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Updating the epidemiological transition model

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Opinions - For Debate

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Abstract

The main feature of the epidemiological transition is a shift in the recorded causes of death from infectious diseases to other morbid conditions. This paper outlines modifications made to Omran's original model and stages of transition, and suggests that without a focus on aetiology and morbidity, these have been basically descriptive rather than explanatory, and potentially misleading because infections have been confirmed as causes of various chronic diseases. Common infections and related immune responses or inflammatory processes contribute to the multifactorial aetiology of morbid conditions that together make a substantial contribution to overall mortality, and infectious causation is suspected for many others because of strong evidence of association. Investigation into possible infectious causes of conditions frequently recorded as the underlying cause of death can be integrated into a framework for comparative research on patterns of disease and mortality in support of public health and prevention. A theory of epidemiological transition aimed at understanding changes in disease patterns can encompass the role in different conditions and chronic diseases of infections contracted over the life course, and their contribution to disability, morbidity and mortality relative to other causes and determinants.

Introduction

A fundamental change in the most frequently recorded causes of death, longer life expectancy and an increasing proportion of older people in the population have been characteristic features of the epidemiological transition in Western countries. Interest in the transition model has renewed recently with more cause-specific mortality data becoming available from low- and middle-income countries (LMICs) [1–3]. Integration with the socio-ecological model in epidemiology has been suggested to provide a comprehensive framework for investigating and understanding changing patterns of health and disease [4, 5]. Omran's original paper on 'epidemiologic transition' in 1971 drew attention to profound changes in the cause of death structure, and identified different stages and models of transition [6]. It diverged from the demographic transition model of mortality, fertility and population change by focusing on a shift from one predominant group of diseases, infectious diseases, to 'degenerative and man-made diseases' considered to be distinctly different. More recently, the term 'non-communicable disease' has been widely used for conditions traditionally regarded as having no infectious causes, and 'chronic disease' for those with long duration (usually at least 3 months). However, infectious causes have been confirmed for a significant number of these in recent decades (e.g. gastric cancer, cervical cancer, peptic ulcer), indicating a fundamental weakness in the concept of transition. The false dichotomy on which the original transition model was based reflects the lack of knowledge at the time about the pathogenesis and aetiology of chronic diseases. In contrast, external manifestations and transmission patterns were conspicuous for most acute infectious diseases, single microbial causal agents had been identified and effective methods of control were well established [7].

Infectious diseases are caused by specific pathogenic microorganisms or parasites that are necessary for them to occur and be transmitted. They include those in the International Classification of Diseases (ICD) chapter, 'certain infectious and parasitic diseases', some 'diseases of the respiratory system' (e.g. influenza, pneumonia) and a few local infections classified elsewhere (e.g. urinary tract infections) [8]. Certain infectious diseases can persist beyond a short-term acute phase into an active chronic phase, become inactive but potentially active or cause some other morbid condition. Infectious diseases have now been superseded by other acute and chronic conditions as the most frequently recorded causes of death in Western countries. Comparison of cause of death structures over time or between populations is based on certification of the underlying cause of death – the condition or event that initiated the fatal sequence of morbid events [8]. This paper considers the implications of research into infectious causation of morbid conditions for the epidemiological transition model, which has undergone much revision and is still used as a framework for research on changing patterns of disease and mortality in support of public health and prevention.

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Development of models with stages of transition

A new infectious disease environment was experienced when groups of humans began to live in settled communities based on agriculture and the domestication of animals. Some researchers refer to this as the first epidemiological transition, with Omran's 'epidemiologic transition' the second, and emerging and resurgent infectious diseases viewed as a third transition [9–11]. Omran's transition has also been viewed as the first of three stages in a health transition characterised by efforts to control infectious diseases, cardiovascular disease and conditions associated with old age, respectively [12]. The response of health systems to changing patterns of disease was included in the health transition model of multiple determinants of health [13]. Omran regarded health as a dependent variable in epidemiology, with 'epidemiologic transition' encompassing changing patterns of disease and health [14].

Much of the critique and modification of Omran's 'theory' has focused on transition models and stages with supposedly characteristic disease profiles, although his other propositions have also been reviewed recently [1–4]. He initially identified three models of transition: the 'western model' based on the experience of England and other Western countries, an 'accelerated model' for Japan and other countries that experienced a more rapid transition during industrialisation and a 'delayed model' for developing countries where the decline in infectious disease mortality was more recent [6]. He later added a fourth 'transitional variant' of the delayed model in which rapidly declining mortality was followed relatively quickly by fertility decline, which occurred in developing countries with well-organised family planning services [15].

Omran originally identified three stages of 'epidemiologic transition' – the 'age of pestilence and famine', the 'age of receding pandemics' and the 'age of degenerative and man-made diseases' [6]. In the 'age of pestilence and famine', mortality remained at very high levels for thousands of years [16]. Plague pandemics caused massive mortality crises in England from the 14th through the 17th century, but after the last major outbreak in the 1660s, additional measures were taken to prevent the disease from re-entering the country. In the mid-18th century when the long-term decline in overall mortality began, endemic infectious diseases caused most deaths, particularly smallpox, tuberculosis, typhus, typhoid, dysentery and other diarrhoeal diseases [17]. In the 20th century, global pandemics of influenza (1918–1919) and human immunodeficiency virus (HIV)/AIDS undermined the idea of an earlier 'age of receding pandemics' that was distinct. The delineation and description of stages, and the lack of clarity about the beginning and end of the whole transition have been much criticised [18, 19]. The epidemiological transition considered here is fundamentally linked with the decline in mortality from infectious diseases and efforts to control them – an ongoing global challenge.

Omran generalised that the predominant influence on the decline in infectious disease mortality in Western countries was social and economic development [6, 14, 15]. He concurred with McKeown's explanation that with few effective treatments available before antibiotics in the 1940s, the main cause of the decline in mortality was improvement in the 'standard of living', particularly nutrition [20, 21]. However, neither McKeown nor Omran presented evidence of changes in food consumption or economic indicators that might support this hypothesis. Fogel concluded that improved nutrition was the main cause of increased longevity on the basis of historical evidence of anthropometric changes [22], but did not take into account the physiological benefits for children who experienced fewer episodes of severe infectious disease. The 'standard of living/nutrition hypothesis' does not explain the many differences in the timing of the decline in death rates for particular infectious diseases and age groups, as discussed elsewhere [17]. The evidence suggests the overall decline in infectious disease mortality was largely due to preventive and public health measures – smallpox vaccination, quarantine and isolation; clean drinking water; sanitation – sewerage, drainage, street cleaning and refuse collection; hygiene – hospital, obstetric, domestic and personal; improved quality of food and milk; methods to prevent pregnancy; smaller families and households which reduced transmission rates; and education for mothers about infant and child care. Successive generations experienced fewer episodes of severe acute infectious disease, which most likely contributed more to the increase in life expectancy than improvements in people's economic circumstances, 'standard of living' and nutrition [17].

Between the mid-19th and mid-20th centuries, cardiovascular diseases and cancers became increasingly predominant as causes of death recorded under national registration in England and Wales. The relative contribution to overall mortality increased as death rates from infectious diseases declined and more people survived to ages at which these conditions and other chronic diseases are more likely to occur following exposure to various environmental risks. The proportion of deaths attributed to all cardiovascular diseases increased to over 50% by the 1970s, although the death rate declined from the early 1950s [23]. A decline in the coronary heart disease (CHD) death rate from the 1970s in most Western countries led to new stages of transition being identified, including a fourth stage of 'delayed degenerative diseases' in which the risk of dying shifts to much older adult ages [16], a fifth stage of 'obesity and inactivity', marked by a rapid increase in obesity/overweight and mental disorders associated with survival to older ages [24], and a concurrent phase of risky sexual behaviours and life styles in the 1980s [25].

In a final update of his transition model, Omran clarified which diseases and conditions he regarded as 'man-made', including those caused by transport accidents, radiation, industrial and chemical hazards, and contaminated food. He added a fourth stage to his original three – the 'age of declining cardiovascular mortality, ageing, lifestyle modifications, emerging and resurgent diseases', and a speculative fifth stage [14]. Others viewed emerging infectious diseases as a separate stage in Omran's transition [26], or a new transition, as mentioned [9–11]. More than 50 new pathogens and infectious diseases have been identified in recent decades, including HIV, community-acquired methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile* colitis, Ebola virus disease, severe acute respiratory syndrome, Legionnaires' disease and Lyme disease [27].

Divergence from the western transition model

New infectious diseases and resurgent diseases such as tuberculosis undermined expectations that measures to control infectious diseases would mean inevitable linear progression through the epidemiological transition experienced in the West. Mortality did decline in most developing countries in the 20th century, although the onset, rate and continuity of decline differed considerably. The evidence suggests that the decline was due mainly to the importation of successful health interventions from the West, rather than changes in economic circumstances [28–30]. In the

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1950s and 1960s, rapid decline in mortality was achieved in many LMICs, including some of the poorest where there was little economic growth, which has been attributed to the implementation of basic health and social programmes driven by the political and social will to achieve greater equity [31]. Mortality from infectious diseases was reduced in most developing countries through safer drinking water, environmental sanitation, hygiene measures, education, basic mother and child health services, immunisation, and after the 1940s, simple treatment measures including antibiotics and oral rehydration salts. The experience of epidemiological transition differed widely between countries, regions and local areas, and between social, cultural, ethnic and socio-economic groups, which exacerbated mortality differentials [32, 33].

Kunitz recognised the value of generalisations about epidemiological transition, but warned against a historicist assumption that the stages would be the same everywhere. He advocated research into social, cultural and behavioural determinants of health and disease to inform the development of appropriate health strategies [34]. Based on data from Latin America, Frenk *et al.* formulated a 'protracted and polarised' variant of the non-western transition model, in which epidemiological change varies between population sub-groups and overlap of stages persists [13]. Omran suggested that the stages overlapped more in non-western populations, and identified rapid-, intermediate- and slow-transition models to describe their delayed mortality and fertility transitions [14].

Data on cause-specific mortality recently available for many LMICs have confirmed doubts about the universality and predictability of epidemiological transition in terms of linear progression through defined stages [1, 3]. Santosa *et al.* reviewed evidence from 136 studies in 48 countries to assess deviation from Omran's western model. The analysis identified wide differences in the timing of stages of transition among LMICs and sub-populations, and other features of mortality change that were not consistent with Omran's propositions. Despite criticisms of the epidemiological transition model, it is still used by many researchers as a framework for studies of changing patterns of disease and mortality, and the review suggested a more comprehensive evidence-based theory was needed focusing on the mechanisms underlying changes in cause-specific mortality [3].

Defo reviewed critiques and limitations of Omran's transition theory, including the focus on recorded causes of death but not morbidity and its causes, oversimplification of transition patterns, the inflexibility of a stage-wise linear approach and lack of attention to the role of poverty in different patterns of disease and mortality among population sub-groups and geographical areas [1, 2]. In many parts of Africa, an initial decline in mortality from the 1950s, reflecting the measures to control infectious diseases and other health interventions, stalled. A sustained shift in disease profiles did not occur and HIV/AIDS became a leading cause of death contributing to a decline in average life expectancy in some countries [2]. Health systems ill-equipped to deal with the burden of acute infectious diseases face a growing burden of other conditions and chronic diseases, co-morbidities and injuries. Defo suggested that basically descriptive transition models had not provided an explanatory framework, and proposed a multilevel model to guide research into mechanisms underlying exposure, occurrence and interactions between infectious diseases and other conditions over the life course, at the individual-, household- and macro-level [1].

Zuckerman *et al.* suggested that the epidemiological transition model can be integrated with the 'socio-ecological model', which incorporates inter-related systems influencing health, including the policy, economic and socio-cultural context, behaviour and biological systems down to the molecular and genetic level [5]. Wider determinants differentially impact population sub-groups distinguished by ethnicity and culture, educational level, socio-economic status or material circumstances [4]. The socio-cultural, material and ecological context into which children are born and interact affects their physical and mental development, and socially patterned factors perpetuate disparities in health and life expectancy [35]. The socio-ecological model characterised by a life course perspective, generational influences and multi-level determinants of health and disease provides a framework for intervention on public health reaching beyond individual- and biological-level risks [36].

The time dimension of the epidemiological transition model also complements evolutionary ecological perspectives on the changing relationship between humans and pathogens. Natural selection can affect morbidity patterns over the long term – for example, historical exposure of populations to falciparum malaria probably supported continuing prevalence of the sickle-cell allele that causes deleterious anaemia in homozygotes, as it protects heterozygotes against this infectious disease. The deleterious allele that causes cystic fibrosis protects against *Salmonella typhi*, the cause of typhoid fever, which may have contributed to continuing prevalence of the chronic disease [7]. The hygiene hypothesis suggests improvements in sanitation, hygiene and public health in populations that are now more affluent reduced gut flora and exposure in childhood to certain microorganisms critical for the development of immuno-regulatory functions, which might explain the increased incidence of chronic inflammatory diseases – allergic diseases such as asthma, and autoimmune diseases such as type-1 diabetes [5, 37]. An evolutionary ecological perspective also contributes to understanding the emergence of new infectious diseases. Human contact with animals has exposed people to new pathogens that can evolve the capacity for inter-human transmission, as in the 'first epidemiological transition'. HIV/AIDS and various human T-lymphotropic viruses associated with certain cancers have been linked with pathogens that infect other primates [5].

Infections and multifactorial aetiology

An epidemiological transition theory aimed at understanding not just describing changing patterns of morbidity and mortality can encompass evolutionary, environmental, economic, socio-ecological, cultural, behavioural and genetic influences on the relationship between humans and microorganisms, and their contribution to the development of morbid conditions over the life course relative to other factors. Infections can cause chronic disease, other conditions and disability in susceptible hosts in different ways – through progressive tissue pathology, organ decomposition or an immune or inflammatory response to persistent infection; the initial stages of infection may cause permanent deficit or disability (e.g. poliovirus-induced paralysis); or infection indirectly predisposes to chronic sequelae (e.g. maternal infection during pregnancy increasing the risk of neurologic or pulmonary deficit in infants) [38].

The appropriate methods for confirming infectious causation of morbid conditions and investigating multifactorial aetiology have been contentious. Methods are based on a pragmatic definition of a causal relationship – an association between categories of events or characteristics in which alteration in the frequency or quality of one is followed by a change in the other [39]. Criteria and guidelines for establishing whether a specific microorganism

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has a causal role in a morbid condition date back to Koch's postulates for assessing possible causal agents of infectious diseases. These required a consistent and constant association between a suspected causal pathogen and a disease, its isolation from an infected host, growth in pure culture, inoculation into a healthy host producing symptoms of the original disease and re-isolation from hosts infected in this way. Difficulties for investigating possible microbial involvement in conditions traditionally assumed to have non-infectious causes include the ubiquity of some microorganisms, some locating in tissues that are difficult to access, pathogens are no longer present or cannot be cultivated, or long periods before onset of chronic disease preclude testing the pathogen in a healthy host [40].

Hill rejected the idea of rigid criteria for assessing causality and suggested that various aspects of the evidence of association ('viewpoints') could be considered before deciding whether causality is the most likely explanation [41]. These included consistency, strength and specificity of association; existence of a dose–response relationship; exposure to infection preceding disease; an analogous relationship established as causal; and the plausibility of causality in the context of other knowledge about the disease. More recently, a pluralistic approach to assessing causality has been advocated, based on triangulation and integration of evidence from diverse types of study [42]. Despite the complexity of issues around causality and continuing debate over how it can be established, infectious causes have been widely accepted for several morbid conditions based on the evidence from different types of investigation, without strict adherence to Koch's postulates, other criteria or Hill's viewpoints [7, 38].

Various observations can suggest a possible infectious cause of an acute or chronic condition, including pathogens present in diseased tissue, an increased risk of the condition among the immune-suppressed, or a favourable response to antimicrobial therapy. Marshall and Warren basically complied with Koch's criteria when they found a bacillus, later named *Helicobacter pylori*, in almost all samples from patients with active chronic gastritis, duodenal ulcer and gastric ulcer, and after deliberately ingesting the bacilli, Marshall developed peptic ulcer and was successfully treated with antibiotics [43]. In the past, as among today's poor, insanitary domestic environments and large families with overcrowded living conditions would have been conducive to rapid transmission of infection [44]. Clearly, confirmation of infectious causation does not exclude the possibility of other endogenous and exogenous influences on the development of a morbid condition [7].

Infections and major chronic diseases

The confirmation in recent decades of infectious causation of conditions previously regarded as having no infectious causes constitutes a fundamental change in scientific understanding of human–microorganism interactions [7, 27, 40, 45]. A vast amount of research has been conducted into other conditions because of strong evidence of association with infections, and investigation continues into cardiovascular conditions, cancers, digestive, neurological, developmental and mental disorders, allergic, autoimmune or immune-mediated diseases and other conditions [38, 40]. Confirmation of infectious causes of conditions frequently recorded as causes of death can have significant public health implications, particularly if preventive interventions are feasible [46]. A brief consideration of research findings for the largest disease groups, cardiovascular disease and cancer, illustrates the potential significance for cause of death statistics, population disease profiles and the epidemiological transition model.

Many types of investigation and hundreds of studies have been reported on the association between *Chlamydophila pneumoniae* and atherosclerosis, the inflammatory process that contributes to coronary artery disease, stroke and other cardiovascular disorders [47–51]. Possible confounding by common cardiovascular disease risk factors, mixed results in antibiotic trials and evidence of association with other infections has cast doubt on an independent causal role [52–56]. A role in cardiovascular disease is also suggested by the association with CHD and acute myocardial infarction [54, 57], although respiratory infection in general is associated with a higher risk of heart attack or stroke [58]. Consistent evidence of a two- to threefold increase in the risk for acute coronary syndromes within 1–2 weeks of respiratory infection is supportive of a causal relationship based on Hill's viewpoints [59]. Several studies suggest an independent causal role for seasonal influenza in acute myocardial infarction and fatal heart attack [60], and there is some evidence of reduced risk in randomised trials of vaccination for cardiovascular patients [61]. In conjunction with other risk factors such as cigarette smoking, poor diet, harmful alcohol consumption, stress, physical inactivity, obesity/overweight, raised blood pressure, lipids or glucose and low socio-economic status [62, 63], certain common infections may contribute to chronic cardiovascular conditions and potentially fatal acute events. Suggested mechanisms for the latter include pro-coagulant effects, vasoconstriction, endothelial injury and a destabilising effect of inflammation on atherosclerotic plaques leading to embolism and thrombosis [58, 59, 64].

Association between respiratory infections and lung cancer has also been reported. Evidence of a raised risk following *C. pneumoniae* infection, with a dose–response relationship and higher risk for several years, suggests a possible causal role [65, 66]. Causative interactions may occur between infections, non-infectious environmental agents such as tobacco smoke and lung cancer [7]. The immune response in the lungs of smokers may be impaired, allowing infection and related inflammation to persist and damage cells, with an increased rate of cell division in the repair process increasing the risk of mutation [65, 66]. Studies in several countries also report higher risk of lung cancer following tuberculosis, even among non-smokers [67, 68], and pathological studies indicate association with scars caused by infection with *Mycobacterium tuberculosis* [69]. Plausible biological mechanisms include related inflammation damaging DNA, involvement of the tissue repair process in the initiation and survival of cancer cells and immunosuppression [67, 68]. When *H. pylori* was found to be associated with gastric cancer, it was confirmed as a causal agent on the basis of evidence from clinical, ecological and prospective epidemiological studies [70, 71]. Viruses have been confirmed as causal agents in some common cancers, including hepatitis C virus (HCV) in non-Hodgkin's lymphoma; HCV and hepatitis B virus (HBV) in hepatocellular carcinoma; and human papillomavirus (HPV) in cancers linked with sexual activity such as cervical cancer, one of the commonest cancers in women [72]. Epstein–Barr virus (EBV) infects almost everyone and causes lymphomas and nasopharyngeal carcinoma in some cases, often in combination with infections suspected of a role in other cancers [73–76]. So far, an estimated 16% of all new cancers are attributable to the confirmed infectious causal agents mentioned here – 7% in 'developed' regions of the world and 23% in 'less developed' regions [72].

With a vast amount of research in progress into the role of infectious diseases in cancers, cardiovascular disease and most

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other morbid conditions frequently recorded as the underlying cause of death, it is premature to speculate about their contribution to overall mortality. Infectious diseases recorded as the underlying cause of death still make a substantial contribution – about 17% of deaths worldwide are classified as due to 'infectious and parasitic diseases', 'influenza' and 'pneumonia' [77]. For Africa, the proportion has been estimated at 40% [2]. For England and Wales, it is about 6%, although the contribution of infectious diseases to other conditions recorded as the underlying cause of death is not taken into account, and only 4% of deaths are due to external causes and conditions that definitely do not have an infectious cause [78].

Further research and prevention

Advances in laboratory technologies, experimental methods and epidemiological study design have increased the scope for investigating cryptic relationships between infectious diseases and different morbid conditions. The ability to establish links more precisely has overcome some of the difficulties in applying Koch's criteria for causality [7, 27, 38, 46]. Advances in DNA sequencing technology have contributed to understanding genetic susceptibility and numerous rare disorders that altogether affect a large number of people. Genome-wide association studies have revealed a vast number of common DNA variations linked with the risk of developing common chronic diseases, although most variations identified so far relate to a relatively small incremental risk [79]. Identification of a genetic causal factor does not rule out the possibility of infectious causation, and interactions between genetic, infectious and non-infectious environmental factors can be involved [7, 45]. Screening for microorganisms suspected or confirmed as causes of chronic disease will allow their contribution to morbidity and mortality relative to other causal factors and determinants to be investigated [80]. Inclusion of rigorous laboratory techniques in surveillance systems and in the design of epidemiological studies facilitates longitudinal investigation. Long-term follow-up can identify the optimal time for prevention or treatment of infection to disrupt the development of a chronic disease in hosts with genetic susceptibility, co-morbidities or other risk factors [38, 46]. Many life style-related risks for developing chronic disease are well established, although further investigation at the individual level could contribute to a more complete understanding if past and current infections are taken into account.

Prevention focused on life style-related health risks is recognised as a priority for global action on chronic disease – tobacco control, reducing harmful consumption of alcohol and promoting healthier diets and physical activity [81]. As the burden of chronic disease and disability increases, many people in low-income countries will not have access to expensive treatments available to those in other countries. Although they are much more likely to die from infectious diseases than people in high-income countries [33], they are increasingly exposed to health risks common to various other conditions. Marketing campaigns promote foods with high fat, sugar and salt content, and tobacco companies target women and children in low-income countries using strategies banned in some industrialised countries [82]. Those better off may adopt unhealthy consumption patterns earlier, but they respond more quickly when information becomes available on how to avoid health risks [83]. An understanding of socio-cultural context is necessary for the development of appropriate health education interventions at the community- and national-level. Prevention of chronic diseases is a priority for both high- and low-income countries in view of the future costs for treatment and health care for a growing number of older people. Low-income countries require resources to meet this challenge in addition to those required for the control of infectious diseases in support of global health [82].

International efforts to control infectious disease face major challenges, including antimicrobial resistance, emerging diseases, warm climate diseases, pandemic diseases such as influenza, the persistence in poor countries of infectious diseases that used to cause high mortality in the West, and infectious diseases that may not be severe, but are now known to cause other morbid conditions. Much ill health and disability in low-income countries is a consequence of early childhood infections that are largely preventable, such as malaria, meningitis, Japanese encephalitis, diarrhoeal diseases, parasitic diseases and trachoma [46]. Following the success of smallpox eradication, immunisation programmes have been highly effective for the prevention of childhood infectious diseases worldwide, including measles, whooping cough, diphtheria and poliomyelitis. The scope is expanding as new vaccines become available and the focus shifts from early childhood to a life course approach [84]. Inclusion of HBV vaccine in childhood immunisation programmes has reduced the incidence of liver cancer in some countries where it was once common, although high infection rates persist in parts of Asia and Africa [46]. Maternal–infant transmission of HBV is preventable through vaccination [85], and vaccines effective against HPV are available for the prevention of cervical cancer [86].

The protective effect of HPV vaccines against breast cancer is under investigation, although establishing causality is difficult as co-infections may be involved [74–76]. Clinical trials of vaccination against respiratory infections in both LMICs and high-income countries could provide evidence regarding any protective effect against cardiovascular conditions and acute events [46]. Effective influenza vaccination for older people is particularly important given the risk of stroke or heart attack for those with underlying cardiovascular conditions [64]. As children are often the source of adult respiratory infections, evidence that vaccinating children against influenza may reduce the risk of cardiovascular events among older people invites further investigation [87]. Studies of preventive interventions against tuberculosis in populations with high prevalence could assess any impact on the incidence of lung cancer. Immunisation could become cost-effective for reducing the prevalence of infectious diseases that cause other morbid conditions, particularly when the pathogen may be a causal agent in more than one, such as EBV, *H. pylori* and *C. pneumoniae*. Possible interactions between *H. pylori* infection and other non-infectious environmental agents such as tobacco smoke and smoked foods suggest possibilities for the prevention of stomach cancer in low-income countries through behaviour change, improved hygiene and better sanitation [7, 88, 89]. Reducing the incidence of *H. pylori* infection in childhood could reduce the risk of both stomach cancer and peptic ulcer later in life [46]. Early detection and antimicrobial treatment of pharyngitis can prevent rheumatic fever, the inflammatory manifestation of group A streptococcal infection that can lead to rheumatic heart disease, a common cause of death among young adults in low-income countries [46, 85].

The relative contribution to overall mortality of rheumatic heart disease, stomach cancer and other diseases with predominantly early life determinants has declined in England, partly reflecting past interventions benefiting children's health [63]. Experiences in childhood are critical for life chances and adult health, and

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investment in child health and education is now a recognised priority for action on the social determinants of health [32]. Health inequalities in England reflect large socio-economic differentials for chronic diseases such as CHD and respiratory disease linked with socially patterned factors acting over the life course, or mainly after childhood in the case of lung cancer [63]. Males and females living in socio-economically deprived neighbourhoods in England had much higher death rates in 1999–2003 than those living in less deprived areas in the same region, with particularly wide differentials at ages 15–64 years for these diseases [90]. Socio-cultural processes perpetuate health risks such as poor diet and smoking in materially and socially disadvantaged groups, contributing to persistent health inequalities [35, 63].

Conclusions

Although mortality differentials persist between socio-economic groups within high- and low-income countries [32, 90, 91], human beings in general have benefited from improvements in child survival and life expectancy. Public health and preventive measures aimed at protecting people from severe infectious diseases are likely to have contributed most to the decline in mortality [17], and the ongoing global epidemiological transition is fundamentally linked with efforts to control infectious diseases. Apart from setbacks in materially poor or remote populations affected by severe infectious diseases, and in countries undergoing rapid political, economic and social change, human intervention has resulted in a transition characterised by lower child mortality, an upward shift in age at death, increased life expectancy, a higher proportion of older people in the population and a reduction in the proportion of deaths for which an infectious disease is recorded as the underlying cause.

In the past, epidemiological transition models, with little focus on aetiology, have been basically descriptive rather than explanatory, and possibly misleading because infectious diseases cause a variety of potentially fatal morbid conditions. Infectious causation has been confirmed through clinical, observational and epidemiological studies, and is suspected for many other conditions because of strong evidence of association. Possible infectious causes are being investigated for most of the morbid conditions now frequently recorded as causes of death [38, 40]. Conditions found to have infectious causation may still be recorded as the underlying cause of death – the disease or condition initiating the morbid process leading to death. The infectious disease can be recorded as an antecedent or coexisting condition where appropriate, and multiple-cause coding allows comparative statistical analysis of these conditions. Certification based on the ICD guidelines for distinguishing the underlying cause from other conditions is the basis for the cause-specific mortality statistics widely used to inform public health policy [8]. A framework for comparative research on disease and mortality profiles and epidemiological transition could be based on five broad groups of underlying cause of death — infectious diseases (diseases only caused by microorganisms), other conditions with an identified infectious cause, conditions that can have an infectious or non-infectious cause, conditions for which infectious causes are not ruled out and conditions that are definitely not caused by infectious disease. Further research into infectious and other causes of conditions frequently recorded as the underlying cause of death or an antecedent will determine the degree to which the earlier dichotomous view of epidemiological transition is altered by empirical evidence.

Infections interact with non-infectious environmental agents and genetic factors over the life course, and a better understanding of chronic diseases and co-morbidities in terms of the balance between these biological-level causes requires integrated research. Humans have evolved as social as well as biological beings [35], and knowledge of socio-ecological and historical context will contribute to a more comprehensive understanding of disease causation at both the individual- and population-level [92]. Life style, culture, social and economic circumstances, and access to material resources, education and health services affect the risk of morbid conditions developing, and contribute to mortality differentials between national populations and between sub-groups [32, 35, 63, 93]. Some measures that could reduce health inequalities or benefit whole populations lie beyond the scope of traditional public health policy, requiring changes in social, economic or environmental policies, and in human activities that affect health [94, 95]. Within the sphere of public health policy, the control of infectious diseases and prevention of serious illness are key objectives. A better understanding of the contribution of infections to acute and chronic conditions, disabilities and mortality relative to other causes and determinants, will inform the development of targeted preventive interventions and broader health strategies. The infectious disease environment continues to have a major ecological influence on health globally. New pathogens are emerging, severe forms of infectious disease are resurgent or persistent, and common infections and related immune or inflammatory responses contribute to conditions that together account for a substantial proportion of overall morbidity and mortality. A theory of epidemiological transition aimed at understanding not just describing changing patterns of disease and mortality can encompass the role in different morbid conditions of infections contracted over the life course.

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