CHAPTER 2. THE IMPACT OF POPULATION GROWTH ON THE EPIDEMIOLOGY AND EVOLUTION OF INFECTIOUS DISEASES

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Abstract. It is generally expected that in developing countries the epidemiological transition, with improved health and lower mortality rates, will eventually lead to a demographic transition with lower fertility rates. The reductions in mortality characterising the epidemiological transition are often associated with controlling the infectious diseases within populations, which leaves the chronic diseases associated with old age, cancer and heart disease dominating the causes of death. However, if the demographic transition does not occur quickly, populations can grow rapidly, creating an increased potential for spread of infectious disease. These infectious diseases could, in turn, increase death rates amongst young people and reverse the epidemiological transition. The relationship between population growth, size and infection depends upon the changes in contact pattern associated with there being more people. If facilities can keep pace with growth, then the increase in contact rates can be kept to a minimum, and the potential reversal in the epidemic transition prevented. This makes development a crucial adjunct to population growth if the global community is not to be increasingly exposed to pandemics of infectious disease. Here we review the epidemiological and demographic theory which relates population growth and infectious disease.

Introduction

The biology of obligate infectious organisms is inextricably linked with the biology and behaviour of their host populations. Organisms that invade another species to gain the building blocks or energy for their survival and reproduction rely on transmission from host to host if they are to succeed. This transmission is a function of the natural history of the infection and the contact patterns of the host [1]. Clearly, the demography of the host population has an enormous role to play in determining both the supply of hosts and the contact patterns between them. Since the opportunities for parasitic organisms

are a function of host demography, changes in host population size, density and structure alter the environment within which pathogens are selected and play a role in their evolution. Concomitantly infectious diseases contribute to the demography of host populations influencing patterns of mortality and fertility. In this review we will describe the different ways in which demographic changes influence the epidemiology of infectious diseases and explore the patterns of population growth and movement that are likely to play an important role in the emergence and re-emergence of infectious diseases.

Parasites, in the current context, include all organisms that live within another organism, and do that organism harm, and include representatives of the prions, viruses, bacteria, fungi, protozoa, helminths and insects. These pathogenic organisms range widely in the frequency and severity of the disease symptoms they cause and the transmission routes through which they spread. The routes of transmission determine how the infections will be influenced by demography, as do the strategies used by the organisms to exploit their niche. Popular writings often depict the infection enjoying an easy life of rich pickings from an unwitting host [2]. In truth, the immune responses of the host and the hurdles to transmission, impose severe selective pressures on the parasites. Thus, there are always strategies employed by the parasite to avoid the immune system, either through racing the production of immune effectors or avoiding them through cryptic or changing surfaces. This tends to generate two types of life histories: either short-lived rapid-reproduction parasites such as the simple viruses and bacteria (e.g. measles, mumps, rubella, influenza and gonorrhoea), or long-lived slow-reproducing infections (e.g. herpes simplex, tuberculosis, syphilis and HIV). Since the resolution of infection within the host destroys that population of infectious organisms, infectious diseases are in part subject to group selection. However, it should be remembered that the individual organism is also competing intra-specifically within the host and that future generations of infection will represent the genotypes of organisms that manage to transmit. In any consideration of evolutionary strategies it is important to remember that evolution is blind. The flu virus does not consider the future problem of widespread immunity following an influenza pandemic and *Neisseria meningitides* does not consider its future success when it invades the host in a selective dead end, with catastrophic consequences for the host and itself. What we observe in nature are either transient epidemics of infectious disease, which spread with short term success, but which will die out, or infectious diseases that have found a strategy to allow them to persist.

In developing our understanding of the interaction between demography and infectious disease epidemiology, it is worth considering the type and quality of evidence available to us, and how we progress from anecdote to general rules and from speculation to theory. A detailed knowledge of the natural history and transmissibility of infections from observational studies, allows us to speculate about how changes in host population structure may have influenced their epidemiology. Historical and archaeological records of population size and organisation, along with evidence of patterns of disease and death, provide examples of coincident changes, including the invasion of new pathogens as civilizations were formed, through to the reductions in disease associated with improved hygiene and living conditions [3]. Other ecological comparisons between populations are instructive, allowing us to compare the success of different types of organism in different locations [4]. Theory has a role to play, since if we can predict patterns of disease based on our hypotheses, we can then

test the hypotheses by comparison with experimental and observational data [5]. In understanding the contribution of infections to demography, records of mortality and its causes are vital. However, in the frequent absence of detailed records we have to rely on theoretical estimates based on what we know of the distribution and consequences of particular infections. This is particularly true of the influence of infectious diseases on fertility where limited numbers of detailed studies have to be related to the global distribution of infections. In studying both the impact of demography on infections and vice versa, general principles are derived from particular examples. However, the examples are never typical since it is specific pathogens such as bubonic plague, tuberculosis, malaria, influenza and HIV that dominate the relationship between infections and demography. Thus, throughout our discussion we have to relate to the particular characteristics of the key pathogens.

Three variables influence the potential for spread of an infection: the duration of infectiousness (D); the contact rate (c); and the likelihood of transmission if there is a contact (p): the duration of infectiousness determines how long an infection stays prevalent to expose others; the contact rate and transmission probability are variables in the transmission from infectious to susceptible individuals [1]. The product of these three variables is termed the basic reproductive number R_0, such that $R_0 = Dcp$ and represents the number of infections caused by one infectious individual in an entirely susceptible population. Thus, the basic reproductive number has to be above one for there to be a risk of an infection spreading. The influence of population size on the contact rate is central to the impact of population growth on infectious disease epidemiology. The incidence of infection is the product of the number of susceptibles (X) and the "force of infection" (λ); the per susceptible risk of acquiring infection, which is a function of the number of infectious individuals (Y) within the population, such that $\lambda = pc\, Y/N$, where N represents the population size.

The Impact of Population Size and Density on Contact Patterns

Whether the growth of a population influences the potential spread of an infectious disease depends upon how the number of individuals influences the patterns of contact and exposure. If population growth leads to greater crowding, more contaminated water supplies, or higher numbers of sexual contacts per person, then the contact rates allowing the transmission of many diseases will increase, making epidemics more likely. Alternatively, if expanding populations have additional geographic space, additional services and no change in sexual norms then the number of contacts can remain constant and no change in risk of epidemics occur. The two types of increase are illustrated in **Fig. 1**. Two extreme patterns have been identified [6]: first "density dependent transmission" in which the number of contacts increases as population size and hence density increase; in its extreme form there is a linear relationship ($c = c_D N$) and the transmission term takes the form

$$X\lambda \equiv Xpc\, Y\!\!\Big/\!_N \equiv Xpc_D N\, Y\!\!\Big/\!_N \equiv Xpc_D Y.$$

In this case $R_0 = Dc_D\, Np$, and hence there is a threshold population size, below which the basic reproductive number is less than one, above which it is more than one. With the transmission term above, the threshold population size for the inva-

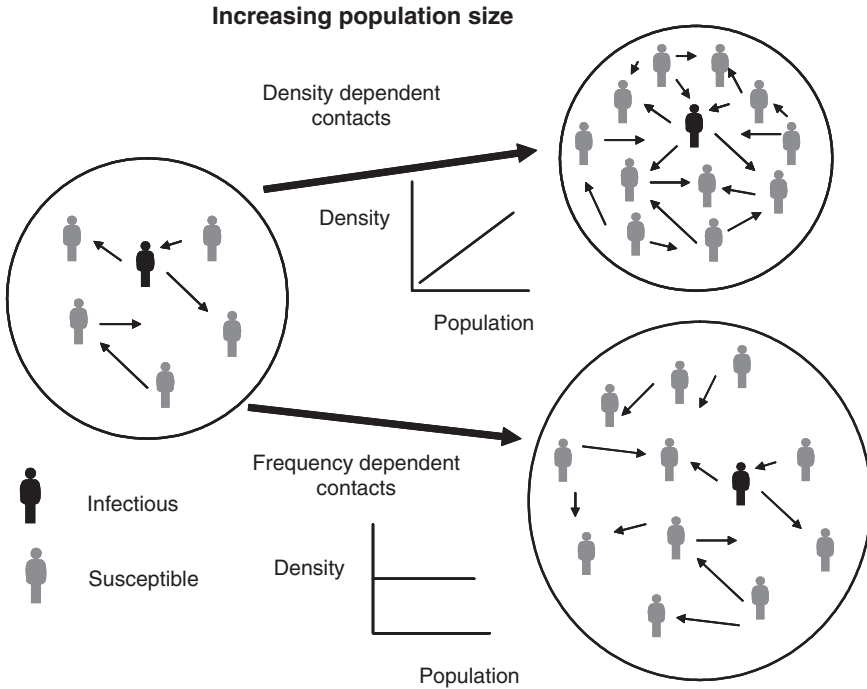**Increasing population size**

Fig. 1. Illustration of the two patterns of population growth: the first, in which density and contacts for infection increase; the second, where density remains constant and contacts remain constant

sion of an infection is given by the equation: $N_T = 1/(Dc_D\,p)$. Thus, the greater the transmission probability and duration of infection the smaller the population size in which an infection can invade. If population size does increase the contact rate, then growing populations will allow epidemics of organisms that have lower transmission probabilities and durations if they cross species barriers or evolve from other pathogenic or commensal organisms. The alternative type of transmission pattern is "frequency dependent transmission" where the rate of contact is independent of population size ($c = c_F$) and the transmission term takes the form $X\lambda = Xpc_F\,Y/N$. In this case there is no threshold population size for the invasion of the population since the basic reproductive number is independent of population size $R_0 = Dc_F\,p$. There has been much debate about which form is "correct", together with evidence from the field and from animal experiments [7, 8]. In reality it is likely that the relationship between population size and contacts will depend upon the local circumstances and the particular routes of transmission. So for example if safe water supplies are guaranteed as a population grows there will be no increased risk of water borne infections; if mosquito breeding sites are not allowed to proliferate than there should be no increase in mosquito vectored pathogens; if people maintain steady numbers of sexual relationships then sexually transmitted infections (STIs) will not increase; if hand washing and food hygiene is maintained then nosocomial infections and directly transmitted faecal orally transmitted infections should not increase; if rates of injecting drug use behaviour do not increase, sterile medical supplies are maintained and blood supplies

are screened, then blood born pathogens should not increase; and, hardest to envisage, if crowding and density of population stay the same, then increased population size should not increase the rate of spread of infections borne in aerosols. However, growing populations place strains on the resources available; where these resources cannot keep pace, rates of contact and risks of epidemics will increase. If, with growing populations, individuals want to take the opportunity to mix in larger social groups or have more sexual partners then the infections which depend upon these forms of contact will thrive. It is likely therefore that growing populations do lead to a greater risk of infectious disease spread, but there are opportunities to combat this trend.

The Supply of Susceptibles Through Birth and Immigration

Analyses of the persistence of measles in cities and islands indicated that there was a threshold population size required for the persistence of the virus (i.e., the consistent presence of infection in the community) [9]. This was initially taken as evidence for a threshold population size for *invasion* and hence a density dependent transmission term. It also supported the belief that larger populations associated with the introduction of agriculture in early human history allowed for the invasion of directly transmitted simple viral infections such as measles and smallpox [10]. However, the ability of an infection to invade a population is not synonymous with the ability of an infection to persist [11]. Either through mortality decreasing population sizes or through inducing acquired immunity, infections are likely to reduce the numbers of susceptibles available to maintain chains of infection. New susceptibles are required to maintain an endemic infection and these susceptibles can be provided by loss of immunity, immigration or births. Thus, large populations and growing populations accrue susceptibles rapidly making it more likely that an infection will be able to persist [12]. A very rapid supply of susceptibles, as is the case for bacterial infections where recovery is back into a susceptible state or in the case of large growing populations, allows a continual high level of incidence. A slow supply of susceptibles is likely to lead to reductions in infection numbers or even stochastic fade out and elimination of the infection. Low numbers of infections will allow a build up of susceptible numbers in the population and new epidemics occur, leading to oscillation between epidemic and interepidemic periods. In a deterministic system we would expect to see damping of the oscillations over time, but epidemics continue because of seasonal variations in contact rates, as occurs with school attendance, and due to stochasticity [1]. The faster the rate of resupply of susceptibles as a function of population size and population growth, the more frequent epidemics will be and the more stable with a regular endemic level of infection the system will be [12].

The need to maintain susceptibles applies in the case of both density dependent and frequency dependent transmission. In the former it is both the number and proportion of the population susceptible that matters. The effective reproductive R_t number is the number of new infections caused by a single infection at any given time and equals 1 at the endemic steady state. The effective reproductive number in a homogeneous population is simply the basic reproductive number times the proportion of the population susceptible.

$$R_t = R_0 \frac{X}{N} = R_0 x.$$

Thus, at the endemic steady state the proportion of the population susceptible x is simply the inverse of the basic reproductive number. As the number of susceptibles increases, an epidemic becomes possible once the proportion susceptible exceeds this inverse of the basic reproductive number. If an infection causes mortality and drives down a population size, but does not induce acquired immunity, the recruitment of numbers to the population is what matters. In the case of frequency dependent transmission a fatal infection that can spread has the potential to drive a population extinct if death rates exceed birth rates, unless something else reduces the spread of infection, such as behaviour change.

The predicted changes of disease incidence have been observed in a detailed analysis of the spatial and temporal patterns of measles incidence within the UK [13]. Here, before the introduction of vaccination, epidemics of measles originated in the large cities of London and Manchester from which they spread as travelling waves. During the "baby boom" years of the 1960s in the UK there was an increased rate of supply of susceptibles, and an even more regular pattern of epidemics every two years was seen. Vaccination when it is introduced greatly increases the time taken for sufficient numbers of susceptibles to accrue and thereby increases the interepidemic period [13]. Within this analysis, Liverpool, prior to vaccination, is particularly interesting since it had higher than average birth rates associated with a large immigrant, Catholic population and consequently had yearly epidemics of measles [12], as had New York [14].

Thus, large and growing populations are more likely to maintain an infection and suffer repeated epidemics prior to vaccination. The mean age of infection also depends upon the frequency of epidemics and the birth rate. A higher rate of births should lead to a higher reproductive number and thereby a lower age of infection. This has been observed in Guinea-Bissau where infection with measles amongst urban children occurred at a lower age than in their rural counterparts [15]. Additionally, the high incidence of meningitis in West Africa reflects the high reproductive number of the bacterial infection in these communities [16]. In growing populations such as these the period between loss of maternally derived antibodies and infection is limited, leaving a limited period for vaccination as children age [17]. This led to efforts to develop a measles vaccine able to immunize children in the presence of maternally derived antibodies (which unfortunately had to be withdrawn following observations of increased non-specific death rates associated with vaccination) [18]. As vaccination becomes widespread, the mean age of infection increases, because susceptible individuals take longer to come into contact with infection, which should allow a greater window of opportunity to vaccinate. However, if there is poor vaccination coverage or efficacy, the growing population makes outbreaks more likely, since the speed of growth in susceptible numbers is greater and the critical number or proportion of the population susceptible is likely to be realised sooner.

The increase in the mean age of infection that follows vaccination programmes can be problematic since for many infections severity increases with age. Examples

include polio infections, where paralysis rates were associated with an increased age of infection with improved hygiene [19]; chickenpox, where encephalitis and pneumonia are associated with infection in teenagers and young adults [20]; mumps, where orchitis is associated with post pubertal infection in males [21]; and rubella, where there is a risk of congenital rubella syndrome when pregnant women acquire infection. Indeed, in Greece—with vaccine coverage rates of less than 50%—there was an increase in the absolute rates of congenital rubella syndrome compared to the period before the vaccination programme was implemented [22].

The Impact of Epidemic and Endemic Disease on Mortality

There is no doubt that infectious diseases are a major cause of mortality in populations, which because of the young age of many of those infected and dying, can contribute to the loss of many life years. In healthy well nourished hosts the fatality rate (the proportion of infections leading to death rather than recovery) associated with the majority of infections is low. When health care provision and nourishment is adequate then mortality associated with infectious diseases is concentrated in those with underlying vulnerability, such as the elderly and immunocompromised, where rates of death from competing causes are high and the demographic impact of the infection is slight [23]. In resource-poor settings deaths from respiratory and diarrhoeal diseases are common in infants and young children. Here it is estimated that measles, malaria, tuberculosis, and pneumococcal infections cause 5 million deaths each year, which is nearly a tenth of global deaths [23]. It is relatively rare for infections to be associated with death in young adults; and it is perhaps particularly their fatality rate in young adults that makes the bubonic plague, syphilis, Spanish flu and AIDS notable historic events [3].

The demographic impact of an infectious disease depends upon the incidence of infection, the fatality rate, the age at which deaths occur and how long lasting the pandemics are. The importance of this last point was neatly captured by Thomas Short, following an analysis of bills of mortality, when he comments that "endemics may reign centuries but not epidemics" [24]. Over the long term a relatively small but continuous increase in mortality rates has a greater effect than acute large scale mortality. This is illustrated in **Fig. 2** where three acute mortality events in an exponentially growing population are compared with increases in the mortality rate over time. The time taken to recover from a given die off will depend upon the subsequent per capita population growth rate and is given by the equation

$$T = \ln (1 - \delta)/-r,$$

where δ is the fraction of the population dying and r is the per capita growth rate. Estimates of the initial mortality associated with the Black Death in Europe in 1347 and 1348 have altered from a high of 85% to a low of 5%, but are now believed to have been around 50% on the basis of records from institutions such as monasteries. However, it was the repeated epidemics, which followed the first and kept returning into the fifteenth century that reduced the populations [25].
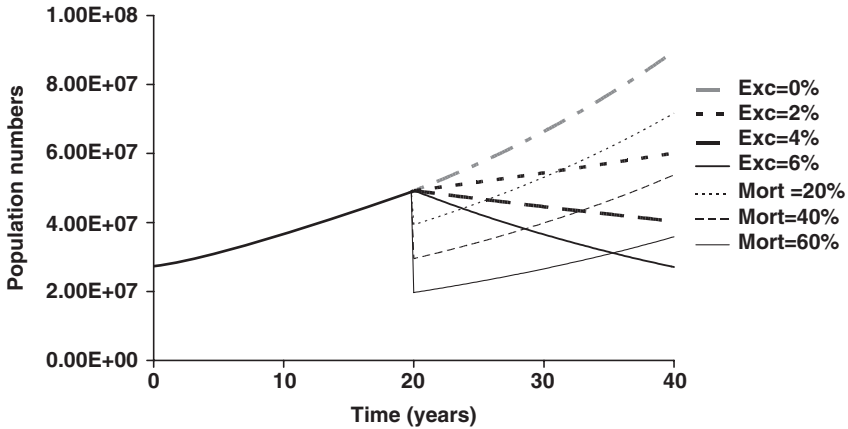
Fig. 2. The impact of infection associated mortality on a population growing at 3% per year. An acute mortality event killing off 20, 40 and 60% of the population (mort) is compared with a continuous 2, 4 and 6% increase in the mortality rate (Exc)

The demographic impact of AIDS is a source of debate. The virus is associated with an almost unprecedented high fatality rate, with seemingly all those infected dying eventually; and the infection is predominantly amongst young adults. This has to be balanced against the length of time it takes for HIV infection to progress to AIDS and death, and the low prevalence of the virus found in many populations. In the absence of treatment HIV takes an average of 10 years to cause death [26], this means that at an endemic state each 10% increase in HIV will increase the death rate by 1%. In addition vertical transmission of HIV to around 30% of children born to infected mothers [27] would lead to rapid childhood death in 3% of births with prevalence at 10% in women attending antenatal clinics. Thus, the prevalences of 30% seen in some locations in sub-Saharan Africa [28] might be expected to reduce a 3% population growth rate to zero. However, such prevalences are only generally observed in urban and semi-urban locations where fertility and birth rates are relatively high and growth rates in the absence of HIV would have exceeded 3% [29]. Thus, predicted negative population growths have not been observed in detailed studies. Furthermore, the observed prevalences are probably at the peak epidemic prevalence. As mortality due to AIDS increases then those initially most at risk of acquiring and transmitting infection are no longer present, and populations tend to reduce their risk behaviours [30, 31]. To maintain over time a given increase in death rates the prevalence of HIV would also have to be maintained. Thus, in a stable population a continued incidence of 3% across the population would be required to maintain a 3% increase in death rates. The AIDS epidemic is likely to reduce life expectancy and growth rates in many developing countries. However, if the death and disease associated with the virus undermines development and health it may delay or prevent the demographic transition and in the long run lead to larger rather than smaller populations.

The Impact of Infectious Diseases on Fertility

A number of infections have the potential to influence fertility as well as mortality. Gonorrhoea and chlamydia can cause pelvic inflammatory disease and lead to scarring of the fallopian tubes, causing sterility. Syphilis and HIV seem to reduce observed fertility in part due to early spontaneous abortions [32, 26]. The use of antenatal screening for syphilis and HIV allow for treatments to reduce neonatal syphilis and vertical transmission of HIV, but these are too late to prevent early foetal loss. The biological proximate determinants of fertility reduce population growth, as observed in Uganda and other African countries [33]. If they are removed, they are likely to be replaced by other proximate determinants limiting fertility, such as increased contraception and abortion [34]). As sexually transmitted infections (STI) are generally transmitted in a frequency dependent fashion (i.e., risk depends upon the distribution of numbers of sexual partners of individuals which are unlikely to be greatly influenced by overall population size [35]), then population growth should have little impact on the spread of these sexually transmitted diseases which reduce fertility. However, there is some evidence of increased risk behaviour in urban populations and among migrant labourers [36]. This, along with the lack of access to timely and appropriate health care and the exchange of sex for material goods and money, would increase rates of sexual partner change and the incidence of STI. Thus if population growth is associated with worsening socio-economic conditions then it could increase infertility along with death rates.

The impact of STIs on fertility depends upon the incidence of infection, the rate of complications and infertility and the age of infection amongst women in relation to their childbearing years. A recent survey of data from sub-Saharan Africa suggested a population attributable decline in total fertility of 0.37% (95% CI: 0.30%, 0.44%) with each percentage point of HIV prevalence [37, 38]. The high incidence of chlamydia in young women, which can lead to permanent primary or secondary sterility, means that it potentially has a major impact on birth rates. However, the actual rates of tubal occlusion are difficult to estimate since natural history studies are clearly unethical, and sterility can be difficult to detect especially if it follows earlier child birth. Assuming that 60% of chlamydial infections lead to salpingitis and that 20% of these develop bilateral tubal occlusion, then 12% of infections would lead to infertility. Then, as seems reasonable, assuming a six month duration of infection the incidence of infection would be twice its prevalence. Thus if women have a 5% prevalence of infection they should have a 10% incidence and a risk of sterility of 1.2% per year. The expected cumulative incidence of infertility as a function of years in the reproductive age classes associated with different incidences of an STI such as chlamydia or gonorrhoea is illustrated in **Fig. 3**. Assuming a constant net birth rate per woman over the 35 reproductive years the reduction in the total fertility rate associated with a particular prevalence of the bacterial STI can be calculated (**Fig. 4**). This relationship clearly depends upon the estimated rates of sterility associated with incident STI infection and the relationship between age specific rates of acquiring infection and births. Since high risk sexual behaviour and risk of STI infection is associated with sexual debut and pre-marital sex [39] our calculations, based on a constant age specific fertility, are likely to be conservative.
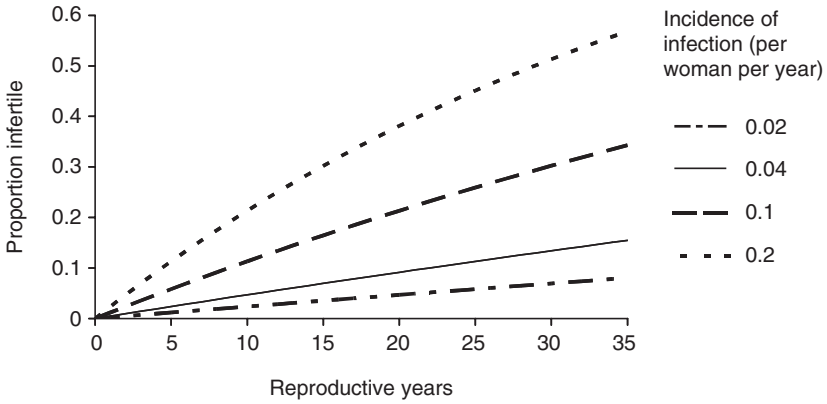
Fig. 3. The relationship between incidence per woman per year and the cumulative rate of infertility assuming that new infections are independent of past infection and a 12% risk of infertility for each infection
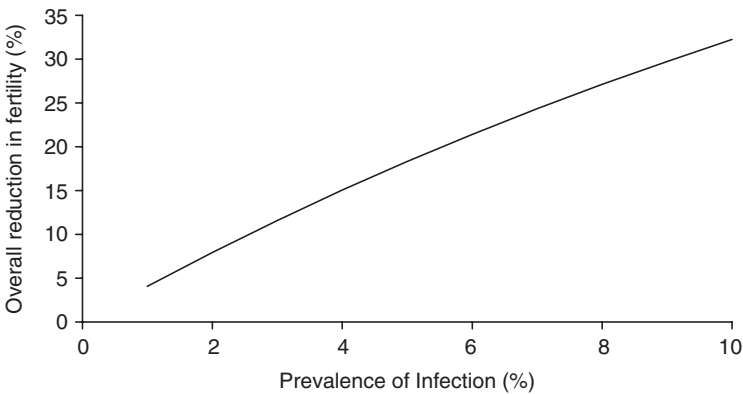

Fig. 4. The reduction in total fertility rate associated with different prevalences of a bacterial STI which causes sterility in 12% of infections and does not induce immunity. The results assume a constant age specific net fertility rate in the absence of sterility and a constant age specific incidence of infection

**The Future: The Epidemiologic and Demographic Transition
and the Re-Emergence of Infections**

Population growth has three major consequences for infectious disease: (1) the sheer scale of cities provides more opportunities for a disease to persist with a rapid supply of susceptibles. (2) The conditions associated with a growing population and

poverty generates increasing contact rates creating the conditions for epidemics. (3) The increases in travel and migration increase global contacts and turn epidemics into pandemics. Surveillance and health systems which are driven by the efficient management of current morbidity are ill equipped to deal with novel overwhelming spread of infections. Recent examples of emerging threats include severe acute respiratory syndrome (SARS) in East Asia [40], Ebola in Central Africa [41], avian flu in East Asia [42], and before that, Pulmonary Hantavirus Syndrome (PHS), which was associated with a 60% fatality rate leading to 51 deaths on its initial emergence [43]. Either these have failed to spread from person to person—or, if, like SARS, they have started inter-human transmission–they have had a low reproductive number and have been identifiable and preventable. (For SARS symptoms appear before infectiousness develops allowing for effective quarantine.) As we can learn from the great pandemics of history, the Black Death in Europe in 1347 and 1348 [3], syphilis in 1495 [44] and influenza in 1917–18 [45], such outbreaks can become devastating pandemics.

The impression is that the number of such events has been increasing, but improvements in modern communication and news network may have made apparent events of limited temporal and geographic scope, which would in the past have gone unnoticed. Such outbreaks are likely to be associated with increasing penetration of and contact with the environment [46], which has been on going for some time. However, the growth of populations may well have increased their frequency.

The possibilities of new pathogens jumping from animal to human increases as the absolute number of contacts with animals increases as human numbers increase and the evolution of novel infection types from non-pathogenic organisms also increases as the population size of the non-pathogenic organisms associated with humans expands. Once they do emerge their wide spread becomes increasingly likely. Large urban centres have grown rapidly in Asia and South America, and such expansion is expected to continue over the next few decades, with megacities, where the population is over 10 million appearing in India, China, Brazil and Indonesia (**Table 1**) [47]. These large populations provide places within which infections are likely to thrive. There is also the greatly increased connectivity of the world's population, with increasingly frequent and increasingly rapid travel. With air travel the majority of the world's population live within 36 hours journey time of each other [48].

Table 1. The number of cities with populations greater than 10 million [47].

	1950	1975	2000
Africa	0	0	0
Asia	0	1	8
Latin America	0	2	4
Europe	0	0	0
Japan	0	1	2
North America	1	1	2

Population growth along with the young, poorly resourced communities it creates is a major concern for both the local health and wellbeing of the populations, but also for global health. To tackle the symptoms, improved surveillance, quarantine and containment facilities in health care, along with the capacity for rapid aetiological research and the development of diagnostics and treatments are required to combat infectious disease. However, to tackle the cause, population growth needs to be accompanied by the provision of housing and services to reduce contact patterns, and by good vaccination coverage and health care; and the demographic transition needs to slow the growth of populations.

References

1. Anderson, R. M. & May, R. M. (1991). *Infectious diseases of humans: Dynamics and control*. (Oxford: Oxford University Press)

2. Nikiforuk, A. (1993). *The fourth horseman: A short history of epidemics, plagues and other scourges*. (London: Phoenix)

3. McNeill, W. H. (1976). *Plagues and peoples*. (New York: Penguin Books)

4. Ewald, P. W. (2002). *Plague time: The new germ theory of disease*. (New York: Anchor Books)

5. Little, T. J. & Ebert, D. (2001). Temporal patterns of genetic variation for resistance and infectivity in a Daphnia-microparasite system. *Evolution; International Journal of Organic Evolution*, *55*(6), 1146–1152

6. McCallum, H., Barlow, N. & Hone, J. (2001). How should pathogen transmission be modelled? *Trends in Ecology and Evolution*, *16*(6), 295–300

7. de Jong, M. C. M., Diekmann, O. & Heesterbeek, H. (1995). How does transmission of infection depend on population size? (In D. Mollison (Ed.), *Epidemic models: Their structure and relation to data* (pp. 84–94). Cambridge: Cambridge University Press)

8. Begon, M., Bennett, M., Bowers, R. G., French, N. P., Hazel, S. M. & Turner, J. (2002). A clarification of transmission terms in host-microparasite models: Numbers, densities and areas. *Epidemiology and Infection*, *129*(1), 147–153

9. Black, F. L. (1996). Measles endemicity in insular populations: Critical community size and its evolutionary implication. *Journal of Theoretical Biology*, *11*, 207–211

10. Bartlett, M. S. (1960). The critical community size for measles in the United States. *Journal of the Royal Statistical Society*, *123*, 37–44

11. Anderson, R. M. & May, R. M. (1986). The invasion, persistence and spread of infectious diseases within animal and plant communities. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *314*(1167), 533–570

12. Finkenstadt, B. & Grenfell, B. (1998). Empirical determinants of measles metapopulation dynamics in England and Wales. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, *265*(1392), 211–220

13. Grenfell, B. T., Bjornstad, O. N. & Kappey, J. (2001). Travelling waves and spatial hierarchies in measles epidemics. *Nature*, *414*(6865), 716–723

14. London, W. P. & Yorke, J. A. (1973). Recurrent outbreaks of measles, chickenpox and mumps. I. Seasonal variation in contact rates. *American Journal of Epidemiology*, *98*(6), 453–468

15. Aaby, P., Bukh, J., Lisse, I. M. & da Silva, M. C. (1988). Decline in measles mortality: Nutrition, age at infection, or exposure? *British Medical Journal (Clinical Research Ed)*, *296*(6631), 1225–1228

16. Sultan, B., Labadi, K., Guegan, J. F. & Janicot, S. (2005). Climate drives the meningitis epidemics onset in West Africa. *PLoS Medicine*, *2*(1), e6

17. McLean, A. R. & Anderson, R. M. (1988). Measles in developing countries. Part I. Epidemiological parameters and patterns. *Epidemiology and Infection*, *100*(1), 111–133

18. Aaby, P., Samb, B., Simondon, F., et al. (1996). Five year follow-up of morbidity and mortality among recipients of high-titre measles vaccines in Senegal. *Vaccine*, *14*(3), 226–229

19. Evans, A. S. & Kaslow, R. A. (1997). *Viral infections of humans: Epidemiology and control*. 4th edn. (New York: Plenum Publishing)

20. Garnett, G. P. & Grenfell, B. T. (1992). The epidemiology of varicella-zoster virus infections: A mathematical model. *Epidemiology and Infection*, *108*(3), 495–511

21. Siemer, S. W., Uder, M., Scholz, M., Steffens, J., Jeanelle, J. P. & Humke, U. (1997). Are low vaccination rates responsible for increased incidence of mumps orchitis in adolescents and adults? *Der urologe. Ausg A*, *36*(5), 456–459

22. Panagiotopoulos, T., Antoniadou, I. and Valassi-Adam, E. (1999). Increase in congenital rubella occurrence after immunisation in Greece: Rretrospective survey and systematic review. *BMJ (Clinical Research ed.)*, *319*(7223), 1462–1467

23. The World Bank (1993). World Development Report. Washington

24. Short, T. (1750). *New observations, natural, moral, civil, political and medical, on city, town and country bills of mortality*. (London: Longman & Millar)

25. Platt, C. (1996). *King death: The black death and its aftermath in late medieval England*. (London: UCL Press)

26. UNAIDS Epidemiology Reference Group (2002). Improved methods and assumptions for estimation of the HIV/AIDS epidemic and its impact: Recommendations of the UNAIDS Reference Group on estimates, modelling and projections. *AIDS*, *16*(9), W1–14

27. Dabis, F., Elenga, N., Meda, N., et al. (2001). 18-Month mortality and perinatal exposure to zidovudine in West Africa. *AIDS*, *15*(6), 771–779

28. UNAIDS. AIDS epidemic update (2003). Retrieved from http://www.unaids.org/en/Resources/Publications/Corporate+publications/AIDS+epidemic+update+-+December+2003.asp

29. Sewankambo, N. K., Wawer, M. J., Gray, R. H., et al. (1994). Demographic Impact of HIV-infection in Rural Rakai District, Uganda - Results of a population-based cohort study. *AIDS*, *8*(12), 1707–1713

30. Kamali, A., Quigley, M., Nakiyingi, J., et al. (2003). Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: A community randomised trial. *The Lancet*, *361*(9358), 645–652

31. Kilian, A. H., Gregson, S., Ndyanabangi, B., et al. (1999). Reductions in risk behaviour provide the most consistent explanation for declining HIV-1 prevalence in Uganda. *AIDS*, *13*(3), 391–398

32. Gray, R. H., Wawer, M. J., Serwadda, D., et al. (1998). Population-based study of fertility in women with HIV-1 infection in Uganda. *The Lancet*, *351*(9096), 98–103

33. Garnett, G. P., Swinton, J., Brunham, R. C. & Anderson, R. M. (1992). Gonococcal infection, infertility, and population growth: II. The influence of heterogeneity in sexual behaviour. *IMA Journal of Mathematics Applied in Medicine and Biology*, *9*(2), 127–144

34. Zaba, B. & Campbell, O. M. (1994). The impact of eliminating sterility on population growth. *Sexually Transmitted Diseases*, *21*(5), 289–291

35. Garnett, G. P. & Anderson, R. M. (1996). Sexually transmitted diseases and sexual behavior: Insights from mathematical models. *Journal of Infectious Diseases. 174*(Suppl 2), S150–161

36. Brunham, R. C. (1997). Core group theory: A central concept in STD epidemiology. *Venereology*, *10*(1), 34–39

37. Lewis, J. J. C., Ronsmans, C., Ezeh, A. & Gregson, S. (2004). The population impact of HIV on fertility in sub-Saharan Africa. *AIDS*, *18*(Suppl 2), S35–S43

38. Brunham, R. C., Garnett, G. P., Swinton, J. and Anderson, R. M. (1991). Gonococcal infection and human fertility in sub-Saharan Africa. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, *246*(1316), 173–177

39. Gregson, S., Nyamukapa, C. A., Garnett, G. P., et al. (2002). Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *The Lancet*, *359*(9321), 1896–1903

40. Riley, S., Fraser, C., Donnelly, C. A., et al. (2003). Transmission dynamics of the etiological agent of SARS in Hong Kong: Impact of public health interventions. *Science*, *300*(5627), 1961–1966

41. Leroy, E. M., Rouquet, P., Formenty, P., et al. (2004). Multiple Ebola virus transmission events and rapid decline of central African wildlife. *Science*, *303*(5656), 387–390

42. Normile, D. (2004). Infectious diseases. Stopping Asia's avian flu: A worrisome third outbreak. *Science*, *303*(5657), 447

43. Khan, A. S. & Young, J. C. (2001). Hantavirus pulmonary syndrome: At the crossroads. *Current Opinion in Infectious Diseases*, *14*(2), 205–209

44. Quetel, C. (1990). *History of syphilis*. (Cambridge: Polity Press)

45. Cliff, A., Haggett, P. & Smallman-Raynor, M. (1998). *Deciphering global epidemics*. (Cambridge: Cambridge University Press)

46. Morse, S. S. (1994). The viruses of the future? Emerging viruses and evolution. (In S. S. Morse (Ed.), *The evolutionary biology of viruses*. (pp. 325–335). New York: Raven Press)

47. UN Population Division (2001). *World urbanization prospects: The 2001 revision*. (New York: UN)

48. Habib, N. & Behrens, R. (2000). *Travel health and infectious disease*. (London: Nuffield Trust)