Global Climate Change and Infectious Diseases: Paradigms, Impacts, and Future Challenges

David Harley and Anthony McMichael
National Centre for Epidemiology and Population Health, Australian National University

Introduction

Global climate change as a result of human activity is now accepted as a reality by most people, including an ever-increasing majority of the world's political leaders. Potential impacts on human society and life are diverse, and include effects on industry, farming, transport, and tourism, as well as health. While social disruption and other effects, including extreme weather events and human migration, may ultimately have greater impact on health, infectious disease outcomes are also likely to be significant. The transmission of many infectious diseases is sensitive to climatic conditions, especially temperature and rainfall. However, there is considerable uncertainty and debate about the scale and timing of changes in infectious disease patterns to be expected. There is also very limited evidence of recent changes in infectious diseases that can be attributed, with reasonable confidence, to climate change at this early stage of the process.

In order to determine priorities for research and response, a coherent framework for understanding the relation between climate and infectious diseases is needed. Other priorities include the determination of appropriate measures of climate change effects and appropriate responses to these, and methods for attributing causality.

The scope of this paper is: to discuss transmission mechanisms for infectious diseases as context for understanding likely climate impacts; focusing primarily on vector-borne diseases, to discuss debate regarding assessment of climate impacts on these diseases; and finally to discuss future priorities and directions for research on climate change and infectious diseases.

Transmission mechanisms for infectious diseases with implications for potential climate change effects

1. Background

McMichael and Woodruff (1) define transmission mechanisms for infectious diseases as falling into four categories, direct or indirect transmission of anthroponoses and zoonoses. They review a number of direct and more complex impacts of climate change on host, pathogen and vector. This framework, rather than the more traditional host, agent and environment categorization, is useful in considering effects of climate on infectious disease transmission, and will be adopted here, with the addition of brief discussion of the effects on human behaviour and physiology as they relate to infectious disease risk.

1) Host

Many examples of climate effects on non-human hosts for infectious diseases could be cited. These include, for Ross River virus, the relation between rainfall and reproduction in kangaroos (1, 2). *Oncomelania hupensis*, an important host for *Schistosoma japonicum* in China (3) is sensitive to temperature, in that this is an important determinant for proportion of snails hibernating (4). An outbreak of the *Hantavirus* Puumula virus in Sweden occurred in 2007. While the population of the host, *Myodes glareolus*, the bank vole were high, they were not unusually so, and it is considered that a cause for the outbreak may have been reduced snow cover (which provides cover and food beneath it) leading the voles to seek cover in barns, consequently increasing contact with humans (5).

2) Pathogen

The concept of extrinsic incubation period is well understood for arboviruses, and is the period between ingestion of a blood meal to the presence of virus in the insect's salivary glands; it

is known to be influenced by temperature (6). The possibility that different transmission mechanisms for influenza predominate at different temperatures is raised by experimental work suggesting aerosol transmission is blocked at high temperature (30℃), but that contact transmission is not (7). Temperature also influences development of *Schistosoma japonicum* in *Oncomelania hupensis*, an important snail host (4). High temperatures and precipitation and consequent low swimming pool chlorine levels may have led to an outbreak of pharyngoconjunctival fever associated with *Adenovirus* in North Queensland in 2000 (8). Temperature is an important determinant for prevalence of colonization of chickens with *Campylobacter* in Iceland (9). In cooler areas of the globe the lack of malaria transmission relates to the inability of *Plasmodium* to develop at lower temperatures, rather than temperature effects on the mosquito vector (1).

Some pathogens are known to survive better at low than high temperatures, Rotavirus and respiratory syncitial virus being examples (1). *Cryptosporidium* oocysts maintained at 4 and 15℃ maintain infectivity, but at 20 and 25℃ are completely inactivated after 12 and 8 weeks, respectively (10).

3) Vector

Temperature is known to influence mosquito populations. *Culex annulirostris*, an important vector for Ross River virus (11) is known to be sensitive to changes in temperature in the larval stage, with 100% larval mortality at 10 and 40℃, and with time for larval development ranging from 8.57 to 37 days, at 35 and 15℃, respectively (12). The distribution of *Anopheles farauti*, a malaria vector in Australia, is limited particularly by temperature and humidity (13). The African malaria vector *Anopheles gambiae* develops from larval to adult stages at temperatures between 16 and 34℃, but with high larval mortality towards the upper limit of this range (14).

Ixodes ricinis, a vector for *Borrelia burgdorferi*, the causative agent for Lyme disease, was found at higher densities in 2003-2005 than 1999-2001 at higher altitudes in Neuchatel, Sweden, and this was thought possibly due to higher temperatures (15). Other studies have also suggested climatic variables have or will affect the distribution or ability of this tick to transmit *Borrelia burgdorferi* (16, 17).

4) Human behaviour and physiology

Extensive treatment of this topic is beyond the scope of this paper. Human migration is one possible consequence of climate change (18) and this potentially could alter patterns of infectious disease indirectly. The movement of immunologically naïve populations to areas of increased arbovirus risk is an obvious issue arising from this (19). Television and air-conditioning lower risk for American arbovirus diseases (20). Given the importance of nutrition to immune function another indirect consequence, if climate change influences nutrient availability as it certainly will, is that some populations will be at increased risk for infectious diseases (21). It has been speculated that drought conditions, by necessitating increased domestic water storage, may have facilitated mosquito breeding and human contact with the vector (*Aedes aegypti* or *albopictus*), precipitating a 2004 epidemic of Chikungunya in Lamu, Kenya (22). Here, climatic conditions may have precipitated a change in behaviour and a consequent alteration in vector abundance, rather than directly affecting the latter.

2. Implications

The clear implication of the above is that climate change could influence the occurrence of infectious diseases. More difficult to determine, though, is whether climate change has and how much it will in future, influence the occurrence of infectious diseases, the topic for the next section.

Assessing the impact of climate change on infectious diseases

1. Vector-borne diseases

Rogers and Randolph (23) discuss the theoretical basis for assessing putative associations between climate change and vector-borne diseases. The basic reproductive number (R_0) determines whether disease cases increase or decrease in a population. In the case of vector-borne diseases R_0 is determined by: the ratio of vectors to vertebrate hosts; transmission coefficients between vectors and vertebrates, and vertebrates and vectors; biting rate of vectors on the host of interest; mortality rate of vectors; extrinsic incubation period for the infection in the vector; and the rate of recovery from infection for the vertebrate host. Because arthropods are sensitive to temperature and other climatic variables, and because all except one (rate of recovery from infection for the vertebrate host) of the parameters that determine R_0 for vector-borne diseases are related to vector ecology, biology, or physiology, one would

expect changes in climate to influence the incidence of vector-borne diseases.

They also point out, however, that the direction of change is difficult to predict, and urge caution in correlating climate and disease data (the "mindless correlation of one dataset with another that is all too prevalent in the climate change literature") without careful thought, particularly because of the inconsistency in both types of data through time and space (because of the increasing numbers of weather stations worldwide through time, concentration of stations around cities, secular trends of increasing disease incidence due to improved diagnostic technologies, and so on). Rogers and Randolph suggest "climate change should have occurred at the right time, in the right place and in the 'right' direction (according to our current understanding of climate/disease linkages)" if it is to be considered the probable cause for a change in vector-borne disease cases. While not diametrically opposed, an alternative view is that the precautionary principle (see, for example McMichael, 2001 (24)) should be applied when assessing all effects of climate change, and that recent increases in vector-borne disease frequency should be assumed to be due to climate change.

1) Malaria

Hay *et al.* analysed global malaria data for 1900 to 2002 (25). These data demonstrated a decrease in the geographical area supporting malaria, but a substantial increase in the number among the world's population at risk for malaria. Further, projections for population increase to 2010 indicated a further 400 million births in the geographical area supporting malaria transmission at the time of the analysis.

Writing in 2002, Hay *et al.* analysed data from the East African Highlands, including climatic variables (temperature, rainfall and vapour pressure) and number of months suitable for malaria transmission (26). They concluded that in the period 1911 to 1995 there was no significant change in vapour pressure or temperature at their study sites, and a temporal increase in rainfall at only one of four sites. They also found no change in number of months suitable for malaria transmission, and concluded that an observed increase in malaria transmission is most parsimoniously explained by factors other than climate change (26). However, this conclusion has been criticized by Patz *et al.* (27) on the basis of the distribution of meteorological stations used to collect climate data and also because Hay and his co-workers ignored the influence of climate variability (as opposed to merely changes in the mean for climatic variables) on malaria. Hay and his colleagues have responded to these criticisms (28). Pascual *et al.* (29), using the same climate input data, drew the opposite conclusion to Hay *et al.* (26), concluding that the biological significance of observed temperature changes would be amplified in mosquito population changes, and that climate cannot be ruled out, along with other factors including *Plasmodium falciparum* drug resistance and land use changes, as a driver of malaria incidence.

Tanser *et al.* (30), using a modeling approach, predicted an altitudinal, but little latitudinal, increase in malaria transmission in Africa to 2100, and also a prolongation of the transmission season in some areas, though there is skepticism and robust debate on this issue (e.g. Reiter *et al.*, 2004 (31)). Rogers and Randolph note the increase in malaria in Africa, but attribute this to changes in land use and land cover, and most importantly in their view, to *Plasmodium* drug resistance, rather than climate change (23).

Clearly, at this point in time, the evidence on malaria is inconclusive. Debate is likely to continue.

2. Tick-borne encephalitis virus

Rogers and Randolph (23) describe varying patterns of disease increase for Tick-borne encephalitis (TBE), a *Flavivirus*, in Europe. In Sweden, a "3-fold step increase" was observed from 1983 to 1986 (from their Figure the number of cases per year before this increase was always less than 50, but afterward was generally over 50, with approximately 100 cases in 1994) with fairly stable case numbers until 2000, and approximately 100 cases per year, on average, through the years 2000 to 2004. In Slovenia, Croatia and Hungary, cases of TBE changed little from the mid-1970s, until there was a 60-70% decrease in Croatia and Hungary from 1997. In Eastern Europe there was a dramatic increase in 1992 or 1993, "the Czech Republic and Slovakia suffered 2-fold increases, Estonia a 5-fold increase, and Poland, Lithuania and Latvia increases of an order of magnitude each." Since 1999 in Latvia, the increase has been largely reversed, possibly due to vaccination. As well, the increase in TBE incidence increase varied markedly in different regions within each of these countries. Rogers and Randolph conclude that while climate change may have played a role in the TBE

increase, no factors have been identified that explains both spatial variation and temporal discontinuities in the incidence of the disease. They also point to increased abundance of tick hosts, deer particularly, and sociological changes since the collapse of communism as possible contributors. While undoubtedly these factors have played a role, evidence from another author (Eisen 2007) presents data suggesting that *Ixodes ricinis*, a vector of TBE, increased its range to the North and its abundance in central Sweden from the early 1980s to the early 1990s (32).

1) Dengue

Dengue is transmitted by *Aedes aegypti* and *albopictus* (33). There seems no doubt that the range for dengue epidemics is expanding, with epidemics in Tahiti and Singapore (33) and increasing numbers of epidemics in North Queensland, Australia (34). Halstead does not accept the suggestion that climate change will increase the incursion of dengue into temperate regions (35), but Hales *et al.* writing in 2002 on the basis of modeling using vapour pressure is a predictor variable for dengue, concluded that "geographical limits of dengue fever transmission are strongly determined by climate" and that climate change will substantially increase the proportion of the global population at risk from dengue (36).

2) Chikungunya

Initially described in Tanzania in 1952 (37) Chikungunya, an *Alphavirus* transmitted in epidemics by *Aedes aegypti* and *albopictus*, has subsequently caused periodic outbreaks in Asia and the Pacific (38) but in 2005 and 2006 came to prominence when it caused an epidemic, probably involving about 250,000 infections, on the Indian Ocean Island or Reunion (39). The epidemic also involved other Indian Ocean Islands including Mayotte (40). There have also been a large number of infections (1.39 million reported in 2006) in India (41) and a small outbreak in Italy (42, 43). While it is admitted other factors may have played a role, there has been speculation for a causal role for climate change in the Italian outbreak (44). Townson and Nathon point to the importance of the spread of *Ae. albopictus* for the increased range of Chikungunya, without discussing any potential relation to climate (45).

3) Ross River virus

Ross River virus is a mosquito-borne *Alphavirus* (11). There is a substantial literature on the relation between climatic variables and Ross River virus disease frequency, though the relation of specific environmental factors and disease differs by geographical area (46-51). Findings by Tong *et al.* also suggest expanding range in Queensland, with an increase in the number of jurisdictions in which the disease has been notified through time (52). Human behaviours are known to affect risk for RRV disease (53). This and the complexity of RRV ecology and epidemiology will make it a challenge to determine to what extent climate change is the cause of changes in disease frequency. Disease frequency may also change differentially in different geographical areas because of this (54).

2. Other infectious diseases

1) Diarrhoeal diseases

Some evidence exists on the effects of temperature on diarrhoeal diseases. For example, Checkley *et al.* found that a 1℃ increase in temperature led to an 8% increase in hospitalization for paediatric diarrhoeal disease in Lima, Peru (55). Matsuda *et al.* also found that climatic variables predicted Cholera cases in Bangladesh, particularly maximum temperature (56). Singh *et al.* (57) found effects positive associations between increased temperature and rainfall, and adult diarrhoeal disease incidence, on Pacific Islands.

Rotavirus infections are generally more common in cool than hot conditions (1). On a short time scale, an Australian study has shown a reduction in hospitalisations of children under five for Rotavirus diarrhoea following warmer weather in three Australian cities (Brisbane, Canberra, and Melbourne) (58), although interestingly the reverse (warmer weather associated with increased incidence) was found in Dhaka, Bangladesh above a threshold of 29℃ (59). But these authors also found, in their crude analysis, increased incidence with decreasing temperature in the lower temperature range, producing a U-shaped relationship, the relation at lower temperatures disappearing after adjustment for humidity, seasonal patterns, between-year variations, river level, and public holidays (59).

In Massachusetts relations were determined between temperature and cases of *Giardia*, *Salmonella*, *Campylobacter*, *Shigella*, Hepatitis A and *Cryptosporidium* (60). Daily incidence for *Campylobacter* and *Salmonella* peaked 2-14 days after the peak in ambient temperature, and the others, aside from Hepatitis A, peaked after longer delays of approximately 40 days (60). D'Souza *et al.* found that monthly *Salmonella*

notifications in five Australian cities were positively associated with mean monthly temperature in the previous month (61).

2) Respiratory infections

There are clear seasonal patterns in transmission of influenza in temperate and cold climates, but not the tropics (62). The possibility that transmission mechanism may be effected by temperature has already been alluded to above as a possible mechanism for this observation (7). Research in France has demonstrated lower influenza infection and mortality rates with warmer weather (63). The possibility exists that numbers of deaths in the elderly, and morbidity amongst younger people as a result of influenza may decrease in cold and temperate latitudes with global warming, but whether this occurs will depend on other host and environmental factors, including physiological adaptation of the host, improvements in vaccine efficacy, and others.

3) Schistosomiasis

Schistosoma japonicum in China is a zoonotic disease, with cattle and buffalo as reservoir hosts (3). Projections for schistosomiasis in China predict expansion to the North with an additional 783,883 km^2 at risk for the disease by 2050 on the basis of projected climate changes (4).

3. Current state of knowledge on climate and infectious disease relations

There is good evidence from basic laboratory science and epidemiology that temperature and other climatic variables influence both infectious disease incidence and potential determinants for incidence, including vertebrate hosts of zoonoses, and mosquito and other arthropod vectors, among others. The emergence of new diseases has created much interest in recent years, with zoonoses prominent among these (64). Less clear is whether climate change has yet significantly influenced infectious disease incidence, and what the likely impacts are in future.

Future priorities and directions for research on climate change and infectious diseases

There is a need to strengthen methodologies and research effort directed at elucidating the relation of infectious diseases and climate change. Methodological challenges include the perhaps competing needs of scientific rigour on the one hand, and pragmatism on the other; in relation to the former there is considerable difficulty involved in disentangling the effects of complex epidemiology and ecology from those of climate change, and in the case of the latter there may be a need for a "paradigm shift" relating to the need, perhaps, to accept a lesser weight of proof given the now accepted importance of climate change to human health.

There is a need to standardise the methodology used for geographic mapping of vector-borne diseases. Taking RRV as an example, the work by Gatton *et al.* on outbreaks uses a specific definition for such outbreaks ("the number of notifications received within a LGA in each season was compared with that expected based on a measure of the long-term incidence rate for the LGA and the corresponding population. Outbreaks were declared if there was a 〈1% chance of obtaining the observed number based on a Poisson model") (46). Tong *et al.* used localities (suburbs or townships) as their unit of study (52). The comparison is perhaps unfair, given the different research questions addressed by these researchers. But there is a need, if we are to understand and quantify the impact of climate change on vector-borne diseases, for agreed upon, standardised measures of disease frequency accessed from a uniform (and well understood) dataset. The same is also true for vectors – uniform National and International measures of vector species and densities using predetermined trapping localities and methods are needed if the relation of climate to vector abundance, and thence to disease frequency, is truly going to be measured, understood, and responded to.

There is a need for ongoing fundamental research on the climatic determinants of vector distribution and abundance, and on the relation between extrinsic incubation period and pathogen transmissibility, and climatic variables.

The information developed from fundamental research on climatic effects on vectors and disease transmission will feed into the development and testing of mathematical models for vector-borne diseases. Such models should allow more accurate prediction of likely secular trends in disease frequency and forecasting of outbreaks in specific geographical areas on the basis of recorded climate parameters.

A related issue is the need to determine who, precisely, is most impacted by the effects of climate change on vector-borne

diseases. Malaria is by far the most important vector-borne disease globally, and as Hales and Woodward (65) point out, those most impacted by projected prolongation of the transmission season are among those who have contributed least to global climate change. While there is clearly inequity here, only the collection of robust data on where, how, and who malaria and other vector-borne diseases have their impact will have a significant impact on adaptation to the effects of climate change, and perhaps more optimistically, to lessening the extent of climate change.

Analogous arguments apply for other infectious diseases. Much debate and research effort has been applied to vector-borne diseases, but climate effects on respiratory infections and food and water-borne diseases are also probable, so the likely consequences of climate change for these diseases is also a priority area. Given the importance of diarrhoeal diseases as causes for deaths of children under five in the developing world (66) these diseases clearly require greater attention. Indeed, greater research effort in the area of infectious disease and climate change generally is needed in the developing world. Another need is to determine priorities, given the superficially competing needs for practical population health programs in the developing world on the one hand, and climate change mitigation and adaptation on the other.

Conclusion

While there are considerable challenges, if we accept that mitigation of climate change will have limited impact, and will not reverse the changes already seen, then the world must adapt to the changes, including in infectious disease incidence, which will occur as a result. There is considerable uncertainty about the extent of climate change, and hence even greater uncertainty regarding changes in infectious disease incidence, particularly given that factors other than climate change about which there is also uncertainty, will also impact on incidence. However, if reasonable decisions regarding changes in demand for primary prevention and treatment of infectious diseases are to be made, efforts must continue to understand the relation between climate and the myriad infectious diseases afflicting humankind.

References

1) McMichael AJ, RE Woodruff, Climate change and infectious diseases, in The Social Ecology of Infectious Diseases, K.H. Mayer and H.F. Pizer, Editors. 2008, Elsevier: Amsterdam. p. 378-407.
2) Strahan RE, The Complete Book of Australian Mammals. 1991: The Australian Museum and Cornstalk Publishing.
3) Ross AG, et al. Schistosomiasis in the People's Republic of China: prospects and challenges for the 21st century. *Clinical Microbiology Reviews* 14(2):270-295, 2001
4) Zhou XN, et al. Potential Impact of Climate Change on Schistosomiasis Transmission in China. *Am J Trop Med Hyg* 78(2):188-194, 2008
5) Pettersson L, et al. Outbreak of Puumala Virus Infection, Sweden. *Emerging Infectious Diseases* 14:808-810, 2008
6) Hardy, J.L., Susceptibility and resistance of vector mosquitoes, in The arboviruses: Epidemiology and ecology, T.P. Monath, Editor. 1988, CRC Press: Boca Raton, Florida. p. 87-126.
7) Lowen AC, et al, High Temperature (30{degrees}C) Blocks Aerosol but Not Contact Transmission of Influenza Virus. *J Virol* 82:5650-5652, 2008
8) Harley D, et al., A primary school outbreak of pharyngoconjunctival fever caused by Adenovirus type 3. *Communicable Diseases Intelligence* 25:9-12, 2001
9) Guerin MT, et al. Temperature-related risk factors associated with the colonization of broiler-chicken flocks with Campylobacter spp. in Iceland, 2001-2004. *Preventive Veterinary Medicine* 86(1-2):p14-29, 2008
10) King BJ, et al., Environmental Temperature Controls Cryptosporidium Oocyst Metabolic Rate and Associated Retention of Infectivity. *Appl Environ Microbiol* 71:3848-3857, 2005
11) Harley D, A. Sleigh, and S. Ritchie, Ross River virus transmission, infection and disease: a cross-disciplinary review. *Clinical Microbiology Reviews* 14:909-932, 2001
12) McDonald G, et al, The effect of temperature on the population growth potential of Culex annulirostris Skuse (Diptera: Culicidae). *Australian Journal of Ecology* 5:379-384, 1980
13) Sweeney AW, et al. Environmental factors associated with distribution and range limits of malaria vector Anopheles farauti in Australia. *Journal of Medical Entomology* 43: 1068-1075, 2006
14) Bayoh MN and SW Lindsay, Temperature-related duration of aquatic stages of the Afrotropical malaria vector mosquito Anopheles gambiae in the laboratory. *Medical and Veterinary Entomology* 18:174-179, 2004
15) Gern L, F. Morán Cadenas, C. Burri, Influence of some climatic factors on Ixodes ricinus ticks studied along al-

titudinal gradients in two geographic regions in Switzerland. *International Journal of Medical Microbiology* 298 (Supple 1):55-59, 2008
16) Gray JS, Ixodes ricinus seasonal activity: Implications of global warming indicated by revisiting tick and weather data. *International Journal of Medical Microbiology* 298 (Supple 1):p19-24, 2008
17) Materna J, et al. The vertical distribution, density and the development of the tick Ixodes ricinus in mountain areas influenced by climate changes (The Krkonose Mts., Czech Republic). *International Journal of Medical Microbiology* 298(Supple 1):p25-37, 2008
18) McMichael AJ, RE Woodruff, S. Hales, Climate change and human health: present and future risks. *The Lancet* 367 (9513):p859-869
19) Patz JA. and WK. Reisen, Immunology, climate change and vector-borne diseases. *Trends in Immunology* 22:171-172, 2001
20) Gahlinger PM, WC Reeves, MM Milby, Air conditioning and television as protective factors in arboviral encephalitis risk. *American Journal of Tropical Medicine and Hygeine* 35:601-610, 1986
21) Black RE, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 371(9608):243-260, 2008
22) Chretien JP, et al. Drought-associated Chikungunya emergence along Coastal East Africa. *Am J Trop Med Hyg* 76:405-407, 2007
23) Rogers DJ, S.A. Randolph, Climate change and vector-borne diseases. *Advances in Parasitology* 62:345-384, 2006
24) McMichael, A.J., Impact of climatic and other environmental changes on food production and population health in the coming decades. *The Proceedings of the Nutrition Society* 60:195-201, 2001
25) Hay SI, et al. The global distribution and population at risk of malaria: past, present, and future. *Lancet Infectious Diseases* 4:327-336, 2004
26) Hay S, et al. Climate change and the resurgence of malaria in the East African highlands. *Nature* 415:905-909, 2002
27) Patz JA, et al. Climate change (Communication arising): Regional warming and malaria resurgence. *Nature* 420 (6916):627-628, 2002
28) Hay SI, et al.Climate change (Communication arising): Regional warming and malaria resurgence. *Nature* 420 (6916):628-628, 2002
29) Pascual, M., et al., Malaria resurgence in the East African highlands: Temperature trends revisited 103:5829-5834, 2006
30) Tanser FC, B Sharp, and D. le Sueur, Potential effect of climate change on malaria transmission in Africa. *Lancet* 362(9398):1792-1798, 2003
31) Reiter P, et al. Global warming and malaria: a call for accuracy. *The Lancet Infectious Diseases* 4:323-324, 2004
32) Eisen L. Climate change and tick-borne diseases: A research field in need of long-term empirical field studies. *International Journal of Medical Microbiology* 298(Supple 1):12-18, 2005
33) Halstead, S.B., Dengue. *The Lancet* 370:1644-1652, 2007
34) Hanna JN, R.S., Richards AR, Taylor CT, Pyke AT, Montgomery BL, Piispanen JP, Morgan AK, Humphreys JL, Multiple outbreaks of dengue serotype 2 in north Queensland, 2003/04. *Australian and New Zealand Journal of Public Health* 30:220-225, 2006
35) Halstead SB, Dengue Virus-Mosquito Interactions. *Annual Review of Entomology* 53:273-291, 2008
36) Hales S, et al. Potential effect of population and climate changes on global distribution of dengue fever: an empirical model. *The Lancet* 360:830-834, 2002
37) Ross RW, The Newala epidemic. III. The virus: Isolation, pathogenic properties and relationship to the epidemic. *Journal of Hygiene* 54:177-191, 1956
38) Pialoux G, et al., Chikungunya, an epidemic arbovirosis. *The Lancet Infectious Diseases* 7:319-327, 2007
39) Renault P, et al. A Major Epidemic of Chikungunya Virus Infection on Reunion Island, France, 2005-2006. *Am J Trop Med Hyg* 77:727-731, 2007
40) Sissoko D, et al. Outbreak of Chikungunya fever in Mayotte, Comoros archipelago, 2005-2006. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 102: 780-786, 2008
41) Mavalankar DSP, Bandyopadhyay T, Parmar J, Ramani KV. (serial on the Internet). Mar (date cited)., Increased mortality rate associated with chikungunya epidemic, Ahmedabad, India. *Emerg Infect Dis* 14:412-415, 2008
42) Chretien JP and K.J Linthicum/ Chikungunya in Europe: what's next? *The Lancet* 370:1805-1806, 2007
43) Rezza G. et al. Infection with chikungunya virus in Italy: an outbreak in a temperate region. *The Lancet* 370:1840-1846, 2007
44) Chikungunya reaches northern Italy: effect of global warming? *Arch Dis Child* 93:312, 2008
45) Townson H. and MB Nathan, Resurgence of chikungunya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 102:308-309, 2008
46) Gatton M, B Kay and P Ryan, Environmental predictors of Ross River virus disease outbreaks in Queensland, Australia. *Am J Trop Med Hyg* 72:792-799, 2005
47) Hu W, et al., Development of a predictive model for Ross River virus disease in Brisbane, Australia. *Am J Trop Med Hyg* 71:129-137, 2004
48) Hu W, et al. Exploratory spatial analysis of social and environmental factors associated with the incidence of Ross River virus in Brisbane, Australia Am J Trop Med Hyg 76:814-819, 2007
49) Tong S, et al. Climate variability and Ross River virus

transmission. *J Epidemiol Community Health* 56:617-621, 2002
50) Woodruff, R., et al., Predicting Ross River Virus Epidemics from Regional Weather Data. *Epidemiology* 13:384-393, 2002
51) Woodruff, R., et al., Early Warning of Ross River Virus Epidemics: Combining Surveillance Data on Climate and Mosquitoes. *Epidemiology* 17:569-575, 2006
52) Tong S, et al. Geographic variation of notified Ross River virus infections in Queensland, Australia, 1985-1996. *Am J Trop Med Hyg* 65:171-176, 2001
53) Harley D, et al. Risks for Ross River virus disease in tropical Australia. *International Journal of Epidemiology* 34:548-555, 2005
54) Russell RC, Mosquito-borne arboviruses in Australia: the current scene and implications of climate change for human health. *Int J Parasitol* 28:955-69, 1998
55) Checkley W, et al. Effects of EI Niño and ambient temperature on hospital admissions for diarrhoeal diseases in Peruvian children. *The Lancet* 355:442-450, 2000
56) Matsuda F, et al. Prediction of epidemic cholera due to Vibrio cholerae O1 in children younger than 10 years using climate data in Bangladesh. *Epidemiology and Infection* 136:73-79, 2008
57) Singh RB, et al. The influence of climate variation and change on diarrheal disease in the Pacific Islands. *Environmental Health Perspectives* 109:155-159, 2001
58) D'Souza RM, G Hall, NG Becker. Climatic factors associated with hospitalizations for rotavirus diarrhoea in children under 5 years of age. *Epidemiology and Infection* 136: 56-64, 2008
59) Hashizume M, et al. Rotavirus infections and climate variability in Dhaka, Bangladesh: a time-series analysis. Epidemiology and Infection 136:1281-1289, 2008
60) Naumova EN, et al. Seasonality in six enterically transmitted diseases and ambient temperature. *Epidemiology and Infection* 135:281-292, 2007
61) D' Souza RM, et al. Does Ambient Temperature Affect Foodborne Disease? *Epidemiology* 15:86-92, 2004
62) Lofgren E, et al. Influenza Seasonality: Underlying Causes and Modeling Theories. *J Virol* 81:5429-5436, 2007
63) Viboud C, et al. Association of influenza epidemics with global climate variability. *European Journal of Epidemiology* 19:1055-1059, 2004
64) Jones KE, et al. Global trends in emerging infectious diseases. *Nature* 451:990-993, 2008
65) Hales S, A Woodward. Climate change will increase demands on malaria control in Africa. *The Lancet* 362: 1775-1775, 2003
66) UNICEF, The State of the World' s Children 2008: Child Survival. New York: UNICEF, 2007