
Past mortality from infectious diseases and current burden of allergic diseases in England and Wales

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SUMMARY

This study documents the changes in mortality in England and Wales over the last 100 years as a possible explanation for our increasingly allergy-prone Western society. A total of 53 million computerized recorded deaths, which occurred from 1901 to 2000 were analysed retrospectively. Childhood mortality decreased by 98%, from 40·6% of total annual deaths in 1901 to 0·9% in 2000. In 1901, 36·2% of all deaths and 51·5% of childhood deaths were from infectious diseases. By contrast in 2000, 11·6% of all deaths and only 7·4% of childhood deaths were from infectious diseases. Infectious diseases were a significant cause of childhood mortality in British cities until about 40 years ago. Several factors, including vaccination, antibiotics and improved sanitation have contributed to this trend. Survival of individuals with heightened immunity to infections may have led to natural selection of allergy-prone individuals in England and Wales. However, the relationship between changes in rates of infection and allergy is complex and not fully understood.

INTRODUCTION

Allergic diseases (eczema, asthma, hay fever and food allergy) are increasingly common, affecting up to 20–50% of people living in the West [1]. The hygiene hypothesis proposes that lack of childhood exposure to certain microbes in our modern society has resulted in loss of immune tolerance to usually innocuous substances (foods, mites, aeroallergens) [2–4].

This study aims to build on this hypothesis. We propose that although recent changes to our environment play a role in the phenotypic expression of hypersensitivity disorders, the environmental pressure faced by our urban ancestors may be a factor that has impacted on our propensity to these diseases. The model is not a new one. For example, it is well accepted that thalassaemia is more common in

southern Europeans because of survival pressures their ancestors faced from malaria, an environmental microbe which was common in those parts of the world until recently [5, 6]. It is the past moulding of southern European's genetic makeup and not the recent eradication of malaria that has caused the current prevalence of haemoglobinopathies in these communities. We predict that studying the factors that influenced the survival of our urban ancestors will result in a better understanding of this complex group of polygenic disorders. It is easy to forget that only a few centuries ago, our ancestors moved *en masse* from their relatively small rural communities to large, overcrowded towns and cities, where premature death from infectious diseases such as cholera, dysentery and tuberculosis was commonplace [7, 8]. For example, in eighteenth-century London one in three babies died before the age of 2 years and only one in two survived to reproductive age [8]. In the absence of vaccines or antibiotics, and considering factors such as nutrition and socio-economic status, individuals

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who were able to mount more effective immune responses to infections were more likely to have survived. The primary aim of this study is to document trends in mortality of children prior to reproductive age during the last century.

METHODS

The UK Government Mortality Statistics Unit has recently published a complete set of computerized raw records of all deaths in England and Wales from 1901 to 2000, including details of age and cause of death for each year in that century [9]. Data from the early years had been entered manually from paper records of the day. Data from later years were taken directly from the computer systems at the Office for National Statistics (ONS, formerly the Office of Population Censuses and Surveys). The International Classification of Diseases (ICD) was introduced in 1900 and was used in the tabulation of mortality statistics in England and Wales since 1911. In all there have been nine revisions of the international classification, up to 2000. Each of these provides codes for cause of death, which differ, in varying degrees, from the previous revision. During the period 1901–10, an unnumbered list of causes was used in England and Wales in place of the new International Classification, which had not yet been widely adopted.

In this study, raw data incorporating records from 53·1 million deaths that occurred during the last 100 years in England and Wales were analysed using the Microsoft[®] Access 2000 programme (Microsoft Corp., Redmond, WA, USA). Further statistical analysis was performed using SPSS 10.1 (SPSS Inc., Chicago, IL, USA). The major focus of this study is deaths from infectious diseases. Thus, people dying from infectious diseases, particularly gastrointestinal infections, tuberculosis and respiratory viruses (measles, influenza and chickenpox) were analysed separately. Deaths from accidents and from cancer are used as non-infectious controls. For these analyses, ICD codes for each of the nine periods were individually reviewed and comparable codes used to provide consistent datasets for the overall time period examined.

RESULTS

Population trends in England and Wales from 1901 to 2000

From 1901 to 2000 the total population in England and Wales increased steadily from 31·6 to 51·9 million

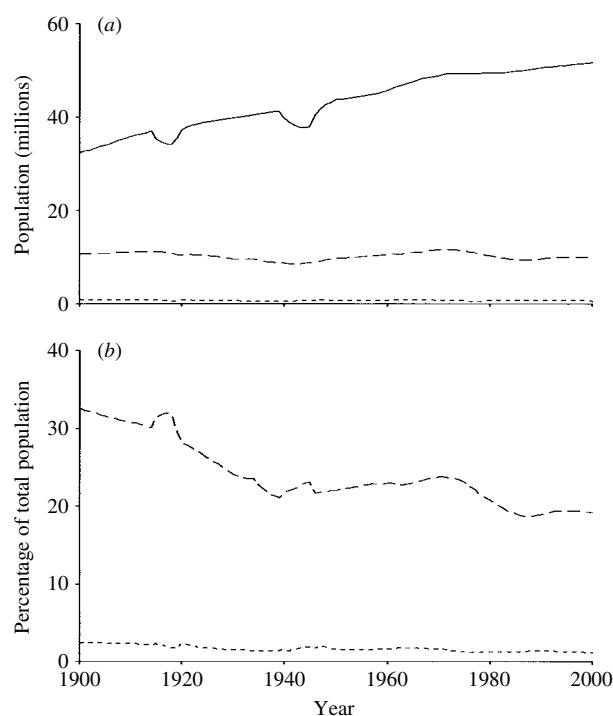


Fig. 1. Changes in population of England and Wales between 1901 and 2000. (a) Total population (continuous line); children 0–14 years old (dashed line); 0–1 year old (dotted line). (b) Percentage of population aged 0–14 years old (dashed line); 0–1 year old (dotted line).

(increase of 64%) except for dips coinciding with the two world wars. In contrast, during the same time period the number of children under 15 years old remained remarkably constant at around 10 million (Fig. 1a). The percentage of the total population who were children therefore decreased from 32·7 to 19·1% (Fig. 1b). Although the number of infants <1 year old has varied significantly over the century, oscillating between 548 000 and 872 000, there has been a similar downward trend in this age group, where infants made up 2·5% of the population in 1901, but only 1·2% in 2000.

Trends in childhood mortality in England and Wales from 1901 to 2000

The total annual number of deaths, although fluctuating across a baseline, particularly during the first half of the century, has remained relatively constant ($521\,000 \pm 44\,000$), while the number of deaths in children <15 years old has decreased by 98% from 223 738 (40·6% of total annual deaths) in 1901 to 4794 (0·9%) in 2000 (Fig. 2). For the first half of the century, 60% of deaths in children occurred in

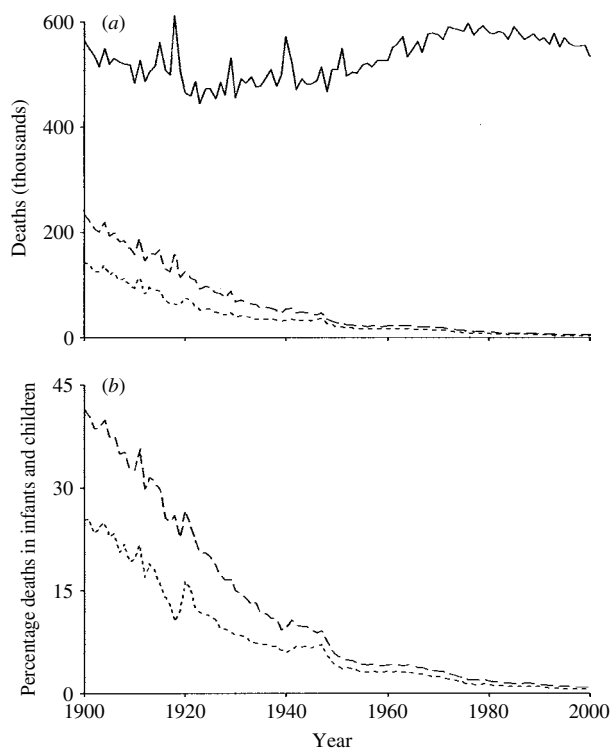


Fig. 2. Deaths in England and Wales between 1901 and 2000. (a) Total deaths (continuous line); deaths in children aged 0–14 years old (dashed line); deaths in children aged 0–1 year old (dotted line). (b) Percentage of total annual deaths occurring in children 0–14 years old (dashed line); 0–1 year old (dotted line).

infants <1 year old, while in the second half of the century the percentage has increased to 70–80% of childhood deaths.

Deaths from infectious diseases between 1901 and 2000

Infectious diseases accounted for a large percentage of deaths in the earlier part of the century (Figs 3 and 4). In 1901 there were 200 398 deaths from infectious diseases (36.2% of all deaths), of which 115 228 deaths occurred in children <15 years old (51.5% of deaths in this age group). By contrast in 2000, there were 62 521 deaths from infectious diseases (11.6% of total deaths), but only 359 of the deaths were in children <15 years old. In contrast to the impact of infectious diseases on childhood mortality, particularly in the first half of the century, the impact of other causes of death, e.g. accidents and cancer has always been small. The proportion of children in any year of the century dying from cancers has never been more than 0.03% and from accidents has never been more than 0.06%. Over the last 30 years infections have

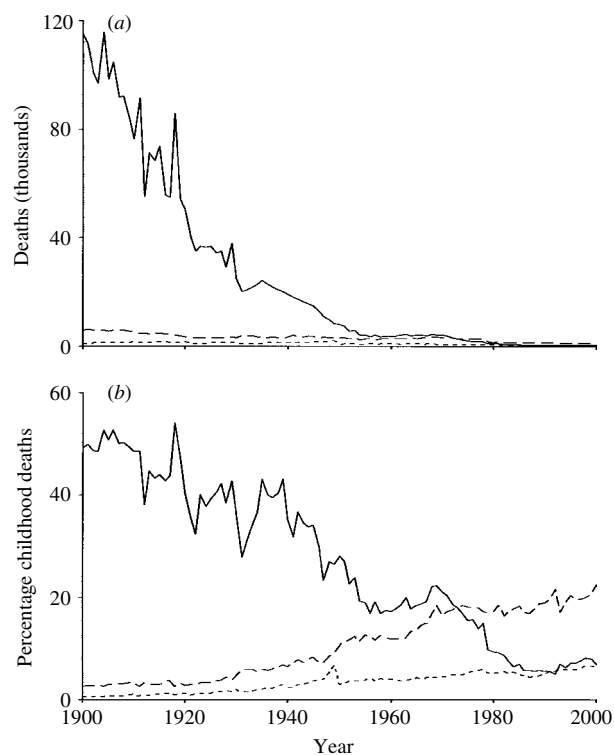


Fig. 3. Childhood deaths from infectious and non-infectious causes. (a) Deaths from infectious diseases (continuous line); accidents (dashed line); cancer (dotted line). (b) Percentage of childhood deaths due to infectious diseases (continuous line); accidents (dashed line); cancer (dotted line).

decreased to such an extent that they now cause the same number, or even less deaths than either accidents or cancers (Fig. 3).

In terms of the types of infections, gastrointestinal infections accounted for 35 257 deaths in 1901 (17.6%) and 81% of these were in children <15 years. Tuberculosis killed 55 328 people in 1901 and 28% were <15 years. By 2000 there were only 370 deaths from tuberculosis, <1% in children. Respiratory tract-acquired infections such as measles, influenza and chickenpox resulted in 9798 (4.4%) childhood deaths in 1901 and only 5 deaths in 2000. The 1918 influenza epidemic was an exceptional year with 24 919 childhood deaths.

Survival beyond childhood

A child born in 1900 had a 25% risk of dying before reaching 15 years old (12% risk of dying from an infectious disease). By 1948, the risk of dying in childhood had decreased to 3% and by 1986 the risk was only 1/100 (Fig. 5).

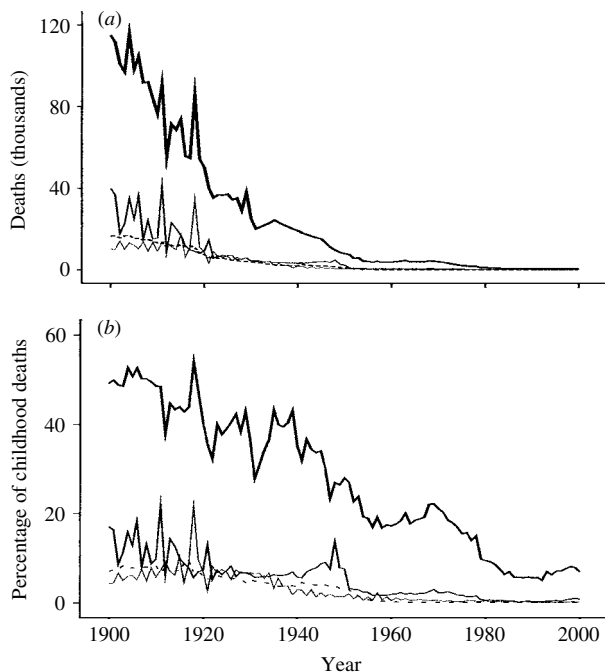


Fig. 4. Childhood deaths from different infectious diseases. (a) Total deaths from infectious diseases (thick continuous line); gastrointestinal infections (thin continuous black line); tuberculosis (dotted line); respiratory viruses (measles, influenza, chickenpox) (thin continuous grey line). (b) Percentage of childhood deaths due to infectious diseases (thick continuous line); gastrointestinal infectious (thin continuous black line); tuberculosis (dotted line); respiratory viruses (measles, influenza, chickenpox) (thin continuous grey line).

DISCUSSION

The publication in 2004 of computerized raw mortality data by the UK Government Mortality Statistics Unit provided a unique opportunity to tailor analyses of the mortality statistics of England and Wales between 1901 and 2000 in order to accurately address specific health-related questions. Our analyses of these data demonstrate that even 100 years ago, people living in Western society had a substantial risk of dying before reaching reproductive age and it was only during the last 40 years that childhood mortality has decreased to its current low levels. Overall childhood mortality has decreased 98% over the last century. In England and Wales in 1901 there was a 25% risk of dying before the age of 15 years and 60–70% of these deaths occurred in infancy. Half of the deaths in children were due to infectious diseases, and gastrointestinal infections and tuberculosis made up a significant proportion of these. In contrast, deaths from accidents and cancers did not have a significant impact on population dynamics.

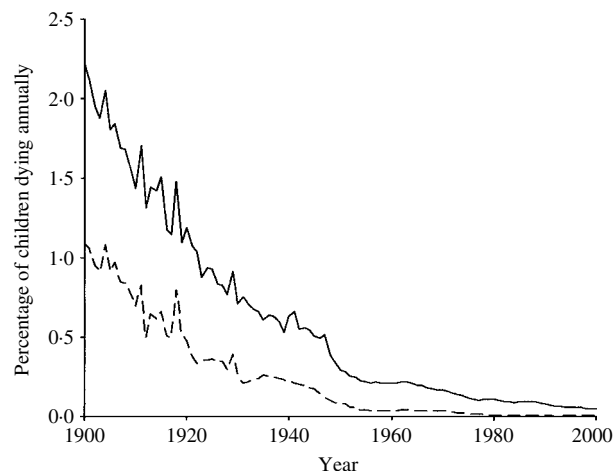


Fig. 5. Percentage of children aged 0–14 years who die each year. All causes (continuous line); infectious diseases (dashed line).

There are a number of factors that have contributed to this dramatic reduction in childhood mortality, each of which needs to be considered within the time frame. Improvements in sanitation, as well as immunization programmes and the advent of antibiotics have all had an impact on survival to reproductive age in England and Wales over the last 100 years. The number of children dying of infectious diseases decreased by 87% from 115 000 in 1901 to 15 102 in 1945, with the greatest decline occurring in the first 30 years of the century, when major improvements to housing and sanitation were being implemented. By 1901, vaccination had already had a major impact on deaths from smallpox with only 346 deaths (0.2% of all deaths from infectious diseases) recorded that year. The first BCG vaccine for humans was made available in 1927, by which time childhood deaths from tuberculosis in the United Kingdom had decreased by 72% from 16 500 in 1901 to 4556 in 1927. Antibiotics became available after the end of the Second World War.

Thus, with the expansion of urbanization and very high population density over the last few centuries, communicable diseases have had a substantial effect on mortality rates, leading to the deaths of 10–15% of children prior to reproductive age. In keeping with Darwin's theory of natural selection, one might expect this to lead to the survival of human beings with heightened immune responses, not only to infectious diseases, but also an unusual or 'atopic' immune hypersensitivity to antigens in general. If this hypothesis were correct, then why has the increased prevalence of atopic diseases only become apparent

since the 1960s [4, 10]? One explanation could be that a reduction in the exposure to 'protective' non-pathogenic environmental microbes has only occurred in the last few decades, unmasking the genetic atopic tendency. An alternative explanation is that children who died of infectious diseases a century ago actually had the atopic tendency and that their survival has led to a higher prevalence of symptomatic atopic diseases. This explanation is, however, unlikely, because if this were true, not only would one have expected atopic diseases to have become more prevalent much earlier than the 1960s, but as atopic dermatitis is usually a disease of infancy, one would have expected a higher prevalence of this disease even 100 years ago [4, 10].

A limitation of all descriptive epidemiological study is that although it may suggest an association, one is unable to draw a logical conclusion of cause and effect. However, if our hypothesis were correct, we would expect that there will be a spontaneous levelling out and then a slow reversal of trends in immune hypersensitivity (allergic) diseases. There is already growing evidence from many Western communities that the incidence of atopic diseases is levelling out or decreasing (e.g. United Kingdom [11], Switzerland [12], Australia [13], Singapore [14]). One would expect this trend to continue without any active intervention.

Recent evidence suggests that genetic factors associated with a heightened immune response to infectious diseases are associated with an increased risk of immune hypersensitivity diseases. For example, although toll-like receptors and their cytoplasmic second messengers are now recognized as being very important in initiating our innate immune response to a variety of pathogens (e.g. Gram-positive and Gram-negative bacteria, mycobacteria) and also in influencing our propensity to allergic diseases [15–18], other genetic factors that heighten our immune responses to infection and thus help to protect us from certain infectious disease (e.g. those determining regulatory T cell activity: TGF- β 1, and IL-10 gene polymorphisms) also increase our propensity to hypersensitivity diseases [19–22].

In summary, this study highlights the fact that although in England and Wales today, almost all children will survive to adulthood, it was only 100 years or a few generations ago that one quarter of all people died before reaching reproductive age. Furthermore, half of these deaths were due to infectious diseases, particularly gastrointestinal infections and tuberculosis. Whether the effect of rapid

urbanization over the last few centuries has caused the natural selection of individuals with not only heightened immunity to infections but also immune hypersensitivity disorders such as allergic diseases cannot be determined with any certainty from this study. It is, however, a hypothesis which deserves further study and validation.

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