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THE WELFARE COST OF ANTIMICROBIAL RESISTANCE – TUBERCULOSIS AS AN ILLUSTRATIVE EXAMPLE

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ABSTRACT

The recent increase in antimicrobial resistance has received concern from the government and media. The twentieth century history of tuberculosis in England and Wales presented here shows that some of the more extreme apocalyptic scenarios are unlikely. The paper shows that preventive medicine can play a major role; that the threat should reduce the use of antimicrobials; and the scope for government to intervene with sound public health policies. The paper also estimates the value of twentieth century health gains associated with eliminating tuberculosis in England and Wales to be worth at least $127 billion, which provides a warning about the potential gains that could be lost without initiatives to prevent antimicrobial resistance.

KEY WORDS

Antimicrobial resistance, tuberculosis, twentieth century, England and Wales, mortality, morbidity

JEL CLASSIFICATION

I11, I18, J17

The welfare cost of antimicrobial resistance – tuberculosis as an illustrative example

CONTEXT

The development of resistance by organisms to antimicrobials is a natural phenomenon. In fact, there is evidence of resistance to most antimicrobials within years of their discovery. The problem in the twenty-first century is that this resistance is coinciding with the reduction in new therapies to replace ineffective ones. Antimicrobials are used widely across the healthcare service: from treating specific infections to surgery, radiotherapy, and chemotherapy. As a result some maintain that many modern advances in medicine could be lost if antimicrobial resistance continues to increase.

Antimicrobials were mainly responsible for the big reductions in deaths and illness caused by infectious diseases in high-income economies from the 1940s. Today infectious diseases remain a major policy concern as a result of evidence about increasing antimicrobial resistance. That is the ability of microorganisms to mutate and resist antimicrobials. The World Health Organisation claims: 'resistance to common bacteria has reached alarming levels in many parts of the world and … in some settings, few, if any, of the available treatments options remain effective for common infections' (WHO 2014). David Cameron has warned that antimicrobial resistance could 'cast the world back into the dark ages of medicine'.[1] A worst case, apocalyptic, scenario put forward by Smith & Coast (2012) postulates a situation of most, if not all, antimicrobials becoming ineffective and the resultant loss of many advances in medical care that antimicrobials have enabled: the list is vast and ranges from advances in surgical procedure to cancer chemotherapy in addition to the more obvious infectious diseases.

Although current levels of antimicrobial resistance are small, and as a result the economic or welfare loss is minor, much of the concern pertains to future predictions and the greater scope for managing antimicrobial resistance now. Antimicrobial resistance is analogous to global warming in the sense that there is widespread agreement about the potentially disastrous consequences of both, but because those consequences are not immediate, little is done about them. With this in mind, a better historical appreciation of what health gains are now in danger of being lost and what alternative solutions could be resurrected is needed. Although antimicrobial resistance is extremely unlikely to undo all the gains achieved in eradicating and reducing the prevalence of infectious disease in the developed world, 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 paper focuses on tuberculosis, which represents one of the most prominent diseases in the developed world during the first half of the twentieth century, and continues to represent a key source of mortality and morbidity in the developing world today.

The historical account of tuberculosis presented here generates more sanguine conclusions about future health associated with antimicrobial resistance. Although the timing and magnitude of resistance is difficult to predict, by using historical evidence associated with tuberculosis, it is possible to highlight that there are numerous coping strategies. In fact, in developed economies significant falls in mortality from tuberculosis had already occurred before antibiotics were invented. Numerous other factors—public health measures, personal hygiene, better nutrition, and later

[1] 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.

vaccination programmes—were responsible for these earlier declines. Hence, much of the decline in tuberculosis occurred before the introduction of efficacious therapy (streptomycin) in the middle of the twentieth century. These developments are explained and evaluated in the following sections.

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'[2] or an 'anti longevity force'[3]. When tuberculosis was not resolved in death survivors were often 'stigmatised and ostracised for the rest of their lives'[3]. By the close of the twentieth century England and Wales tuberculosis sufferers' lives 'were altered very little'[4].

In the twenty-first century some of these gains appear to be in jeopardy with the emergence of multi-drug resistant tuberculosis. The incidence and spread of multi-drug resistant tuberculosis is of concern to both the developed and developing world[4]. The predictions for the future situation with tuberculosis drug resistance and, more generally, antimicrobial resistance vary widely. In order to contemplate the potential future burden of tuberculosis antimicrobial resistance 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 antimicrobial resistant tuberculosis in the twenty-first century and implications for the future. Hence, the results below provide a broad illustrative range of estimates about the possible future economic burden of antimicrobial resistance regarding tuberculosis.

TUBERCULOSIS IN TWENTIETH CENTURY ENGLAND AND WALES

Medical therapy represents the most important driver of improved quality of life associated with tuberculosis after 1950. Iseman (1994) heralded that 'one of the most important achievements of modern medicine has been the development of therapy for tuberculosis'[5]. By 1947 streptomycin was being distributed in small quantities in the UK. Moreover, within a few years of the streptomycin revolution, the impetus for further developments in the treatment of tuberculosis had yielded positive results. Para-amino-salicylic acid (1948) and Isoniazid (1952) provided the necessary partners to streptomycin, such that when patients were treated with therapy combining all three antibiotics, not only were they cured of the disease but there was no (initial) emergence of resistance. The National Health Service provided access to therapy to all tuberculosis sufferers. Bryder (1988) claims that 'this success can be measured in the surplus of hospital beds that was evident by 1955 and the closure of many former tuberculosis treatment centres, and although drug treatment still required hospitalisation the treatment time had been significantly reduced'[3].

Other important medical advances associated with tuberculosis are prevention (BCG) and screening (radiography). BCG (Bacille Calmette and Guerin) was not administered widely in England until the

[2] Macnalty A. A Report on Tuberculosis, Including an Examination of the Results of Sanatorium Treatment. In: Health Mo, editor. London: HMSO; 1932

[3] Dublin L, Whitney, J. On the costs of tuberculosis. Quarterly Publications of the American Statistical Association. 1920; 17(132):441-50.

[4] WHO. Anti-tuberculosis Drug Resistance Surveillance Geneva. 2000.

[5] Iseman M. Evolution of Drug Resistant Tuberculosis: A Tale of Two Species. Proceedings of The National Academy of Science. 1994;91:2428-9.

1950s, arguably because of scepticism among British physicians about its efficacy[6]. However, by the 1970s the BCG was providing a protection level of about 75 percent[7].

A final area of improved medical technology was radiography. Mass Miniature Radiography was introduced in 1943, under the recommendations of the Medical Research Council. The contribution of mass miniature radiography was in the examination of large groups of apparently healthy individuals. During the 1940s an active case rate of 1 per 1,000 was discovered among those previously unsuspected of having tuberculosis[8].

TUBERCULOSIS EPIDEMIOLOGY

The epidemiology of tuberculosis is influenced by two important factors: exposure and susceptibility. Exposure is a result of M. tuberculosis being transmitted between an infectious patient and susceptible contacts via droplet nuclei that are expelled by coughing, sneezing and other forceful respiratory activities[9]. In order to develop the disease a victim must have contact with a source case.

The probability of transmitting tuberculosis depends upon: the infectiousness of the carrier (quantity expelled), environment of exposure, duration of exposure, virulence of the organism, and susceptibility of the contact. The chain of transmission can be stopped by isolating patients with the active disease (pre 1950 this was the common solution) and starting effective anti-tuberculosis therapy (which became increasingly effective and commonplace from the 1950s).

The outcome of exposure is dependent upon individual susceptibility to disease. A number of conditions are associated with altered host immunity and increase the risk of developing tuberculosis, e.g. HIV infection, extremes of age, immunosuppressive therapy, cancer, end stage renal disease, diabetes, severe malnutrition and some upper gastrointestinal surgeries[10]. In addition, injection drug use is associated with an increased risk of developing tuberculosis (for reasons that are not well described). Close contacts (i.e. persons with prolonged, frequent or intense contact) are at highest risk of becoming infected.

During the twentieth century this infection rate (i.e. the chance of an individual being infected after close contact with a contagious tuberculosis agent) fell to about 22 percent from a level much closer to 100, largely as a result of improvements in standards of living.

METHODS FOR ESTIMATING THE VALUE OF C20 TUBERCULOSIS IMPROVEMENTS

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

[6] Citron K, Raynes, R., Berrie, J. Tuberculosis today. In: Security DoHaS, editor. London: HMSO; 1981.
[7] Bannon M. BCG and Tuberculosis. Archives of Disease in Childhood. 1999;80:80-3.
[8] Bryder L. Below the magic mountain: A social history of tuberculosis in twentieth century Britain. Oxford: Clarendon Press; 1988.
[9] Johns Hopkins Centre for Tuberculosis Research (2005). Retrieved 24 February 2005, from: http://www.hopkins-id.edu/diseases/tb/tb_class.html
[10] Ibid

quality of life aspects and evaluating these based on available evidence[11]. The introduction of efficacious therapy changed the epidemiology of tuberculosis and the most important quality of life variables: before 1950 government and charities had the most influential role and after 1950 medical developments were of primary importance. This transformation and numerous other more nuanced changes in the morbidity burden of tuberculosis are captured by the key quality of life aspects that contribute to generating the overall QALY. The results about the QALY weights for tuberculosis in 1900, 1950 and 2000 are presented in Table 1.

[Table 1]

Table 1 indicates that in 1900 the collection of health and welfare standards of living meant that the typical tuberculosis sufferer only enjoyed about 30 percent of a healthy life year. Government legislation only aimed to control the spread of tuberculosis instead of providing any welfare or medical support. There was no cure for tuberculosis and treatment was protracted. As a result tuberculosis sufferers experienced a very limited ability to lead a normal life. The only reduction on the morbidity burden was generated by charities, for example, they funded the majority of sanatoria treatment[12]. By the year 2000 the quality of life associated with tuberculosis morbidity to increase to a level that represents about 80 percent of a full healthy life year. This boost was largely facilitated by the availability of a cure for tuberculosis around the middle of the twentieth century. The government contributed to improved quality of life through provision of treatment for the population under the National Health Service Act of 1948. As a result of the discovery and availability of a cure for tuberculosis the ability to lead a normal life improved markedly, for example, as a result of much shorter treatment durations and a prognosis that usually pertained to morbidity rather than mortality.

The QALY results presented in Table 1 provide the summary quantitative index about the burden of tuberculosis morbidity. This can be combined with data about the prevalence of tuberculosis in order to generate a quantitative morbidity measure. This morbidity measure can be combined with mortality data in order to provide a more accurate health measure for tuberculosis. Once this methodology has been applied to England and Wales in 1900 and 2000 it is possible to calculate the number of life years that have been gained as a result of the decline in tuberculosis mortality and morbidity.

There are some weaknesses associated with the methodology. The primary drawback is that the results can only ever be approximates. Additional shortcomings are associated with the QALY: deriving the QALY is an intricate and lengthy process, which yields a result that is open to criticism. Another weakness is generated by the contentions associated with the 'Value of a Statistical Life' (VSL) function, which is unavoidable. However, these weaknesses do not invalidate the results, which provide novel estimates about the magnitude of the value of virtually eliminating one of the most prominent diseases of the twentieth century in England and Wales.

[11] 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 K. The Contribution of Improved Health to Standards of Living Growth in Twentieth Century England and Wales. London: London School of Economics and Political Science; 2006.

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

RESULTS ABOUT THE VALUE OF TUBERCULOSIS ELIMINATION IN C20 ENGLAND AND WALES

Table 2 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, when the tuberculosis death rate per 10,000 population was less than 0.1, tuberculosis mortality had been virtually eliminated. In comparison to all mortality causes in twentieth century England and Wales, tuberculosis accounted for 11 percent of all deaths in 1901 and 0.07 percent in 2000[13].

[Table 2]

Tuberculosis prevalence – as defined by notifications to the medical officer – also experienced a significant decline over the twentieth century. However, this data needs to be analysed with much caution due to the strong prospect of under and uneven reporting. Although this distortion is more pronounced in earlier years it should be regarded as applicable to the entire twentieth century, because despite repeated efforts to improve reporting, there were still likely to be many undetected and unreported cases. Although problematic, notifications under reporting are not thought to be significant enough to distort the overall trend of decline over twentieth century England and Wales, which is reported in Table 3.

[Table 3]

Table 3 shows the decline in tuberculosis morbidity during the twentieth century followed by a slight increase between 2000 and 2012. The tuberculosis notification rate, or morbidity 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 the tuberculosis notification 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[14]. 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 sufferers[15,16]. This also explains the increase during the twenty-first century.

The above analysis has highlighted the extensiveness of the mortality and morbidity decline of tuberculosis, in terms of the fall in the death rate (Table 2) and the notification rate (Table 3) and the gains associated with quality of life (QALY) when suffering from tuberculosis (Table 1). These developments can be better highlighted through considering the aggregate number of additional life years that have been generated as a result of the falling tuberculosis death and notification rate, and the improved quality of life (QALY) associated with tuberculosis as the twentieth century unfolded. Table 4 presents this calculation.

[13] 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.
[14] Bryder L. Below the magic mountain: A social history of tuberculosis in twentieth century Britain. Oxford: Clarendon Press; 1988.
[15] Joint Tuberculosis Committee of the British Thoracic Society. Control and Prevention of Tuberculosis in the UK: Code of Practice 2000. Thorax. 2000:887-901.
[16] Bannon M. BCG and Tuberculosis. Archives of Disease in Childhood. 1999;80:80-3.

[Table 4]

Table 4 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 QALYs presented in Table 1 presents the proportion of a healthy life year lived when suffering from tuberculosis. In order to consider the proportion of a healthy life year lost when suffering from tuberculosis, the inverse QALY or 1 - QALY needs to be calculated. The sum of the mortality and morbidity calculation gives the number of life years gained due to the decline of tuberculosis. For example, in 1901 there were 58,930 tuberculosis deaths (or lost life years). And 70,000 people reported as suffering from tuberculosis. In 1901 the typical tuberculosis sufferer only experienced 0.33 of a healthy life year and as such lost 0.67 of a healthy life year. The aggregate loss is equal to 46,900 (70,000 * 0.67). Therefore, the life years lost as a result of tuberculosis mortality and morbidity in 1901 = 105,830 (58,930 + 46,900).

To calculate the number of additional healthy life years that have been generated by the amelioration and virtual elimination of tuberculosis during the twentieth century, the difference between the number of healthy life years lost in 1901 or 1950 and 2000 needs to be identified. This is estimated to be 104, 425 (105,830 – 1,405) additional life years between 1901 and 2000. Hence, as a result of mortality and morbidity improvements 104,425 life years were spared of tuberculosis between 1901 and 2000.

In order to add greater significance to the results presented in Table 4 the number of additional life years that have been gained can be valued by applying 'Value of a Statistical Life' (VSL) functions. This concept is applied widely in regulatory economics to denote the value placed on the policies that can reduce the statistically expected risk of death[16]. Estimates about the 'Value of a Statistical Life' 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'*[17]. Sceptics also question the simplified implementation and over generalisation[18]. One of the most 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 'Value of a Statistical Life'[19]. Miller (2000) estimates the 'Value of a Statistical Life' (VSL) to be between $1.22 and $1.84 million in twentieth century England, which represents a mid range estimate[20]. In order to add validity to the results Miller's (2000) lower bound estimate of the VSL of $1.22 million will be used[21].

[Table 5]

[17] Jones-Lee M. The Economics of Safety and Physical Risk. New York and Oxford: Basil Blackwell; 1989.
[18] Laxminarayan R, Klein, E., Dye, C., Floyd, K., Darley, S., Adeyi, O. Economic Benefits of Tuberculosis Control. The World Bank; 2007.
[19] Jones-Lee M. The Economics of Safety and Physical Risk. New York and Oxford: Basil Blackwell; 1989.
[20] Miller T. Variations between Countries in Values of Statistical Life. Journal of Transport Economics and Policy. 2000;34:169-88.
[21] Ibid

The results in Table 5 are calculated by valuing the number of healthy life years gained (Table 4) with the VSL. Several points stand out from Table 5: 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 antimicrobial resistance and the associated consequence of multi-drug resistant tuberculosis.

TUBERCULOSIS IN C21 WITH ANTIMICROBIAL RESISTANCE

The issue of antimicrobial resistance has received increasing attention as the twenty-first century unfolded. Although the process of natural selection encourages microorganisms to adapt to environmental pressures, the use of antimicrobial therapies can accelerate this natural process, whereby resistant ones soon eliminate sensitive microorganisms. Although there remains much uncertainty about the development of resistance and the extent to which resistance is permanent, there is concern that over time there is no reason to suspect that resistance will not occur to all antimicrobials the only question is to what level[22].

At the same time the number of new therapeutics has been declining, organisms such as *S. Aureus* and *E. faecium* have been acquiring resistance to multiple therapies. This is also true for tuberculosis; multi-drug resistance is defined as resistance to at least isoniazid and rifampicin[23]. The incidence and spread of multi-drug resistant tuberculosis is of concern to both the developed and developing world[24]. For example, in the USA, multi-drug resistant tuberculosis epidemics have been reported in New York and Florida[25], while in Africa the incidence of multi-drug resistant tuberculosis continues to spread dramatically and extensively[26]. Tuberculosis is still a leading cause of death in sub-Saharan Africa, and in large parts of Africa, tuberculosis is epidemic because of the increased susceptibility conferred by HIV infection[27]. 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 to treat per patient[28].

As multi-drug resistant tuberculosis becomes more commonplace some of the gains associated with tuberculosis in the twentieth century (presented in Tables 1-5) 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 multi-drug resistant tuberculosis. This is a general issue associated

[22] Andersson, D. The ways in which Bacteria Resist Antibiotics. International Journal of Risk & Safety in Medicine. 2005; 17: 111-16
[23] Arias, C. et al. Antimicrobial-resistant bugs in the 21st century – a clinical super-challenge. The New England Journal of Medicine. 2000; 360: 5: 439-43
[24] WHO. Anti-tuberculosis Drug Resistance Surveillance Geneva. 2000.
[25] Park, M. et al. Outcome of multi-drug resistant tuberculosis patients, 1983-1993. American Journal of Respiratory Critical Care Medicine. 1996; 153: 317-24
[26] Davies, G. Et al. 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. 1999; 3: 799-804
[27] Maartens, G & Wilkinson, R. Tuberculosis. Lancet. 2007; 15: 370: 96074: 2030-433
[28] Chaulk, C. et al. Directly observed therapy for treatment completion of pulmonary tuberculosis. Journal of the American Medical Association. 1998; 279: 943-48

with antimicrobial resistance. One indication about the potential magnitude of the problem can be gleaned from considering the nature, timing and distribution of antimicrobial resistance. 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[29]. This distribution is summarised in Figure 1. 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[30].

[Figure 1]

Hence, it is extremely difficult to predict the path that multi-drug resistant tuberculosis and total-drug resistant tuberculosis will follow. One very approximate approach 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 is more plausible than 1901-2000 because even without efficacious therapy, there have been improvements in standards of living and prevention (BCG) that would very roughly approximate the situation in 1950. The efficacy of the BCG vaccine continues to be debated. Clinical trials have shown protection against tuberculosis that varies from zero to over 70 percent[31]. For this reason the results have not been adjusted to reflect the BCG in the second half of the twentieth century, and as such they should be considered as an upper bound. This upper bound estimate, which represents the mortality and morbidity gains associated with tuberculosis between 1950 and 2000, is presented in the final row of Table 5 as $35 billion.

The lower bound can be estimated by considering the current situation with multi-drug resistant tuberculosis. Table 6 provides a lower bound indication about the current burden of multi-drug resistant tuberculosis in the UK.

[Table 6]

This calculation considers only an altered morbidity burden. This seems most plausible given that multi-drug resistant tuberculosis tends to be resolved in longer treatment times and not mortality. This is largely due to comprehensive treatment artillery against tuberculosis; first line drugs include isoniazid, rifampicin and pyrazinamide[32]. Second-line agents are used by specialists in certain situations (e.g. resistance and intolerance) and include amikacin, capreomycin, cycloserine,

[29] Austin, D. & Anderson, R. Transmission dynamics of epidemic Methicillin-resistance Staphylococcus aureus and Vancomycin-resistant Enterococci in England and Wales. The Journal of Infectious Disease. 1999; 170: 883-91

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

[31] 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 percent. Conversely, in the 1960s the World Health Organisation carried out a large double-blind controlled trial of 360,000 people in Madras and found that more of those vaccinated with BCG got tuberculosis than those who were not vaccinated. Colditz, G. Et al. Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature. 1994; 271: 9: 698-702. Bailey, G. Et al. Tuberculosis prevention trial, Madras. Indian Journal of Medical Research. 1980; 72: 1-74

[32] British National Formulary.

macrolides and quinolones[33]. Streptomycin is unlicensed and now rarely used in the UK. The proportion of multi-drug resistant tuberculosis cases was 1.6 percent in the UK in 2012[34]. Currently and for the foreseeable future, the key issue seems to be one of increased morbidity rather than mortality from total-drug resistant tuberculosis. The burden of which is estimated to be $1.9 billion. This is calculated in Table 6 by applying a VSL function to the number of life years that have been burdened with multi-drug resistant tuberculosis in 2013.

To put these results into context Table 7 presents some very initial estimates about the burden of methicillin-resistant Staphylococcus aureus (MRSA), and Box 1 provides a very brief case study about methicillin-resistant Staphylococcus aureus.

[Table 7]

[Box 1]

The recent results about the burden of methicillin-resistant Staphylococcus aureus are much higher than tuberculosis. For example, the burden of methicillin-resistant Staphylococcus aureus between 1993 and 2011 is estimated to be $17 billion. This is primarily because methicillin-resistant Staphylococcus aureus currently causes mortality and multi drug resistant tuberculosis currently is only an issue of morbidity. However, if the early issues of total drug resistant tuberculosis continue then the burden of tuberculosis could indeed become of a similar or even greater order of magnitude to methicillin-resistant Staphylococcus aureus.

Hence, at a very rough initial approximation, the cost of antimicrobial resistance associated with tuberculosis is somewhere in the region of $1.9 billion as we are currently at the early or lag phase. With a worst case scenario (at time x + n on the distribution in Figure 1) we will move closer to an economic burden of many more billions of dollars. Therefore, the sigmoid distribution also highlights the need for policy before the lag phase is complete. During the lag phase, policies aimed at controlling resistance will help to curtail antimicrobial resistance. Once time x + n has been reached, only policies which reduce transmission of the organism will (generally) be valuable as a means of reducing the impact of resistance on health. The effect of policies which reduce antimicrobial usage will at this point have a limited impact. Policies aimed at reducing transmission will never avoid all the ill health associated with a resistant organism, whereas policies which avoid the emergence of resistance could potentially avoid all additional ill health associated with the resistant organism[35].

Unfortunately, the policies which are likely to be easiest to evaluate are not likely to produce an optimal long-term outcome given the importance of remaining at lower points on the sigmoid curve (shown in Figure 1) because of the apparent irreversibility of much resistance and the potentially severe harm which could be imposed as a result. This reality also frustrates the results of economic impact studies. Because during the lag phase the results will be much lower and hence likely motivate less spending. This is highlighted by comparing the lower bound results from Table 6 ($1.9 billion) with the upper bound estimates in Table 5 ($35 billion). Thus, policies to reduce transmission

[33] Ibid
[34] Annual Report on tuberculosis surveillance in the UK; Health protection report.
[35] Ibid

may seem more cost-effective and the evidence for them may be much stronger, but the implication of pursuing such policies would be that, over time, more and more antimicrobials would reach high equilibrium levels of resistance, and the option for using alternative antimicrobials would gradually be lost, and the impact on morbidity and mortality could be devastating[36]. Some experts go so far as to state that an increase in antimicrobial resistance coupled with a fall in the number of new antimicrobial drugs suggests an "apocalyptic scenario may be looming"[37].

The sigmoid distribution is also important for explaining the relatively small results of economic impact studies. One of the reasons that antimicrobial resistance has received less attention than many other issues in health economics is because these numbers are lower than estimates of the economic burden from other (modern) diseases: such as Cutler's estimates and other estimates for cancer, heart disease, etc. One of the reasons that current estimates about the burden of antimicrobial resistance are low is because much of the literature evaluates antimicrobial resistance on an incremental cost basis, and according to Smith & Coast (2013) this masks the most critical economic burden, which is a potential scenario of antimicrobial resistance leading to the loss of many advances in medical care that antimicrobials have enabled: the list is vast and ranges from advances in surgical procedure to cancer chemotherapy. I.e. According to Smith & Coast (2013) none of the studies consider the bigger picture- where antimicrobial resistance jeopardises the entire health care system, and not just infectious diseases, like tuberculosis. I.e. many more times as costly as the upper bound, $35 billion, result presented here.

SUMMARY

Hence, organisms develop resistance to antimicrobials, and increasingly are developing resistance to multiple therapies, rendering these antimicrobials ineffective. At the same time, the once prolific pipeline bringing new antimicrobials into clinical practice is faltering[38]. We are therefore 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[39]. This problem is compounded by the nature and timing of the antimicrobial resistance issue. As such the relatively small results for multi-drug resistant tuberculosis, presented in Table 6, should not lull us into a false sense of security or complacency with regard to policy and initiatives to prevent the increase in antimicrobial resistance. That being said, the history of tuberculosis presented here shows that some of the more extreme apocalyptic scenarios being aired in media are unlikely. Partly because, as in the past, preventive medicine (including vaccination) and public health measures can play a major role; partly because the threat should result in the reduced use of antimicrobials; and partly because the potential role for government to intervene with sound public health policies.

[36] Ibid

[37] Smith, R. & Coast, J. The true cost of antimicrobial resistance. British Medical Journal. 2013; 346: f1493

[38] Smith, R. & Coast, J. 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.

[39] Cars, O. et al. Meeting the challenge of antimicrobial resistance. British Medical Journal. 2008; 337: 726-28

TABLES

Table 1: Tuberculosis (Quality Adjusted Life Year) QALY, 1900, 1950 and 2000[40]

Year	Tuberculosis QALY value
1900	0.33
1950	0.67
2000	0.83

[40] Hickson K. The Contribution of Improved Health to Standards of Living Growth in Twentieth Century England and Wales. London: London School of Economics and Political Science; 2006.

Table 2: Number of tuberculosis deaths and tuberculosis deaths rate per 10,000 population in England and Wales, 1901-2000 (calculated from Office for National Statistics 2003[41])

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

[41] 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 3: Number of tuberculosis notifications and tuberculosis notifications per 10,000 population in England and Wales, 1901-2012 (compiled from Citron et al 1981[42], Watson et al 1991[43], Joint Tuberculosis Committee of the British Thoracic Society 2000[44], Office for National Statistics 2003[45], Statutory Notifications of Infectious Diseases 2014[46])

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

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Table 4: 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 5: Calculation of the value of life years gained due to improved tuberculosis mortality and morbidity in England and Wales, 1901-2000 and 1950-2000

	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

Table 6: Number of drug resistant tuberculosis cases and associated QALY cost, 2013[47]

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

Note: cases includes isoniazid resistant and multi-drug resistant tuberculosis
Note: using 1950 QALY to simulate antimicrobial resistance

[47] Compiled from Enhanced Tuberculosis Surveillance: Centre for Infectious Disease Surveillance and Control, Public Health England

Table 7: WTP to show the welfare cost of antimicrobial resistance: MRSA, England and Wales, 1993-2011[48]

Year	Age-standardised rates per million population		Number of deaths			VSL (int. $ million)	WTP (int. $ million)
	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**

[48] Calculated from ONS Deaths involving MRSA, England and Wales, 1993-2011: http://www.ons.gov.uk/ons/rel/subnational-health2/deaths-involving-mrsa/2007-to-2011/stb----mrsa.html

BOXES

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

S. aureus is a common type of bacteria found on the skin and in the nostrils of about one third of healthy people without it causing any harm[1]. 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 Meticillin; and again resistant strains developed soon after, and spread rapidly during the 1990s[2]. Hence, Meticillin-resistant Staphylococcus aureus (MRSA) is a type of Staphylococcus bacteria 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[3]. 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[4]. Rates have continued to fall since 2008[5]. For example, in 2012 there were 934 MRSA bacteraemia reports; a 21 percent reduction from 2011[6]. 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 Lives' initiative in 2007[7]), decolonization (see below) have been shown to have a prominent role in this reduction. This highlights the importance of maintaining careful surveillance[8].

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[9]. For example, numerous studies have reported successful control of endemic and epidemic MRSA in an ICU setting with the use of decolonization agents[10]. 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[11].

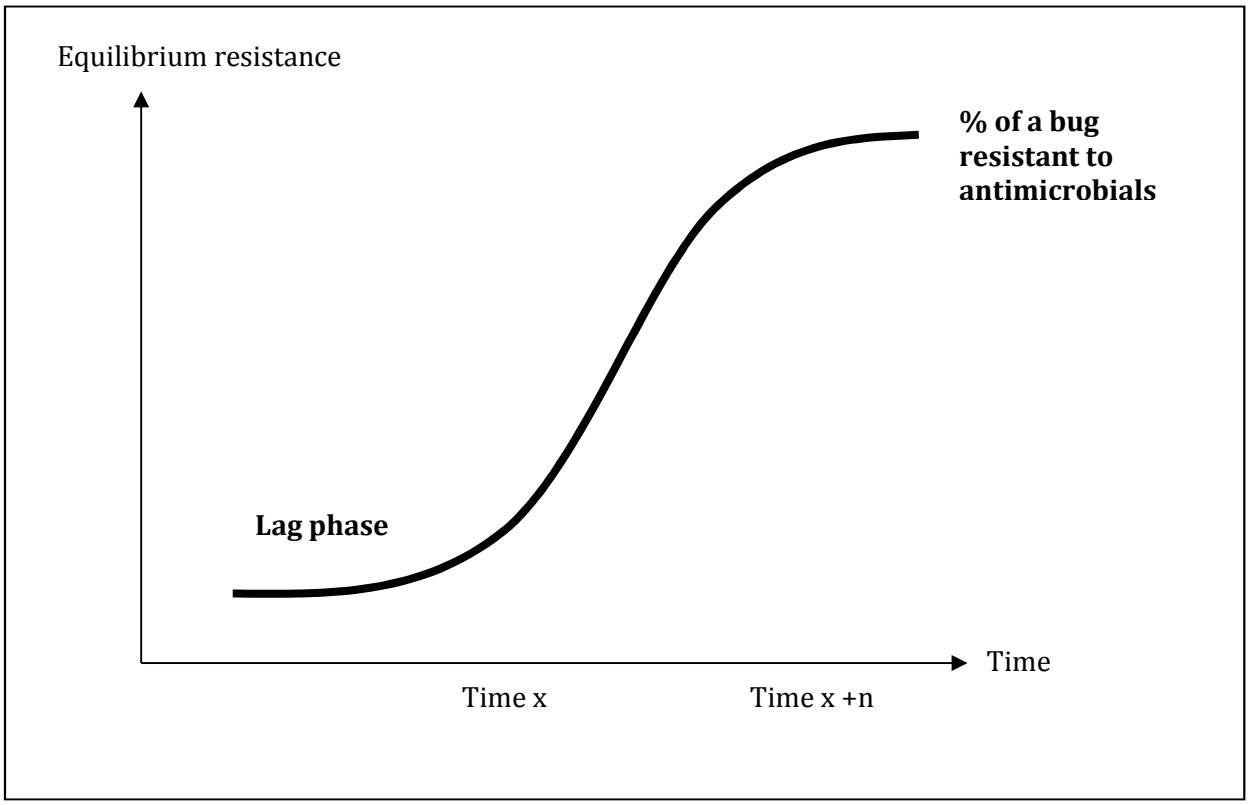
Available evidence on the efficacy of decolonization, predominantly from ICU studies, combined with the introduction of national guidelines endorsing its implementation as part of a new performance management culture in the NHS, supports the proposal that the widespread uptake of decolonization has made 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.

[1] HPA 2010
[2] ONS 2014
[3] Ibid
[4] Pearson et al 2009
[5] Ellington et al 2010
[6] ONS 2013
[7] Department of Health 2010
[8] Edgeworth 2010
[9] For example see: Batra et al 2010, Cunningham et al 2007, Thompson et al 2009, Gould et al 2007.
[10] For example see: Raineri et al 2007, Thompson et al 2009, Sandri et al 2006, Girou 1998, Ridenour et al 2007
[11] Batra et al 2010

FIGURES

Figure 1: The development of antimicrobial resistance over time



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The welfare cost of antimicrobial resistance – tuberculosis as an illustrative example