

The effects of early life infections on health in adulthood remains hotly debated (Finch & Crimmins 2004, 2005). However although there are clear cases of specific pathways from childhood infection to adult disease, as in the case of rheumatic fever and valvular heart disease or *Heliobacter pylori* infection and stomach cancer, at the population level life expectancy at older ages bears little relationship to childhood levels of infection, and elderly cohorts in countries such as Japan and Italy with relatively high levels of historic childhood mortality now enjoy some of the highest life expectancies (Barbi & Vaupel 2005; see also Davenport 2013). The synergies between different causes of death remains an under-researched area but one that is key to understanding the implications of both control and loss of control of infectious diseases.

[Figures 7, 8 about here]

Improvements in mortality after 1870 were associated with very profound social changes in European and neo-European societies and defy monocausal explanations. Explanations fall largely into two camps, those invoking rising living standards especially improved nutrition as a consequence of rising real incomes (e.g. McKeown 1977; Floud et al. 2011), and those who attribute the bulk of improvement to preventative public health measures (e.g. Szreter 1988; Hardy 1993). Predictably, the evidence is ambiguous. Anthropometric measures of nutritional status, usually adult height, are used often to infer nutritional gains. However attained adult height is a complex measure that reflects the net outcome of food inputs and the demands of work and disease burden integrated over childhood and adolescence. Therefore the steady rises in heights of military conscripts in continental European populations over the nineteenth century probably reflect both the declining burden of infectious diseases and rising food intake (whereas the more improbable fluctuations in heights of English recruits and convicts probably reflect fluctuations in the extent of economic alternatives to crime and soldiery in the absence of a conscript army: Bodenhorn, Guinnane & Mroz, 2014). Similarly, the fairly poor chronological and spatial matches between sanitary reforms and other preventative measures and improvements in

mortality from waterborne and other infectious diseases have provided little direct evidence of the mechanisms by which public health measures exerted some of their undoubted effects (Hardy, 1993; Woods, 2000). The ubiquity of mortality improvements in European and neo-European populations at very different levels of income, development and life expectancy in the late nineteenth and early twentieth centuries points to the potential multiplicity of pathways and perhaps to the importance of fertility decline and education (Riley, 2001; Woods, 2000).

1.4. The Antimicrobial Era, 1940+

The first efficacious antimicrobial may have been quinine, in use against malaria from at least the sixteenth century in Bolivia and Peru. Disinfectants that killed pathogens formed a key part of the antiseptic movement that contributed to falling rates of wound infection. Anti-toxins (antibodies) against diphtheria and tetanus were developed in 1890 and salvarsan against spirochaete infections, notably syphilis, was discovered in 1909. However most attempts to treat infections with antimicrobial drugs were unsuccessful before the 1930s. The discovery of the bactericidal properties of protonsil in 1931 led to the proliferation of related 'sulfa drugs' that came into wide use in Europe and the USA by the late 1930s. Sulfa drugs were effective against a narrow but important range of bacterial infections, including the streptococcal strains responsible for puerperal fever in recently delivered women and streptococcal wound infections, but not the streptococcal strains that cause scarlet fever. Their impact on maternal mortality was dramatic (Loudon, 1992; Figure 7) and they also proved effective in treating pneumonia but had no impact on tuberculosis.

Penicillin was developed in the 1930s and widely used from 1942. It proved effective against wound infections and was widely deployed in the closing stages of WWII by the American and British armies. However the greatest impact of penicillin-type drugs was the discovery in 1946 that streptomycin cured tuberculosis. Although tuberculosis death rates had already improved profoundly (Figure 6) streptomycin and subsequent combination therapy (introduced in the face of the very rapid evolution of resistant tuberculosis strains) were key in definitively eliminating tuberculosis as a major cause of mortality and morbidity in developed countries.

[Figure 7 about here]

Although hailed as wonder drugs and despite the demographic importance of tuberculosis, the direct impact of antimicrobial technologies on historical trends in mortality appears surprisingly slight (Figures 1, 6). In the English population infectious diseases had been controlled to a great extent by 1940 using methods that prevented transmission or raised population resistance (rather than *cured* infection per se). These older methods of disease control were further enhanced in the second half of the twentieth century by the development or implementation of new vaccines against a range of infectious diseases (Table 2). For example the Bacillus Calmette-Guérin (BCG) vaccine against tuberculosis was developed in the 1920s, but only brought into routine use in Britain in 1953. Antibiotics, BCG and surveillance were used in a three-pronged strategy to identify and treat those infected to reduce transmission, and to immunise the population against infection. BCG immunisation was discontinued in Britain in 2005 but remains routine in 157 countries (Zwerling *et al*., 2011), and has been reintroduced in high risk areas of London (NHS, 2013). BCG is protective against tuberculosis disease in infants but the efficacy of BCG against adult respiratory forms of the disease varies with latitude and age at immunisation, with efficacy ranging from zero at low latitudes to 60 - 80 per cent protection at latitudes above 40 degrees (Mangtani *et al*., 2014).

The overt impact of antibiotics in developed country populations was limited by prior falls in infectious disease mortality (Riley, 2001). Nevertheless a superficial consideration of the timing of declines in specific infectious causes of death masks the **enormous dependence of many medical technologies on prophylactic or curative antibiotics for their success**. Before 1950 surgery remained a very dangerous procedure, despite very significant developments in sterile procedures and wound treatment. Many of the gains in survival from heart disease and cancers in the last fifty years depended and continue to depend on surgical interventions that would have involved substantial risk before the advent of penicillin (Smith & Coast 2012, 2013). Chemotherapy, which reduces the patient's resistance to infection, also relies on the prophylactic use of antibiotics to reduce the risk of opportunistic infections, as does organ transplant technology. The enormous shift in the distribution of deaths from the youngest ages to the oldest (Figure 4c) means that continuing gains in life expectancy can only be achieved (or indeed preserved) by these types of technologies that are underpinned by the ability to prevent or treat adventitious infections.

1.5. The Global Surge in Life Expectancy 1950+

While the health gap between rich and poor nations remains very wide, it has narrowed over the last century. Figure 9 compares trends in the log values of income per head and life expectancy at birth (a common proxy for a community's health) in

India, representing low-income countries, and Sweden, representing high-income countries, since 1900. Note that while the proportionate gap in income per head is wider now than a century ago, the gap in life expectancy has narrowed significantly. That narrowing of the health gap has been mainly due to the radical reduction in India of deaths from infectious diseases including plague and malaria. The narrowing also explains why measures of human wellbeing that incorporate demography imply less inequality than those relying on income alone (Becker *et al*. 2003).

In developing countries the process of infectious disease control, so drawn out in England, was compressed into the twentieth century and enormously accelerated by the availability of medical and public health technologies and knowledge. Unfortunately we have relatively little insight into mortality trends in most countries before the 1950s at the earliest. However it is clear from the very rapid rates of population growth already evident by the mid-twentieth century that there must have been significant falls in mortality before 1950. In India for instance large upswings in mortality caused by famine, bubonic plague and smallpox diminished substantially after 1920. Dyson and Das Gupta (2001) attributed this stabilisation of mortality to colonial policies that improved food distribution, monitored plague outbreaks and increased smallpox vaccination coverage. A similar stabilisation of mortality after 1920 is evident in Jamaica, where a precocious public health administration, education and registration system facilitated rapid gains in life expectancy from this date, with the fastest gains in the period 1925 – 40 (Riley, 2005). The control of smallpox and plague in nineteenth century Jamaica probably contributed to the relatively favourable level of life expectancy in Jamaica by 1920 (35 years). However in Africa especially the progressive eradication of smallpox, culminating in the WHO global campaign from 1950 to 1980, must have had an effect on populations with hitherto low rates of vaccination as profound as that in early nineteenth century Europe.

Mortality declines are better documented from the mid-twentieth century (when the U.N. began to publish systematic country-level data[4]). Gains were particularly rapid in the 1950s and 1960s in Asia, the Caribbean and Latin America but the underlying drivers appear to have been diverse (Livi-Bacci, 2001; Riley 2001). Improved food supplies, the spread of immunisation programmes especially against smallpox, typhoid and yellow fever, control of plague, improved sanitation and the advent of DDT in insect control were all factors. However rising educational levels and changes in the status of women also explain much of the variation between populations (Caldwell 1986; Riley 2005) (see section 3). In populations where malaria and other insect-borne diseases were major causes of morbidity and mortality then the combination of public drainage works and widespread applications of the insecticide DDT could as much as halve mortality (e.g. Livi-Bacci 2001: 139). The area of the world

[4] See the WHO Mortality Database: http://www.who.int/healthinfo/mortality_data/en/

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). These factors acted both to stabilise mortality by reducing epidemic mortality and famine-related infectious disease mortality and to raise life expectancy rapidly, producing a global convergence in life expectancies (Figure 10).

[Figures 9, 10 about here]

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).

The very diverse pathways to improved health traced by developing country populations, and the rapid cascade of medical advances and synergies between immunisation, drug therapies, nutrition and sanitation, make it very difficult to assess the role of any single intervention. The contribution of antimicrobial drugs is most evident in the success of anti-malarial treatments and more recently anti-retroviral therapy in reducing HIV transmission and mortality. The persistent importance of diseases eminently treatable by antibiotics indicates the continuing scope for better-targeted access to antibiotics in reducing especially child mortality.

1.6. Mortality and Morbidity

The previous section has focussed on mortality primarily because this measure is more common in historical records and because life expectancy is a relatively unambiguous measure of well-being. However most infections result in illness without death. Infectious diseases vary very substantially in the ratio of illness to fatalities they cause (Table 1), and in the duration of morbidity (ill-health) they evoke. Some infectious diseases, such as plague, typhus and smallpox, can kill otherwise robust children and adults rapidly. Others, including most macro-parasitic infections, malaria and tuberculosis, are chronic and cause sustained debility. Some infections can leave survivors permanently disfigured or disabled, as in the cases of crippling by polio or blindness by trachoma. It is likely for instance that between episodes of terrifying plague epidemics European populations experienced relatively good health in the fifteenth century as a consequence of low population densities and relatively high wages, and the apparent lack of significant chronic effects of plague on survivors. Conversely Riley argued on a rather tenuous empirical basis in his book *Sick not dead* (1997) that as mortality rates fell in the English population after 1870 the prevalence of ill-health actually rose (for an alternative view using similar sources see Harris et al. 2012).

It is often assumed that the historical shift from infectious to 'degenerative' diseases as the main causes of death was necessarily accompanied by a significant lengthening of the period of life spent in ill health as chronic diseases came to account for an ever-increasing proportion of deaths. Although disability is difficult to measure especially in a comparative context, WHO estimates of disability by cause give little support to this assumption. Between 1990 and 2010 years lost both to disability and to premature mortality fell on an age-adjusted basis (Murray *et al.*, 2012). The connections between infectious diseases and non-communicable 'degenerative' diseases outlined earlier meant that levels of chronic non-infectious diseases were also

high in populations with high infectious disease mortality, and both broad categories of disease often declined together (Figure 8). While we cannot estimate historical levels of morbidity with any precision, widespread increases in height associated with reductions in childhood infections and improved nutrition suggest that morbidity in childhood at least has receded dramatically since the 1870s, and this is probably the case for adults too (although the profound impacts of smoking in the twentieth century partially reversed these gains especially in men).

A protracted debate on whether the extension of life expectancy in affluent populations in the twentieth century was accompanied by an expansion or compression of the period of life spent in ill-health has produced mixed results that vary markedly by country (Fries 1989; Olshansky *et al*. 1991; Doblhammer & Kytir 2001). However these studies refer mainly to affluent populations in the late twentieth century and so may fail to capture most of the gains or costs associated with major falls in infectious disease mortality.

In conclusion, the causes of the profound declines in infectious disease mortality before 1940 particularly in developed country populations remain only very partially understood. A better understanding of these factors is essential because in many cases the strategies of disease control they entailed, such as routine surveillance, health education and immunisation, continue to underpin modern health gains, and provide pointers for control of newly emerging infections as well as **areas to be strengthened in the event of a failure of antimicrobial technologies.** These factors are discussed further in section 2.

2. Intervening

This section evaluates the contributions of these technologies, and of improvements in 'living standards' broadly defined as nutrition and housing. Long-run changes in the impact of infectious diseases on mortality and morbidity can be conceptualised as the direct outcome of changes in three factors

(1) **exposure** to pathogens
(2) **resistance** to pathogens
(3) **treatment** of the consequences of infection

While these factors are themselves determined by a plethora of social, economic, ecological and evolutionary factors, these latter exert their effect through changes in exposure, resistance, and cure rates.

2.1. Exposure to Infection

Exposure to infectious diseases depends on a multitude of factors from the microscopic to the global. Most fundamentally it depends on the array of pathogens present, which varies according to geography, environmental and biotic factors, chance inter-species transfers, and patterns of long-distance human interactions. The risk of exposure to pathogens is affected by climate and season, and by the presence of invertebrate vectors (in the case of diseases such as malaria, plague, typhus and bilharzia where insects or snails transfer disease between human hosts) or reservoirs of infection (such as rats or birds and pigs in the cases of plague and influenza). Critical for most infectious diseases is the density and size of human populations and the opportunities for transmission within these congregations. Population size and density are key for a variety of reasons. Airborne diseases that transmit from person to person require frequent contact between individuals for transmission, and diseases that confer immunity require populations sufficiently large that they continue to furnish sufficient non-immune individuals to sustain transmission. In the case of measles, an acute infection which cannot survive outside a human host, it is estimated that an urban population of at least a quarter of a million is required to avoid 'die-out' of epidemics. For waterborne diseases such as dysentery and cholera that are transmitted through faeces, high population densities increase the probability that water sources will be contaminated. Even for diseases with intermediate hosts, such as malaria, the probability that a mosquito will bite an infected human and transmit the malarial plasmodium to another host is obviously density-dependent. Trade and migration increase the range of circulating diseases, while urbanisation and high population densities facilitate transmission. At the individual level poor hygiene (infrequent washing of hands, clothes and utensils) and crowded housing raise exposure levels. For infants breastfeeding dramatically reduces the risk of exposure to contaminated foods.

Much of the dramatic fall in infectious disease mortality before 1870 described in Section 1 can be attributed to reductions in exposure to pathogens. Processes that reduced exposure include quarantine and isolation (especially of plague, typhus and smallpox victims), sanitation (effective disposal of garbage and sewage), hygiene (for example hand-washing and more frequent washing of clothes), mass immunisation, and improvements in wound treatment including antiseptic surgical procedures. Improvements in housing and reductions in family size have probably played major roles in reducing disease transmission. *Breastfeeding* is key to reducing exposure of infants to diarrhoeal diseases (through contaminated alternatives to breast milk) as well as increasing resistance via the anti-microbial properties of breast milk that provide some protection against both gastrointestinal and respiratory infections.

Although *artificial immunisation* acts to increase individual host resistance its key function from a public health point of view is in preventing transmission to uninfected hosts. If a sufficient proportion of the population is immunized then transmission can be halted (so-called 'herd immunity'). The level of immunisation required for herd immunity varies with the infectiousness of the disease. Smallpox, the most lethal single disease of the eighteenth century in north-west Europe, was reduced to a minor cause of death by 1850 by the discovery and, perhaps more crucially, state promotion of routine vaccination of young children (its final eradication by 1980 depended on both vaccination and rigorous surveillance, contact tracing and isolation of those exposed; Fenner et al., 1986). Much of the global decline in childhood diseases such as measles, polio, whooping cough (pertussis) and tetanus since 1950 can be traced to the proliferation of vaccine discoveries in the 1950s and 1960s and to the rigorous implementation of immunisation campaigns. The success of immunisation technologies has depended heavily not only on factors that promote vaccine discovery and development but also on the willingness of states to roll out these technologies to the entire population. For example, smallpox inoculation was an effective precursor of vaccination and where parishes deemed it cost-effective to implement inoculations of the entire population (in preference to paying for nursing and burial of smallpox victims) then it seems to have been very effective in preventing smallpox epidemics (Smith 1987; Razzell 2003). However where, as in British cities, local officials were unwilling to bear the cost of wholesale inoculation then private inoculation was wholly insufficient to reduce smallpox mortality (Davenport et al. 2015). Similarly, polio persists in populations where the reach of the state is limited or where there is widespread mistrust of the state (as in the case of hostility to polio vaccines in parts of India, Pakistan, Afghanistan and northern Nigeria) (Obregon et al. 2009).

The control of insect vectors has been crucial to the decline of insect-borne diseases. The application of DDT (discovered in 1939) to malaria is the most outstanding example. In Sardinia, where an eradication campaign funded by the Rockefeller Foundation led to the application of 10,000 tonnes of DDT between 1946 and 1950, the number of malaria cases plummeted from 75,000 in 1946 to nine in 1951 (Snowden 2006; Percoco 2013). DDT was also widely used in the later stages of World War 2 against typhus-bearing lice and later against *aedes aegypti*, the mosquito responsible for dengue and yellow fever. DDT remains an effective weapon against mosquitoes but its negative impacts on human health and the environment have restricted its use since the 1970s. Earlier efforts at drainage and greater emphasis on hygiene and washing of clothes together with delousing probably drove substantial pre-twentieth century declines in typhus and malaria (Dobson, 1993; Riley, 1983).

Sanitation (water supply, sewage disposal) has undoubtedly played a central role in the reduction especially of diseases spread by faecal contamination of water

and food. Cutler and Miller (2005) argued that the clean water technologies of filtration and chlorination were responsible for reducing mortality in U.S. cities in the second half of the nineteenth century by half. Ferrie and Troesken (2008) broadly corroborate, finding that 30 to 50 per cent of the reduction in mortality in Chicago between 1850 and 1925 was due to cleaner water. This was during a period when the overall death rate in Chicago declined by three-fifths. Evidence of the impact of water supplies and sanitation on mortality in nineteenth century England is more equivocal, perhaps because of large variations in the quality of piped water and sewerage during the long process of developing and refining these technologies, and because access to these services was often on a household rather than neighbourhood basis.

Reductions in exposure to infection were probably especially key in the early phase of mortality decline because of a paradoxical relationship between lethality and disease transmission. The growth of cities and the integration of large population through trade and migration has often been assumed to have resulted in an initial rise in mortality as new diseases were introduced, followed by a gradual process of adjustment and mortality decline as many 'immunising' infectious diseases were reduced to diseases of childhood (e.g. McNeill 1976; Kunitz 1983). The assumption that as various infections were reduced to diseases of childhood they would become more benign rested at least partially on the assumption amongst epidemiologists and evolutionary biologists that the process of accommodation between host and pathogen involved an evolutionary selection for avirulence. In the last 25 years this evolutionary paradigm has been overturned with the recognition of the complexity of selective forces operating on the determinants of virulence.

Virulence is usually associated with rapidity of pathogen multiplication, and therefore there is strong natural selection for high virulence amongst the pathogen population *within* a host. However because virulent pathogens tend to incapacitate their hosts and reduce their mobility, high virulence can limit the transmission of the pathogen *between* hosts *unless* the pathogen has another means of transmission that does not depend on host mobility. Thus Ewald has argued in a very influential series of papers (Ewald 1983, 1991, 2004) that a hierarchy of virulence exists from very lethal diseases transmitted by arthropod vectors (bubonic plague, typhus, malaria, yellow fever) or by water (cholera, typhoid), to pathogens that can persist outside any host and 'sit and wait' for a victim (smallpox, tuberculosis, polio, influenza) down to relatively mild diseases that are transmitted person to person without an intermediate phase and which are therefore necessarily highly infectious (in order to sustain transmission) but also not too disabling to the majority of hosts (measles, whooping cough, scarlet fever, diphtheria, chicken pox, rubella). This hierarchy of virulence is approximated in the chronology of disease control in England (Table 2).

[Table 2 about here]

The association of high lethality with alternatives to rapid person-to-person transmission that do not require high host infectiousness meant that many of the most lethal diseases were not very contagious (Table 2). In terms of the history of infectious disease control, it was fortuitous that the most lethal diseases were those where the chain of transmission was most readily broken by relatively rudimentary policies of quarantine and isolation (plague, typhus and smallpox), by drainage in the case of malaria in northern Europe and by vaccination in the case of smallpox. Smallpox for instance requires only c. 80 per cent vaccination coverage to prevent transmission, compared with c. 95 per cent for measles because of its much higher infectiousness, and this relatively low level of immunisation required was a key factor in the successful eradication of smallpox (Anderson & May, 1991).

Notable in Table 2 is the inclusion of MRSA ((Methicillin-resistant *Staphylococcus aureus*) in recently controlled diseases. A hospital-acquired infection, MRSA is not confined to institutional settings by any need for debilitated hosts, but rather belongs to the class of lethal 'sit and wait' pathogens with high virulence but low transmissibility. MRSA can persist in the environment for months until a host comes within range, with no selection for avirulence (Walther & Ewald, 2004). MRSA is currently treatable by a narrow range of 'front-line' antibiotics, but can also be prevented by stringent hygiene on account of its relatively low infectiousness (see box 1 and section 5.1).

The elimination of plague, smallpox, cholera and typhus depended to a great extent on effective surveillance and quarantine of cases together with measures to disinfect or dispose of contaminated clothes and bedding. Medieval Italian city states established a rigorous if often neglected system of surveillance and quarantine against the plague that included naval blockades of affected ports and an espionage network. Bills of Mortality were first established to give early warning of plague outbreaks and this system was intensified during the cholera epidemics of the nineteenth century and eventually coupled with sanitary inspectors to implement quarantine and cleansing, and extended to include notification of cases as well as deaths. As the SARS episodes and the current Ebola epidemic has demonstrated, surveillance remains absolutely vital to the prevention of epidemics.

2.2. Resistance to Infection

Resistance to infection depends on the immune status of individuals. It depends on previous exposure (in the case of diseases that confer some immunity on survivors), evolutionary processes affecting host/pathogen interactions, and on the

nutritional status and co-morbidity burden of the human host (as well as basic factors such as age and sex). *Co-morbidity* is undoubtedly a key factor affecting host susceptibility to many infections. For example, recurrent diarrhoeal infections undermine nutritional status and increase the risk or impact of infection with other pathogens. Active tuberculosis infection heightens the risks associated with influenza and pneumonial infections. For some diseases, including tuberculosis, pneumonia and leprosy, host nutritional status profoundly affects the ability of the immune system to respond to the pathogenic challenge. However not all infectious diseases are more lethal in malnourished populations. Very lethal diseases such as malaria, bubonic plague and smallpox are able to overwhelm host defences regardless of nutritional status or age (although not specific host immunity), and therefore where they were prevalent they would have reduced substantially the advantages of wealth or adequate nutritional status to survival. Conversely the disruption of transmission of these diseases would have favoured the emergence of socioeconomic differentials in mortality in the nineteenth century, as less virulent diseases more sensitive to host health status became the dominant causes of infectious disease. The dramatic rise in life expectancy over the last two centuries has been associated with widening inequalities in mortality between socioeconomic groups, despite the development of national health services and universal education. Widespread improvements in nutrition and declines in co-morbidities over the last century have increased host resistance to infection and have undoubtedly played a significant part in reducing mortality from diseases such as tuberculosis and pneumonia.

2.3. Treatment of Infections

Treatment has arguably played relatively little role in determining historical trends in mortality and morbidity from infectious diseases before the antibiotic era. However nursing has been key to survival in the case of many diseases by keeping the patient hydrated, nourished and warm (or cool). Nursing quality is often considered a key factor in preventing deaths from measles, many of which result from opportunistic respiratory infections that can be prevented by isolation, hygiene and keeping the patient warm and rested. It has been argued for example that mortality from measles and from the 1918 pandemic flu strain was exceptionally high in some isolated and immunologically naive communities because the simultaneous infection of a high proportion of adults left too few to provide even the most basic needs of the sick (e.g. Boyd, 1999). Breastfeeding was and remains a key means of keeping infants hydrated during acute diarrhoeal episodes, supplemented only since the 1960s by oral rehydration therapy, a relatively cheap and simple treatment for dehydration that has led to major reductions in diarrhoeal mortality. Hygiene, discussed above in the context of reducing exposure, can also be viewed as part of a suite of medical

treatments (aseptic and antiseptic methods) designed to prevent wound infection that evolved in the late nineteenth century in tandem with bacteriology.

The most dramatic advance in the history of treatment was undoubtedly antibiotic therapy. However the development of penicillin and related anti-bacterial drugs grew out of a period of intense experimentation from at least the 1870s that produced anti-toxins against diphtheria and tetanus by the 1890s (recognised by a Nobel prize in 1901: Kantha, 1991), salvarsan against spirochaete infections most notably syphilis (1909), and later sulfa drugs (1930s). Since the 1940s other types of antimicrobial drugs that target malaria and HIV have also had a very major impact (see section 3.3).

Among other effects antibiotics made surgery radically safer and contributed to the profound historical shift in the nature of military casualties. Before the twentieth century infectious diseases such as smallpox, typhus, typhoid, cholera and dysentery not combat wounds accounted for a clear majority of military losses. Accordingly armed forces were often at the forefront of developments in the control of infectious diseases, including smallpox inoculation of troops and militia from the late eighteenth century, vaccination against smallpox (1800+) and typhoid (from the 1900s), and delousing, as well as implementation of aseptic and antiseptic practices in wound treatment. These measures, as well as 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. As a result WWI was the first major war in which more deaths were caused by battle wounds than by epidemic diseases (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). The ratio of battle casualties to fatalities improved markedly with the use of penicillin (in military use by 1942). However antibiotics represented a late contribution to the progressive development since the mid-nineteenth century of medical and logistical processes to prevent wound infection that included rapid treatment, antiseptic and aseptic technologies, and tetanus antitoxin and which had already led to very substantial reductions in the rate of infection and mortality before 1942 (Cooter et al. 1999).

2.4. Successful Interventions: Plague as a Case Study

Plague (*Yersinia pestis*) is the most fearsome of all infectious diseases.[5] 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 for a further three and a half centuries. 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-sectional 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 (Cummins, Kelly and Ó Gráda 2014; Champion 1995). A century or so ago plague was very uneven in its impact in India. 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 (Rao 1994: 2720).

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 (Mital *et al*. 2004; Stenseth *et al.* 2008).

Since the Black Death reduced labour inputs but not those of land or capital, it should have increased wages and output per head (Hirshleifer 1966; Voigtländer and Voth 2013). And, indeed, in Western Europe workers gained while landlords lost.[6] Plague, unlike, say, malaria or HIV/AIDS today (compare Haacker 2002a, 2002b), 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. It is sometimes claimed that the rise in wages that followed the Black Death may have spurred labour-saving innovations such as the printing press and firearms, though this remains rather speculative.

The disappearance of plague from the western world in the early modern era owed nothing to 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. Instead the most

[5] Fears in the recent past and today of SARS (severe acute respiratory syndrome), new influenza strains, and Ebola offer only a faint indication of the terror caused by plague. Plague was perhaps as lethal and easier to transmit than Ebola.

[6] In Eastern Europe the outcome was different because the power of the landed elite to combine led to increased exploitation of the landless masses (Domar 1970).

comprehensive analyses of the disappearance of bubonic plague from Europe suggest that a combination of routine surveillance (such as urban Bills of Mortality), 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 (Slack, 1985). Northern Italian cities devised an elaborate system of *cordon sanitaire* (including naval blockade of effected 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 1648 and from England after the Great Plague of 1665 (Cipolla 1981; Slack 1981; 1985).

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. 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: see Curson 1985; Echenberg 2007). Plague remains endemic in rodent populations in part of the Americas, Africa and Asia and although human cases are now treatable with antibiotics, deaths occasionally occur, as recently in Madagascar (Vogler *et al.* 2013).[7] Although outbreaks are managed on an emergency basis by antibiotic prophylaxis to reduce transmission in contacts, surveillance, pest control and quarantine remain the preferred control options both where outbreaks are still common (such as central Africa) and in preparatory scenarios where it is not (Stenseth *et al*. 2008; Dennis *et al*. 1999).

3. The Links between Income and Health

That better health is linked to economic growth would seem incontrovertible. On the one hand, there is a presumption that higher living standards lead to reductions in mortality and morbidity; on the other hand, surely improved health increases productivity and income. Yet both these links are contested.

In a classic paper Preston (1975) argued that increased incomes accounted for only one-quarter of the increase in life expectancy between the 1930s and the 1960s,

[7] *The Guardian*, 'Bubonic plague outbreak kills 32 in Madagascar', 20 December 2013; BBC News Africa, 'Madagascar plague outbreak kills 40, says WHO', 21 November 2014 [http://www.bbc.com/news/world-africa-30152979]; WHO, *Impact of plague: Human plague cases from 1989 to 2003* [http://www.who.int/csr/disease/plague/impact/en/].

with 'factors exogenous to a country's current level of income' being responsible for the other three-quarters. Those factors ranged from sanitation, public health education, and vector control in poor economies to vaccines, sulfa drugs, and antibiotics in rich economies. Preston illustrated his claim with what became known as 'Preston curves' (figure 11), representing life expectancy for national populations against national per capita income in different periods. In any given year there is a strong relationship between GDP/capita and life expectancy, at least for populations in the lower half of the income distribution. However when comparing across years it is also evident that at any given level of income life expectancy has risen over time, apparently independent of income. Preston's findings tally with Deaton's that between 1850 and 1950 'new ways of addressing health' mattered most, with economic growth playing 'an important, but subsidiary role' (2013: 107) but not the claim that across the world since 1950 there is 'no relationship at all between growth and saving lives' (2013: 109; compare Easterlin 2013; Soares 2007). What matters most today, says Deaton, is not higher incomes but good government. Such claims, which highlight the role of institutions conducive to the spread of medical innovation, run counter to McKeown's famous thesis, broadly supported by Fogel (McKeown 1976; Fogel 2004) that in the past nutrition and higher incomes rather than medical science or public policy were mainly responsible for reduced mortality. But this does not mean that McKeown and Fogel were entirely wrong; unlike Preston and Deaton, their main focus was on the pre-1900 era.

Paralleling Preston's evidence on the relatively minor role of economic growth in mortality declines, Jack Caldwell analysed exceptional gains in life expectancy made by some of the poorest populations in the world, populations he called 'high achievers' (Costa Rica, Sri Lanka and the Indian state of Kerala) (Caldwell 1986). Caldwell argued that relatively egalitarian access to food (or a basic safety net in cases of need), widespread access to basic health services, and the status and autonomy of women were key determinants of good health in these populations. He did not analyse the factors driving similarly impressive gains in a number of poor Communist states (including China and Cuba), but did contrast the very poor performance of a number of oil-rich Muslim states, a pattern which still holds today (Figure 11B).

3.1. Economic impacts

The reduced prevalence or elimination of infectious diseases has had important economic consequences. These vary by disease. Some diseases kill but have little impact on the health of the few victims who survive (plague); others don't usually kill but debilitate those who contract them (hookworm); while others both kill and scar (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 (malaria, influenza).

3.2. Macroeconomic consequences

How improvements in health affect economic performance is controversial. In a simple neoclassical growth framework (compare Haacker 2004), the reduction in the capital-labour ratio resulting from improved survival should depress workers' incomes, but this does not allow for potential increases in savings attendant on reduced medical outlays, nor for indirect gains in human capital attendant on higher survival rates and reduced morbidity. Acemoglu and Johnson (2007, 2013) deny any link between health improvements (proxied by life expectancy) and GDP in the past, arguing that the negative economic impact of population growth trumped any direct health benefits. 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. In pre-transition countries increasing population absorbs the gains, whereas in post-transition countries there are positive growth effects (on the transition see Guinnane 2011).

[Figure 11 here]

Acemoglu and Johnson (2007: 975) concede that their results may not be applicable to today's world, since their focus was on health improvements in the 1940s, i.e. at a time when most LDCs had yet to begin their fertility transition, whereas today few countries today have yet to embark on it (Reher 2004). Ashraf *et al.* (2009) find that Acemoglu and Johnson's results hinge on an implausibly high fertility response to health improvements. When they allow for endogenously falling fertility, the long-run outcome is an improvement in GDP per capita. A cross-country analysis by Weil (2007: 1291-2, 1299-1300) finds that direct effect of moving from the lowest to the highest adult survival rate is output per worker increasing by a factor 1.35, while allowing for the indirect impact of productivity growth on income would roughly double that affect. Several other studies also support the link between health and economic growth. They include Bloom, Canning, and Fink (2013) who argue for a growth dividend through the impact of childhood health on adult productivity. Arora (2000), employing a time-series causality approach to data on ten relatively well-off economies, found that during the twentieth century health improvements added 30-40 per cent to the annual growth rate. Audibert *et al.* (2012), using a range of *DALY*

(Disability-Adjusted Life Years) ariables as proxies for health, find that these variables exert a strong positive impact on GDP growth after a controlling for a range of macroeconomic and institutional variables.

3.3. Malaria

Malaria is a life-threatening disease caused by parasites that are transmitted to mammals via infected female mosquitoes. In 2012, the WHO estimated that there were over two hundred million cases of malaria and 0.6 million deaths – mostly among children living in Africa.[8] Hay *et al*. (2004) claim that malaria is the most important of the parasitic diseases of humans, with 107 countries and territories having areas at risk of transmission containing close to half the world's population (Hay et al. 2000). Of the four varieties of malaria, *Plasmodium falciparum* and *Plasmodium vivax* are the most common, and *P. falciparum* the most fatal. 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.

Mankind'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. Antimicrobials are currently used in a two-pronged approach to malaria, by reducing exposure via insecticidal bed nets and indoor spraying, and via treatment of infected individuals with ACTs. However both insecticides and antimicrobial therapies are threatened by the evolution of insect and plasmodial resistance, and 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.

Estimates of the impact of malaria on productivity and income vary rather widely. In a much-cited study Gallup and Sachs (2001; see too Sachs and Melaney 2002) reckoned that malaria imposed an annual cost in terms of GDP growth foregone of 1.3 per cent on heavily infected countries. But Acemoglu and Johnson (2007) could find no educational or GDP dividend from the eradication of malaria, and Ashraf *et al.* (2014) find that the total eradication of malaria in Zambia, where the disease is widespread, would increase GDP per capita by only 2 per cent in the long run. A commonly noted problem with the Sachs-Gallup approach is that its results may be

[8] http://www.who.int/mediacentre/factsheets/fs094/en/

biased if the geography linked to the prevalence of malaria is also independently associated with lower economic growth. Kiszewski *et al*. (2004) and Carstensen and Grundlach (2006) attempt to control for this and find that both geography and institutions help account for the variation in per capita GDPs, while in another influential study of African underdevelopment Bhattacharyya (2009) found that among several likely explanatory factors, the fallout of malaria mattered the most. McCord and Sachs (2013) return to the issue of how geography impacts on development and still find a role for the malarial ecology index previously applied by Kiszewski *et al*. (2004) and Carstensen and Grundlach (2006).

Other studies on the impact of malaria on productivity include Lucas (2010), Cutler *et al.* (2010), Bleakley (2010), and Barreca (2010). Cutler *et al*. focus on India's anti-malarial campaign in the 1950s and find that a ten percentage point reduction in incidence results in increased in per capita expenditure by 1.5 to 6.8 percentage points and in female primary school attainment and literacy by 2.5 to 5.6 percentage points. Lucas (2010) finds that malaria eradication campaigns in Sri Lanka and Paraguay led to increased educational attainment, with a ten percentage point reduction in incidence leading to increases in years of schooling of 0.1 and in the probability of being literate of 1-2 percentage points, while Bleakley estimates that malaria accounted for 7 to 13 per cent of the income gap between the U.S. North and South c. 1900, and 10 to 16 per cent of that between a group of Latin American economies and the U.S. c. 1950.

4. Welfare Costs

As just noted, the literature is rather equivocal on the link between the burden of infectious disease and GDP. However, GDP is an inadequate measure of the value that we place on health. If the focus is shifted to estimating the welfare or utility benefits from better health, the gains turn out to be much more significant (Weil 2010, 2014; Hickson 2014). Several alternative measures have been proposed, including the United Nations-sponsored Human Development Index, a weighted index of measures of health (measured by longevity), education, and income. This section briefly reviews three of them; Section 4.2 offers a more comprehensive study of the welfare gains associated with the campaign against tuberculosis in Britain.

The Human Development Index (HDI) owes its origin to a request to Amartya Sen to produce a measure of human wellbeing that 'captures in one number an

extremely complex story'.[9] HDI was initially devised as the arithmetic mean of measures of income, education, and health relative to a maximum; since 2010 it is estimated as the geometric mean of such measures. Its theoretical underpinnings have often been criticized (e.g. Kelley 1991; Srinivasan 1994; Ravallion 1997, 2012) but it has endured, and has been invoked, sometimes in modified form, by economic historians as an improvement on GDP per capita (e.g. Costa and Steckel 1997; Crafts 2002, 2003; Prados de la Escosura 2013).[10]

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

One criticism made of HDI is the relatively low value it implicitly places on gains to life expectancy (Ravallion 2011, 2012; Klugman *et al*. 2011a, 2011b; Easterly and Freschi 2010). Other measures that seek to incorporate longevity include those proposed by Usher, Nordhaus, and others, including VSL (value of a statistical life); QALYs (Quality-Adjusted Life Years) and the *DALY*s associated with the World Health Organisation and, recently, the Gates Foundation. While all are an improvement on GDP per capita, they are also subject to several caveats.

[Table 3 about here]

The Canadian economist Dan Usher (1973; see too Nordhaus 1999; Becker *et al*. 2003) proposed an influential and simple way of incorporating changes in life expectancy into the computation of 'real' national income. Usher's reduced form is

$$G_C = G_{\hat{C}} + [1/\beta]G_L$$

[9] Cited in e.g. Jon Gertner, 'The rise and fall of the GDP,' *New York Times*, 30 May 2010. For a review of critiques of HDI see Kovacevic 2010.

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

where the improvements in mortality over time, G_L, are the difference between the growth in actual consumption, G_C, and 'real' consumption, $G_{\hat{C}}$, while $\beta[=G_L/(G_{\hat{C}}- G_C)]$ may be interpreted as the elasticity of life expectancy to income. Note that most applications of this approach assume a β of .25 or 0.45 (e.g. Williamson 1984; Costa and Steckel 1997: 68-70). Table 4 describes the change in 'real' U.S. income as measured by the Usher method.

[Table 4 about here]

The value of a statistical life (VSL) is a measure of people's willingness to pay for reductions in fatal risks from accidents, work-related illnesses, or infectious diseases. In other words, it is a measure of how people value living longer. Studies applying the measure to historical contexts are few (Hickson 2006, 2014). Here the method is applied to a number of historical contexts related to infectious disease in order to obtain rough orders of magnitude for the gains from reduced prevalence or eradication. The measure is also applied below in Section 4.2.

A 'first cut' estimate of the value of a statistical life in Country C in year t may be obtained by calculating (OECD 2012):

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

where Y is GDP, $VSL_{US,2010}$ and $Y_{US,2010}$ refer to present-day US values and η is the income elasticity of demand for staying alive. PPP-adjusted US$ estimates of $Y_{C,\,t}$ may be obtained from the Penn World tables or (for the pre-1950 period) Angus Maddison's historical national accounts estimates.

Applying estimates of VSL in high-income countries to much poorer countries in an earlier era entails an assumption about which income elasticity to use, i.e. what is the proportionate change in VSL resulting from a change in income. Clearly the higher the elasticity η, the more poor economies discount VSL; indeed, some studies yield $\eta>1$, implying that that VSL rises sharply with income (Hammitt and Robinson 2011: 21; Leon and Miguel 2013; Jeuland *et al*. 2013, 2014; but see too Wang and He

2010). In a meta-meta-analysis based mainly on studies in advanced economies Doucouliagos, Stanley, and Viscusi (2014) find that η is 'clearly and robustly inelastic'. Miller (2000) recommends η=1 as the 'best estimate' and a recent OECD report (2012) recommends η=0.8, while Hammitt and Robinson (2011) advise analysts not to rely on a single value but to report outcomes using a range of estimates of η. The following estimates, which are intended to be illustrative, work on the assumption of η=1.

4.1.1. Plague in London

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

What were the welfare gains for London of the disappearance of plague? The VSL methodology offers one way of answering this question. The population of London in 1666 was about 0.5 million. Before the plague's disappearance a crude death rate of 30-32 per thousand implies that epidemics were responsible for an average of 2,500 deaths annually over the previous century. Let us suppose output per head in London was 50 per cent higher than the English average, so about \$1,400[11], versus \$30,490 for the U.S. in 2010. Assuming a U.S. VSL of \$9 million yields a VSL of about \$410,000 for London c. 1665 when η=1. The gain as a percentage of London's GDP was [(2,500)*410,000]*100/(1,400*500,000)], or over 140 per cent of London's GDP. Naturally this huge percentage leaves out of account other economic and demographic impacts of the plague's disappearance.

4.1.2. Smallpox in England

Smallpox spread in Europe in the wake of the Crusades and was already endemic by the sixteenth century. Hard data are lacking on how many deaths were due to smallpox in the period just before inoculation against smallpox became widespread. We assume the rather conservative figure of 5 per cent.[12] The crude death

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

[12] In Sweden as a whole between 1749 and 1773 smallpox was responsible for 13.2 per cent of all deaths, whereas in Stockholm—notorious for its high mortality rate—it accounted for only 7.1 per cent of deaths (Sköld 1996: 546). In the Netherlands, 'in spite of its endemic character, the impact of smallpox on medium-sized cities, small towns and the countryside was of minor

rate in England and Wales c. 1750 was about 27 per thousand, meaning about 150,000 deaths per annum (Wrigley and Schofield 1981: 494, 533). A death rate of 5 per cent from smallpox would mean a total of 7,500.

What would the gains have been from the non-occurrence of those 7,500 smallpox deaths per annum? Again, using η=1, we can estimate as a first approximation:

$$VSL_{ENG1700} = [VSL_{US2010}][Y_{ENG1700}/Y_{US2010}]$$

$$= [\$9{,}000{,}000][1{,}695/30{,}500]$$

$$= [\$9m][0.0556]$$

$$= \$0.5 \text{ million}$$

Given a population of 5.7 million c. 1750 the GDP of England and Wales in terms of current PPP dollars was worth (5,739,364)($1,695), or $9,728 million. Then the estimated welfare benefit in terms of VSL of eliminating smallpox as a percentage of GDP is 39 per cent. This would represent an enormous gain, especially relative to the slow economic growth rates typical of the pre-industrial era.

4.1.3. Malaria in India and China

During the 1950s India's National Malaria Eradication Programme reduced the number of deaths from malaria by nearly half. Between independence (1947) and 1965 the number of deaths fell from 0.8 million to virtually zero. In other words, malaria killed more people in India in 1947 than it kills worldwide today. How did the benefits from virtually eliminating deaths from malaria compare to the eradication of smallpox in England? We note that the population of India c. 1950 was 370 million; the Penn World Tables give GDP per capita (Y) in India in 1950 as $594 (2005 PPP), whereas Y in the US c. 2005 was $41,146. Again working with a US estimate of VSL=$10 million, we can calculate for η=1:

$$VSL_{IND1950} = [VSL_{US2005}][Y_{IND1950}/Y_{US2005}]$$

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importance, being the cause of death for no more than 4 to 5 per cent of total mortality' (Rutten 2011: 189).

= [$9m][594/41146]

= [$9m][0.0144364]

= $130,000

So the welfare gain from eliminating 0.8 million deaths from malaria as a percentage of GDP for η=1 was 47 per cent 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. Estimating the benefits using the VSL approach is as before. In 1950 China's population was 545 million and GDP per head was $448. We use U.S. GDP per head of $30,500 and a VSL of $9 million. This yields a Chinese VSL of $132,000 in 1950. Applied to a million lives with η=1 yields a welfare gain of 56 per cent of 1950 GDP.

In Ceylon (Sri Lanka) a vigorous eradication campaign (see San Francisco Global Health Group/WHO 2012) reduced the number of malaria deaths from an average of 7,500 annually in 1936-45 to 1,500 in the early 1950s. So six thousand lives saved annually in a population of 6.65 million and a GDP per capita of $1,116 in 1945 (Maddison). Assuming η=1 yields VSL=$250,000. So the ensuing welfare gain, using 1945 GDP as denominator, was worth about 20 per cent of GDP.

The preliminary character of these estimates of the welfare gains from eradicating three infectious diseases—plague, smallpox, and malaria—is clear. In particular, the choice of η=1 is controversial: estimates of welfare gains are very sensitive to the elasticity used.[13] Choosing η=1.5 instead of η=1 would reduce the estimated welfare gains from eradicating smallpox in England to 9 per cent of GDP and the gains from eradicating malaria from India in the 1950s to a still significant 5 per cent. Rough as they are, these estimates still point to the significance of the welfare gains associated with three well-known historical examples.

[13] Clearly the higher the elasticity η, the more poor economies discount VSL; indeed, some empirical studies yield η >1, implying that that VSL rises sharply with income (Hammitt and Robinson 2011: 21; Leon and Miguel 2013; but see too Wang and He 2010). In a meta-meta-analysis based mainly on studies in advanced economies Doucouliagos, Stanley, and Viscusi (2014) find that η is 'clearly and robustly inelastic'. Deaton *et al*. (2010) demur, arguing that the income elasticity of demand for healthcare in Africa is high, citing Easterly's finding of large negative responses to user fees for medical care. A full analysis of the sensitivity of these VSL-based estimates to different assumptions about η, age at death, and so on is desirable, but remains a task for another day.

4.2. Tuberculosis: A Case Study

4.2.1 Introduction

The decline and virtual elimination of tuberculosis in England and Wales represents one of the most important and valuable health gains during the twentieth century. In 1901 tuberculosis was regarded as a 'comprehensive sentence of death' (MCNulty, 1932). By the close of the twentieth century tuberculosis sufferers' lives 'were altered very little' (WHO, 2000).

Some of these gains appear to be in jeopardy with the emergence of multi-drug resistant tuberculosis (MDR-TB). The incidence and spread of multi-drug resistant tuberculosis (MDR-TB) is of concern to both the developed and developing world (WHO, 2000). The predictions for the future situation with tuberculosis drug resistance and, more generally, antimicrobial resistance (AMR) vary widely. In order to contemplate the potential future burden of TB AMR it is necessary to first explore the contribution of the virtual elimination of tuberculosis in the twentieth century, after which it will be possible to provide some illustrative calculations about the burden of TB AMR and implications for the future. The results below provide a broad illustrative range of estimates about the possible future economic burden of AMR regarding TB.

4.2.2 Results About the Value of TB Elimination in Twentieth Century England and Wales

Improvements in tuberculosis are evident with mortality and morbidity. Mortality can be measured as the fall in the age-specific death rate. Morbidity measurement is much more complex. An accurate measure of tuberculosis morbidity will consider the burden of tuberculosis in terms of quality of life of sufferers and the number of sufferers or prevalence of tuberculosis. Hickson (2006) summarised the morbidity burden of tuberculosis over the twentieth century by identifying the key quality of life aspects and evaluating these based on available evidence.[14] These are summarised as quality adjusted life year (QALY) weights in Table 5.

[14] Key quality of life aspects: (i) government initiatives and help, (ii) recognition and awareness provided by charities, organisations, and society in general, (iii) medical developments, (iv) the pain and discomfort associated with suffering from tuberculosis, and lastly (v) the ability to lead a normal life, which considers the financial and emotional burden of tuberculosis. From Hickson, 2006.

[Table 5]

Table 5 indicates that in 1900 the collection of health and welfare standards of living meant that the typical tuberculosis sufferer only enjoyed about 30 per cent of a healthy life year. By the year 2000 the quality of life associated with tuberculosis morbidity increased to a level that represents about 80 per cent of a healthy life year. This boost was largely facilitated by the availability of a cure for tuberculosis around the middle of the twentieth century.

Table 6 highlights the significant decline in tuberculosis mortality over the twentieth century. This decline began in the late nineteenth century and gathered pace throughout the twentieth century, such that by 1980 tuberculosis mortality had been virtually eliminated.

Tuberculosis prevalence – as defined by notifications to the medical officer – also experienced a significant decline over the twentieth century. This is reported in Table 7.

[Tables 6 and 7]

Table 7 shows that the tuberculosis notification rate declined markedly over the twentieth century such that by the year 2000 tuberculosis morbidity had been virtually eliminated. Two exceptions to this trend are: (i) between 1940 and 1950 when tuberculosis notifications increased, which is a likely result of National Health Service initiatives at more comprehensive reporting, rather than a genuine worsening in the prevalence of tuberculosis, for example, the utilisation of mass miniature radiography screening (Bryder, 1988). And (ii) between 1980 and 2000 there was stagnation of the decline of tuberculosis prevalence, which is generally considered to be a result of a resurgence of tuberculosis in the homeless, immigrants and AIDS populations (Joint Tuberculosis Committee, 2000; Bannon, 1999). This also explains the increase during the twenty-first century.

These developments can be better highlighted by considering the aggregate number of additional life years that have been generated as a result of improvements associated with tuberculosis as the twentieth century unfolded. Table 8 presents this calculation.

[Table 8]

Table 8 considers the loss of life years in 1901-2000 and 1950-2000 for tuberculosis mortality and morbidity. The mortality component is calculated as the number of deaths in 1901, 1950 and 2000. Morbidity comprises the number of notifications, which is adjusted for the quality of life burden of tuberculosis in 1901, 1950 and 2000. Tuberculosis severity is calculated as the portion of a health life year lost due to tuberculosis. That is, the inverse QALY. The sum of the mortality and morbidity calculation gives the number of life years gained due to the decline of tuberculosis.

In order to add greater significance to the results presented in Table 8 the number of additional life years that have been gained can be valued by applying 'Value of a Statistical Life' (VSL) function. Estimates about the 'Value of a Statistical Life' (VSL) range widely, from several hundred thousand to millions of dollars, which has led some to claim that *'the variation in VSL estimates raises such doubts about their reliability that they are virtually redundant'* (Jones-Lee, 1989). One of the more credible studies was conducted by Miller (2000), who considered a range of estimates, which were applied to a series of statistical analyses in order to estimate a more robust VSL (Jones-Lee, 1989). Miller's (2000) lower bound estimate of $1.22 million will be used here (Jones-Lee, 1989).

[Table 9]

Several points stand out from Table 9: most striking are the values of the mortality, morbidity and subsequent aggregate life years gained from the virtual elimination and amelioration of tuberculosis. The number of additional life years generated by the reduced death rate, prevalence, and quality of life burden of tuberculosis between 1901 and 2000 has been calculated to be worth at least $127 billion, and $35 billion between 1950 and 2000.

Now that the magnitude of twentieth century health gains as a results of the elimination of tuberculosis have been identified it is necessary to consider the extent to which this achievement might be reversed during the twenty-first century as a result of MDR-TB.

4.2.3 TB In the Twenty-First Century With AMR

MDR-TB is defined as resistance to at least isoniazid and rifampicin (Arias, 2000). The incidence and spread of MDR-TB is of concern to both the developed and developing world (WHO, 2000). For example, in the USA, MDR-TB epidemics have been reported in New York and Florida (Park *et al.*, 1996), while in Africa the incidence of MDR-TB continues to spread dramatically and extensively (Davies *et al.*, 1999). This imposes a significant resource burden as the associated treatment costs and QALY burden are substantial. For example, treatment of some patients in the USA has been estimated to cost $1 million (Chaulk *et al.*, 1998).

As MDR-TB becomes more commonplace some of the gains associated with the elimination of tuberculosis in the twentieth century (presented in Tables 5 - 9) will be lost. Unfortunately estimating this loss with any precision is very difficult, not least because of the need for epidemiological forecasts about the probability of MDR-TB. This is a general issue associated with AMR. One indication about the potential magnitude of the problem can be gleaned from considering the nature, timing and distribution of AMR. The relationship between time and the proportion of any particular microorganism that is resistant tends to follow a sigmoid distribution, with 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, followed by a third phase in which the proportion of resistant strains has reached equilibrium (Austin and Anderson 1999). 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 (Coast *et al.* 2000).

One very approximate approach is to estimating the potential losses due to resistance is to consider an upper and lower bound based on available data. The upper bound, worst case, 'apocalyptic' scenario could be approximated by the loss of virtually all tuberculosis gains, between 1950 and 2000. This upper bound estimate is presented in the final row of Table 5 as $35 billion. 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.[15] 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[16]. 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.

The lower bound can be estimated by considering the current situation with MDR-TB. Table 9 provides a lower bound indication about the current burden of MDR-TB in the UK.

[Table 10]

This calculation considers only an altered morbidity burden. This seems most plausible given that MDR-TB tends to be resolved in longer treatment times and not mortality. The proportion of MDR-TB cases was 1.6 percent in the UK in 2012.[17] Currently, and for the foreseeable future, the key issue seems to be one of increased morbidity rather than mortality. The burden of which is estimated to be $1.9 billion. This is calculated in Table 10 by applying a VSL function to the number of life years that have been burdened with MDR-TB in 2013.

To put these results into context Table 11 presents some very initial estimates about the burden of MRSA. The recent results about the burden of MRSA are much higher than tuberculosis. For example, the burden of MRSA between 1993 and 2011 is estimated to be $17 billion. This is primarily because MRSA currently causes mortality and MDR-TB currently is only an issue of morbidity. However, if the early issues of

[15] 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.

[16] 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.

[17] Annual Report on tuberculosis surveillance in the UK; Health protection report.

total drug resistant tuberculosis (TDR-TB) continue then the burden of tuberculosis could indeed become of a similar or even greater order of magnitude to MRSA.

[Table 11]

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

How great is the danger posed by AMR and what can economic historians contribute to understanding it? Expressions of concern and deliberations about antimicrobial resistance (AMR) are not new.[18] Recently the issue has been making the headlines, however, with gloomy warnings from G8 science ministers (2013)[19], the WHO, and others, and media reports of 'as big a threat as terrorism' and 'a ticking time bomb'[20]. The WHO's first global report on AMR (WHO 2014a) offers evidence of increasing resistance by an increasing range of bacteria to antibiotic treatments for intestinal and urinary tract infections, gonorrhea, and MRSA infection.[21] With growing antibiotic usage in humans and animals (Sarmah *et al*. 2006), 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' (WHO 2014a). Smith and Coast (2013) go so far as to state that an increase in AMR coupled with a fall in the number of new antimicrobial drugs means an 'apocalyptic scenario may be looming'.

Such warnings have elicited a response from some concerned parties [e.g. ECDC 2009; RSC 2013; Matlin *et al*. 2014]. Still, AMR has received less attention than many other health-related issues. A key reason for this is that both policymakers and pharmaceutical companies tend to focus on the present or the short-term future. 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

[18] For earlier warnings see Davies *et al*. 1999; Austin and Anderson 1999; White 1999; Department of Health 2013: 9; Arias *et al.* 2000; Health Canada 2002; Harbarth and Emonet 2006.

[19] Clive Cookson, 'G8 ministers pledge to act on bacterial antibiotic resistance', *Financial Times*, June 13, 2013.

[20] 'Antibiotics resistance 'as big a threat as terrorism'—medical chief'', 11 March 2013 (http://www.bbc.com/news/health-21737844).

[21] And there are worries about HIV too. See 'Drug-resistant HIV pandemic is a 'real possibility', expert claims', *Independent*, 22 May 2014 [http://www.independent.co.uk/life-style/health-and-families/health-news/drugresistant-hiv-pandemic-is-a-real-possibility-expert-claims-9420833.html]

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, the potentially disastrous consequences are acknowledged, but because they are not immediate, little is done about them. A case in point is the promising Ebola vaccine shelved in the mid-2000s because outbreaks of the disease seemingly did not pose a major threat at the time.[22]

So far, although it is reckoned that 25,000 die annually in European Union and 'at least 23,000' in the United States from an AMR-related infection (ECDC 2009; CDC 2013)[23], there have been no catastrophic crises due to AMR. Moreover, in England and Wales, MRSA-linked death rates have been falling, due to improved hygiene and infection control; having risen from 2.2 per million for males and 1.0 per cent for females in 1993-95 to 26.5 per million for males and 13.2 per million for females in 2005-07, by 2010-12 they were down to 4.7 per million and 2.4 per million, respectively (see Box 1). In the U.S.A. too, the number of 'invasive MRSA infections in healthcare settings' has been falling (ONS 2013; CDC 2013: 77; compare Song *et al*. 2013). In other words, so far the *demographic* cost of AMR-related conditions in developed economies is perceived as rather small, even though these numbers are the tip of an iceberg that includes many more who die of conditions exacerbated by antibiotic-resistant infection and at least an annual two million people infected with antibiotic-resistant bacteria in the U.S.A.

In addition, in parts of Southeast Asia there is evidence of delayed parasitic resistance of one type of malaria (*P. falciparum*) to the standard 'first line' antimicrobial treatment *artemisinin,* when used as a stand-alone drug. But the impact on prevalence and mortality so far seems modest. Figure 12 describes recent prevalence and mortality from malaria in reportedly drug-resistant countries since 2000.[24] Note the lack of any significant increase in reported deaths in any of the five countries at risk. However, as our earlier discussion of the sigmoidal time-path of microbial evolution of resistance showed, it would be foolhardy to base policy on such data.

[Figure 12 about here]

[22] Denise Grady, 'Without Lucrative Market, Potential Ebola Vaccine Was Shelved for Years', *New York Times*, 23 October.
[23] The ECDC study (p. 13) reckoned the cost in Europe in terms of medical outlays and productivity losses in 2007 at €1.5 billion.
[24]The number of reported cases is given only from 2000 on, since the data for the 1990s seem very suspect.

A second reason is for the delayed response to AMR that antibiotic resistance is a natural and inevitable phenomenon. Methicillin 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).. 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. Similarly, as streptomycin resistance in the treatment of tuberculosis became a problem from the late 1940s on, more effective antibiotics replaced streptomycin in the initial treatment of that disease. The same holds for tetracyclines, streptomycin, penicillin, gentamicin, fluoroquinolones, and, very recently, daptomycin.

So resistance is not an issue per se, but only if the antimicrobial artillery is being consistently updated, as was the case during the second half of the twentieth century. In the past most of that updating has been the product of extended, focused, and commercially oriented research; serendipitous inventions, such as Alexander Fleming's invention of penicillin, are very much the exception. The crux of the present crisis is that the increase in organisms resistant to multiple therapy has *coincided* with the reduction in new therapies coming through the pipeline to replace ineffective therapy (but see below). Moreover, the science involved in generating new treatments is inherently difficult. Presumably all the straightforward discoveries have been made (Shute 2013), which would help explain the lag between a new treatment's discovery and making it operational.

5.1. The Demand for Drugs

It is natural that economic historians, as economists, focus not just on the supply side—the pipeline—but also on the demand side. Current strategies to combat AMR pay lip service to limiting the demand for antimicrobials, and the EU has taken legislative measures to reduce the consumption of antimicrobials in agriculture. But these face opposition from pharmaceutical companies who rely on big sales after discovery in order to recoup substantial R&D costs, and from agriculturalists in places such as the U.S., where reliance on antibiotics is very great. Still, antibiotic usage is amenable to policy choices (Blommaert *et al*. 2013; compare Michel-Lepage *et al*. 2013; Plachouras *et al*. 2008).[25]

A more intelligent approach towards antibiotics usage could increase the shelf life of individual treatments and reduce the incidence of AMR (Shute 2013). However, the trade-off between the misuse of antibiotics and antimicrobial resistance, while

[25] 'More must be done to cut unnecessary antibiotic prescriptions, say experts', *The Guardian*, 5 August 2014.

well established, requires more precision (compare Transatlantic Taskforce 2014; WHO 2014a). Reducing average consumption elsewhere in Europe to, say, the Dutch level would cut the consumption of antibiotics on the continent by almost half. In 2012 11.8 milligrams per thousand inhabitants were consumed outside hospitals in the Netherlands, but 29.3 milligrams in neighbouring Belgium (see Table 12).[26] Much higher consumption of over-the-counter antibiotics in Greece and Italy might suggest that AMR is a bigger problem in those countries than in, say, the Netherlands or Austria, where consumption is low.

The variation in prevalence of resistance across Europe supports the presumption of a correlation between usage and AMR. Figure 13a reports trends in MRSA in a cross-section of European countries since 2000. Note the very low rates of MRSA in the Netherlands and very high rates in Greece and Italy. Figure 13b describes the trends in *E. coli* resistance to fluoroquinolones in the same set of countries; again Greece and Italy perform rather poorly relative to others. Figure 10c plots the relationship between consumption and MRSA in 2012. And indeed, two variables—antibiotics consumption and GDP per capita—'explain' over three-fifths of the variation in MRSA prevalence across Europe in 2012 (compare Blommaert *et al*. 2013, Table 3). Adding GDP per capita squared increases the r-squared value to 0.69. The elasticity of MRSA to consumption is 1.6, an indication of the power of reduced usage to combat MRSA. However, the trade-off between the misuse of antibiotics and antimicrobial resistance, while well established, requires more statistical precision and articulation.

Again, administering antimicrobial drugs to food animals has been linked to the AMR crisis (Maron, Smith, and Nachman 2013; Wallinga and Burch 2013). A recent *BMJ* press release describes the practice of 'additives in feed given routinely, without a prescription, at lower than therapeutic concentrations, for purposes such as growth promotion and to control disease in otherwise healthy animals being raised in crowded or unhygienic conditions that promote disease'.[27] In the U.S. four times as many antibiotics are used on animals as on humans and a recent study of MRSA in U.S.-produced meat and poultry found *Staphylococcus aureus* contamination in nearly half of the samples (Waters et al. 2011).[28] This would be expected to result, other

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

[27] http://www.bmj.com/press-releases/2013/07/09/do-antibiotics-animal-feed-pose-serious-risk-human-health.

[28] In 2011 3.29 million kilograms of drugs were sold for human consumption, whereas 13.77 million kilograms of antibiotics were approved for use in food-producing animals. Between 2009 and 2012 the total for animal use rose from 12.8 million kilograms to 14.7 million kilograms. The figure for human consumption excludes what was administered directly [United States Food and Drug Administration,

things being equal, in more AMR in the U.S. than in Europe (and particularly than in Sweden and Denmark, where the bans on growth-promoting antibiotics have been in force for some time). Indeed, resistance levels seem to be much higher in the U.S. than in Europe: of 4,131 isolates collected by Diekema *et al.* (2014) in a recent nationwide surveillance study, over half (2,093) were MRSA. The gains and the trade-offs from intelligent usage seem worthy of much closer scrutiny.

Related to the last question is the monetary cost of combatting AMR by banning prophylactic and growth-promoting antibiotics in corn-fed livestock production. Initial estimates focusing on antibiotics use in pigs in Denmark suggested that the costs were small but U.S. studies, on the contrary, imply that the costs of shifting to antibiotics-free meat would be significant (WHO 2003; Hayes *et al*. 2001; Capper and Hayes 2012). Other potential trade-offs complicate the outcome: Dumortier *et al.* (2012) suggest that the cost of eliminating antibiotics in food production would increase global greenhouse gas emissions by giving a competitive advantage to grass-intensive livestock systems, but they do not discuss how such emissions might be reduced by increasing the nutritional quality of forage crops.

5.2. The Pipeline

Most accounts of the state of the pipeline are unremittingly bleak. And these are persuasive for two reasons. One is that drug companies have little incentive to invest in new drugs for which demand is very 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'[29] for the unhealthy state of the pipeline, but others too insist that the once prolific pipeline bringing new antimicrobials into clinical practice is faltering (e.g. Smith and Coast 2012). 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. Both in Europe and the US current apprehensions have focused policy-

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http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm261160.htm; *http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm042896.htm*].

[29] 'IFPMA Position on Antimicrobial Resistance' [http://www.ifpma.org/fileadmin/content/Innovation/Anti-Microbical%20Resistance/IFPMA_Position_on_Antimicrobial_Resistance_NewLogo2013.pdf]. See also Association of the British Pharmaceutical Industry [ABPI], AMR: *An Urgent Need for Economic Incentives in a New Economic Model: Principles to Consider* [http://www.abpi.org.uk/our-work/policy-parliamentary/Documents/supplementary_evidence.pdf]; and OHE, 'Innovation, regulation, and antibiotics' [http://news.ohe.org/2014/09/30/innovation-regulation-antibiotics/]. OHE is an affiliate of ABPI.

makers' attention on incentives for the inventors of new microbe-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 (compare Brogan and Mossialos 2013).[30]

But independent assessments of the situation are needed. Although the lack of new effective antibiotics is worrisome, the pipeline has by no means run completely dry (Pucci and Busch 2013; Pucci *et al.* 2014; Nathan and Cars 2014). The number of new FDA-approved drugs targeting infections and infectious diseases averaged a dismal two per annum in 2004-6 and four in 2007-9, but has exceeded eight since then.[31] As of October 2014, there were 38 new antibiotic drugs under development on the FDA's register. If successful, these drugs would go a long way towards alleviating fears of AMR for a while. Some, however, are bound to fail and some are only in the early stages of development,[32] but in November 2013 the Swiss firm Novartis announced a promising new treatment for malaria. And even more significant, given repeated references to the lack of new effective antibiotics against gram-positive bacteria, is that so far in 2014 the FDA have already approved three new Qualified Infectious Disease Products under the GAIN (Generating Antibiotic Incentives Now) legislation passed in 2012. These are Durata's dalbavancin, Cubist's tedizolid, and the new single-dose antibiotic against MRSA, oritavancin, developed by scientists at Duke University (McNamara *et al*. 2013; Corey 2014). All three drugs claim gram-positive power for the treatment of skin infections caused by *Staphylococcus aureus*. Recent news on the treatment of gonorrhoea in the UK and in the USA is also mildly encouraging, on two fronts: there is the prospect of an effective new drug and evidence (from the U.S., at least) of stricter adherence to usage guidelines.[33]

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[30] NIH Directors Blog, 'New strategies in battle against antibiotic resistance', September 18 2014 [http://directorsblog.nih.gov/2014/09/18/new-strategies-in-battle-against-antibiotic-resistance/].

[31] See: http://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/25/infections-and-infectious-diseases.

[32] See: http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2014/03/12/tracking-the-pipeline-of-antibiotics-in-development. Interestingly, as the major pharmaceutical giants abandon investment in new antibiotics, most of the companies developing these antibiotic drugs today are small; indeed, half are 'pre-revenue', in other words they have yet to make any sales.

[33] *BMJ Blogs*, 'Gonorrhoea antimicrobial resistance: is UK antibiotic stewarding policy shows some success (Leslie Goode, Blogmaster), 14 May 2014 [http://blogs.bmj.com/sti/2014/05/14/gonorrhoea-antimicrobial-resistance-is-uk-antibiotic-stewarding-policy-shows-some-success/]; Gus Cairns, 'Drug-resistant gonorrhea rates plummet in US', *NAM AIDSMAP*, 16 June 2014 [http://www.aidsmap.com/Drug-resistant-gonorrhoea-rates-plummet-in-US/page/2860585/].

Importantly, both reductions in antibiotic consumption and the strengthening of public health alternatives to antibiotic use (including vaccination and better hospital hygiene) will slow the development of AMR and increase the window of opportunity for drug discovery.

5.3. 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 context and to suggest ways in which an historical perspective can inform the current discussion. The threat of AMR calls for a multidimensional approach. Scientists have a role in increasing our understanding of resistance and in fast-tracking the development of new therapies, while medical practitioners have a role in influencing usage and behaviour in settings within their control, such as hospitals and clinics. What can economic historians contribute?

First, a consideration of the recent history of infectious disease and its implications for economic growth and economic welfare makes clear the limitations of the conventional practice of evaluating AMR on an incremental cost basis. A historical perspective can be used to estimate the contributions of specific technological and public health interventions, and 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.

See too *NIH News*, 'NIH launches phase 1 clinical trial of novel drug to treat *Clostridium difficile* infection', July 2014 [http://www.niaid.nih.gov/news/newsreleases/2014/Pages/CdifficileTrial.aspx].

Second, 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 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.

Medical history also 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 immunisation). These examples can provide important lessons regarding policy implementation.

To conclude, this survey of the history of infectious disease with reference to AMR can 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.

BIBLIOGRAPHY:

Aaby, Peter, Jette Bukh, Ida Maria Lisse, and Maria Clotilde da Sliva. 1988. 'Decline in measles mortality: nutrition, age at infection, or exposure?', *British Medical Journal (Clin Res Ed)* 296(6631): 1225-8.

Aarestrup, F. 2012. 'Get pigs off antibiotics', *Nature* 486: 465-66.

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.

Acemoglu, Daron and Simon Johnson. 2013. 'Disease and development: a reply to Bloom, Canning, and Fink'. http://economics.mit.edu/files/8698

Adhvaryu, Achyuta R. 2014. 'Learning, misallocation, and technology adoption: evidence from new malaria therapy in Tanzania', *Review of Economic Studies*, forthcoming.

Anand, Sudhir, and Kara Hanson. 1997. 'Disability adjusted life years: a critical perspective'. *Journal of Health Economics* 16: 685-702.

Anderson, R. M. and R. M. May. 1991. *Infectious diseases of humans: dynamics and control,* Oxford: Oxford University Press.

Andersson, D. 2005. 'The ways in which bacteria resist antibiotics', *International Journal of Risk & Safety in Medicine*. 17: 111-16.

Andre, F. E, R, Booy, H. L. Bock et al. 2008. 'Vaccination greatly reduces disease, disability, death and inequity worldwide', *Bulletin of the World Health Organisation* 86[2]: 81-160.

Arias, Cesar A. *et al*. 2000. 'Antimicrobial-resistant bugs in the 21st century – a clinical super-challenge'. *The New England Journal of Medicine*. 360: 5: 439-43

Arora, Suchit. 2001. 'Health, human productivity, and long-term economic growth', *Journal of Economic History*, 61[3]: 699-749.

Ashraf, Nava, Günther Fink, and David N. Weil, 2014. 'Evaluating the effects of large scale Health Interventions in Developing Countries: The Zambian Malaria Initiative, In Sebastian Edwards, Simon Johnson, and David N. Weil, eds. *African Successes: Human Capital* Chicago: University of Chicago Press, forthcoming

[available at: http://ideas.repec.org/h/nbr/nberch/13371.html; Vimeo summary at: http://vimeo.com/8555815]

Audibert, Martine, Pascale Combes Motel, and Alassane Drabo, 2012. ;Global burden of disease and economic growth', Working Papers halshs-00678713, HAL [https://halshs.archives-ouvertes.fr/file/index/docid/678713/filename/2012.pdf].

Austin, D. J. and R. M. Anderson. 1999. 'Transmission dynamics of epidemic Methicillin-resistance Staphylococcus aureus and Vancomycin-resistant Enterococci in England and Wales', *The Journal of Infectious Disease*, 170: 883-91.

Bannon M. J. 1999. 'BCG and Tuberculosis'. *Archives of Disease in Childhood* 80:80-3.

Banthia, Jayant and Tim Dyson. 1999. 'Smallpox in nineteenth-century India', *Population and Development Review*, 25(4): 649-80.

Barbi, Elisabeta and James Vaupel. 2005. 'Comment on "Inflammatory exposure and historical changes in human life-spans" ', *Science* 308, 16.

Barreca, Alan. 2010. 'The long-term economic impact of in utero and post-natal exposure to malaria', *Journal of Human Resources* 45[4]: 865-92.

Batra, R. Et al (2010) Efficacy and limitation of a chlorhexidine-based decolonization strategy in preventing transmission of MRSA in an intensive care unit. Clinical Infectious Diseases 50: 210-7

BBC. 2012. 'Hand hygiene campaign cut superbug infections', 3 May 2012 [http://www.bbc.com/news/health-17942182].

Becker, Gary S., T. Philipson, and R. R. Soares. 2003. 'The quality and quantity of life and the evolution of world inequality', *American Economic Review*95: 277-291.

Bengtsson, Tommy & Frans van Poppel, F. 2011. 'Socioeconomic inequalities from past to present: an introduction'. *Explorations in Economic History*, 48: 343-56

Bergstrom, C. T. and M. Feldgarden. 2008. 'The ecology and evolution of antibiotic-resistant bacteria'. in S. Stearns and J. Koella, eds., *Evolution in Health and Disease, Second Edition.* Oxford University Press.

Bhattacharyya, Sambit. 2009. 'Root causes of African underdevelopment', *Journal of African Economies* 18[5]: 745-80.

Bleakley, Hoyt. 2007. 'Disease and development: evidence from hookworm eradication in the American South', *Quarterly Journal of Economics*, 122(1): 73–117.

Bleakley, Hoyt. 2010. 'Malaria eradication in the Americas: a retrospective analysis of childhood exposure', *American Economic Journal: Applied Economics*, 2(2): 1-45.

Blommaert, A., C. Marais, N. Hens, S. Coenen, A. Muller, H. Goossens, and P. Beutels. 2013. 'Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: a longitudinal observational study', *Journal of Antimicrobial Chemotherapy*, September 29 [http://jac.oxfordjournals.org/content/early/2013/09/27/jac.dkt377.full?sid=cfaab65a-23de-40cc-9332-eef6708d7d97].

Bloom, David, David Canning, and Guenther Fink. 2013. 'Disease and development revisited', IZA WP 7391.

Bodenhorn, Howard, Timothy W. Guinnane, and Thomas A. Mroz. 2013. 'Problems of sample-selection bias in the historical heights literature: a theoretical and econometric analysis', Working Paper 1023, Economic Growth Center, Yale University.

Boucher, Helen W. *et al*., '10 x 20 Progress-Development of New Drugs Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America', *Clinical Infectious Diseases* 56 (2013): 1685-94. [But note that the acknowledgements of potential conflicts of interest at end of this paper take up nearly half a page].

Boyd, Robert. 1999. *The coming of the spirit of pestilence: introduced infectious diseases and population decline among Northwest Coast Indians, 1774 – 1874*, Seattle: University of Washington Press.

Broadberry, Stephen. 2014. *British Economic Growth 1270-1870*. Cambridge: Cambridge University Press.

Breman, Joel G. 2001. 'The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden', *American Journal of Tropical Medicine and Hygiene* 64[1].

Brogan, David M. and Elias Mossialos. 2013. 'Incentives for new antibiotics: the Options Market for Antibiotics (OMA) model', *Globalisation and Health* 9: 58 [http://eprints.lse.ac.uk/51319/1/Mossialos_Incentives_new_antibiotics.pdf].

Brown, Ryan and Duncan Thomas. 2013. 'On the long term effects of the 1918 U.S. influenza pandemic'. Typescript.

Bryder L. 1988. *Below the magic mountain: A social history of tuberculosis in twentieth century Britain*. Oxford: Clarendon Press.

Caldwell, John C. and Peter McDonald. 1982. 'Influences of maternal education on infant and child mortality: levels and causes', *Health Policy and Education,* 2(3-4): 251-67.

Caldwell, John C. 1986. 'Routes to low mortality in poor countries', *Population and Development Review,* 12 (2), pp. 171–220.

Capper, Judith L. and Dermot J. Hayes. 2012. 'The environmental and economic impact of removing growth-enhancing technologies from U.S. beef production', *Journal of Animal Science*, 90[10]: 3527-37.

Cars, O. *et al*. 2008. 'Meeting the challenge of antimicrobial resistance'. *British Medical Journal*. 337: 726-28.

Carstensen, Kai and Erich Gundlach. 2006. 'The primacy of institutions reconsidered: direct income effects of malaria prevalence', *World Bank Economic Review*, 20[3]: 309-339 [version available at: https://www.ifw-members.ifw-kiel.de/publications/the-primacy-of-institutions-reconsidered-the-effects-of-malaria-prevalence-in-the-empirics-of-development/kap1210_revised.pdf].

CDC [Centers for Disease Control and Prevention]. 2013. *Antibiotic/Antimicrobial Resistance: Threat Report 2013* [available at:

http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf].

Cervellati, Matteo and Uwe Sunde. 2011. 'Life expectancy and economic growth: the role of the demographic transition', *Journal of Economic Growth*, 16(2): 99-133.

Champion, Justin A.I. 1995. *London's dreaded visitation: the social geography of the Great Plague in 1665*, London: Historical Geography Research Group.

Charlton, John and Michael Murphy. 1997a. *The Health of Adult Britain 1841-1994: Volume I*, London: HMSO.

Charlton, John and Michael Murphy. 1997b. *The Health of Adult Britain 1841-1994: Volume II*, London: HMSO.

Chaulk, C. *et al*. 1998. 'Directly observed therapy for treatment completion of pulmonary tuberculosis', *Journal of the American Medical Associatio*n 279: 943-48

Cipolla, Carlo M. 1981. *Fighting the Plague in Seventeenth-Century Italy*. Madison: University of Wisconsin Press.

Citron K, R. Raynes, and J. Berrie. 1981. *Tuberculosis today*. In: Security DoHaS, editor. London: HMSO.

Cleland, J. and C. Wilson. 1987. 'Demand theories of the fertility transition: an iconoclastic view'. *Population Studies*, 41[1]: 5-30.

Coast, J. *et al*. 2000. 'Superbugs II: How should economic evaluation be conducted for interventions which aim to contain antimicrobial resistance?' *Health Economics*. 11: 637-47.

Col, N. F., and R. W. O'Connor. 'Estimating worldwide current antibiotic usage: report of Task Force 1'. *Review of Infectious Diseases* 1987; 9 (suppl 3): S232–43

Colditz, G., T. F. Brewer, C. S. Berkeley, M. E. Wilson, E. Burdick, H. V. Fineberg, and T. Mosteller. 1994. 'Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature', *Journal of the American Medical Association*, 271[9]: 698-702.

Cooter, Roger, Mark Harrison, and Steve Sturdy, eds. 1999. *Medicine and Modern Warfare*. Clio Medica 55, Amsterdam, Rodopi.

Corey, Ralph. 2014. 'Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections'. *New England Journal of Medicine* 370: 2180-2190, June 5.

Costa, Dora L. and Richard H. Steckel. 1997. 'Long-term trends in health, welfare, and economic growth in the Unites States.' In Richard H. Steckel and Roderick Floud, eds. *Health and Welfare during Industrialization.* Chicago: University of Chicago Press, pp. 47-90.

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 [available at SSRN: http://ssrn.com/abstract=879194]

Creighton, Charles. 1894. *A history of epidemics in Britain*, vol. II, Cambridge.

Crosby, Alfred. 1972. *The Columbian Exchange: Biological and Cultural Consequences of 1492*. Westport, Conn.: Greenwood.

Cummins, Neil, Morgan Kelly, and Cormac Ó Gráda.2014. 'Living standards and plague in London, 1560–1665', *Economic History Review,* forthcoming.

Cunningham, R. Et al (2007) Effect on MRSA transmission of rapid PCR testing of patients admitted to critical care. The Journal of Hospital Infection 65: 24-8

Curson P. H. 1985. *Times of Crisis: Epidemics in Sydney 1788-1900*. Sydney: Sydney University Press.

Cutler, David M. 2008. 'Are we finally winning the war on cancer?', *Journal of Economic Perspectives*, 22[4]: 3-26.

Cutler, David M. and Grant Miller. 2005. 'The role of public health improvements in health advances: the twentieth century United States', *Demography* 42[1]: 1-22.

Cutler, David, Winnie Fung, Michael Kremer, Monica Singhal, and Tom Vogl. 2010. Early-life malaria exposure and adult outcomes: evidence from malaria eradication in India. *American Economic Journal: Applied Economics* 2(2): 72–94.

Davenport, Romola J (2007) Annual deaths by cause, age and sex in England and Wales, 1848-1900 [dataset]. Economic and Social Data Services (SN5705)

Davenport, Romola J. 2013. 'Year of birth effects in the historical decline of tuberculosis mortality: a reconsideration', *PLoS ONE* 8(12): e81797.

Davenport, Romola J. 2014. 'The first stage of the epidemiological transition in British cities: a comparison of Manchester and London, 1750-1820', Working Paper (http://research.ncl.ac.uk/pauperlives/)

Davenport, Romola J., Jeremy P. Boulton and Leonard Schwarz. 2015 'Urban inoculation and the decline of smallpox in eighteenth-century cities – a reply to Razzell', *Economic History Review* (in press).

Davies, G. *et al*. 1999. 'Emergence of multi-drug resistant tuberculosis in a community-based directly observed treatment programme in rural South Africa'. *International Journal of Tuberculosis and Lung Disease*. 3: 799-804.

Davis, Kingsley. 1956. ' The amazing decline of mortality in underdeveloped areas'. *American Economic Review Papers & Proceedings*, 46[2]: 305-18.

De Vries, Jan. 1984. *European Urbanization, 1500-1800*. London: Methuen.

Deaton, Angus. 2013. *The Great Escape*. Princeton: Princeton University Press.

Deaton, Angus, Jane Fortson, and Robert Tortora. 2010. 'Life (evaluation), HIV/AIDS, and Death in Africa', in E. Diener, J. Helliwell, and D. Kahneman, eds. *International Differences in Wellbeing*, Oxford: Oxford University Press, pp.105-36.

Depetris-Chauvin, Emilio and David N. Weil. 2013. 'Malaria and early African development: evidence from the sickle cell trait', NBER Working Paper No. 19603.

Dennis, David T., Kenneth L Gage, Norman Gratz, Jack D. Poland, and Evgueni Tikhomirov. 1999. *Plague Manual: Epidemiology, Distribution, Surveillance, and*

Control. WHO [http://www.who.int/csr/resources/publications/plague/WHO_CDS_CSR_EDC_99_2_EN/en/].

Department of Health (2010) Screening for MRSA. A strategy for NHS trusts: A summary of best practice.

Department of Health (UK). 2013. *UK Five Year Antimicrobial Resistance Strategy* [https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf].

Diekema, D. J., S. S. Richter, K. P. Heilmann, C. L. Dohrn, F. Riahi, S. Tendolhar, J. S. McDanel and G. V. Doern. 2014. 'Continued emergence of USA300 methicillin-resistant Staphylococcus aureus in the United States: results from a nationwide surveillance study', *Infection Control and Hospital Epidemiology* 35(3): 285-92.

Doblhammer, Gabrielle and J. Kytir. 2001. 'Compression or expansion of morbidity? Trends in healthy-life expectancy in the elderly Austrian population between 1978 and 1998', *Social Science and Medicine*, 52(3), pp. 385–391

Dobson, M. J. 1997. *Contours of Death and Disease in Early Modern England.* Cambridge: Cambridge University Press.

Domar, Evsey D. 1970. 'The Causes of Slavery or Serfdom: an Hypothesis', *Journal of Economic History*, 30[1]: 18-32.

Doucouliagos, Hristos, T. D. Stanley, and Kip Viscusi. 2014. 'Publication selection bias and the income elasticity of a value of a statistical life'. *Journal of Health Economics* 33: 67-75.

Dublin L, and J. Whitney. 1920. 'On the costs of tuberculosis'. *Quarterly Publications of the American Statistical Association*. 17(132): 441-50.

Dyson, Tim. 1997. 'Infant and child mortality in the Indian subcontinent, 1881-1947', in Alain Bideau, Betrand Desjardians and Héctor Pérez Brignoli (eds) *Infant and child mortality in the past*, Oxford: Clarendon Press, pp.109-134

Dyson, Tim. 2010. *Population and Development: the Demographic Transition*. London: Zed.

Dyson, Tim and Monica Das Gupta. 2001. 'Demographic trends in Ludhiana district, Punjab, 1881-1981: an exploration of vital registration data in colonial India', in Ts'ui-jung Liu, James Lee, David Sven Reher, Osamu Saito and Wang Feng (eds.) *Asian population history*, Oxford: Oxford university Press, pp. 79-104.

Easterlin, Richard. 1998. *Growth triumphant. The twenty-first century in historical perspective*. Ann Arbor: University of Michigan Press.

Easterlin, Richard. 2013. 'Cross-sections are history', *Population and Development Review* 38[S1]: 302-08.

Easterly, William and Laura Freschi. 2010. 'The first law of development stats: whatever our bizarre methodology, we make Africa look worse'. *Aid Watch*, December 2.

Echenberg, Myron J. 2002. '*Pestisredux*: the initial years of the third bubonic plague pandemic, 1894-1901' *Journal of World History*, 13[2]: 429-449.

Echenberg, Myron. 2007. *Plague Ports: The Global Urban Impact of Bubonic Plague: 1894–1901*. Sacramento: New York University Press.

ECDC (European Centre for Disease Control). 2009. *The Bacterial Challenge: Time to React*. ECDC: Stockholm [http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf].

Edgeworth, J. (2011 Has decolonization played a central role in the decline in UK MRSA transmission? A focus on evidence from intensive care. Journal of Antimicrobial Chemotherapy 66: ii41-ii47

Ellington, M. et al (2010) Decline of EMRSA-16 amongst Meticillin-resistant Staphylococcus aureus bacteraemia in the UK between 2001 and 2007. Journal of Antimicrobial Chemotherapy 65: 446-68

Ewald, Paul W. 1983. 'Host-parasite relations, vectors, and the evolution of disease severity', *Annual Review of Ecology and Systematics*, 14, pp. 465-85,

Ewald, Paul W. 1991. 'Transmission modes and the evolution of virulence', *Human Nature*, 2(1), pp. 1-30.

Ewald, Paul W. 2004. 'Evolution of virulence', *Infectious Disease Clinics of North America*, 18, pp. 1-15.

Fenner, F., D. A. Henderson, I. Arita, Z. Ježek, and I. D. Ladnyi. 1988. *Smallpox and its eradication,* Geneva: World Health Organisation.

Ferrie, Joseph and Werner Troesken. 2008. 'Water and Chicago's mortality transition, 1850-1925', *Explorations in Economic History*, 45[1]: 1-16.

Fewtrell, Lorna, Rachel B. Kaufmann, David Kay, Wayne Enanoria, Laurence Haller and John M. Colford Jr. 2005. 'water, sanitation, and hygiene interventions to reduce diarrhoea in less developed countries: a systematic review and meta-analysis', *Lancet Infectious Diseases*: 5: 42-52.

Finch, Caleb E. and Eileen M. Crimmins. 2004. 'Inflammatory exposure and historical changes in human life-spans', *Science* 305, 17 September.

Finch, Caleb E. and Eileen M. Crimmins. 2004. 'Response to comment on "inflammatory exposure and historical changes in human life-spans" ', *Science* 308, 17 June.

Floud, Roderick, Robert W. Fogel, Bernard Harris, and Sok Chul Hong. 2011. *The Changing Body: The Changing Body: Health, Nutrition, and Human Development in the Western World since 1700.* Cambridge: Cambridge University Press.

Fogel, Robert W. 2004. *The escape from hunger and premature death, 1700-2100: Europe, America, and the Third World*, Cambridge: Cambridge University Press.

Fries, J.F. 1989. 'The compression of morbidity: Near or far?' *Milbank Memorial Foundation Quarterly*, 67, pp. 208–232

Gage, T. 1993. 'The decline of mortality in England and Wales 1861-1964: decomposition by cause of death and component mortality', *Population Studies* 47: 47-66.

Gallup, J. and Jeffrey Sachs. 2001. 'The economic burden of malaria', *American Journal of Tropical Medicine and Hygiene* 64S: 85–96.

Girou, E. et al (1998) Risk factors and outcomes nosocomial infections: results of a matched case-control study of ICU patients. American Journal of Respiratory and Critical Care Medicine 157: 1151-8

Gould, I. Et al (2007) Topical antimicrobials in combination with admission screening and barrier precautions to control endemic MRSA in an intensive care unit. International Journal of Antimicrobial Agents 29: 536-43

Graham, Jay P, John J. Boland, and Ellen Silbergeld. 2007. 'Growth Promoting Antibiotics in Food Animal Production: An Economic Analysis', *Public Health Reports* 122(1): 79–87.

Guinnane, Timothy W. 2011. 'The historical fertility transition: a guide for economists', *Journal of Economic Literature* 49[3]: 589-614.

Haacker, Markus. 2004. 'HIV/AIDS: the impact on the social fabric and the economy', in M. Haacker, ed. *The Macroeconomics of HIV/AIDS* Washington, D.C.: International Monetary Fund [http://www.imf.org/external/pubs/ft/aids/eng/chapter2.pdf].

Haacker, Marcus. 2002a. 'The economic consequences of HIV/AIDS in sub-Saharan Africa', International Monetary Fund Working Paper 02/38.

Haacker, Marcus. 2002b. 'Modeling the macroeconomic impact of HIV/AIDS', International Monetary Fund Working Paper 02/195.

Hammitt, James K. and Lisa Robinson. 2011. 'The income elasticity of the value per statistical life: transferring estimates between high and low income countries'. *Journal of Benefit-Cost Analysis* 2[1]: 1-27 [http://www.regulatory-analysis.com/hammitt-robinson-VSL-income-elasticity.pdf].

Harbarth, Stephan and Stéphane Emonet. 2006. 'Navigating the World Wide Web in Search of Resources on Antimicrobial Resistance', *Clinical Infectious Diseases* 43[1]: 72-78.

Hardy, Anne. 1988. 'Urban famine or urban crisis? Typhus in the Victorian city', *Medical History*, 32(4), pp. 401-25

Hardy, Anne. 1993. *The epidemic streets*, Oxford, Clarendon Press.

Harper, Kristin N., Molly K. Zuckerman, Megan L. Harper, John D. Kingston' and George J. Armelagos. 2011. 'The origin and antiquity of syphilis revisited: an appraisal of old world pre-Columbian evidence for treponemal infection' *American Journal of Physical Anthropology* 146[S53]: 99-133 [http://onlinelibrary.wiley.com/doi/10.1002/ajpa.21613/abstract].

Harris, Bernard, Martin Gorsky, Aravinda Meera Guntupalli and Andrew Hinde. 2012. 'Long-term changes in sickness and health: further evidence from the Hampshire Friendly Society', *Economic History Review*, 65(2): 719-45.

Hawker, Jeremy, Sue Smith, Gillian E. Smith, Roger Morbey, Alan P. Johnson, Douglas M. Fleming, Laura Shallcross, and Andrew C. Hayward. 2014. 'Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995–2011: analysis of a large database of primary care consultations', *Journal of Antimicrobial Chemotherapy*, August 4 [http://jac.oxfordjournals.org/search?fulltext=jeremy+hawker&submit=yes&x=8&y=4].

Hay, Simon I., David J Rogers, Jonathan F. Toomer, and Robert W. Snow. 2000. 'Annual *Plasmodium falciparum* Entomological Inoculation Rates (EIR) across Africa: Literature Survey, Internet Access, and Review'. *Transactions of the Royal Society for Tropical Medicine and Hygiene* 94(2):113-27.

Hay, Simon I., C. A. Guerra, A. J. Tatem, A. M. Noor, and R. W. Snow. 2004. 'The global distribution and population at risk of malaria: past, present, and future'. *Lancet Infectious Diseases*, 4[6]: 327-36.

Hayes, Dermot, Helena H. Jensen, Lennart Backstrom, and Jacinto Fabiosa. 2001. 'Economic impact of a ban on the use of over-the-counter antibiotics in swine rations', *International Food and Agribusiness Management Review*, 4: 81-97.

Health Canada. 2002. *Antimocrobial Resistance: Developing a Common Understanding* ('issue identification paper') [http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/pubs/amr-ram_issue-enjeux-eng.pdf].

Health Protection Agency (2010) MRSA information for patients.

Hickson Kerry. 2006. 'The contribution of improved health to standards of living growth in twentieth century England and Wales', London: London School of Economics and Political Science.

Hickson, Kerry. 2014. 'The GDP value of twentieth-century health improvements in developed economies: initial estimates for England'. *Review of Income and Wealth* 60[2]: 385-99.

Hirshleifer, Jack. 1966. 'Disaster and recovery: the Black Death in Western Europe', Santa Monica: Rand Corporation.

Hobcraft, John. 1993. 'Women's education, child welfare and child survival: a review of the evidence', *Health Transition Review*, 3(2): 159-73.

Hotez, Peter, Jeff Bethony, Maria Elena Bottazzi, Simon Brooker, and Paulo Buss. 2005. Hookworm: 'The great infection of mankind', *PLoS Medicine* 2(3): e67. doi:10.1371/journal.pmed.0020067.

Howse, K. 2006. 'Increasing life expectancy and the compression of morbidity: a critical review of the literature'. *Oxford Institute of Ageing working paper* no. 206.

Iseman M. 1994. 'Evolution of Drug Resistant Tuberculosis: A Tale of Two Species'.

Proceedings of The National Academy of Science. 91: 2428-9.
Jannetta, Ann Bowman. 1987. *Epidemics and mortality in early modern Japan*, Princeton N.J.: Princeton University Press.
Jannetta, Ann Bowman. 2001. 'Public health and the diffusion of vaccination in Japan', in Ts'ui-jung Liu, James Lee, David Sven Reher, Osamu Saito and Wang Feng (eds.) *Asian population history*, Oxford: Oxford university Press, pp. 292-305.
Jeuland, Marc S. Ozdemir, D. Fuente, M. Allaire, D. Whittington. 2013. 'The long-term dynamics of health benefits from improved water and sanitation in developing countries', *PLoS ONE* 8(10): e74804.
Jeuland, Marc, S. Ozdemir, D. Fuente, M. Allaire, and D. Whittington. 2013. 'Economic losses from poor water and sanitation: past, present, and future', in Bjorn Lomborg, ed. *How Much have Global Problems Cost the World? A Scorecard from 1900 to 2050.* Cambridge: Cambridge University Press.
Joint Tuberculosis Committee of the British Thoracic Society. 'Control and Prevention of Tuberculosis in the UK: Code of Practice 2000'. *Thorax*. 887-901.
Jones-Lee M. 1989. *The Economics of Safety and Physical Risk*. New York and Oxford: Basil Blackwell.
Kannisto, Väinö, Mauri Nieminen and Oiva Turpeinen. 1999. 'Finnish life tables since 1751', *Demographic Research*, 1(1) (DOI: 10.4054/DemRes.1999.1.1)
Kantha, Sachi Sri. 1991. 'A centennial review: the 1890 tetanus antitoxin paper of von Behring and Kitasato and the related developments', *Keio Journal of Medicine*, 40(1): 35-9.
Kelley, Alan. 1991. 'The Human Development Index: handle with care.' *Population and Development Review* 17[2]: 315-24.
Kelly, Morgan & C. Ó Gráda. 2014. 'Living standards and mortality since the middle ages', *Economic History Review* 67(2): 358-81
Kesztenbaum, Lionel and Jean-Laurent Rosenthal. 2014. 'Income versus sanitation; mortality decline in Paris, 1880-1914' [https://ideas.repec.org/p/hal/psewpa/halshs-01018594.html].
Kiszewski, A., A. Mellinger, A. Spielman, P. Malaney, S. E. Sachs and J. Sachs. 2004. A global index representing the stability of malaria transmission. *American Journal of Tropical Medicine and Hygiene* 70[5]: 486-98.
Klugman, Jeni, Francisco Rodríguez, and Hyung-Jin Choi. 2011a. 'The HDI: New controversies, old critiques'. *Journal of Economic Inequality* 9(2): 249–288.
Knodel, John E. 1987. 'Starting, stopping, and spacing during the early stages of the fertility transition: the experience of German village populations in the 18th and 19th centuries', *Demography*, 24[2]: 143-62.
Klugman, Jeni, Francisco Rodríguez, and Hyung-Jin Choi. 2011b. 'Response to Martin Ravallion', *Journal of Economic Inequality* 9: 497–499.
Kovacevic, Milorad. 2010. 'Review of HDI Critiques and potential improvements.' UNDP Research Paper Number 2010/33.

Kunitz, Stephen J. 1983. 'Speculations on the European mortality decline', *Economic History Review*, 36(3), pp. 349-64.

Landers, John. 1992.'Historical epidemiology and the structural analysis of mortality', *Health Transition Review* 2(Supp) pp. 47-75

Landers, John. 1993. *Death and the metropolis: studies in the demographic history of London, 1670–1830,* Cambridge: Cambridge University Press.

Laxminarayan R., E. Klein, C. Dye, K. Floyd, S. Darley and O. Adeyi. 2007. *Economic Benefits of Tuberculosis Control*. Washington D.C.: The World Bank.

Laxminarayan, Ramanan. 2014. Antibiotic resistance: balancing conservation against innovation, *Science*, 345: 1299, 12 September.

Le Roy Ladurie, Emmanuel. 1973. *'Un concept: l'unification microbienne du monde (XIVe - XVIIe siecles).* Geneva: Société Suisse d'Histoire.

Lee, James, Wang Feng and Cameron Campbell. 1994. 'Infant and child mortality among the late imperial Chinese nobility: implications for two kinds of positive check', *Population Studies*, 48(3), pp.395-411.

Leon, Gianmarco and Edward Miguel. 2013. 'Transportation Choices and the Value of a Statistical Life'. NBER Working Paper No. 19494.

Livi-Bacci, Massimo. 2001. *Population and nutrition*, Cambridge: Cambridge University Press.

Livi-Bacci, Massimo. 2001. *A concise history of world population*, 3rd edn., Oxford: Blackwell.

Lodise, Thomas P. and Peggy S. McKinnon. 2007. 'Burden of methicillin-resistant *Staphylococcus aureus*: focus on clinical and economic outcomes', *Pharmacotherapy*. 27[7]: 1001-12.

Løkke, Anne. 2012. 'The antibiotic transformation of Danish obstetrics. The hidden links between the decline in perinatal mortality and maternal mortality in the mid-twentieth century', *Annales de Démographique*, 123: 205-24.

Loudon, Irvine. 1992. *Death in childbirth: an international study of maternal care and maternal mortality 1800-1950,* Oxford: Clarendon Press.

Lucas, Adrienne. 2010. 'Malaria eradication and educational attainment: evidence from Paraguay and Sri Lanka', *American Economic Journal: Applied Economics* 2[2]: 46-71.

Maartens, G. and R. Wilkinson. 2007. 'Tuberculosis'. *Lancet*. 15: 370: 96074: 2030-433.

McCord, Gordon C. and Jeffrey D. Sachs. 2012. 'Development, structure, and transformation: evidence on comparative economic growth', NBER Working Paper 19512.

McKeown, Thomas and R. G. Brown. 1955. 'Medical evidence related to English population changes in the eighteenth century', *Population Studies*19**:** 119–41.

McKeown, Thomas. 1976. *The Modern Rise of Population* London: Edward Arnold.

Macnalty Arthur S. 1932. *A Report on Tuberculosis, Including an Examination of the Results of Sanatorium Treatment*. London: HMSO.

McNamara C. W. *et al.* 2013. 'Targeting Plasmodium PI(4)K to eliminate malaria', *Nature*, 504, 248–253, 27 November. doi: 10.1038/503186a.

McNeill, W. H. 1976. *Plagues and Peoples.* New York: Anchor.

McNeill, W.H. 1980. 'Migration patterns and infection in traditional societies' In Stanley NF & Joske RA (eds.) Changing *disease patterns and human behaviour* (London: Academic Press, pp. 28-36

McWeeney, E. J. 1915. 'On immunity against infectious disease with special reference to anti-typhoid inoculation', *Journal of the Statistical and Social Inquiry Society of Ireland*, XIII: 231-254.

Mackenbach, J. P. and C. W. N. Looman. 1988. 'Secular trends of infectious disease mortality in the Netherlands, 1911-1978: quantitative estimates of changes coinciding with the introduction of antibiotics', *International Journal of Epidemiology* 17[3]: 618-24.

Mangtani, P., I. Abubakar, C. Ariti, P. Mangtani, I. Abubakar, C. Ariti, et al. 2013. Protection by BCG against tuberculosis: a systematic review of randomised controlled trials. *Clinical Infectious Diseases,* 58, pp. 470-80.

Maron, Dena F., Tyler J. Smith and Keeve E. Nachman. 2013. 'Restrictions on antimicrobial use in food animal production: an international regulatory and economic survey', *Globalization and Health*, 9:48 [http://www.globalizationandhealth.com/content/9/1/48].

Mastrantonio, Paola, Fabrizio Barbanti, and Patrizia Spigaglia. 2008. 'Hypervirulent antibiotic-resistant Clostridium difficile in Europe', *Microbial Ecology in Health and Disease*, 20: 210-212.

Matlin, S. A. *et al*. 2014. *AMR—An Urgent Global Health Problem: A Brief for Policy-Makers.* Graduate Institute Global Health Programme and Chatham House Centre on Global Health Security [http://graduateinstitute.ch/files/live/sites/iheid/files/sites/globalhealth/shared/2014/events/PB_AMR2014_final.pdf].

Mercer, Alex. 1990. *Disease, mortality and population in transition,* Leicester: Leicester University Press.

Michel-Lepage, A., B. Ventelou, A. Nebout, et al. 2013. Cross-sectional survey: risk-averse French GPs use more rapid-antigen diagnostic tests in tonsillitis in children. *BMJ Open* [http://bmjopen.bmj.com/content/3/10/e003540.full.pdf].

Miller, T. 2000. 'Variations between Countries in Values of Statistical Life' *Journal of Transport Economics and Policy*, 34: 169–88.

Mittal, V., U. V. Rana, S. K. Jain, K. Kumar, I. S. Pal. R. C. Arva, R. L. Ichhpujani, S. Lal, S. P. Agarwal. 2004. 'Quick control of bubonic plague outbreak in Uttar Kashi, India', *Journal of Communicable Diseases*. 36[4]: 233-9.

Mukandvire, Zindoga, David L. Smith and J. Glenn Morris. 2003. 'Cholera in Haiti: reproductive numbers and vaccination coverage estimates', *Scientific Reports*, 3(997), DOI: 10.1038/srep00997.

Murphy, Marion, Colin P. Bradley, and Stephen Byrne. 2012. 'Antibiotic prescribing in primary care, adherence to guidelines and unnecessary prescribing—an Irish perspective', *BMC Family Practice* 13:43 [http://www.biomedcentral.com/1471-2296/13/43].

Murray, Christopher J. L. 1994. 'Quantifying the burden of disease: the technical basis for disability-adjusted life years.' *Bulletin of the World Health Organisation* 72(3): 429-445.

Murray, Christopher J., T. Vos, R. Lozano, M. Naghavi, A.D. Flaxman. C. Michaud et al. 2012. 'Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990 – 2010: a systematic analysis for the Global Burden of Disease Study 2010, *Lancet*, 380(9859): 2197-223.

Nathan, Carl and Otto Cars. 2014. 'Antibiotic Resistance — Problems, Progress, and Prospects', *New England Journal of Medicine*, October 1, DOI: 10.1056/NEJMp1408040.

NHS (National Health Service). 2013. 'Report on BCG policy and provision in London, February 2013' (http://www.networks.nhs.uk)

Nordhaus, William D. 1999. 'The health of nations', in Kevin Murphy and Robert Topel, eds. *Measuring the Gains from Medical Research*. Chicago: University of Chicago Press.

Ó Gráda, Cormac. 2009. *Famine: A Short History*. Princeton: Princeton University Press.

OECD. 2012. *Mortality Risk Valuation in Environment, Health and Transport Policies.* Paris: OECD.

Oeppen, Jim. and J. W. Vaupel. 2002. 'Broken limits to life expectancy,' *Science* 296[no. 5570]: 1029-1031.

Office for National Statistics (2013) Death involving MRSA: England and Wales, 2012.

Office for National Statistics (2014) Death involving MRSA: Wales, 2013.

Olshansky, S. J., M. A. Rudberg, B. A. Carnes, B. A. Cassel and J. A. Brady. 1991. 'Trading off longer life for worsening health: The expansion of morbidity hypothesis', *Journal of Aging and Health*, 3, pp. 194–216

Omran, A. R. 1971. 'The epidemiologic transition: a theory of the epidemiology of population change'. *Milbank Memorial Fund Quarterly*, 49(4): 509-538.

(ONS) Office of National Statistics. 2003. 'Twentieth Century Mortality: 100 Years of Mortality Data in England and Wales by Age, Sex, Year and Underlying Cause', CD-ROM.

ONS. 2010. *Guidance for Doctors Completing Medical Certificates of Cause of Death in England and Wales* [http://www.gro.gov.uk/images/medcert_July_2010.pdf].

ONS. 2013. *Deaths Involving MRSA 2008 to 2012* [http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-314063].

Nathanson, Neal and O. M. Kew. 2010. 'From emergence to eradication: the epidemiology of poliomyelitis deconstructed', *American Journal of Epidemiology* 172[11]: 1213-29.

Nunn, Nathan and Nancy Qian. 2010. 'The Columbian Exchange: A History of Disease, Food, and Ideas'. *Journal of Economic Perspectives* 24[2]: 163–88.

Obregón, Rafael, Ketan Chitnis, Chris Morry, Warren Feek, Jeffrey Bates, Michael Galway and Ellyn Ogden. 2009. 'Achieving polio eradication: a review of health communication evidence and lessons learned in India and Pakistan', *Bulletin of the World Health Organisation*, 87: 624-30.

Park, M. *et al.* 1996. 'Outcome of MDR-TB patients, 1983-1993'. *American Journal of Respiratory Critical Care Medicine*. 153: 317-24.

Pearson, A. et al (2009) Voluntary and mandatory surveillance for MRSA bacteraemia in England. Journal of Antimicrobial Chemotherapy 64: Supp 1: 1-7

Percoco, Marco. 2013. 'The Fight Against Disease: Malaria and Economic Development in Italian Regions', *Economic Geography* 89[2]: 105-125.

Plachouras, D., D. Kavatha, A. Antoniadou, E. Giannitsioti, G. Poulakou, K. Kanellakopoulou, and H. Giamarellou 2010. 'Dispensing of antibiotics with prescription in Greece, 2008: another link in the antibiotic resistance chain', *Eurosurveillance* 15[7], 18 February.

Podolsky, Scott H. 2005. 'The Changing Fate of Pneumonia as a Public Health Concern in 20th-Century America and Beyond'. *American Journal of Public Health* 95(12): 2144–2154.

Prados de la Escosura, Leandro. 2010. 'Improving human development: a long run view', *Journal of Economic Surveys* 24: 842-94.

President's Council of Advisors on Science and Technology. 2014. *Report to the President on Combatting Antibiotic Resistance*.

Preston, Samuel H. 1975. 'The changing relation between mortality and level of economic development', *Population Studies*, 29(2): 231-248.

Preston, Samuel H. 1976. *Mortality Patterns in National Populations.* London: Academic Press.

Preston, Samuel H. And Etienne van der Walle. 1978. 'Urban French mortality in the nineteenth century', *Population Studies*, 32(2): 275-97.

Pucci, Michael J. and Karen Busch. 2013. 'Investigational antimicrobial agents of 2013'. *Clinical Microbiological Reviews*, 26[4]: 792-821 [http://cmr.asm.org/content/26/4/792.full].

Pucci, Michael J., Malcolm G. P. Page, and Karen Bush. 2014. 'Cautious optimism for the antibacterial pipeline', *Microbe Magazine*, April [http://www.microbemagazine.org/index.php?option=com_content&view=article&id=6663:cautious-optimism-for-the-antibacterial-pipeline&Itemid=1597].

Raineri, E. et al (2007) MRSA control in an intensive care unit: a 10 year analysis. The Journal of Hospital Infection 67: 308-15

Rao, Mohan. 1994. Plague: the fourth horseman. *Economic and Political Weekly*. 29[42]: 2720-1, October 15 [http://www.jstor.org.ucd.idm.oclc.org/stable/pdfplus/4401904.pdf?acceptTC=true&jpdConfirm=true].

Ravallion, Martin. 1997. 'Good and bad growth: the human development reports', *World Development*, 25(5): 631-38.

Ravallion, Martin. 2012. 'Troubling trade-offs in the Human Development Index', *Journal of Development Economics*, 99[2]: 201-9.

Razzell, Peter. 2003. *The conquest of smallpox: the impact of inoculation on smallpox mortality in eighteenth century Britain* (2nd edn), Caliban Books.

Reher, David S. 2004. 'The demographic transition revisited as a global process' *Population, Space, and Place* 10[1]: 19-41.

Reid, Alice. 1997. 'Locality or class? Spatial and social differentials in infant and child mortality in England and Wales, 1895-1911', in C.A. Corsini & P.P. Viazzo, eds. *The Decline of Infant and Child Mortality: The European Experience: 1750-1990*, The Hague: Martinus Nijhoff, pp. 129-154.

Reves, Randall. 1985. 'Declining fertility in England and Wales as a major cause of the twentieth century decline in mortality' American Journal of Epidemiology, 122(1), pp. 112-26

Ridenour, G. Et al (2007) Selective use of intranasal mupirocin and chlorhexidine bathing and the incidence of MRSA colonization and infection among intensive care unit patients. Infection Control and Hospital Epidemiology 28: 1155-61

Riley, James C. 1983. *The eighteenth-century campaign to avoid disease*, London: Macmillan.

Riley, James C. 1997. *Sick not dead: the health of British workingmen during the mortality decline,* Baltimore: John Hopkins University Press.

Riley, James C. 2001. *Rising life expectancy: a global history*. Cambridge: Cambridge University Press.

Riley, James C. 2005. *Poverty and life expectancy: the Jamaica paradox*. Cambridge: Cambridge University Press.

RSC (Royal Society of Chemistry). 2013. *Response to the House of Commons Science and Technology Committee 'Call for Evidence: Antimicrobial Resistance'* [http://www.rsc.org/globalassets/04-campaigning-outreach/realising-potential-of-scientists/research-policy/global-challenges/rsc-written-evidence-on-amr.pdf]

Rutten, Willibrord. 2011. 'The demographic history of smallpox in the Netherlands', in Theo Engelen, John R. Shepherd, and Yang Wen-Shan, eds. *Deaths at Opposite Ends of the Eurasian Continent* Amsterdam: Aksant, pp. 184-97.

Sachs, Jeffrey and Pia Malaney. 2002. The economic and social burden of malaria. *Nature* 415: 680-65, 7 February [available at: http://www.nature.com/nature/journal/v415/n6872/full/415680a.html].

Sandri, A. et al (2006) Reduction in incidence of nonsocomial MRSA infection in an intensive care unit: role of treatment with mupirocin ointment and chlorhexidine baths for nasal carriers of MRSA. Infection Control and Hospital Epidemiology 27: 185-7

Sarmah, A. K., M. T. Meyer, and A. B. A. Boxall. 2006. 'A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment', *Chemosphere* 65:725-759.

Selgelid, Michael J. 2008. 'Ethics, tuberculosis, and globalization', *Public Health Ethics* 1[1]: 10-20.

Shaw, Brent. 1996. 'Seasons of death: aspects of mortality in ancient Rome', The *Journal of Roman Studies*, 86: 100-38.

Shute, Joe. 2013. *Too Much of a Good Thing*. London: Telegraph Media Group [http://s.telegraph.co.uk/graphics/projects/antibiotic-resistance/].

Sköld, Peter. 1996. *The Two Faces of Smallpox: A Disease and Its Prevention in Eighteenth and Nineteenth Century Sweden*. Report No. 12, Demographic Database Umeå: UmU Tryckeri [http://www.diva-portal.org/smash/get/diva2:531050/FULLTEXT02.pdf].

Slack, Paul. 1981. 'The disappearance of plague: an alternative view', *Economic History Review*, 34[3]: 469-476.

Slack, Paul. 1985. *The Impact of Plague in Tudor and Stuart England*. London: Routledge & Kegal Paul.

Smith, J.R. 1987. *The speckled monster: smallpox in England, 1670-1970, with particular reference to Essex*. Chelmsford, Essex Record Office.

Smith, Richard and Joanna Coast. 2012. *The economic burden of antimicrobial resistance: Why it is more serious than current studies suggest.* 2012. Technical Report. London School of Hygiene & Tropical Medicine, London.

Smith, Richard and Joanna Coast. 2013. 'The true cost of antibacterial resistance', *British Medical Journal* 346: f1493, 11 March.

Smith, Richard and James Oeppen. 2006. 'Place and status as determinants of infant mortality in England c. 1550-1837', in E. Garrett, C. Galley, N. Shelton, and R. Woods, eds. *Infant Mortality: A Continuing Social Problem*. Aldershot: Ashgate.

Snowden, Frank M. 2006. *The Conquest of Malaria: Italy, 1900-1962*. New Haven: Yale University Press.

Soares, Rodrigo R. 2007. 'On the determinants of mortality reductions in the developing world', *Population and Development Review*, 33[2]: 247-87.

Song, Xiaoyan, Jonathan Cogen, and Nalini Singh. 2013. 'Incidence of methicillin-resistant *Staphylococcus aureus* infection in a children's hospital in the Washington metropolitan area of the United States, 2003 – 2010', *Emerging Microbes & Infections* **2**, e69; doi:10.1038/emi.2013.69 Published online 9 October.

Srinivasan, T. N. 1994. 'Human development: a new paradigm or reinvention of the

wheel?' *American Economic Review* 84[2]: 238-43.

Statutory Notifications of Infectious Diseases (NOIDS). 2014. *Enhanced Tuberculosis Surveillance: Centre for Infectious Disease Surveillance and Control*. Public Health England.

Stenseth, Nils Christian, Bakyt B. Atshabar, Mike Begon, Steven R. Belmain, Eric Bertherat, Elisabeth Carniel, Kenneth L. Gage, Herwig Leirs, and Lila Rahalison. 2008. 'Plague: Past, Present, and Future', *PLOS Medicine*, January 15 [http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0050003].

Szreter, Simon. 1988. 'The importance of social intervention in Britain's mortality decline c.1850-1914: a reinterpretation of the role of public health', *Social History of Medicine,* 1, pp. 1-37/

Transatlantic Taskforce on Antimicrobial Resistance. 2014. Progress Report [http://www.cdc.gov/drugresistance/pdf/TATFAR-Progress_report_2014.pdf].

Tatem, A. J., D.J. Rogers, and S.I. Hay. 2006. 'Global Transport Networks and Infectious Disease Spread,' *Global Advances in Parasitology* 62: 293-343 [available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3145127/].

Thompson, D. et al (2009) Decline in the rates of MRSA acquisition and bacteraemia in a general intensive care unit between 1996 and 2008. The Journal of Hospital Infection 71: 314-9

Union of Concerned Scientists. 2004. *Hogging It! Estimates of Antimicrobial Abuse in Livestock (2001)* [http://www.ucsusa.org/food_and_agriculture/our-failing-food-system/industrial-agriculture/hogging-it-estimates-of.html#.VE0T9mYZ09Y].

UNICEF. 2012. *Pneumonia and diarrhoea: tackling the deadliest diseases for the world's poorest children*. UNICEF.

Usher, Dan. 1973. 'An imputation to the measure of economic growth for changes in life expectancy', in Milton Moss, ed. *The Measurement of Economic and Social Performance* New York: Columbia University Press, pp. 193-226.

Van Boeckal, Thomas P., Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, and Ramanan Laxminarayan. 2014. 'Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data', *Lancet Infectious Diseases*, 14(8): 742-50.

Vogler, Amy J., F. Chan, Roxanne Nottingham, Genevieve Anderson, Kevin Drees, Stephen M. Beckstrom-Sternberg, David M. Wagner, Suzanne Chanteau, and Paul Keim. 2013. 'A decade of plague in Mahajanga, Madagascar: insights into the global maritime spread of pandemic plague' *mBio* 4[1]: e00623-12, February 12 [available at: https://www.researchgate.net/publication/235604636_A_decade_of_plague_in_mahajanga_madagascar_insights_into_the_global_maritime_spread_of_pandemic_plague].

Voigtländer, Nico and Hans-Joachim Voth, 2013. 'The three horseman of riches: plague, war, and urbanization in early modern Europe', *Review of Economic Studies*, 80(2): 774-811.

Vynnycky E, Fine PEM. 1997. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiology and Infection*, 119, pp. 183-201

Wallinga, D. and D. Burch. 2013. 'Does adding routine antibiotics to animal feed pose a serous risk to human health?', *British Medical Journal* 347: f4214.

Walter, John and Roger Schofield. 1989. 'Famine, disease and crisis mortality in early modern society', in Walter, John and Roger Schofield (eds.) *Famine, disease and the social order in early modern society*, Cambridge: Cambridge University Press: pp. 1-72.

Walther, B.A. and P. W. Ewald. 2004. 'Pathogen survival in the external environment and the evolution of virulence' *Biological Reviews*, 79: 849-69.

Wang, Hua and Jie He. 2010. 'The value of statistical life: a contingent investigation in China'. World Banks Policy Research Working Paper 5421 [http://elibrary.worldbank.org/doi/book/10.1596/1813-9450-5421].

Waters, Andrew E., Tania Contente-Cuomo, Jordan Buchhagen, Cindy M. Liu, Lindsey Watson et. al. 2011. 'Multi-drug resistant *Staphylococcus aureus* in US meat and poultry', *Clinical Infectious Diseases*, 52 (15 May): 1-5.

Watson J, K. Fern, and S. Whitmore. 1991. 'Notifications of Tuberculosis in England and Wales, 1982-1989', *Communicable Disease Review* 1(2): R13-R20.

Weil, David. N. 207. 'Accounting for the effect of health on economic growth', *Quarterly Journal of Economics*. 122[3]: 1265-1306.

Weil, David N. 2010. Endemic Diseases and African Economic Growth: Challenges and Policy Responses. *Journal of African Economies* 19[s3]: 81-109.

Weil, David N. 2014. Health and Economic Growth, in Philippe Aghion and Stephen Durlauf, eds. *Handbook of Economic Growth*, vol. 2.

Weir, David. 1989. 'Markets and mortality in France, 1600-1789', in Walter, John and Roger Schofield (eds.) *Famine, disease and the social order in early modern society*, Cambridge: Cambridge University Press: pp. 201-234.

White, N. J. 1999. 'Avoiding a malaria disaster'. *The Lancet*. 353: 1965–67.

Williamson, J. G. 1984. 'British mortality and the value of life, 1781-1931', *Population Studies*, 38 (1): 157-172.

Woods, Robert. 2000. *The Demography of Victorian England and Wales*. Cambridge: Cambridge University Press.

World Health Assembly 2014. *Draft global action plan on antimicrobial resistance: Draft for consultation with Member States October 2014*.

World Health Organisation (WHO). 2000. *Anti-tuberculosis Drug Resistance Surveillance*. Geneva: WHO.

WHO. 2003. *Impacts of Antimicrobial Growth Promoter Termination in Denmark: the WHO's International Review Panel's Evaluation* [http://www.who.int/gfn/en/Expertsreportgrowthpromoterdenmark.pdf].

WHO. 2014a. *Antimicrobial Resistance: Global Report on Surveillance 2014* [http://www.who.int/drugresistance/documents/surveillancereport/en/].

WHO. 2014b. 'Fact sheet on tuberculosis' [http://www.who.int/mediacentre/factsheets/fs104/en/].

WHO. 2014c. 'Nigeria is now free of ebola virus transmission' http://www.who.int/mediacentre/news/ebola/20-october-2014/en/

WHO. 2014d. *Global Health Estimates* [http://www.who.int/healthinfo/global_burden_disease/en/].

WHO. 2014e. *Millennium Development Goals (MDGs): Fact sheet N°290* Updated May 2014 [http://www.who.int/mediacentre/factsheets/fs290/en/].

Wilson, Chris. 2011. 'Understanding global demographic convergence since 1950', *Population and Development Review*, 37[2]: 375-88.

Wrigley, E. A. and R. Schofield. 1981. *The Population History of England 1541-1871: A Reconstruction*. London: Arnold.

Wrigley E. A., R. S. Davies, J. E. Oeppen and R. S. Schofield. 1997. *English population history from family reconstitution 1580-1837*, Cambridge: Cambridge University Press.

Zwerling, Alice, Marcel A. Behr, Aman Verma, Timothy F. Brewer, Dick Menzies, and Madhukar Pai. 2011. 'The BCG World Atlas: A Database of Global BCG Vaccination Policies and Practices', *PLoS Medicine* 8[3]: e1001012.

Box 1
Methicillin-resistant *Staphylococcus aureus* (MRSA): A brief case study

Staphylococcus aureus is a common type of bacterium found on the skin and in the nostrils of about one third of healthy people without it causing any harm[34]. In the community the majority of MRSA infections are skin infections while in hospital settings MRSA causes life-threatening bloodstream infection (bacteraemia), pneumonia, and surgical site infections. Most strains of *S. aureus* are sensitive to commonly used antibiotics. However, some strains have developed resistance to the antibiotics and often require different types of antibiotics to treat them. Most *S. aureus* strains first developed resistance to penicillin in the 1950s. Later chemists developed methicillin; and again resistant strains developed soon after, and spread rapidly during the 1990s.[35] Hence, methicillin-resistant *Staphylococcus aureus* (MRSA) is a type of *Staphylococcus* bacterium that is resistant to beta-lactam antibiotics. *Staphylococcus aureus* bacteria can cause mild to life threatening disease if there is an opportunity for it to enter the body through broken skin or invasive surgical procedures and medical devices.

Deaths involving *S. aureus* and MRSA statistics have been produced by ONS for each year since 1993. Figures for recent years show a large decrease in the number and age-standardised death rate of deaths involving *S. aureus* and MRSA. This trend is consistent with the decrease in incidence data. The decrease is due in part to interventions which are targeted at improving hospital-based infection control practices[36]. In April 2001 the UK Government introduced mandatory reporting of MRSA bacteraemia. During the initial two years there was little change in rates of bacteraemia, but from September 2006 rates declined dramatically to reach a reported 57 percent reduction by June 2008[37]. Rates have continued to fall since 2008[38]. For example, in 2012 there were 934 MRSA bacteraemia reports; a 21 percent reduction from 2011[39].

Figure 14 shows this decline in MRSA mortality since the ONS started monitoring the disease in 1993. Of particular interest is the magnitude of the decline in 'resistant MRSA' mortality, which by 2013 was a fraction of the peak in 2005. Hand hygiene, contact precautions, active surveillance cultures (where cultures are taken from patients on admission to the ICU- a measure supported by the Department of Health where this was recommended for all patients entering the ICU as part of the 'Saving

[34] HPA 2010
[35] ONS 2014
[36] Ibid
[37] Pearson et al 2009
[38] Ellington et al 2010
[39] ONS 2013

Lives' initiative in 2007[40]), decolonization (see below) have been shown to have a prominent role in this reduction. This highlights the importance of maintaining careful surveillance[41].

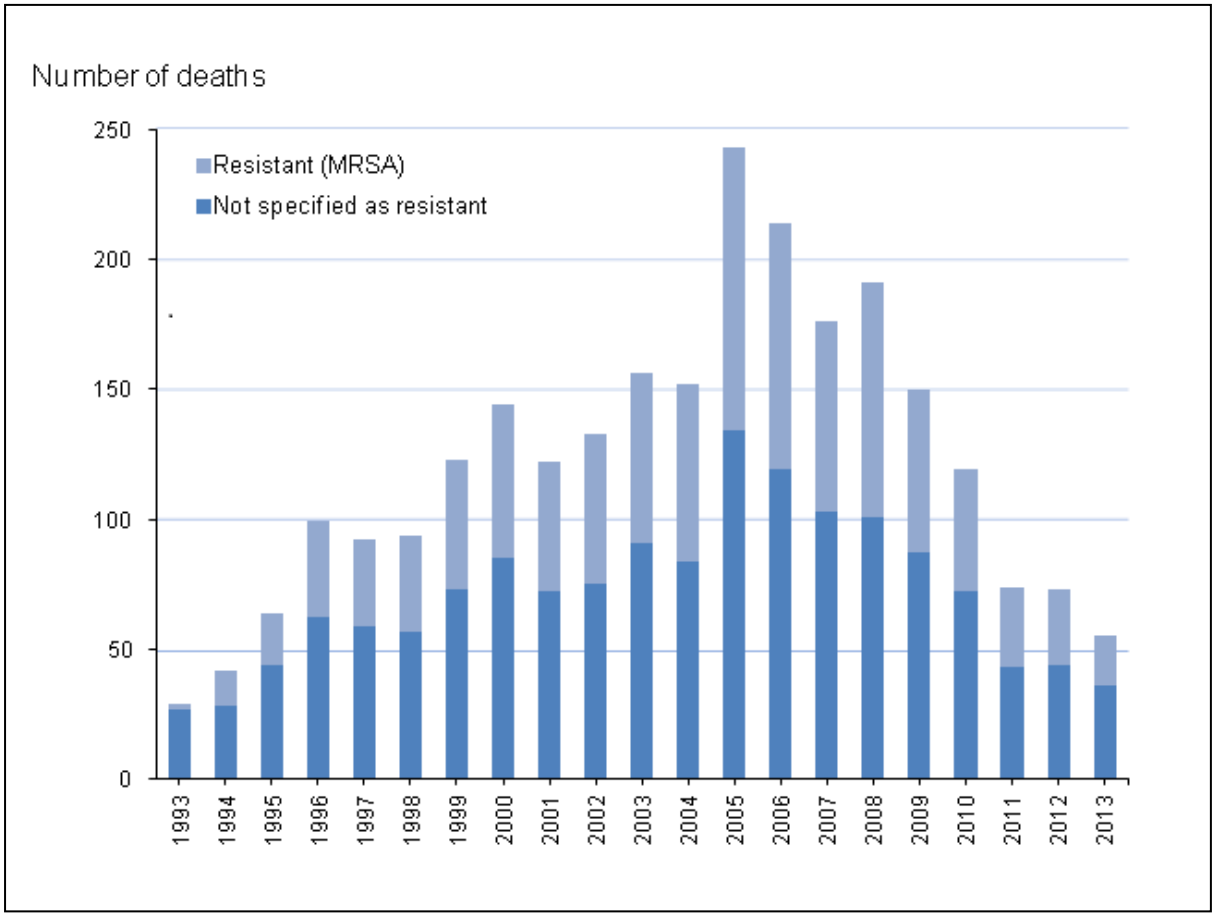
Decolonization is another strategy for preventing MRSA transmission in the hospital setting (usually intensive care unit). It entails the use of antiseptics or antimicrobials as surface decolonization agents, to reduce the bacterial load on patients' skin, which reduces the chance of transmission of MRSA. Numerous studies have also highlighted the prominent role decolonization has played in reducing MRSA in the healthcare setting[42]. For example, numerous studies have reported successful control of endemic and epidemic MRSA in an ICU setting with the use of decolonization agents[43]. Batra et al (2010) found that there was an immediate 70 percent reduction in the transmission of susceptible MRSA strains with the introduction of a universal chlorhexidine-based antiseptic protocol[44].

Available evidence on the efficacy of decolonization, predominantly from ICU studies, combined with the introduction of national guidelines endorsing its implementation as part of a new performance management culture in the NHS, supports the proposal that the widespread uptake of decolonization has made a key additional contribution to the decline in MRSA, such that decolonization, hand hygiene and ASC explain the significant decline in MRSA in the UK over the last decade.

Hence, similar to the findings for tuberculosis, MRSA also provides a vivid counter example to predictions of an apocalyptic scenario looming due to antimicrobial resistance. Indeed, what MRSA highlights is that despite increased antimicrobial resistance, there has been a decline in mortality. This has been achieved without novel antimicrobials. Much like tuberculosis at the beginning of the twentieth century, alternative public health interventions have delivered a decline. What the trends and history of both diseases highlights is the role for government public health interventions and how far reaching these basic infection prevention and control measures can be in combating antimicrobial resistance.

[40] Department of Health 2010
[41] Edgeworth 2010
[42] For example see: Batra et al 2010, Cunningham et al 2007, Thompson et al 2009, Gould et al 2007.
[43] For example see: Raineri et al 2007, Thompson et al 2009, Sandri et al 2006, Girou 1998, Ridenour et al 2007
[44] Batra et al 2010

Figure 14: MRSA mortality, England and Wales, 1993-2013



Source: ONS 2014

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.

Table 2 – see end of report

Table 3. HDI and GDP per capita in Britain, 1870-2013						
ear	1] HDI	[2] GDP per head	Per iod	Relative Contribution (percentage of total)		
				Y	*E*	*L*
870	.476	3,190				
913	.628	4,921	187 0-1913	1 4.2	5 4.1	31 .7
950	.762	6,939	191 3-1950	1 4.6	6 3.3	2 2.1
013	.923	23,50 0	195 0-2013	4 4.0	3 9.5	16 .5

Source: Crafts 2002: 396-7; Maddison website [http://www.ggdc.net/maddison/oriindex.htm]

Note: GDP per head is measured using 1990 international Geary-Khamis dollars; education component estimated using years schooling as a proportion of 15 years (assumed to be 3 years in 1870).

Table 4. The rise in U.S. 'real' incomes, 1870-1950		
Year	β =0.25, r=0.05	β =0.45, r=0.10
1870	62	148
1910	634	975
1950	3,150	2,572

Source: Costa and Steckel 1997: 69

Note: r is the discount rate used. The Usher estimates are in real 1958 US dollars.

Table 5: Tuberculosis (Quality Adjusted Life Year) QALY, 1900, 1950 and 2000[45]

Year	Tuberculosis QALY value
1900	0.33
1950	0.67
2000	0.83

Table 6: Number of tuberculosis deaths and tuberculosis deaths rate per 10,000 population in England and Wales, 1901-2000

[45] Hickson, 2006.

Year	Number of tuberculosis deaths	Tuberculosis deaths rate per 10,000 population
1901	58930	18.1
1920	36342	9.8
1940	27814	7.0
1950	15969	3.6
1960	3435	0.8
1980	605	0.1
2000	370	0.07

Source: Office for National Statistics. Twentieth Century Mortality: 100 Years of Mortality Data for England and Wales by Age, Sex, Year and Underlying Cause. CD Rom. 2003.

Table 7: Number of tuberculosis notifications and tuberculosis notifications per 10,000 population in England and Wales, 1901-2012

Year	Number of tuberculosis notifications	Tuberculosis notifications rate per 10,000 population
1901	70000	21.5
1920	60500	16.2
1940	35000	8.8
1950	42000	9.6
1960	21000	4.6
1980	6000	1.2
2000	6087	1.2
2012	8194	1.4

Sources: compiled from Citron *et al*. 1981, Watson *et al*. 1991, Joint Tuberculosis Committee of the British Thoracic Society 2000, Office for National Statistics 2003, Statutory Notifications of Infectious Diseases 2014

Table 8: Calculation of life years gained due to the amelioration and elimination of tuberculosis in England and Wales, 1901-2000 and 1950-2000

Year	Number of lost life years from mortality	Number of notifications (prevalence)	Proportion of a healthy life year lost (1 – QALY)	Number of lost life years from morbidity	Number of life years lost from mortality and morbidity	Number of life years gained
1901	58930	70000	(1 - 0.33) = 0.67	46900	105830	
1950	15969	42000	(1 – 0.67) = 0.33	13860	29829	
2000	370	6087	(1 - 0.83) = 0.17	1035	1405	
Number of life years gained 1901-2000 (1901 life years lost – 2000 life years lost)						**104425**
Number of life years gained 1950-2000 (1950 life years lost – 2000 life years lost)						**28424**

Table 9: Calculation of the value of life years gained due to improved tuberculosis mortality and morbidity in England and Wales, 1901-2000 and 1950-2000[46]

	Life years gained			VSL (int. $ million)	Value of life years gained (int. $ million)		
Period	Mortality	Morbidity	Mortality and morbidity		Mortality	Morbidity	Mortality and morbidity
1901-2000	58560	45865	104425	1.22	71443	55956	127399
1950-2000	15599	12825	28424	1.22	19031	15647	34678

[46] VSL values for 1950-2000 need to be more accurate

Table 10: Number of drug resistant TB cases and associated QALY cost, 2013

Age group	Cases	Proportion of a healthy life year lost (1 – QALY)	Number of lost life years from morbidity	VSL (int. $ million)	Value of life years lost (int. $ million)
0-14	62	(1 - 0.67*) =			
15-44	2931				
45-65	964				
65+	649				
Sum	4606	0.33	1520	1.22	1854

Source: compiled from Enhanced Tuberculosis Surveillance: Centre for Infectious Disease Surveillance and Control, Public Health England

Note: cases includes isoniazid resistant and multi-drug resistant tuberculosis

Note: using 1950 QALY to simulate AMR

Table 11: WTP to show the welfare cost of antimicrobial resistance: MRSA, England and Wales, 1993-2011

	Age-standardised rates per million population		Number of deaths			VSL (int. $ million)	WTP (int. $ million)
Year	**Males**	**Females**	**Males**	**Females**	**Sum**		
1993	1.0	0.4	29	22	51	1.22	62
1994	1.7	0.8	52	38	90	1.22	110
1995	4.0	1.7	116	82	198	1.22	242
1996	5.7	2.6	166	132	298	1.22	364
1997	7.3	3.6	216	170	386	1.22	471
1998	7.6	3.8	231	178	409	1.22	499
1999	9.0	4.1	278	202	480	1.22	586
2000	12.2	5.9	382	284	666	1.22	813
2001	12.7	6.5	405	326	731	1.22	892
2002	14.6	6.9	468	326	794	1.22	969
2003	16.6	8.8	541	427	968	1.22	1181
2004	19.4	9.0	655	483	1138	1.22	1388
2005	25.8	14.4	891	758	1649	1.22	2012
2006	26.8	13.2	947	705	1652	1.22	2015
2007	26.3	11.8	953	640	1593	1.22	1943
2008	18.2	10.3	667	563	1230	1.22	1501
2009	11.7	5.9	444	337	781	1.22	953
2010	6.8	3.7	271	214	485	1.22	592
2011	5.4	2.4	217	147	364	1.22	444
Sum 1993-2011							**17035**

Table 11. Antibiotic consumption in the community (primary care sector) in Europe: 2003 and 2012		
Country	*2003*	*2012*
Austria	12.48	13.98
Belgium	23.80	29.76
Bulgaria	15.54	18.47
Croatia	--	21.72
Cyprus	--	29.71
Czech Republic	16.70	17.54
Denmark	13.52	16.43
Estonia	11.08	11.74
Finland	18.71	19.46
France	28.86	29.68
Germany	13.90	14.87
Greece	31.32	32.39
Hungary	19.14	13.61
Iceland	19.55	22.11
Ireland	20.12	23.02
Italy	25.61	27.56
Latvia	--	13.02
Lithuania	--	16.19
Luxembourg	28.58	27.86
Malta	--	22.48
Netherlands	9.79	11.34
Norway	15.61	16.92
Poland	--	22.63
Portugal	25.11	22.66
Romania	--	30.40
Slovakia	27.64	20.02
Slovenia	16.99	14.30
Spain	18.93	20.87
Sweden	14.66	14.07
United Kingdom	15.14	20.06
Source: ECDC		

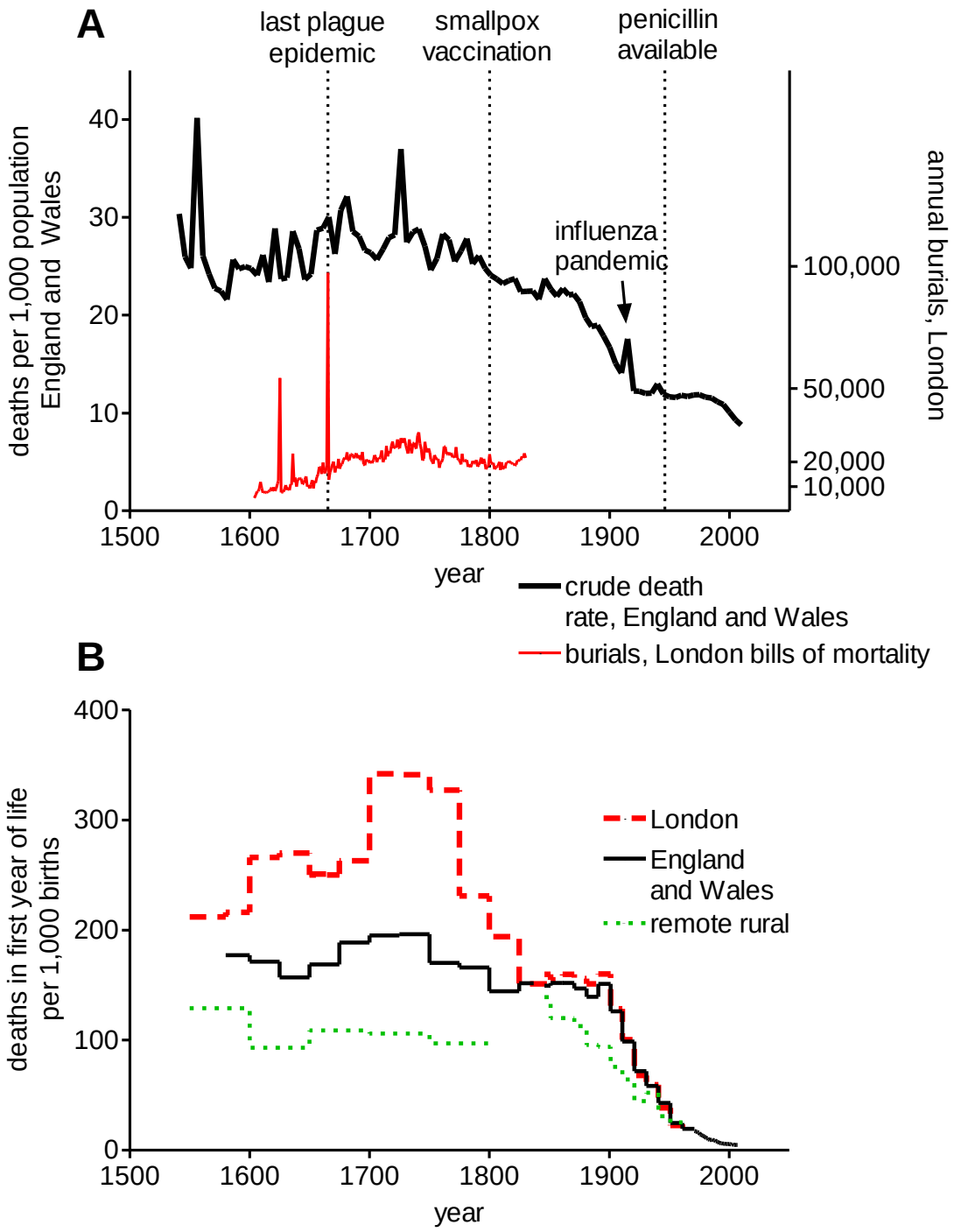


Figure 1. Long-run trends in crude death rates (A) and infant mortality (B) in England.

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

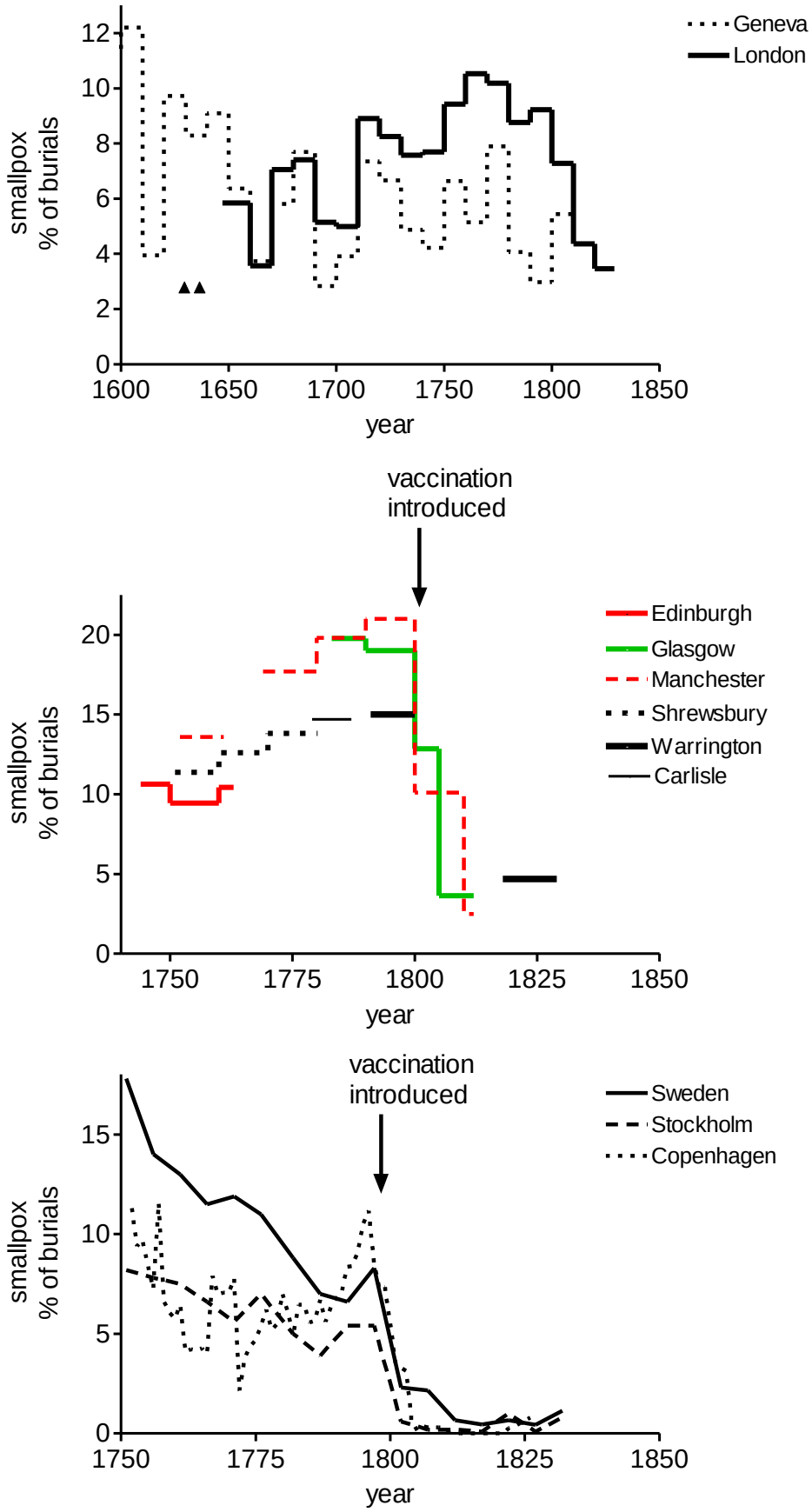


Figure 2. Smallpox percentage of all burials in England, Sweden, Geneva and Copenhagen.

Sources: Perrenoud, 1980; Sköld, pp. 52, 541-57; Creighton, 1894, pp. 436-7, 456, 461, 531, 535, 568; Vaccination Commission, pp.107-8.

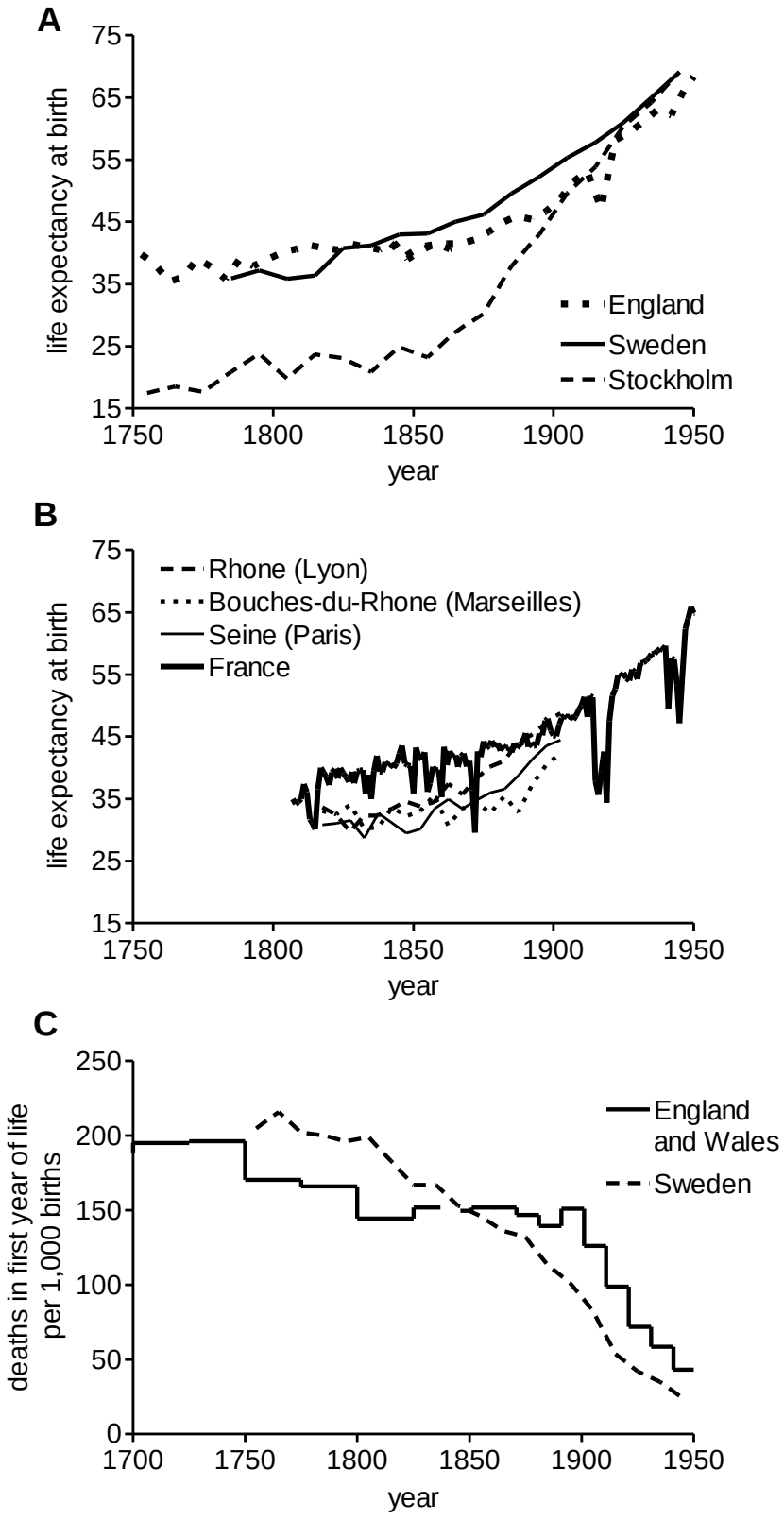


Figure 3. National and urban life expectancy (A,B) and infant mortality (C) in England, Sweden and France.

Sources: Human Mortality Database; Sköld, 1996; Preston & van der Walle, 1978.

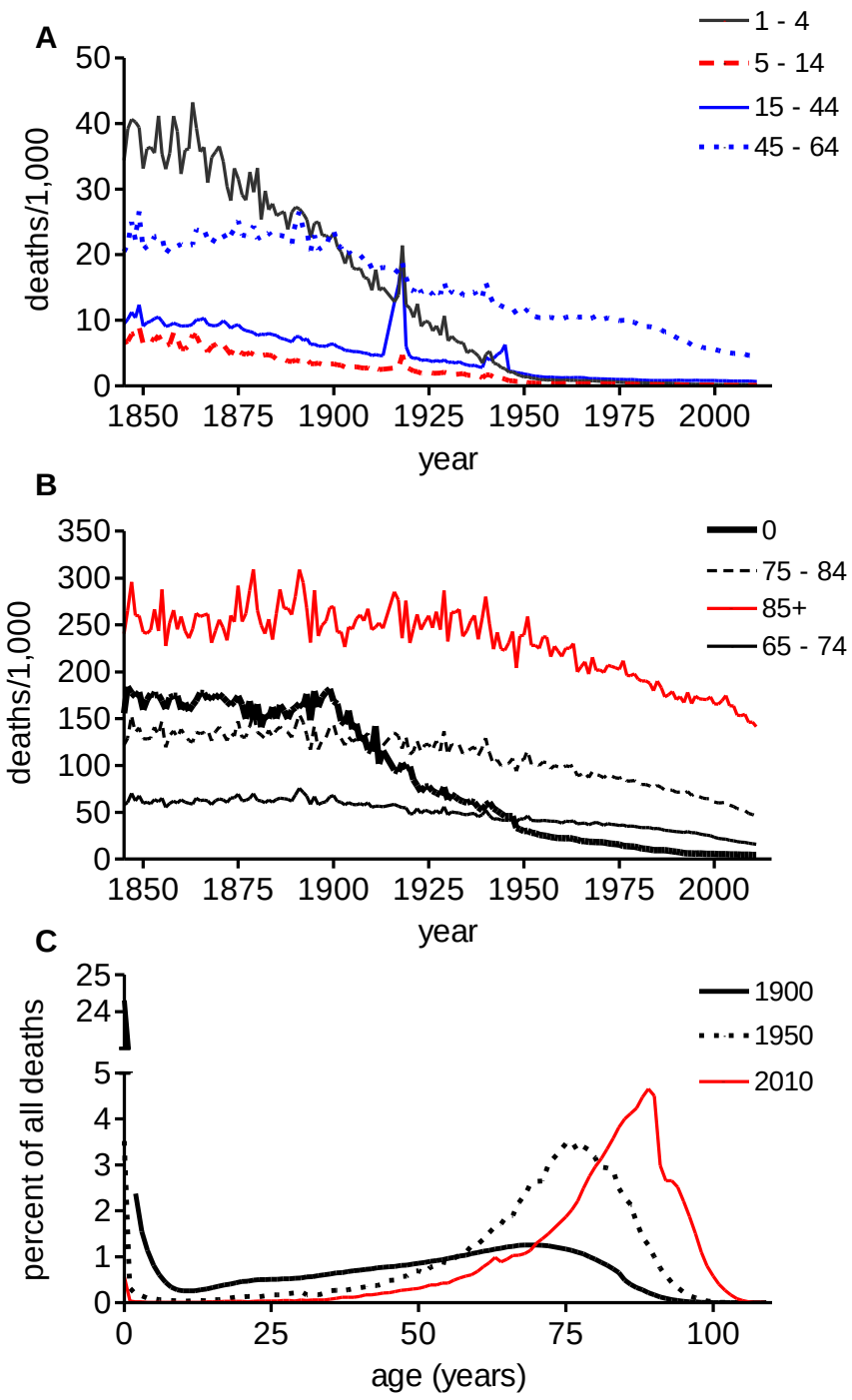
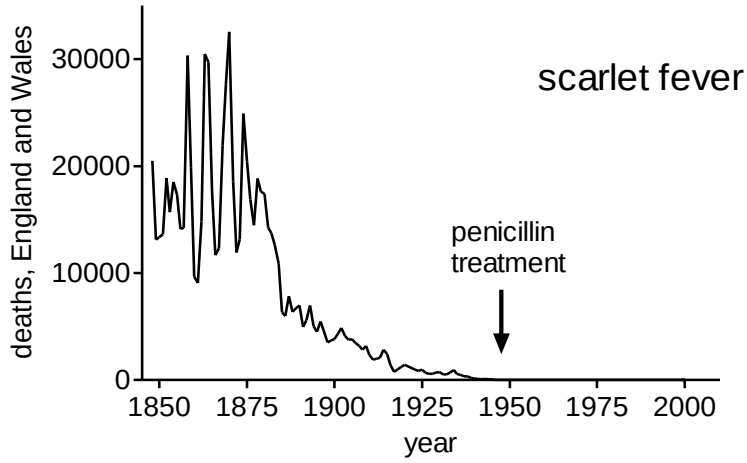


Figure 4. Age-specific death rates (A, B) and percentage age distribution of deaths, England & Wales.

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


scarlet fever
deaths, England and Wales
30000
20000
10000
0
penicillin
treatment
1850
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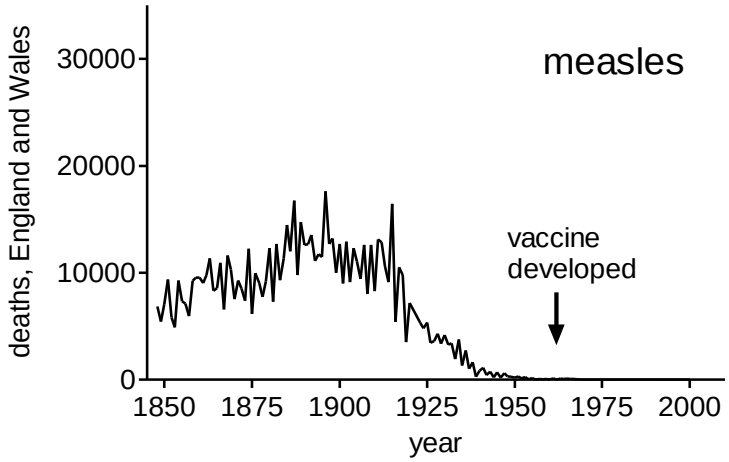
1900
1925
1950
1975
2000
year


measles
deaths, England and Wales
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vaccine
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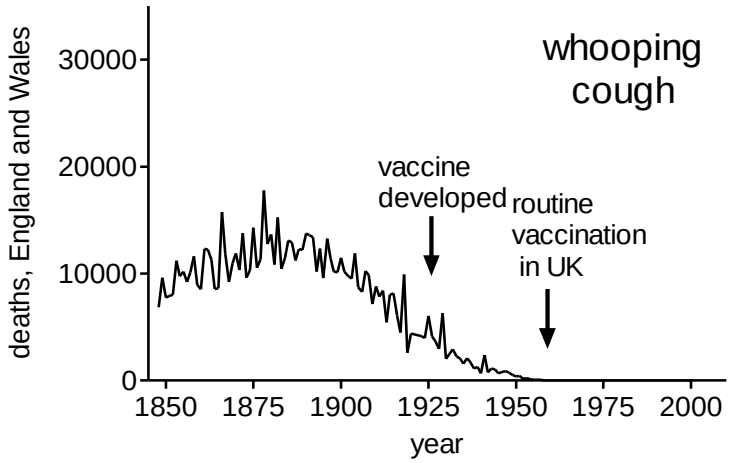
whooping
cough
deaths, England and Wales
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in UK
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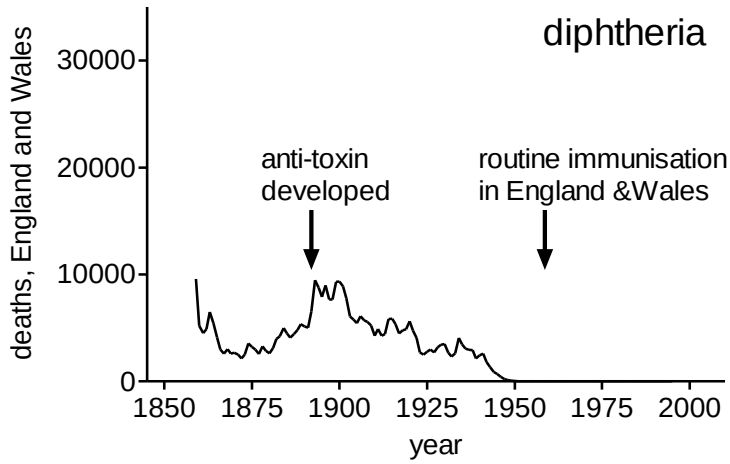
diphtheria
deaths, England and Wales
30000
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10000
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anti-toxin
developed
routine immunisation
in England &Wales
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Figure 5. Deaths from the main childhood infections (excluding diarrhoeal deaths), England and Wales.

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

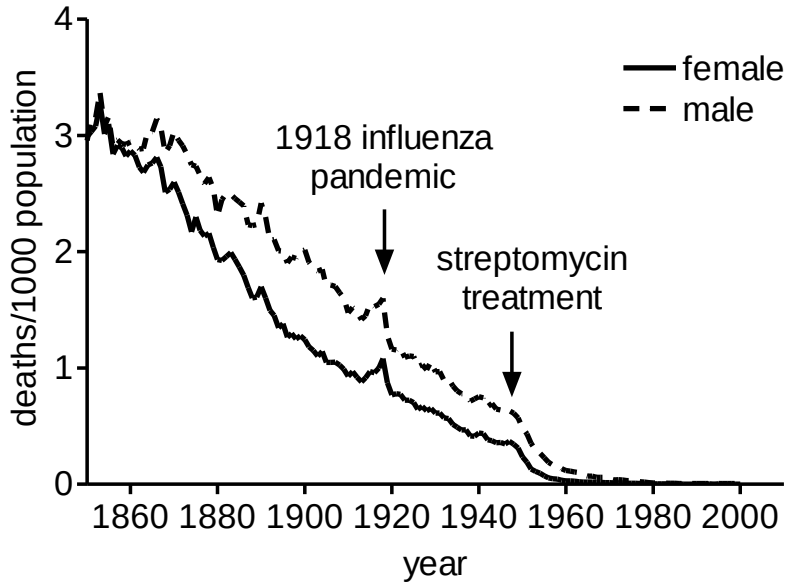

Figure 6. Tuberculosis mortality in England and Wales, age-standardised to the U.K. population in 2000.

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

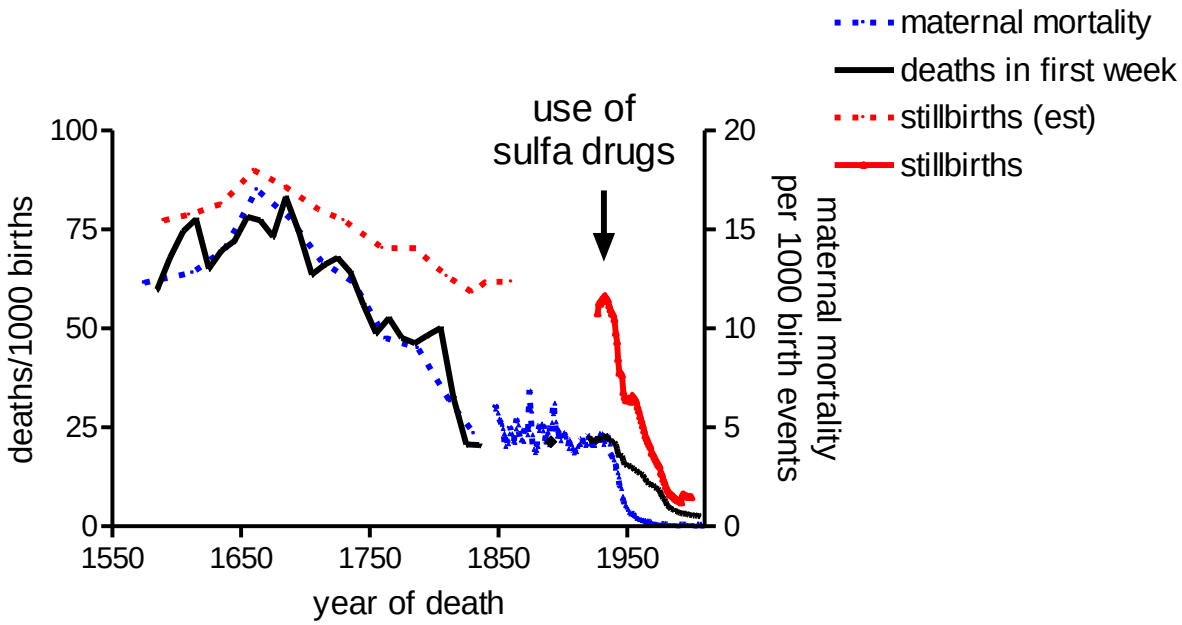

Figure 7. Maternal, early neonatal and late foetal (stillbirth) mortality, England (1680 – 1840) and England and Wales (1848 – 2000).

Sources: Wrigley et al. 1997; GapMinder(http://www.gapminder.org/)

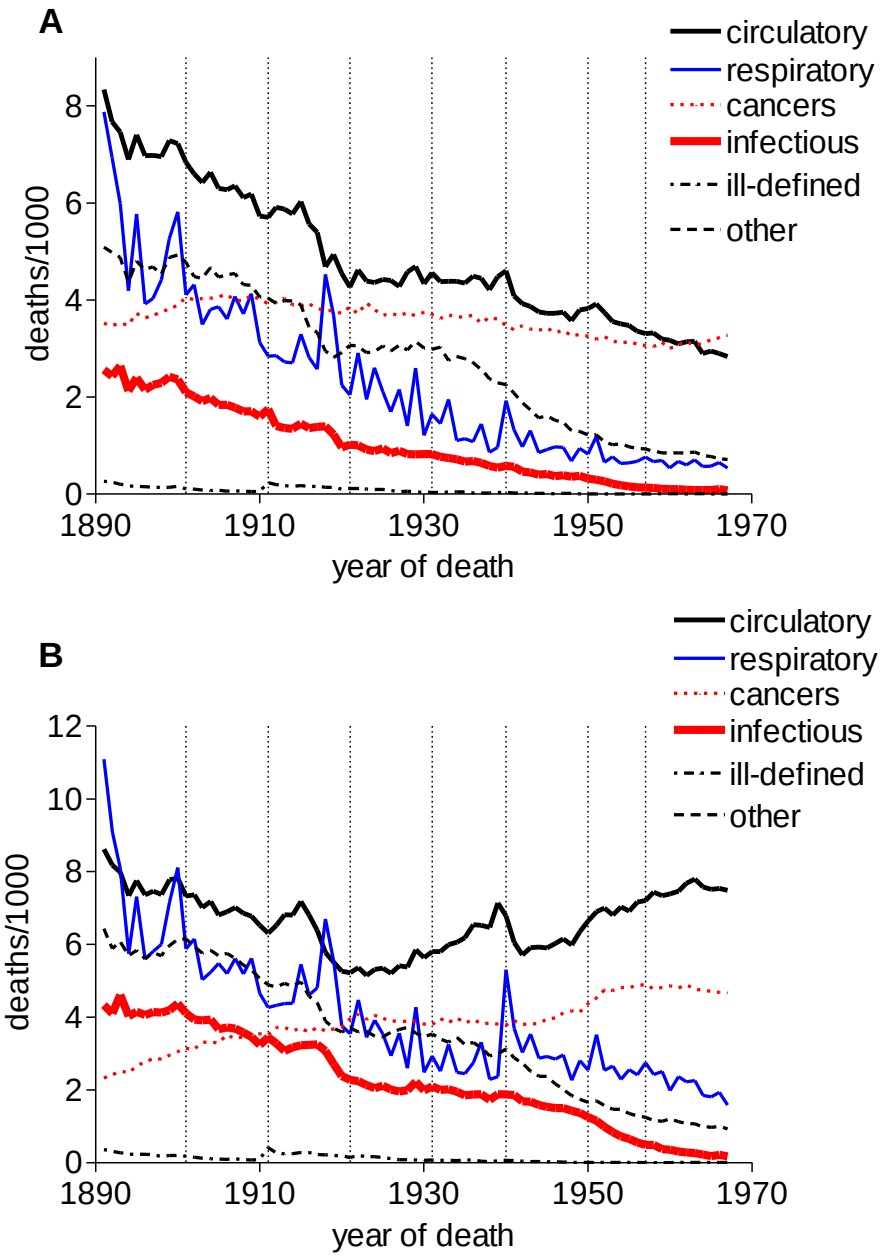

Figure 8. Annual death rates by category of cause, females (A) and males (B) aged 55-59, England and Wales. Vertical lines indicate revisions in the coding of causes of deaths.

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

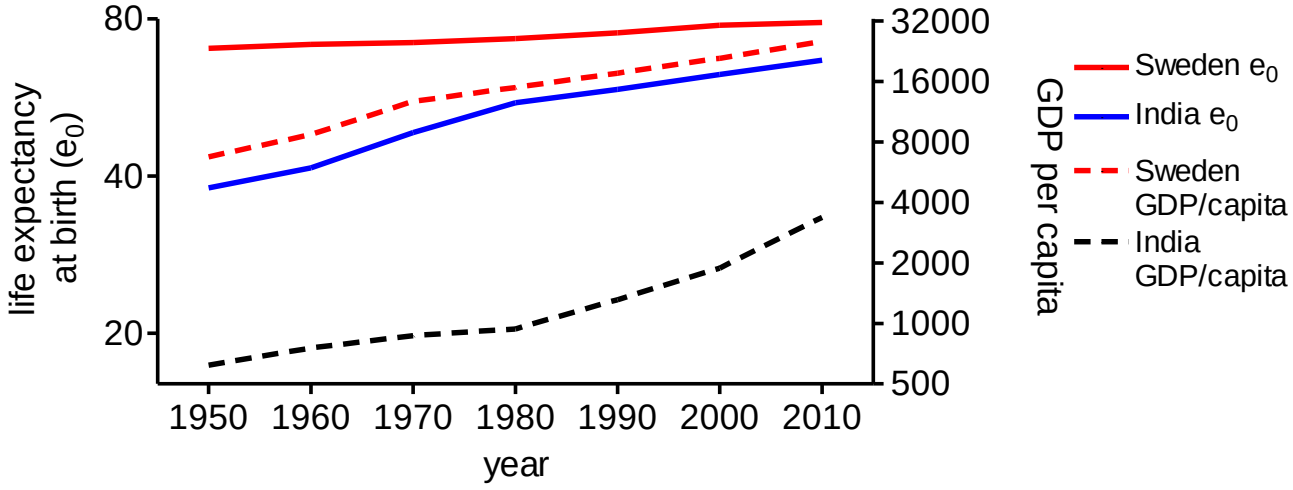

Figure 9. Income per capita and life expectancy at birth, India and Sweden

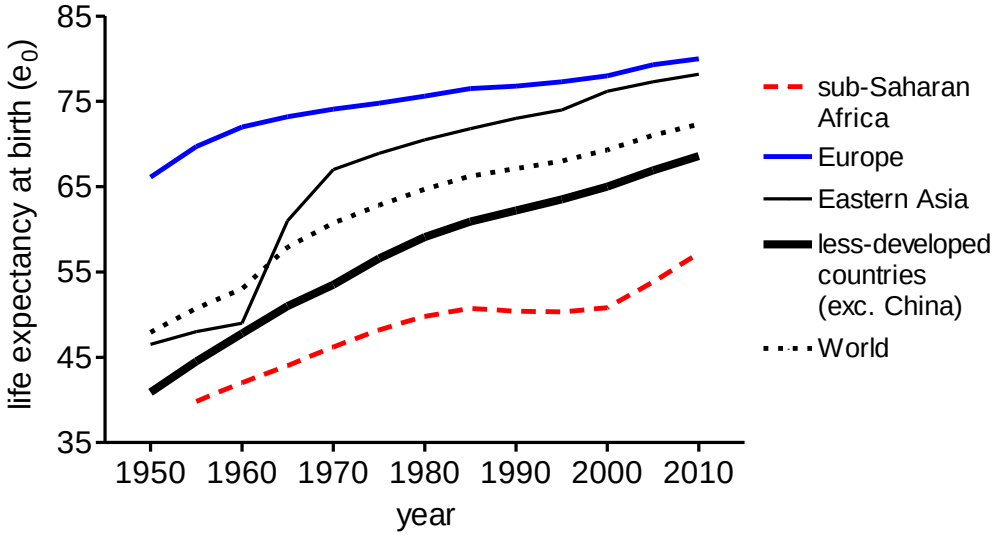

Figure 10. Global convergence in life expectancy at birth, 1950 – 2000

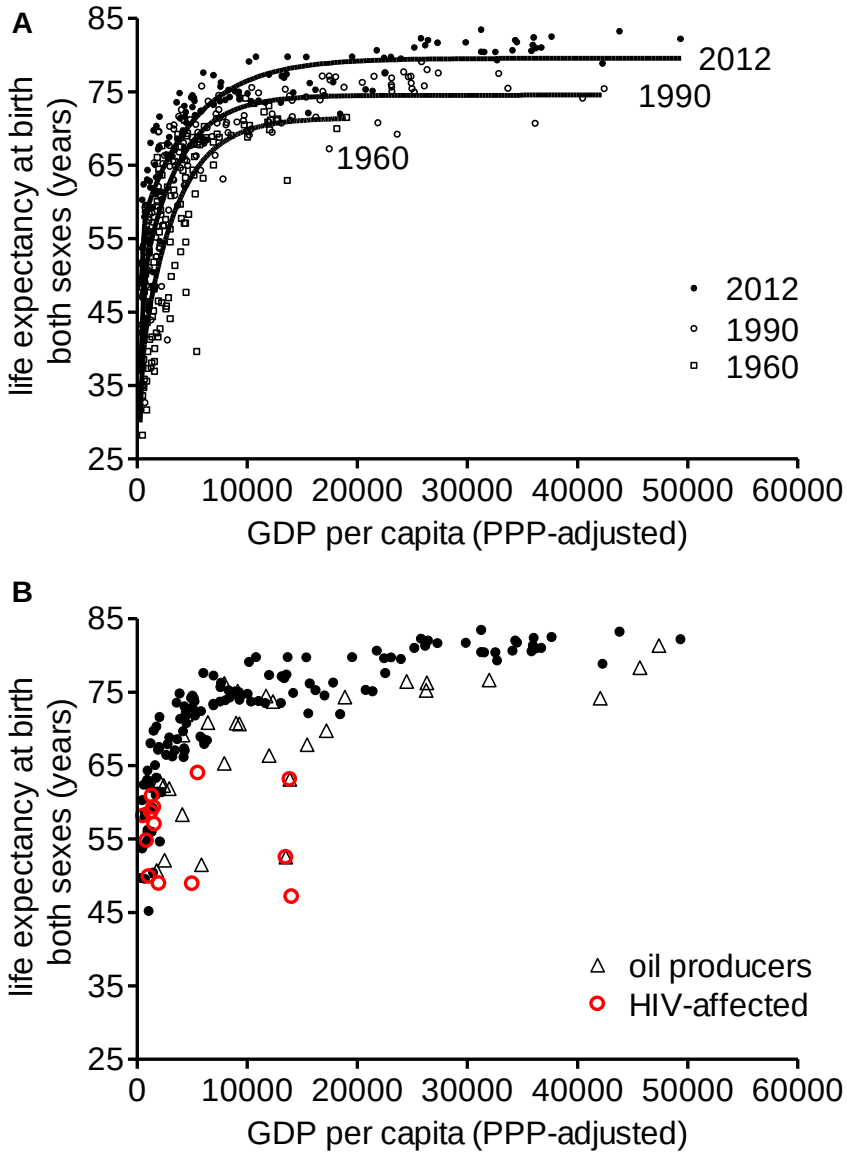

Figure 11. 'Preston curves' of national life expectancy by income (GDP per capita). States deriving more than 10% of GDP from oil rents and populations with HIV prevalence > 5% in 2012 (panel B).

Sources: http://www.gapminder.org/ accessed 03 Nov 2014; http://www.indexmundi.com/facts/indicators/NY.GDP.PETR.RT.ZS/rankings accessed 03 Nov 2014; CIA World Factbook, 2011

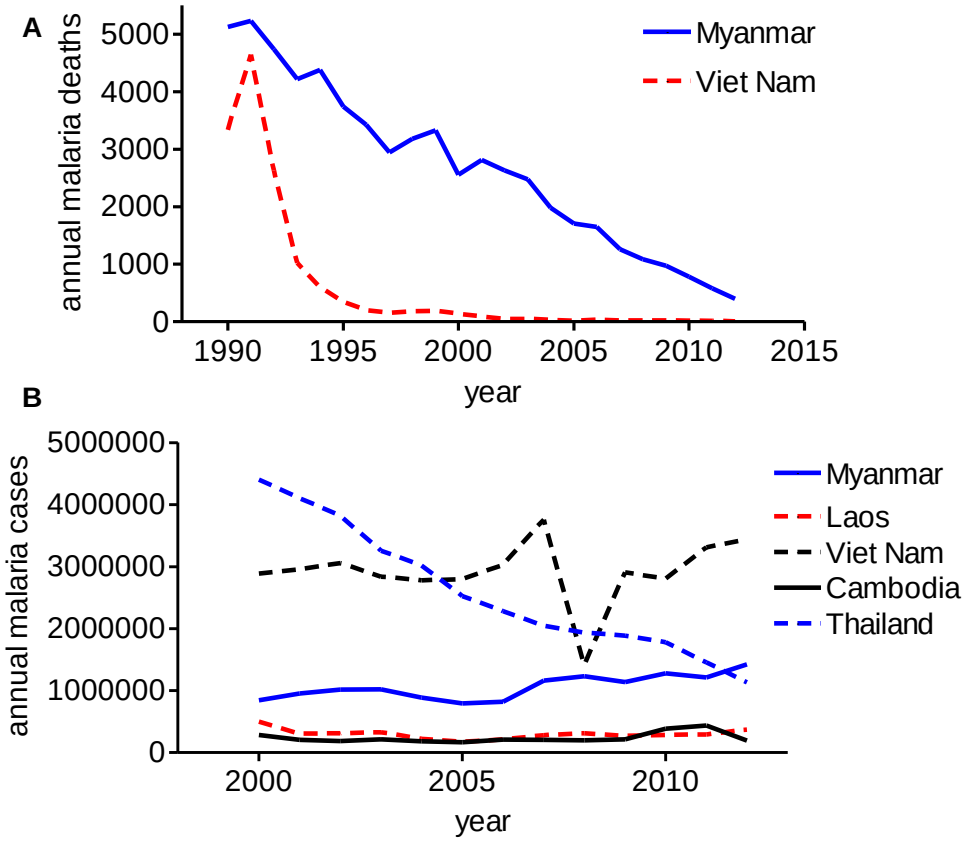

Figure 12. Reported Deaths and Suspected Cases in Southeast Asia

Source: WHO, *World Malaria Report 2013,* Annexes 6D and 6E

http://www.who.int/malaria/publications/world_malaria_report_2013/en/

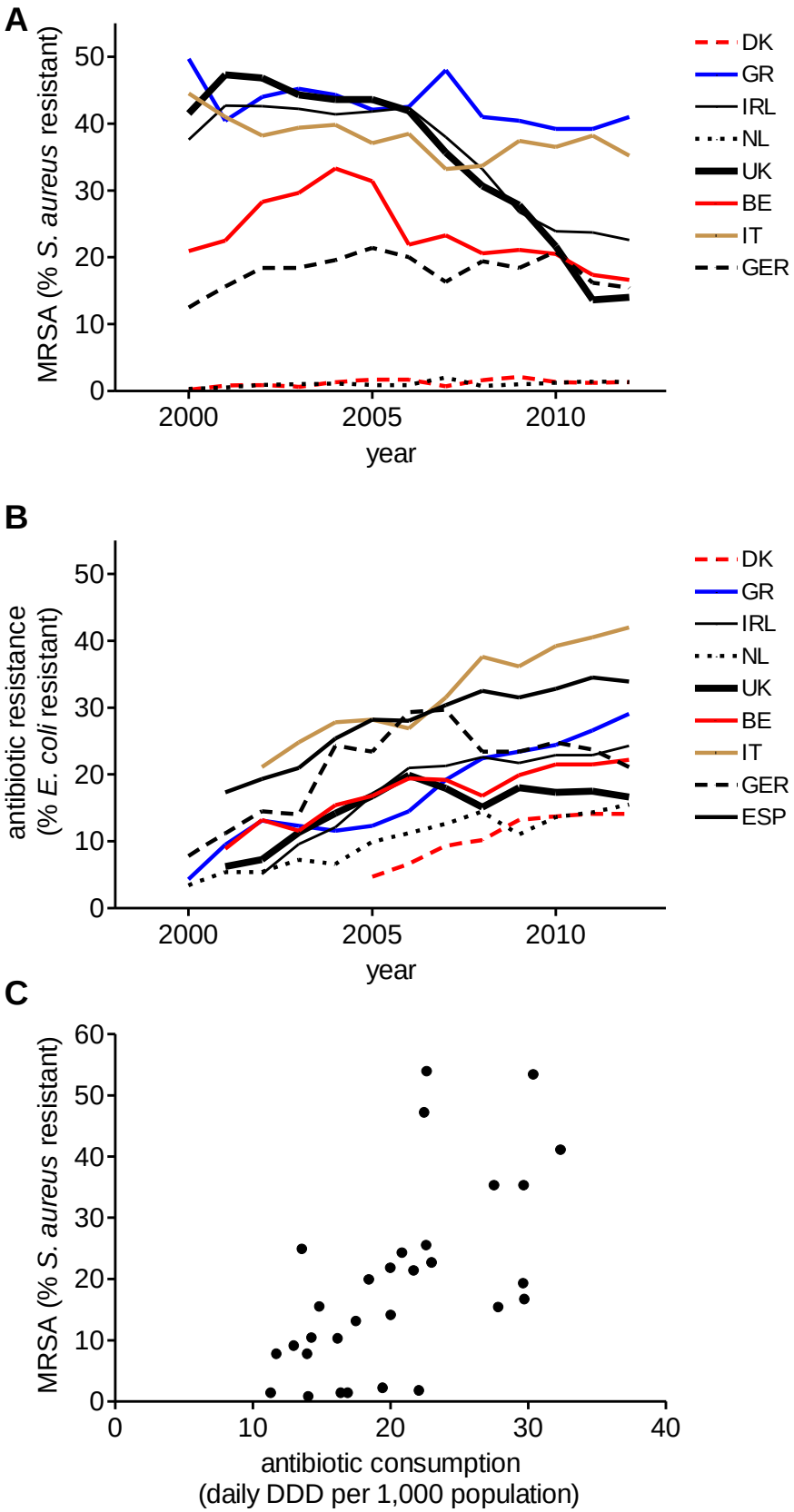

Fig. 13 Antibiotic resistance in *Staphyloccocus aureus* (A) and *E. coli* (B) in Denmark (DK), Greece (GR), Ireland (IRL), Netherlands (NR), U.K., Belgium (BE), Italy (IT) and Germany (GER) 2000 – 2012, and antibiotic resistance according to antibiotic consumption by country in 2012 (C).
Source: ECDC

Table 2. Major diseases and their prevention and treatment, with estimates of infectiousness ('R_0') and case-fatalities (in absence of treatment).

disease	pathogen	type	mode(s) of transmission	R_0[47]	case-fatality	prevention	date	treatment	date
Diseases reduced or eliminated before 1750									
bubonic plague	*Yersinia pestis*	gram-negative bacterium	flea bite	1.1-1.2 [48]	20 - 60%	quarantine, isolation	from C15th in Europe	antibiotics	1946 (streptomycin)
Diseases reduced or eliminated 1750 - 1870									
typhus	*Rickettsia prowazekii*	gram-negative bacterium	louse faeces in open wound	low	20 % [49]	quarantine, isolation, hygiene, DDT to kill lice.	C18th reductions	antibiotics	1948 (chloramphenicol)
						Vaccine	1943 (not currently in production)		
smallpox	variola major	virus (DNA)	airborne, exudate	3.5 – 6 [50]	10-20% [51]	quarantine, isolation	C17th?, C18th	none	
						Inoculation	C18th	none	
						vaccination	1798	none	

[47] Ro is the 'basic reproductive number', an estimate of the number of infections caused by a single infected individual in a completely susceptible population. It is notoriously difficult to measure particularly for diseases that involve an intermediate host (such as insect-borne infections) or chronic stages (such as tuberculosis).
[48] Nishiura et al., 2012
[49] Ewald, 1983
[50] Gani & Leach, 2001
[51] Fenner et al., 1988; Walther & Ewald, 2004

cholera	*Vibrio cholerae*	gram-negative bacter-ium	mainly water-borne (faecal contamination)	1.1 - 2.6 (Haiti outbreak, 2010)[52]	15.7 [53]	water purification, notification and isolation of cases	last epidemic in Britain 1866 (1890s in continental Europe). Still endemic in south Asia	oral rehydration	1968
typhoid	*Salmonella typhae*	gram-negative bacter-ium	mainly water-borne (faecal contamination)	2.8 - 7 [54]	5-8 - 9.7[38]	water purification, isolation of cases. Vaccine	reduced in importance over the course of the C19th in England. 1897[55]	antibiotics, oral rehydration	1948 (chloramphenicol); 1968 (ORT)
malaria	four *Plasmodium* strains	protozoan	mosquito bite	estimates very variable	1- 30% in epidemics [56]	reduction in mosquito host populations (drainage, DDT) and prevention of bites (bednets, insecticide)	eliminated in England by early C20th. Very large global reductions through DDT use 1940s+	quinine, chloroquine, artemisinin and combination therapies	quinine used in Bolivia and Peru at least since C15th
<u>Diseases reduced or eliminated 1870-1940</u>									
yellow fever	flavivirus	virus (RNA)	mosquito bite	1.1 - 5.9 [57]	1 - 16 % [34]	reduction in mosquito host populations	early C20th, used successfully during Panama	none	

[52] Mukandvir et al., 2013
[53] Ewald, 1991
[54] Pitzer et al., 2014
[55] Used by the Japanese army in 1905 in the Japanese-Russian war, making it the first army to suffer more deaths from battle wounds than disease. Variable efficacy.
[56] Carter & Mendis, 2002
[57] Favier et al., 2006

						(drainage, DDT) and prevention of bites (bednets, insecticides)	canal construction		
						vaccination	1936, used by US army WWII		
tuberculosis	*Mycobacterium tuberculosis*	gram-positive bacterium	airborne, exudate	1.0 < R0 < 8.9 [58]	5 % [59]	BCG vaccination	1921 (routine use in England 1953)	antibiotics	1946 (streptomycin)
measles	Rubeola	virus (RNA)	airborne	5 – 18 [60]	0.007 % [44]	vaccination	1963	none	
scarlet fever	*Streptococcus pyogenes*	gram-positive bacterium	airborne	6 - 8 [13] (C20th)	2 - 6 % in late C19th[61]		apparent decline in virulence 1870+	antibiotics	1942 (penicillin)
whooping cough	*Bordetella pertussis*	gram-negative bacterium	airborne	7 - 18 [45]	0.1 % [44]	vaccine	1947	antibiotics	1946 (streptomycin)
Diphtheria	*Corynebacterium diphtheriae*	gram-positive bacterium	airborne, exudate	4 - 5 [45]	0.2 % [44]	vaccination (with 'anti-toxin')	1890, but used widely only from 1940s.	antitoxin and antibiotics (latter largely to prevent transmission)	

[58] Sanchez & Blower, 1997
[59] Walther & Ewald, 2004
[60] Anderson & May, 1991: 70
[61] Lancaster, 1991: 114

Diseases reduced or eliminated after 1940									
poliomyelitis	poliovirus	virus (RNA)	mainly water-borne (faecal contamination)	5 - 7 [45]	0.15 % [62]	vaccination	1954, 1957	none	
Pneumonia	Streptococcus pneumoniae	gram-positive bacter-ium	airborne and exudate		0.036 %[44]	vaccination	1975	Sulphonamide, penicillin	1937, 1944
chickenpox	Varicella zoster	gram-negative bacter-ium	airborne	7 - 12 [45]	0.003%[7]	vaccine	1975	none	
MRSA	*Staphylococcus aureus*	gram-positive bacter-ium	person to person, exudate	low [63]	15 - 60% [64]	hygiene	Reductions in hospital-acquired infections from 1880s due to aseptic and antiseptic surgical techniques and improvements in wound treatment	antibiotics	sulfa drugs (1930s) penicillin (1942). Rapid evolution of resistance

[62] Nathanson & Kew, 2010 (case-fatalities for paralytic cases multiplied by 100 for average seroconverters/case)
[63] Cooper et al., 2012
[64] McKinnon & Lodise, 2007