The first stages of the mortality transition in England: a perspective from evolutionary biology[1]

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Abstract

This paper examines the origins of the Mortality Revolution from an evolutionary point of view, in terms of the trade-offs between virulence and disease transmission. For diseases that are transmitted person-to-person and cannot persist outside a host then there is evidence of strong selective pressure against high host lethality. However for pathogens which don't depend on their human host for transmission or can persist outside a human host (including plague, typhus, smallpox and malaria) then the conflict between virulence and dispersal is reduced. Importantly, the properties that permitted these diseases to be so lethal also made it easier for relatively weak interventions to break the chain of disease transmission. The early control of these major diseases was associated with large reductions in mortality, but also shifted the distribution of causes of death towards the less virulent diseases of the extremes of age and of poverty.

Key words: demographic transition, mortality transition, evolutionary biology, smallpox, vaccination.

JEL classification: I14 (health and inequality); I15 (health and economic development); I18 (Government policy, regulation, public health); N33, N93 (Europe: pre-1913)

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Introduction

A recent CAGE publication, 'Health, well-being and antimicrobial resistance: insights from the past for the present', addressed the importance of an understanding of the historical impact and control of infectious diseases for estimates of the likely impact of widespread failure of antibiotic therapies (Davenport et al., 2014). The current working paper focuses on a claim made in that publication that long-run trends in infectious disease mortality could be explained at least partially by a consideration of the evolutionary biology of individual infectious diseases. It focuses on the first stages of mortality decline (1600 – 1850), and on England, because the English population is the only for which we have reliable estimates of population and mortality rates before the mid-eighteenth century. Readers are referred to the first publication for consideration of the period c.1300 – 2000 and for a global perspective.

1. The first stage of the epidemiological transition in England

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 in England, 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. Demographic historians date the beginnings of the demographic transition and secular mortality decline from the late eighteenth century, and locate it in the North Sea basin region. Figure 1 shows long-run life expectancy and infant mortality estimates for England and for Sweden. In both populations life expectancy was relatively high by historical standards, and rose between 1750 and 1820. The Swedish population experienced almost unbroken improvements in life expectancy from the late eighteenth century to the present. However the English rise in life expectancy c.1750-1820 was braked by rapid urbanisation in especially the middle decades of the nineteenth century. The fact that English life expectancy did not *reverse* in this period is remarkable given the historically unprecedented growth and redistribution of the population into urban centres in this period. Indeed the stagnation of life expectancy in the aggregate probably conceals

improvements in mortality in both the growing urban and the dwindling rural sector of the population (Woods, 1985).

The early origins of the mortality transition are often overlooked, preceding as they did the sanitary reforms and economic growth of the second half of the nineteenth century and the rise of curative medicine in the twentieth. However the apparently unremarkable rise in life expectancy at the aggregate level in England before 1870 (Figure 1) concealed very profound changes in the structure of mortality, processes that were in fact initiated in the seventeenth century. Five main changes occurred.

1.1 Reductions in the volatility of mortality

Figure 2 illustrates annual crude death rates (deaths per 1,000 population) for the English population 1540 - 1870, and total annual burials for London 1604 - 1830. The largest spikes in mortality coincided with plague epidemics. However the impact of plague diminished from the mid-fifteenth century, and plague disappeared from Scotland after 1647, from England after 1666, and from western Europe after the 1720s. Nonetheless substantial volatility persisted into the early eighteenth century in England, and only after the 1740s did major crises at the national level cease.

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 escape from famine, and much of the attenuation of burial volatility reflects the progressive attenuation of the link between food prices and mortality swings (Wrigley & Schofield, 1989). The positive relationship between food prices and mortality weakened over the seventeenth century and disappeared at the national level after 1750, reflects progressive improvements in the distribution of food via greater market integration, and the operation of the English poor laws (Wrigley & Schofield, 1989; Kelly & Ó Gráda, 2014).

1.2. Shifts in the age structure of mortality

The progressive reduction in the volatility of mortality was not however 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. Before the mid-eighteenth century adult mortality was historically high relative to infant and child mortality. This feature is very unusual in modern populations, to the extent that none of the standard model life tables derived from nineteenth and twentieth century populations can be used approximate the early modern English population (Wrigley et al., 1997). However by the early nineteenth century the English population had attained a more typical 'model west' pattern of age-specific mortality, with mortality concentrated in early childhood and late adulthood. This profound shift in the age structure of mortality is documented in Figure 3. Importantly, mortality moved in different directions for adults and children. Amongst adults mortality declined from c.1700, even as mortality worsened for infant and children. After 1750 there was progressive improvement in survival of older children (ages 3+), and mortality became concentrated in early childhood (ages 1 -2).However mortality of infants (in the first year of life) followed a more unusual trajectory, rising before 1750 and declining thereafter. When mortality in this age range is decomposed into neonatal (first month) and post-neonatal (ages 1-11 months) periods then it is clear that older infants continued to experience worsening mortality together with one and two year olds. Very young infants on the other hand experienced improvements in survival that were chronologically very similar to adults, suggesting that mortality in the first month of life was more closely related to maternal health than at later ages (when infectious diseases dominated mortality).

1.3. Increases in mortality differentials by social status

The fall in life expectancy of the English population between 1650 and 1750 (Figure 1) coincided with a period of rising real wages; conversely, higher life expectancy before 1650 and after 1750 was associated with falling real wages (Wrigley and Schofield, 1989). The apparently *negative* association between living standards and life expectancy identified in the English population before 1800 is borne out by the lack of evidence for gradients 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). For England we have only fragmentary evidence before the late nineteenth century. 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). This may reflect the tendency of the wealthy to spend more time in towns, where risk of infection was higher, or the dysfunctional consumption and sporting habits of the aristocracy. Mortality was highest in urban populations despite the higher incomes and greater food security associated with towns, and mortality was lowest in those remote rural communities where prolonged maternal breastfeeding was the norm (Farr, 1865; Wrigley & Schofield, 1989, Wrigley et al., 1997). Early plague epidemics affected rich and poor districts of London equally, but by the seventeenth century the poorer parishes bore the brunt of plague mortality, probably because the wealthy were more able to flee the city, rather than because they enjoyed greater immunity (Cummins et al., 2014; Champion, 1995). Infant and child mortality were apparently lower in wealthier London parishes in the late sixteenth and early seventeenth century, but converged with rates in poorer suburban parishes over the century, probably as a result of a reduction in the tendency of higher status families to send young children to be nursed in the countryside, where their deaths, if they occurred, went unrecorded in their natal urban parish (Newton, 2011). Mortality rates amongst London Quaker infants and children were as high as those estimated for the population of the London Bills as a whole in the seventeenth and eighteenth centuries, despite the relative affluence of Quakers (Landers, 1993). In a study of mortality in the first two years of life across the social spectrum in the London parish of St. Martin in the Fields there was no evidence of a social gradient in mortality in the period 1752-1812, once rates were corrected for the effects of missing children (Davenport, unpubl). Using smaller samples, Razzell and Spence found no differences in mortality of infants and children by social status in London before the mid-nineteenth century, and higher mortality amongst men of higher status (Razzell & Spence, 2006, 2007).

By the late nineteenth century however infant mortality displayed a clear status gradient in the English population. Infants born to fathers in the highest of the five tiers of the occupational classification system (class I) experienced half the risk of infants born to fathers in class V (Reid, 1997). The advantages of rural remoteness persisted however, and infants of agricultural labourers, one of the poorest of occupational groups, were at even lower risk than those born to fathers of the highest social class. Moreover within a given settlement social gradients in infant mortality remained slight, suggesting that it was the ability of higher status groups to locate to more salubrious residential areas that conferred the most advantage, rather than nutritional intake or household characteristics (Reid, 1997). Suburbanisation and residential segregation by income were characteristic of the nineteenth century, and must have contributed to the widening of social differences in mortality. However early modern towns were characterised by

the very close residential proximity and intermingling of rich and poor, a situation that made the selective avoidance of disease more difficult.

1.4 Disappearance of the 'urban graveyard' phenomenon

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 (Landers, 1992). 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). 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. English towns and cities appear to have been particularly lethal in the century 1650-1750, and larger urban centres functioned as 'demographic sinks' in this period. Burials exceeded baptisms every year, and where age-specific mortality rates have been estimated these indicate very high levels of mortality amongst infants and young children (with infant mortality rates of 250 – 450 per thousand births), consistent with a demographic regime that was dependent on in-migration to avoid population demise (Figure 4; Landers, 1993; Galley, 1998; Newton, 2011; Davenport, 2014).

After 1750 the balance of baptisms to burials seems to have improved progressively in many towns, with profound falls in infant and child mortality in London (Landers, 1993; Davenport, 2014) and in smaller market towns (Wrigley et al., 1997; Davenport, 2014.). In London infant mortality fell from 35 – 40 % in the first year of life in the 1740s to the national average of c. 16 % by 1850, and mortality also improved markedly for older children (at ages where there was little improvement at the national level – Figure 3). The exceptional lethality of London in the period 1650-1750 appears to have been due largely 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). The profound falls in infant mortality after 1750 coincided with a lengthening of birth intervals that most pronounced in wealthier families with

the shortest birth intervals, suggesting a pronounced lengthening in the period of maternal breastfeeding (which delays conception of a subsequent child) (Landers, 1993; Davenport, 2014). This shift in birth intervals is consistent with more anecdotal evidence of changing attitudes to breastfeeding amongst elite women. Conversely, the (lethal) tendency of wealthier families to employ wet-nurses or to hand feed their infants before the nineteenth century would have served to undermine or reverse status gradients in survival particularly in urban populations.

Much of the lethality of even minor towns in the period 1650 – 1750 is also attributable to smallpox. Smallpox was a major cause of death especially in northern English towns in the eighteenth century. 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 (Figure 5). Although inoculation, the forerunner of vaccination, appears to have made little headway in English cities (Davenport et al., 2011, 2015) the advent of vaccination had a profound effect on smallpox mortality, and must have made a major contribution to improving urban mortality rates (Landers, 1997).

1.5 Changes in causes of death

The four changes outlined above in the patterns of mortality in the English population were associated with, and driven in a proximate sense by, changes in the structure of causes of death. Causes of death were not recorded systematically before the introduction of civil registration in 1837, and the only long-run record of causes of death in England is provided by the London Bills of Mortality, which provide a continuous series from 1603-1830, but relate only to the metropolis. Otherwise we are dependent on notes in parish registers, and on occasional runs of cause of death recording that become more frequent in parish registers after c.1780. Plague and smallpox burials were often recorded in burial registers that otherwise contained few other details. Although historical nosologies are very problematic to interpret, smallpox was relatively safe from misdiagnosis because it was both distinctive and well-known. The main diagnostic confusion was with chickenpox, a relatively benign infection that rarely resulted in a burial. Causes of death can sometimes also be inferred, with great caution, from the seasonality and age patterns of burials. Here we focus on the major infectious diseases that are widely considered to have declined in England in the century before 1850.

The most obvious change in the disease environment between the medieval period and the nineteenth century was the disappearance of plague from England after 1666. The arrival of plague in Britain in 1348-9 caused a dramatic fall of perhaps 30 – 50% of the population, and repeated recurrences of plague prevented sustained population recovery for several centuries. The final disappearance of plague after 1666 made a significant contribution to the stabilisation of especially urban mortality in the late seventeenth century (Figure 2).

As plague receded smallpox seems to have become a more significant cause of death (Carmichael & Silverstein, 1987). Smallpox was probably the most lethal single disease of the eighteenth century. We do not have estimates of smallpox mortality for England as a whole, but in Sweden, a much more thinly populated and lightly urbanised society, smallpox accounted for 8-15 % of all deaths nationally in the second half of the eighteenth century (Sköld, 1996). By 1850 smallpox accounted for just over 1 % of deaths in England, a figure that probably reflects the profound effect of vaccination (Figure 5), it is likely that smallpox accounted for a much nmore significant proportion of deaths nationally before 1800, although its impact was geographically very uneven [see section 3.4].

Typhus, a disease associated particularly with social dislocation and with extreme overcrowding and lack of sanitation (hence its synonyms 'famine fever', 'ship fever' and 'gaol fever'), was probably a factor in many of the mortality spikes associated with high food prices and the subsistence migration that often accompanied food shortages (Creighton, 1894; Galloway, 1985). Over the course of the eighteenth century typhus epidemics appear to have been confined increasingly to urban populations (Creighton, 1894; Hardy, 1988), and typhus did not occasion major mortality events nationally after the 1740s. However it remained a common episodic cause of the 'fevers' noted in urban mortality records in the second half of the eighteenth century. There were widespread outbreaks of typhus 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. Hardy argued that typhus was endemic, but rarely epidemic, in cities of Victorian Britain until the late 1860s, but virtually disappeared after that date (Hardy, 1988).

Malaria was a cause of highly localised mortality excess in early modern England. Dobson credited it as the main cause of the very high mortality associated with low-lying mainly coastal areas (the Fens, the Thames and the coastal marshes of southeast England, and to a less extent the Somerset Levels, the Ribble district in Lancashire and Holderness in Yorkshire), where burials routinely exceeded baptisms and net immigration was required to sustain the mainly rural populations (Dobson, 1989). However Dobson argued that malarial mortality declined in

the late eighteenth century, and that gains in life expectancy after 1750 were particularly rapid and impressive in those areas where mortality had been highest as a consequence of malaria (Dobson, 1989; 1997).

By the mid-nineteenth century, when the Registrar-General began reporting annual cause of death statistics, the major infectious causes of death were 'childhood' diseases (especially measles, whooping cough and scarlet fever), diarrhoeal and respiratory diseases (affecting mainly children especially during weaning, and the elderly), and tuberculosis, which killed infants and children and, in respiratory form, young adults (McKeown, 1976; Woods, 2000). Some of these diseases, especially the 'childhood' infectious diseases, had probably increased not only their share of mortality but their absolute rates. Notably absent as major causes were the most feared of eighteenth century epidemic diseases, smallpox and typhus, despite the huge increases in urban populations, population densities and interconnectedness that should, all else equal, have amplified mortality rates and urban epidemics.

There was therefore a progressive shift in epidemiological terms from a regime in which very lethal epidemic diseases such as plague, typhus, malaria and smallpox made a major contribution to mortality rates, to a nineteenth century pattern of infectious disease mortality dominated by endemic childhood and chronic infections (including tuberculosis).

2. The proximate determinants of infectious disease mortality

How are we to explain the profound changes in the pattern of mortality that occurred in the English population between the eighteenth and the nineteenth centuries? Recent explanations fall into three major categories, that focus (sometimes non-exclusively) on (1) nutritional status of the population; (2) the role of autonomous factors such as climate or pathogenic variations; and (3) the role of economic integration in reducing dearth-associated mortality and increasing circulation of infectious diseases. Human agency, in the form of preventative public health measures or medicine, has been invoked to explain the disappearance of plague and the decline of smallpox and, more recently, neonatal mortality, but is not a major explanatory variable.

This paper seeks to apply insights from evolutionary biology to understanding the mortality transition and the role of preventative efforts in the early stages of the mortality transition. As a prelude to discussion of recent theoretical developments in evolutionary biology

we discuss first the proximate determinants of infectious disease mortality, through which any social and biological factors must operate.

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 both the particular pathogens present in the environment, and factors that bring humans and pathogens into contact. The presence of pathogens varies according to geography, chance inter-species transfers, the presence, where necessary of intermediate vectors, and patterns of long-distance human interactions. The risk of exposure to these pathogens depends on human activities, climate and season. For most infectious diseases the size and density of human populations are key in providing opportunities for infection and transmission. 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 (Bartlett, 1960; Cliff et al., 1993). 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 the risk

of exposure. For infants breastfeeding dramatically reduces the risk of exposure to contaminated foods.

Processes that reduced exposure include quarantine and isolation, reductions in numbers of animal vectors, 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. Reductions in over-crowding and in family size have probably played major roles in reducing disease transmission since the 1870s (Reves, 1985). *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'). 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).

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. Age plays a very important role in resistance to many diseases. Infants and young children lack immune experience (although very young infants are often protected by maternal antibodies to specific infections). Infants and young children are also small and have high surface-to-volume ratios, making them more susceptible to dehydration, body temperature extremes and depletion of resources than older larger individuals. Conversely, older adults tend to accumulate conditions (co-morbidities) that increase their risk of complications from infection. 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 these reasons mortality related to diarrhoeal and respiratory infections is concentrated at the extremes of age, in a pattern similar to all-cause mortality.

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 generally 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 adequate nutritional status to survival (Kunitz, 1983; Livi-Baci, 1991).

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.

We next discuss pathogen-specific determinants of the relative efficacy of these difference means of control, from an evolutionary viewpoint.

3. Mortality declines from an evolutionary perspective

Evolutionary biology has long influenced historical interpretations of the epidemiological consequences of population growth, long-distance trade and urbanisation. In particular the very influential work of William McNeill argued that the growth of cities and the integration of large populations through trade and migration resulted in an initial rise in mortality as new diseases were introduced, followed by a gradual process of accommodation between host and pathogen that involved a decline in pathogen virulence. Thus as once rare epidemic diseases became childhood diseases they also became less lethal. In this scenario both the rise and fall of mortality in England c. 1600 – 1820 could be explained as a consequence of an epidemiological integration that resulted in higher exposure to infectious diseases, but also, eventually, reduced the lethality of these diseases (e.g. McNeill 1976; Kunitz 1983; Walter & Schofield, 1989). This assumption was based on then current evolutionary biological models that assumed a necessary evolutionary trade-off between virulence and transmission. However over the last 30 years this evolutionary paradigm has been overturned with the recognition of the complexity of selective forces operating on the determinants of virulence. For diseases that do not depend solely on person-to-person transmission then the barriers to high virulence may be slight. Conversely, and critically for early efforts at disease control, these alternative methods of disease transmission may be relatively easy to disrupt. We demonstrate the application of this theory to historical patterns of infectious disease mortality by comparing those diseases that declined in incidence before 1850 with those that came to dominate in the nineteenth century.

Evolutionary theory predicts that different selective forces operate on within-host and between-host competition between pathogens. Within a host, there is usually selection for rapid multiplication of the pathogen. For a given dose of infection, there may be genetic variation between the individual pathogen units (viral particles, bacterial cells etc). This variation may arise through random mutations occurring after infection, or may derive from variation already present in the infectious dose. Where this variation affects the multiplication rate then those variants that reproduce fastest will come to dominate the intra-host population of the pathogen, and will be more likely than less abundant variants to be transmitted. This selection for rapid multiplication has implications for lethality, because morbidity and lethality (jointly, virulence) are usually directly associated with the number of pathogens. Thus virulence is usually associated with rapidity of pathogen reproduction, 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, and/or disfigure them in ways that warn other hosts to avoid the infectious individual, high virulence should

limit the transmission of the pathogen *between* hosts. Since the survival of any pathogen depends ultimately on the ability to sustain transmission, there is strong selection against virulence in these cases.

A key new insight of the last thirty years, initiated by the biologist Paul Ewald, is that evolutionary selection against virulence depends critically on transmission mode. He argued in a very influential series of papers (Ewald 1983, 1991, 2004, Walther & Ewald, 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).

Table 1 presents a summary of the characteristics of some of the major pathogens responsible for infectious disease mortality in England before 1950, ranked by the date of their initial decline or, for plague, disappearance. There is a clear hierarchy in virulence, from plague through typhus, malaria, smallpox, cholera and typhoid, to the 'childhood' diseases, that corresponds to the progressive decline of mortality from these diseases. Tuberculosis at first glance does not fit neatly within this model, since it is a disease of moderately high lethality that showed no evidence of declines in mortality before the 1870s. However together with sexually transmitted diseases tuberculosis combines person to person transmission with both chronic and latent states that provide relatively long windows of transmission compared with acute infections, and that make interventions to prevent transmission more difficult. Debate over the relative contributions of improving nutrition, isolation of the clinically ill, autonomous change in the pathogen and lower densities within houses remains unresolved.

Importantly, high virulence was generally associated with relative insensitivity to the health status of the host, and so highly lethal diseases affected adults as well as children, and were socially relatively unselective. Diseases that are less virulent tend to be lethal only at the extremes of life, where small size and immunological naiveté or the accumulation of co-morbidities increase vulnerability, or in individuals who are immune-compromised by malnutrition. These differences therefore probably explain some of the curious age pattern of mortality in the English population before 1750, and the apparent absence of strong gradients in mortality before the nineteenth century. We expand these points below through a

consideration of the characteristics of specific diseases, and the factors that were important in their control.

3.1 Plague

The causal agent of medieval and early modern plagues remains debated, despite the recovery of DNA identifiable as the modern plague bacterium, *Yersinia pestis*, from medieval plague burials. In the classic account of plague, the bacterium is transmitted by rat fleas that, having unwittingly caused the deaths of their rat hosts, bite humans. The human victim sickens within a few days, develops fever, severe pain and buboes, and case-fatality rates vary from 20 to 60% (in the absence of antibiotic therapy: Table 1). The plague bacterium is not usually transmitted directly person to person (unless the infection assumes a rare pneumonic form) and so the hideous appearance and supine state of the human host does not necessarily limit transmission of the pathogen. A single infected flea may bite a number of humans and rodent vectors, and infected fleas and rodents can move between non-ambulatory human victims to spread the disease. Moreover *Y. pestis* can also persist outside a flea or mammalian host, and so the death of a host does not necessarily prevent transmission. A number of medieval and early modern outbreaks were blamed on infected cloth or wool and specific quarantine restrictions were often placed on cloth and yarn products (Slack, 1985; Harrison, 2012). While the association of cloth with infection may have overlooked the presence of infected rats or lice in the cargo, there is also evidence for long-term persistence of plague bacteria in soil (e.g. Eisen et al., 2008). The complex transmission pathway of plague, involving non-human vectors and persistence outside a host, means that there has probably been little selection for avirulence with respect to human hosts, because humans are not an important pathway for plague transmission.

Plague epidemics were associated with very high mortality and with little evidence of attenuation with age or nutritional status. Moreover plague did not confer immunity on survivors, thus leaving open the possibility of re-infection. Where estimates of ages of victims in pre-modern plague epidemics can be made, the distribution of deaths tends to resemble the composition of the population, with high mortality amongst adults as well as children. Medieval plagues also show little evidence of social selectivity, and the emergence of variations in mortality by social status probably reflect the evolution of early warning systems such as the London bills of Mortality, and the superior ability of the rich to flee the foci of infection (Cummins et al., 2014; Champion, 1995). Plague appears to have been sufficiently lethal as to over-ride variations in host size, age and nutritional status.

While the causes of the disappearance of plague remain hotly contested, the most plausible account of its disappearance from Britain is that of Paul Slack. Reviewing the evidence from early modern plague outbreaks in England Slack concluded that quarantine efforts, although incomplete and rudimentary by later standards, were sufficient to prevent the introduction of plague from infected ships in most cases The efficacy of quarantine derived not from its thoroughness but from the relative weakness of the chains of transmission of plague from infected ships to the English population. He concluded that attempts to isolate victims by boarding them up in houses were generally ineffective because such measures failed to contain the rat vectors, and probably served mainly to infect the families of those incarcerated with already infected victims. However the isolation of the sick away from residential areas in pest houses, a measure adopted in the 1665/6 epidemic, was probably effective in reducing infection in the early stages of an outbreak (Slack, 1981: 1985).

3.2 Typhus

Classic louse-borne typhus is caused by the bacterium *Rickettsia prowazekii*. The louse is infected by biting an infected human, and then excretes the bacteria in its faeces. These can infect another human if the faeces enter the bloodstream through a wound caused for example by the louse bite itself or by scratching it. Human lice are not very mobile and typhus is usually transmitted between human hosts in conditions of overcrowding. However *R. prowazekii* can also persist in lice faeces for years, especially at low temperatures, and infection from fomites from infected clothing and bedding was probably a secondary mode of transmission. Typhus is an under-studied disease but is considered one of very few diseases that is actually more lethal to adults than children (Zinsser, 1935). It is also unusual among insect vector-borne diseases in being more common in winter months, because of its dependence on close contact for transmission. High mortality of adults relative to children and a winter peak are therefore key markers used to identify the presence of typhus in historical mortality crises. Although associated with famine and forced migration and more generally with urban poverty, typhus has no clear association with nutritional status of victims (Luckin, 1984; Hardy, 1988). Typhus was generally associated with overcrowding and ext poverty or war, but the apparent social gradient in mortality probably reflected higher exposure amongst the poor rather than any protective effect of superior nutritional status amongst the wealthy. Doctors in particular often fell victim during typhus outbreaks in the late eighteenth and early nineteenth centuries, as a consequence of the expansion of infirmaries and hospitals and domicile attendance upon the poor.

Typhus was a much feared disease, particularly in northern towns where it seems to have had the greatest impact, and amongst military personnel. Individuals with 'fever' were excluded from the hospitals established in the eighteenth century for fear of contagion, although it was recognised that patients often developed fever after admission for other reasons. Perceptions of rising fever mortality in rapidly growing northern towns in the late eighteenth century prompted the establishment of fever hospitals designed specifically to isolate typhus and other fever cases amongst the urban poor (Pickstone, 1985). Poor law authorities increasingly took responsibility for removing fever victims to hospital and with burning the clothes and whitewashing the dwellings of fever cases (Pickstone, 1985; Hardy, 1988). Hardy argued that an intensification of these efforts, including the permanent closure of recalcitrant 'fever nests', was finally sufficient to break the cycle of typhus endemicity in London in the 1870s.

Public concern with the prevention of fever transmission was preceded and influenced by developments in military hygiene, that produced impressive falls in military morbidity and mortality from non-combat related infectious disease in the period 1750-1825. Major typhus epidemics in the 1740s and 1750s on British naval ships led to concerted efforts to improve ventilation on ships, and to improve hygiene by washing and delousing recruits (Riley, 1989). The apparent efficacy of these efforts led to their adoption more widely in prisons and on long-distance voyages, wand were associated with significant improvements in survival of prisoners, slaves and recruits (Riley, 1989). It remains unclear to what extent isolation and destruction of clothing helped to reduce the transmission of typhus, and the proliferation of cheap cotton from the late eighteenth century may also have played a key role. Falls in the price of clothing meant that poorer people could afford several sets of clothes, and this allowed more frequent washing of clothes, especially of undergarments where lice were most abundant. The same may have applied to bed linen, another source of both lice and bacteria.

3.3 Malaria

The malarial parasite is carried in the gut of infected mosquitoes that can fly between mammalian hosts, ingesting the pathogen from the host bloodstream and releasing it into the bloodstream of the next host. The parasite persists in the bloodstream of infected human hosts, providing a reservoir for ongoing infection of mosquitoes where the mosquito life cycle is seasonal, such as the marshlands of early modern England. Malaria is caused by four species of the *Plasmodium* genus, and Dobson concluded that the endemic form in England was probably *P. vivax*, spread by the mosquito *Anopheles atroparvus* a species tolerant of the brackish waters

of most English coastal marshlands. *P. vivax* is considered less virulent than *P. falciparum,* the primary agent of malarial mortaltiy in Africa, but is nonetheless associated with a very significant burden of morbidity and mortality in Asia (Baird, 2013).

P. falciparum-induced malaria is very lethal to infants but induces transient immunity and so is less lethal in older children and adults where exposure is sufficiently high. However where malarial infection is episodic rather than persistent (as in areas with high in-migration from non-malarial areas) then malaria may be more severe in adults than children (Olliaro et al., 2008). *P. falciparum* is better studied than *P. vivax* and the extent to which these patterns are true of the form that may have been endemic in England remains unclear.

The relationship between malaria and nutritional status is complex, and poorly understood. Severe bouts of malaria cause weight loss, and may drive associations between stunting and malaria. Additionally, the malarial parasite requires iron and other micronutrients for optimal growth and therefore deficiencies in these nutrients can provide protection against clinical infection.

While the rapid decline of malarial mortality in the late eighteenth and early nineteenth centuries is not debated, the causes of this decline remain unclear. Dobson attributed the decline to a confluence of factors that included increased use of quinine, declines in mosquito populations caused by large-scale drainage programmes, and a shift in the relative availability of human and cattle hosts for the mosquito and its parasite that shifted the burden of infection onto cattle. Dobson was hesitant to attribute the decline specifically to drainage, because mosquitoes remain abundant in England today. Nonetheless the areas affected by 'ague' were subject to extensive drainage programmes in the eighteenth and nineteenth centuries, and much of the land thus drained was used for more intensive grazing than had been possible on the wetlands. Thus drainage may both have reduced mosquito numbers (by reducing habitat extent) and reduced the dependence of mosquitoes on humans for food (Riley, 1989). A recent study of the final phase of malarial decline in England, 1840 – 1910, concluded that both drainage and increasing cattle densities made major contributions to malarial mortality decline in this period (Kuhn et al., 2003). In any case the dependence of the malarial parasite on its mosquito vector meant that factors affecting the abundance or diet of the mosquito were sufficient to reduce transmission to humans.

3.4 Smallpox and measles

The 'sit and wait' character of smallpox probably explains much of its historical impact. Although it is often described in popular accounts as extremely infectious, in fact smallpox was not very infectious compared with most common childhood diseases (Table 1). Comparison with measles provides a great deal of insight into the particular lethality of smallpox in historical populations. Smallpox and measles are similar in many ways. Both are relatively stable viruses with have similar incubation (or latent) periods of 10-12 days, and both confer lifelong immunity. Both viruses are transmitted primarily by airborne droplets, but smallpox can persist in dried droplets or scabs for years, whereas the measles virus breaks down very rapidly outside a human host and therefore requires rapid very rapid host-to-host transmission. Additionally, estimates of the infectiousness of smallpox are much lower than for measles (Table 1).

Smallpox was also much more lethal than measles, with case-fatality rates of between 10 and 30 per cent for the Variola major strain that probably circulated in Europe until the early twentieth century. Measles by contrast is associated with case-fatality rates of less than 5 % in historical populations. Measles is lethal mainly to very young children, although in conditions of overcrowding or social collapse then adult mortality may be significant.

The high infectiousness of measles, the lifelong immunity it confers and and the inability of the virus to persist outside a host, means that measles cannot persist in circulation in small populations. Rather it produces very rapid epidemics that infect almost all susceptible individuals, and then burn out for lack of further susceptible individuals. Bartlett estimated that a population of at least a quarter of a million was required to provide a sufficient supply of susceptible individuals (through births) to maintain measles circulating in the population without requiring introduction (Bartlett, 1960). However Black, restricting his study to island populations, argued that a population of around half a million was required to give an even chance of persistence in the absence of regular reintroduction from other populations (Black, 1966). This dependence on continuous transmission and large populations raises interesting questions about the history of measles before the rise of large cities.

London was the only English city with the potential to sustain measles in endemic form before the nineteenth century (Cliff et al., 1993). Weekly counts of burials attributed to measles suggest that measles was present in a majority of weeks each year by the late seventeenth century, and erupted in regular three yearly epidemics (Figure 6). London had a population of perhaps 350,000 by 1650, and had grown to 959,000 by 1801. By the 1840s its population had

reached 2.36 million and measles deaths occurred every week, with an epidemic cycle of approximately 96 weeks, consistent with the increase over the period 1660 to 1900 in the size and replenishment rate of susceptible children (Brownlee, 1918). Outside London no urban centres were large enough to sustain measles without regular reintroduction, and measles appears to have remained a regular but not endemic disease before the nineteenth century. However as other large cities and conurbations developed in the course of the nineteenth century then measles epidemics increased in frequency nationally. Its' higher case-fatality rates amongst young children meant that as the disease circulated more frequently and the average age at infection fell then measles mortality increased, and was highest in large cities and high population densities (Woods, 2000).

Smallpox on the other hand appears to have faced fewer natural barriers to establishment in small historical populations than measles. It was a very regular cause of death in both London and Manchester in the mid-eighteenth century, with roughly biannual epidemics in both places despite the huge difference in size (Manchester had a population of around 20,000 in 1750). Smallpox mortality rates were similar in both centres (Davenport et al., 2015). More surprisingly, smallpox appears to have circulated relatively freely through communities in the north of England and in mainland Scotland, and was a major cause even in small towns (Figure 3). The relatively low infectiousness of smallpox meant that it did not infect all susceptible individuals during an epidemic, and its ability to persist apparently made it possible for the disease to meander through areas of low density and dispersed settlement, such as was typical of much of northern Britain and Sweden (Brunton, 1990; Razzell, 2003; Sköld, 1996).

The relatively low infectiousness of smallpox may however also have made it relatively easy to control the disease. Smallpox required 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), together with isolation of sufferers and contact tracing (Fenner et al., 1988). Smallpox is the only human disease to have been successfully eradicated, and attempts to eliminate measles continue to founder on the requirement for extremely high rates of compliance with immunisation programmes. In the case of smallpox even very partial vaccination schemes were sufficient to cause a substantial lengthening of smallpox epidemic cycles and a dramatic reduction in mortality from the disease (Krylova, 2011).

Surprisingly, even before the advent of vaccination it appears that towns and villages in southern Britain were able to avoid smallpox for very long periods. Figure 7 maps the

distribution of smallpox burials identified so far in eighteenth century burial registers, by the proportion of smallpox burials that were adult. The pattern is very striking. Adults comprised less than 5 % of smallpox victims in northern settlements, but at least 10 % of victims in the south. The presence of adult victims is an indicator of the frequency of smallpox epidemics in these settlements, or in the places where migrants to these places originated. In London 20 % of smallpox victims were adult in the mid-eighteenth century, and these were mostly migrants who had grown up in areas where smallpox was a rare disease before migrating to London (Davenport et al., 2011). In Manchester by contrast less than 5 % of smallpox victims were adults, and this fell to 1 % after c. 1770 (Davenport et al., 2015). This difference in the susceptibility of adults probably reflects the migration fields of the two cities, with London drawing most of its migrants from southern counties where smallpox was rare and epidemic, and Manchester drawing migrants from areas where smallpox was already endemic.

The curious pattern of smallpox mortality evident in Figure 7 suggests that in southern England many villages and even towns were able to avoid smallpox epidemics for long period, a phenomenon borne out by anecdotal accounts (Razzell, 2003). This is surprising given the generally higher population densities and more integrated market economy of this region. These areas were also keenest in the adoption of inoculation, the forerunner of vaccination. Inoculation was more dangerous than vaccination because it involved infection with a low dose of smallpox virus. This raised the risk both to the individual being inoculated, and to the community if the inoculation itself triggered an outbreak. Some communities banned the practice of inoculation for this reason. However many communities undertook 'General inoculations' that involved inoculation of all those who had already had smallpox, including the poor who were inoculated at parish expense (Smith, 1987; Razzell, 2003). This expedient was usually adopted when smallpox threatened, and was probably very effective at reducing smallpox mortality and the frequency of epidemics in areas where inoculation was popular. There is however no evidence that inoculation was practiced to any extent in northern England, consistent with the high mortality from smallpox evident in those northern settlements for which we have data. The avoidance of smallpox by many southern villages and towns is testament both to the vigilance of parochial officials in responding to the threat of approaching smallpox epidemics, and to the relatively low infectiousness of smallpox. Paradoxically this property of smallpox allowed it to persist at low population densities where measles could not, but also made it relatively easy to avoid or control by partial and rudimentary means.

Conclusion

While a positive association between income and life expectancy is virtually ubiquitous in modern populations, the evidence for this association in historical populations is ambiguous, particularly before the nineteenth century. Stephen Kunitz argued that poverty only emerged as major determinant of mortality levels once crisis mortality occasioned by plague and typhus was controlled by human intervention and epidemic diseases such as smallpox and measles were reduced to disease of childhood in the course of the economic and political integration that occurred over the eighteenth century in Europe (Kunitz, 1983). This paper examined these shifts in the major infectious causes of death over the period 1600 – 1850 in England from an evolutionary point of view. For diseases that are transmitted person-to-person, confer immunity and cannot persist outside a host then there is evidence of strong selective pressure against high host lethality (measles is the classic example). These diseases are most lethal in individuals whose immunity is low (young children, the ill and the malnourished). However for pathogens which don't depend on their human host for transmission and/or can persist outside a human host then there is less selection for low virulence. This category includes some of the most destructive epidemic diseases in early modern England (plague, typhus, smallpox and malaria). In these cases case-fatality rates appear to have been high even in relatively well-nourished and robust adults, and therefore these diseases were relatively non-selective with respect to poverty, except where wealth facilitated avoidance of infection (for example by fleeing plague or paying for smallpox inoculation). Here we argue that not only were these socially non-selective diseases particularly lethal, but the characteristics that made them so lethal also made it easier for relatively weak interventions to break the chain of disease transmission. Therefore the most deadly epidemic diseases were also those most easily controlled by preventative actions, including quarantine, isolation and immunisation. The early control of these major diseases was associated with large reductions in mortality, but also shifted the distribution of causes of death towards the less virulent diseases of the extremes of age and of poverty (diarrhoeal diseases, measles and other childhood infections, certain respiratory diseases and tuberculosis). This shift was amplified by the increases in population size, densities and connectedness associated with urbanisation and industrialisation, that favoured transmission of highly infectious person-to-person diseases of moderate lethality, such as measles.

It was no accident that the most lethal diseases of early modern England were also 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, and by inoculation and vaccination against smallpox. These measures were all

preventative, and acted to reduce exposure to disease. Reductions in the most lethal diseases would have reduced the volatility of mortality (together with reductions in the dearth-related events that triggered these epidemic episodes), and shifted the age pattern of mortality to the extremes of life, as well as reduced the lethality of cities and increased the advantages of wealth and superior nutritional status. This is not to claim that the control of these very lethal diseases, deliberate or otherwise, was the sole factor in producing these changes in mortality patterns. Rather the aim is to explore the potential disease specificity of the mechanisms proposed to underlie some of the major explanations of mortality decline, especially those based on the endemicisation of epidemic diseases or improvements in nutritional status. In particular, while increasing epidemiological integration of the English population was probably a major force driving mortality patterns, it can account better for *rises* in mortality in the seventeenth and eighteenth centuries, and of especially childhood infections in the nineteenth, than for observed declines in overall mortality, especially in urban areas, after 1750. The assumption that endemicisation of diseases should necessarily have produced in the long run a more benign mortality regime via the attenuation of virulence (McNeill, 1977; Kunitz, 1983) is inconsistent with the sustained lethality of some of the most important pathogens of the eighteenth century. Similarly, explanations that attribute the lion's share changes in mortality to changes in mean nutritional status of the population against an unchanging disease environment or 'mortality risk surface' (Floud et al., 2011) ignore the dramatic changes in the disease environment occasioned by the control of smallpox, which owed nothing to improvements in host resistance.

Life expectancy stagnated between c.1820 and 1870 in England, and the mortality decline that ensued after 1870 required more heroic additional means of disease control, including improvements in sanitation and housing that reduced exposure, and rises in host nutritional status, that increased host resistance. These factors were sufficient to drive enormous falls in infectious disease mortality before the advent of modern antimicrobial treatments, and they remain key to preventative efforts to control infectious diseases now. However some of the diseases that cause most concern with respect to the potential failure of antimicrobial agents, including MRSA, are characterised by high lethality but low person-to-person transmission (Walther & Ewald, 2004). The efficacy of relatively limited historical measures that disrupted disease transmission serve as a reminder of the continued importance of basic hygiene and of surveillance, isolation and contact tracing techniques that first developed during the plague era.

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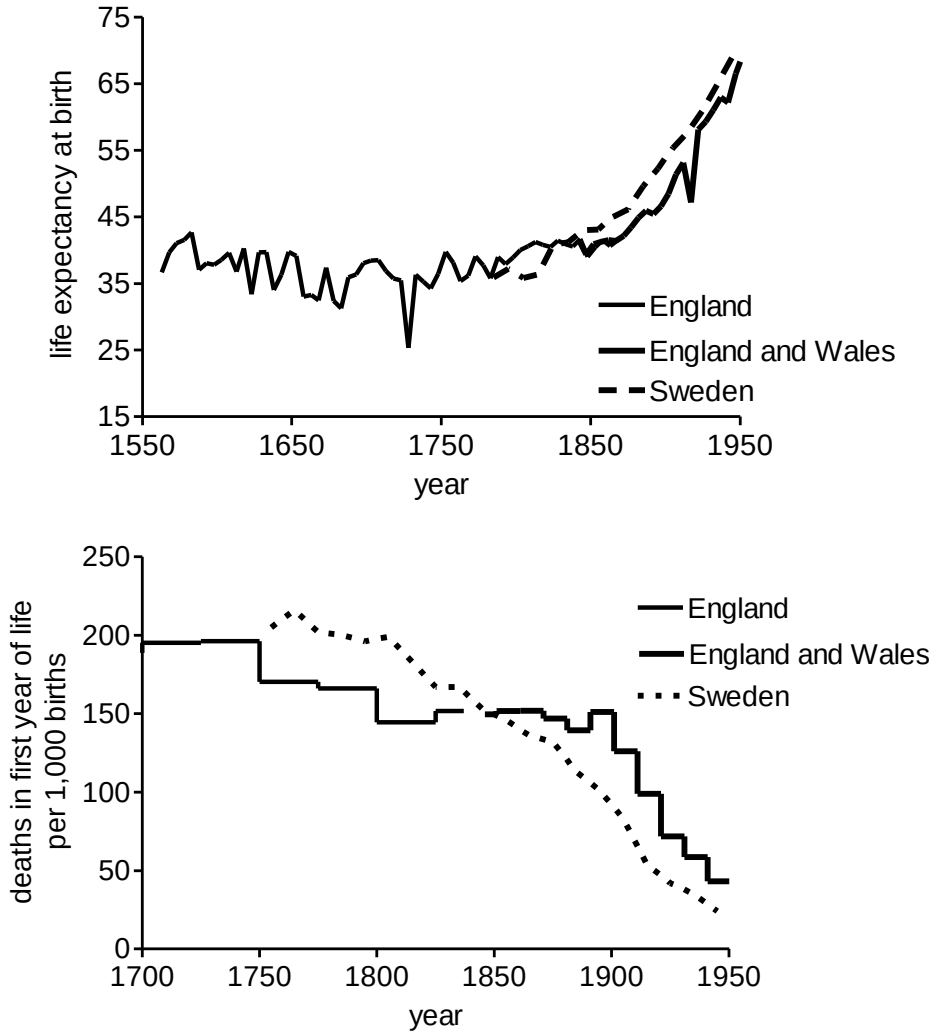

Figure 1. Life expectancy at birth (upper panel) and infant mortality (deaths in the first year of life per 1,000 births: lower panel) in England (England and Wales after 1837) and Sweden.

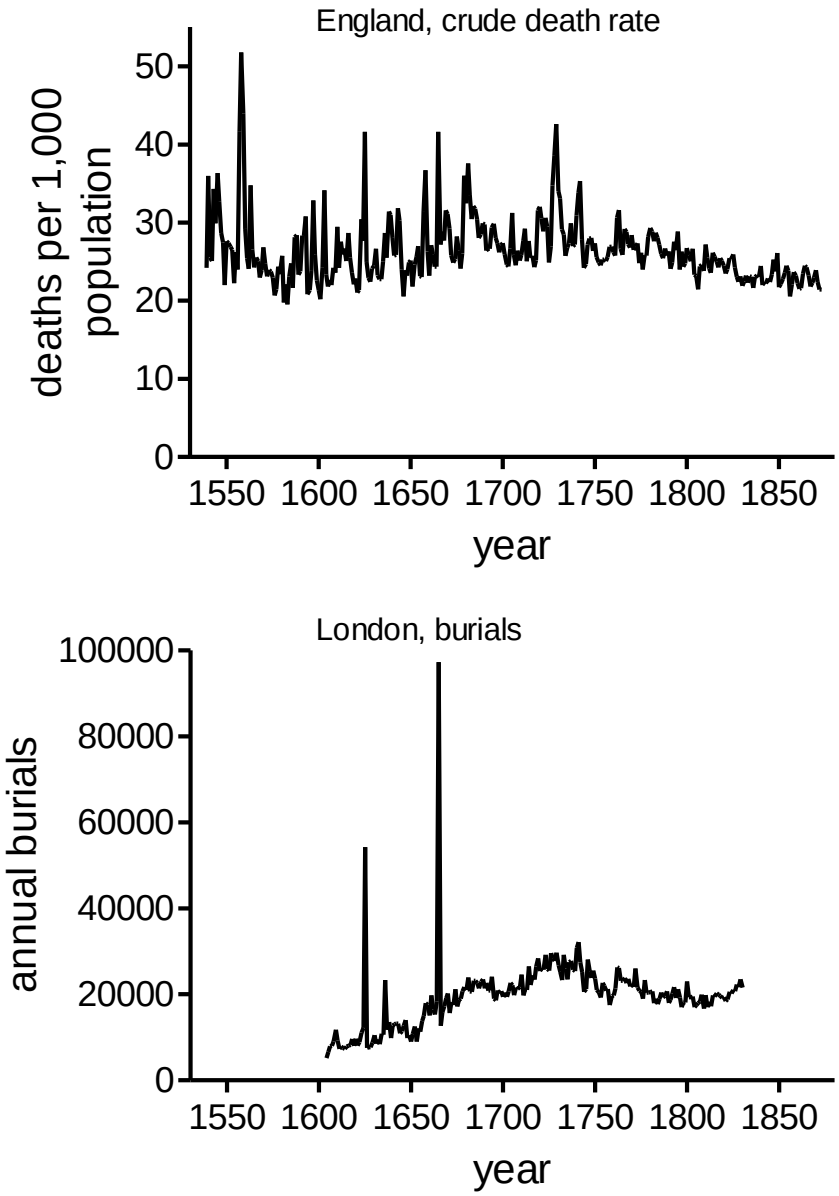

Figure 2. Annual crude death rate for England (upper panel) and annual burial counts for London (area covered by the London Bills: lower panel).

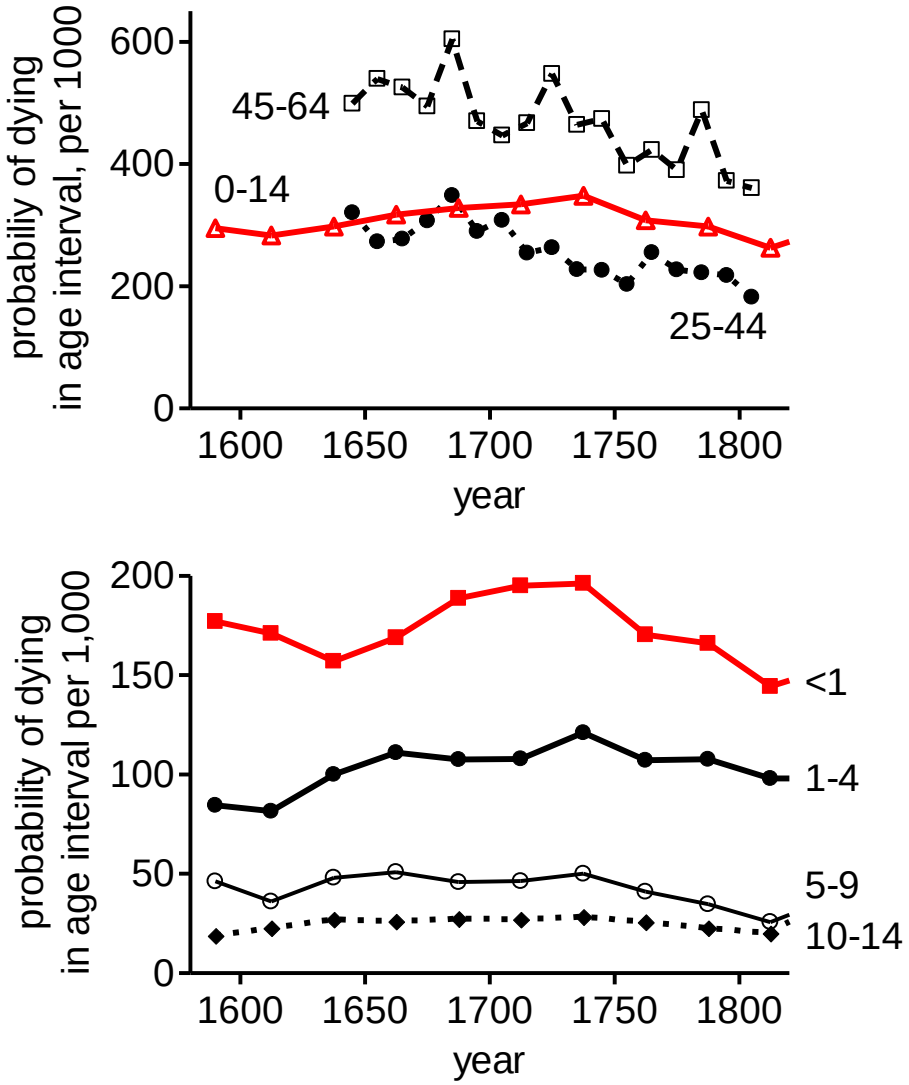

Figure 3. Age-specific probabilities of dying, England.

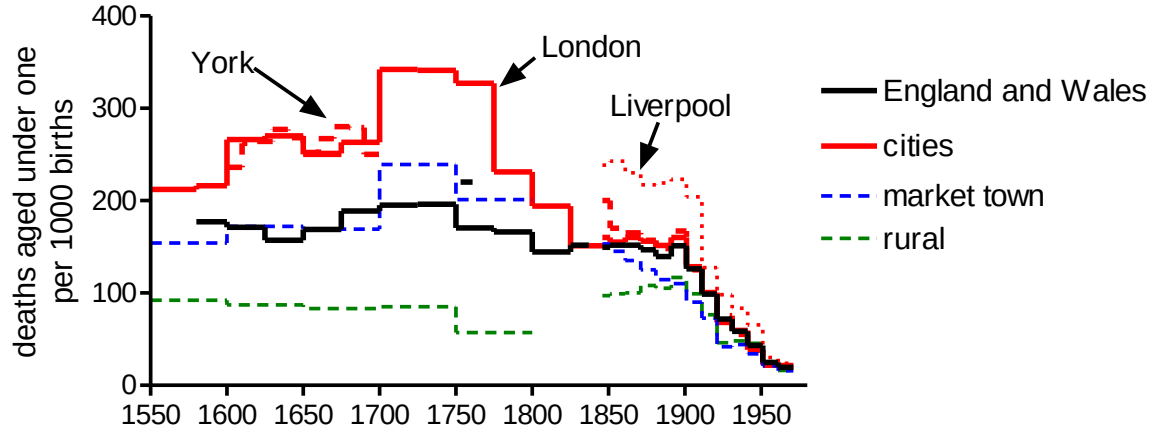

Figure 4. Infant mortality in urban and rural settlements, England.

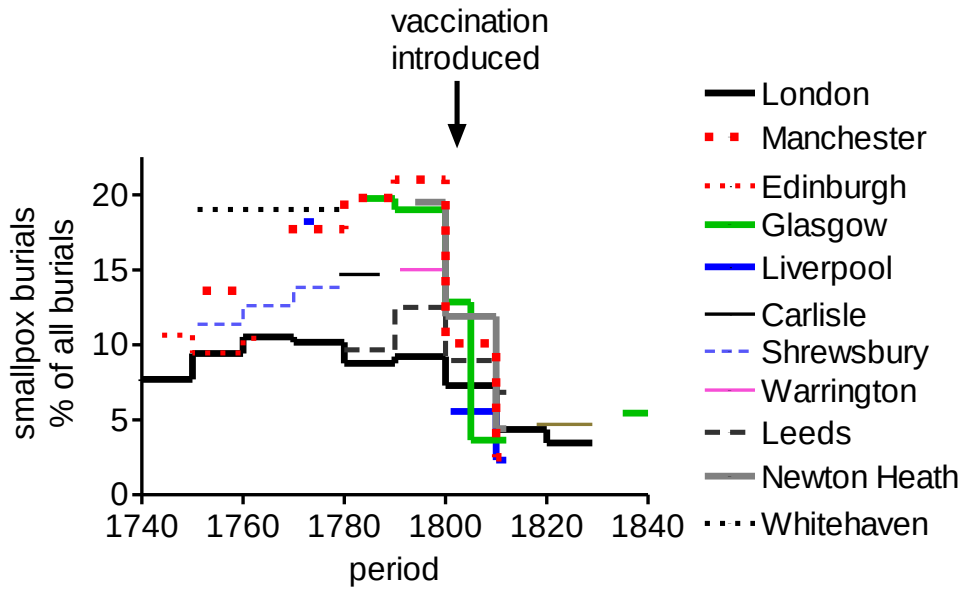

Figure 5. Smallpox in British towns and cities, 1740-1840.

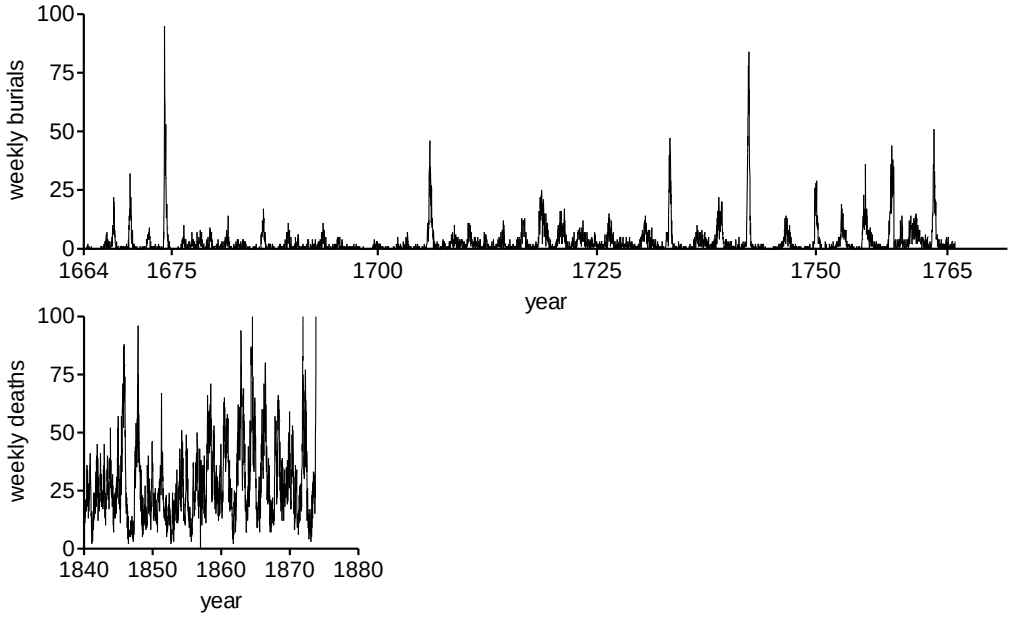

Figure 6. Weekly measles burials in London, 1664 – 1765 and 1840-1873.

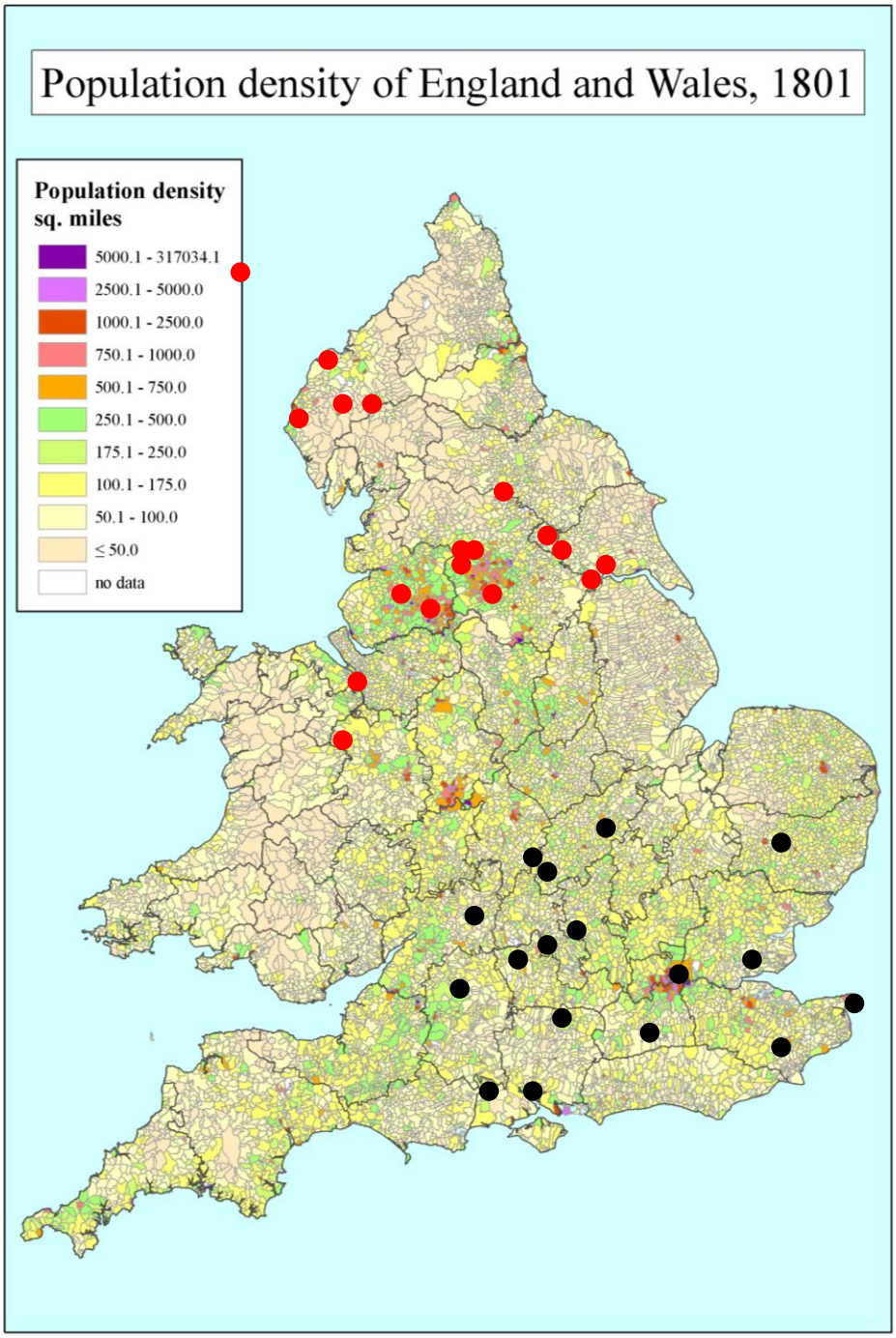

Figure 7. Smallpox burials in eighteenth century Britain by place and percentage adult. Black dots represent settlements where adults (aged ten years and over) comprised 10 % or more of smallpox burials; red dots indicate settlements where adults comprised less than 5 % of burials.

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Table 1. 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[2]	case-fatality	prevention	date	treatment	date
<u>Diseases reduced or eliminated before 1750</u>									
bubonic plague	*Yersinia pestis*	gram-negative bacter-ium	flea bite	1.1-1.2 [3]	20 - 60%	quarantine, isolation	1666, England	antibiotics	1946 (streptomycin)
<u>Diseases reduced 1750 - 1870</u>									
typhus	*Rickettsia prowazekii*	gram-negative bacter-ium	louse faeces in open wound	low	20 % [4]	quarantine, isolation, hygiene, DDT to kill lice. Vaccine	C18th reductions 1943 1943 (not currently in production)	antibiotics	1948 (chloramphenicol)
smallpox	variola major	virus (DNA)	airborne, exudate	3.5 – 6 [5]	10-20% [6]	quarantine, isolation Inoculation	C18th C18th	none	

[2] 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).
[3] Nishiura et al., 2012
[4] Ewald, 1983
[5] Gani & Leach, 2001
[6] Fenner et al., 1988; Walther & Ewald, 2004

						vaccination	1798		
cholera	*Vibrio cholerae*	gram-negative bacter-ium	mainly water-borne (faecal contamination)	1.1 - 2.6 (Haiti outbreak, 2010)[7]	15.7 [8]	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 [9]	5-8 - 9.7[38]	water purification, isolation of cases. Vaccine	reduced in importance over the course of the C19th in England. 1897[10]	antibiotics, oral rehydration	1948 (chloramphenicol); 1968 (ORT)
malaria	four *Plasmodium* strains	protozoa n	mosquito bite	estimate s very variable	1- 30% in epidemic s [11]	reduction in mosquito host populations (drainage, DDT) and prevention of bites	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

[7] Mukandvir et al., 2013
[8] Ewald, 1991
[9] Pitzer et al., 2014
[10] 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.
[11] Carter & Mendis, 2002

						(bednets, insecticide)			
<u>Diseases reduced 1870-1940</u>									
tuberculosis	*Mycobacterium tuberculosis*	gram-positive bacter-ium	airborne, exudate	1.0 < R0 < 8.9 [12]	5 % [13]	BCG vaccination	1921 (routine use in England 1953)	antibiotics	1946 (streptomycin)
measles	Rubeola	virus (RNA)	airborne	5 – 18 [14]	0.007 % [44]	vaccination	1963	none	
scarlet fever	*Streptococcus pyogenes*	gram-positive bacter-ium	airborne	6 - 8 [13] (C20th)	2 - 6 % in late C19th[15]		apparent decline in virulence 1870+	antibiotics	1942 (penicillin)
whooping cough	*Bordetella pertussis*	gram-negative bacter-ium	airborne	7 - 18 [45]	0.1 % [44]	vaccine	1947	antibiotics	1946 (streptomycin)

[12] Sanchez & Blower, 1997
[13] Walther & Ewald, 2004
[14] Anderson & May, 1991: 70
[15] Lancaster, 1991: 114

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)	
Diseases reduced or eliminated after 1940									
poliomyelitis	poliovirus	virus (RNA)	mainly water-borne (faecal contamination)	5 - 7 [45]	0.15 % [16]	vaccination	1954, 1957	none	
Pneumonia	Streptococcus pneumoniae	gram-positive bacterium	airborne and exudate		0.036 %[44]	vaccination	1975	Sulphonamide, penicillin	1937, 1944
chickenpox	Varicella zoster	gram-negative bacterium	airborne	7 - 12 [45]	0.003%[7]	vaccine	1975	none	
MRSA	*Staphylococcus aureus*	gram-positive bacterium	person to person, exudate	low [17]	15 - 60% [18]	hygiene	Reductions in hospital-acquired infections from 1880s due to aseptic and antiseptic surgical	antibiotics	sulfa drugs (1930s) penicillin (1942). Rapid evolution of resistance

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

		techniques and improvements in wound treatment