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CONTENTS

EXECUTIVE SUMMARY

Maintaining biodiversity underpins the stability of ecosystems and the services that they supply to the community, such as food, drinking water, clean air, control of disease and raw materials for the development of medicinal drugs. These are essential to human health.

The objective of this literature study is to provide an overview of existing information concerning the impacts of changes in biodiversity and ecosystems on two services related to human health: regulation of infectious diseases and provision of medicines.

Human infectious diseases

The review focuses on infectious diseases in the human population, in particular vector-borne diseases (VBD), because, as pointed out in the Millennium Ecosystem Assessment:

- these diseases are highly sensitive to changes in the natural environment, i.e. environmental conditions affect both the infectious pathogens and the insects and other intermediate hosts that transmit them;
- many such infections are related to specific ecosystems (such as forests and wetlands);
- VBDs are major killers, causing approximately 1.4 million deaths per year worldwide. Due to the increasing impact of biodiversity changes they are expected to represent the largest share of the future disease burden.

The VBDs included in the review were selected on the following criteria:

- the direct impact of biodiversity and changes in ecosystems on their spread;
- their current high frequency and incidence on human health (VBDs affect over 700 million people every year worldwide);
- the occurrence of outbreaks outside their traditional areas (the so-called emerging diseases) and reappearance in areas where these diseases were considered eradicated or contained (the so-called re-emerging diseases).

The diversity of species of intact ecosystems can protect mankind against the emergence and spread of infectious diseases. Disease transmission cycles are generally kept in equilibrium by population limiting processes (such as acquired immunity to infectious disease, predation and competition for food) and by the carrying capacity limits of habitats for hosts and vectors.
In stable ecosystems each species occupies a particular position or *niche* and in so doing impedes the invasion of “foreign” species which may form part of an infectious disease cycle, either as predators, prey, hosts, vectors or parasites.

There is increasing evidence that greater species richness may decrease the spread of pathogens to humans. Species rich communities are more likely to be populated by highly competitive species which leave fewer vacant niches for possible invasion by species carrying infectious agents. Recent data indicate that higher host diversity (synonymous with species richness) may decrease the risk of disease through a “dilution effect”, i.e. a reduced likelihood that “vectors” (organisms which carry pathogens) come in contact with pathogen hosts.

However, although a greater diversity of hosts can reduce transmission rates of particular diseases, they may also harbour additional pathogens. The relative role of species richness

versus species composition remains to be clarified, as changes in the level of biodiversity affect not the number of species but also their composition.

Alteration of natural ecosystems through human activity influences the distribution and incidence of vector-borne infectious diseases. Alterations to ecosystem are diverse and often interrelated. They include introduction of alien species; loss, fragmentation and deterioration of habitats; changes in the distribution and availability of surface water; changes in agricultural practice, urbanisation and other changes in land use. Ecological alterations directly or indirectly affecting the populations of the pathogen, the vector, or the nonhuman hosts of the pathogen and the context within which they interact, may disrupt their complex relationships, destabilise natural equilibrium and alter the epidemiology of vector-borne diseases. Conditions for disease transmission may be enhanced or transmission cycles disrupted.

Links between biodiversity change and infectious diseases of humans occur at all levels of biology, from genetics of individual organisms to the structural diversity of habitats.
Any disturbance in an ecosystem can induce:

- genetic changes in disease pathogens (e.g. change in pathogen virulence),
- changes in population dynamics of vectors or hosts species (abundance, diversity, composition, distribution), changes in the community (predation, competition, population density, etc.),
- changes in structural diversity (structure, complexity of habitats, size, fragmentation and distribution, area- species relationships).

Changes to an environment brought about by human activity can drive selection processes of vectors and pathogens leading to the expansion of those vector and strains suited to the new environmental conditions. An example of newly evolved pathogens include newly re-assorted influenza strains. The potential for mutability allows pathogens to switch hosts migrating into a new ecological niche. This ‘‘host transfer” is easier at the interface between wild communities and agricultural communities with high population densities of humans, domestic animals, and crops, where higher is the vector-host contact rate.

Some human infectious diseases are linked to population dynamics of vectors, hosts and pathogens, e.g. high risk or incidence of Lyme disease and West Nile virus may be closely associated with changes in the diversity or composition of animal hosts, which in turn is associated with certain types of habitat destruction and fragmentation.
The transmission of major human infectious vector-borne diseases such as malaria and yellow fever can be fairly described as connected to structural diversity. Changes in plant and habitat complexity, habitat fragmentation and alteration, particularly of forests and wetlands, linked to human settlements and activities, can create new breeding sites for the vector or alter the distribution, density and behaviour of reservoir host and their interactions with humans and increase contact with vectors.

Vector-borne infections of humans create the highest disease burden and will continue to do so in the future. This disease burden is concentrated in the poorest regions of the world, where VBDs are not only a result but also a cause of poverty. Malaria alone is responsible for approximately 11% of the total disease burden in Africa, while all VBDs combined account for less than 0.1% of the burden in Europe.
VBDs have long-term negative consequences on the social well-being and economic performance of low income countries, affecting human resources, inequality, education,

productivity and learning capacity. Such diseases incur wide social and economic costs and prevent economic development, perpetuating the “poverty trap”.
In developed countries infectious diseases of humans imply high costs resulting from absence from work, medical care, hospitalisation and rehabilitation. Of particular note is the high cost of vaccination programmes to prevent possible pandemic outbreaks from new influenza strains.

Medicines

Biodiversity loss diminishes the supplies of raw materials for traditional medicine and for drug discovery. Biological diversity, particularly plants, is a key source of medical products. Between 50,000 and 70,000 plant species are known to be used in traditional and modern medicine worldwide and almost every class of drug includes a model structure derived from nature. The loss of species could have immediate negative effects if it involves species currently used for medicinal purposes, and could also reduce the opportunity for the future discovery of new natural products which have medicinal properties if it involves species not yet studied for their pharmaceutical potential or even undiscovered. For example, tropical rainforests contain at least half of all world species, but less than 5% of tropical plant species have been studied for their pharmaceutical potential. This leaves great potential for even more discovery, but also the potential for great loss as rainforests are felled around the globe and unstudied species are lost to extinction. It is estimated that biodiversity loss is leading to the loss of about three potential new medicines each year.

Valuing biodiversity as a source of medicines could help towards economic sustainability of nature conservation. The economic value of medicines is considerable and in many parts of the world expenditure on traditional and complementary medicine is not only significant but growing rapidly. Moreover, herbal treatments are internationally highly lucrative. Although not included in formal national accounting, the use of medicinal plants makes a significant contribution to productive activities, incomes, and well-being in some communities. Biodiversity also remains a major source of bioactive compounds for modern medicine.

CHAPTER 1

Introduction

1.1 Purpose of this review

Human health and biodiversity are inextricably linked. An ecosystem with a high biodiversity ensures the regulation of interactions between predators, prey, hosts, vectors and parasites, so providing mechanisms for controlling the emergence and spread of infectious diseases. Maintaining or restoring human health with naturally based medicines depends on the existence of the species from which they are derived.

Changes in biodiversity and ecosystems cause, both directly and indirectly, changes in the services ecosystems provide, including disease regulation and provision of medicines.

In recent years, an increasing number of studies have focused on the importance of biodiversity in regulating diseases and as a source of raw material for medicines. This literature review examines the existing knowledge on the relationship between changes in biodiversity and ecosystems and human infectious diseases, the supply of medicines and their respective socio-economic impact.

The starting point of the study is the identification of key questions to be addressed:

- How do changes in biodiversity and ecosystems lead to human infectious diseases?
- Which human infectious diseases are most affected by changes in biodiversity and ecosystems?
- What information is available on the current incidence of these infectious diseases?
- What studies and publications are available regarding the socio-economic impact of human infectious diseases?
- What is the cost of this impact in terms of Gross Domestic Product, Disability-Adjusted Life Year and Quality-Adjusted Life Year?
- Is there a way to measure the value of ecosystem services in reducing or containing infectious diseases?
- Are there reliable sources of information on the dependence of traditional and modern medicine on biodiversity?
- Are there reliable figures on the importance of known and undiscovered species for the production of pharmaceuticals?
- What is the existing and future value of medicines derived from nature?

Two conceptual models have guided the literature study. The first (figure 1.1) shows the links between human activities, ecosystem change and human infectious diseases, in particular those that are carried out by vectors.

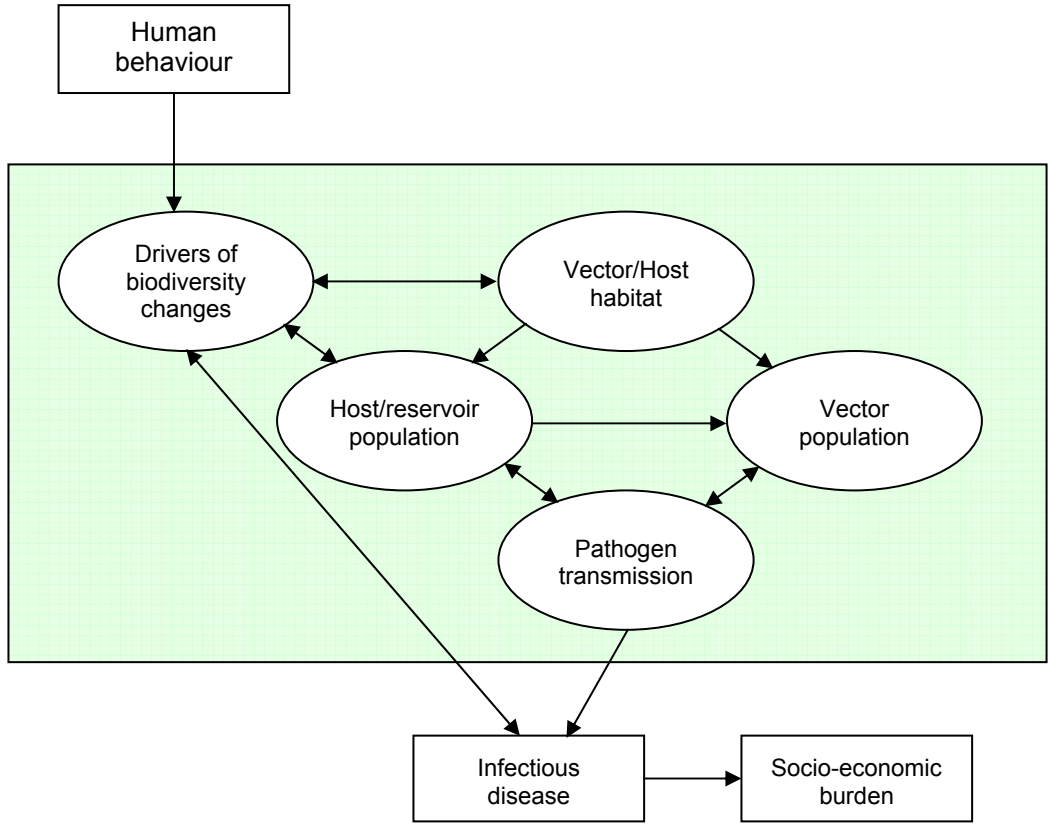


Figure 1.1. Schematic overview of the inter-linked relationships between human behaviour, ecological modifications and changes in infectious disease incidence. A **vector** is an insect or any living carrier that transmits an infectious agent. A **host** is an organism that harbours a pathogen. A **reservoir** is the long-term host of the pathogen of an infectious disease.

The second (fig 1.2) shows the links between biodiversity, traditional and modern medicine and their economic value.

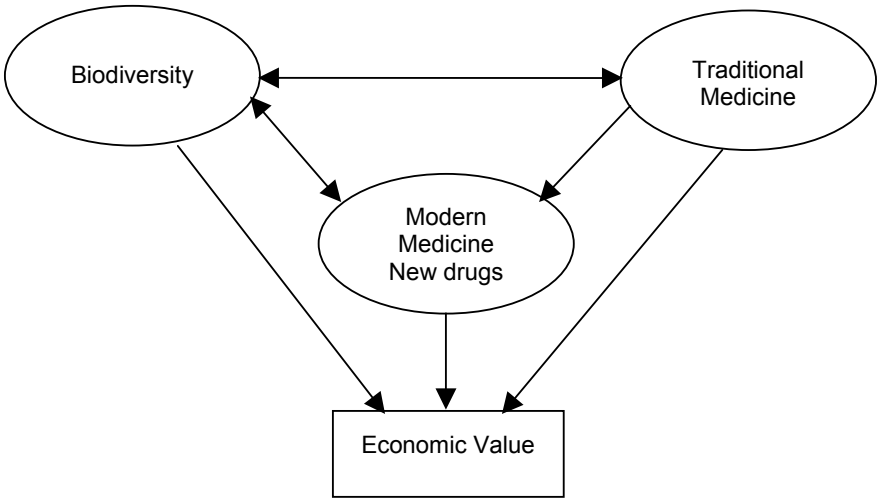


Figure 1.2. The relationships between biodiversity, traditional and modern medicines and their economic value.

The review is divided into 5 sections:

The **first chapter** provides an introduction to the concept of biodiversity and ecosystem services and their relation to human health.

The **second chapter** focuses on nine human infectious diseases, considered to have in their ecology and epidemiology a strong relation with biodiversity and ecosystems.

The **third chapter** examines the social and economic burden of the human infectious diseases identified in chapter 2. It includes a brief description of several methodologies used to evaluate social and economic burdens and estimate the direct and indirect costs of the diseases.

The **fourth chapter** shows how medicines are connected to biodiversity and how the decline in biodiversity will have an adverse impact on the development of medicines. It also provides an overview of some studies on the existing and future value of biodiversity for medicine.

The **concluding** paragraphs sum up the findings of the preceding chapters and provide a series of suggestions for future research.

1.2 Biodiversity and ecosystem services

Biodiversity, or biological diversity, is an umbrella term used to describe the variety of life on Earth. It specifically means "the variety and variability of biological organisms" (Wilson and Peter, 1988). The United Nations Convention on Biological Diversity similarly defines biodiversity as the "*variability among living organisms from all sources including,* inter alia*, terrestrial, marine and other aquatic ecosystems and the ecological complexes of which they are part; this includes diversity within species, between species and of ecosystems*".

The number of species living on earth is still unknown. Estimates, using different methodologies, indicate a very wide range of between 3 and 100 million species (Thomas, 1990; Grassle, 1989; Grassle *et al*., 1990). However, most scientists believe it to be closer to 10 million. Approximately 1.75 million species have been named so far (Millennium Ecosystem Assessment, 2005).

"At the ecosystem level, biodiversity refers to the varied assemblages of species that characterize deserts, forests, wetlands, grasslands, lakes, rivers, agricultural and other landscapes. Each ecosystem consists of living creatures interacting with one another and with the air, water, and soil around them. […] *It is the combination of life forms and their interactions with one another, and with the physical environment, that has made Earth habitable for humans. Ecosystems provide the basic necessities of life (e.g., food, water and the very air we breathe), offer protection from natural disasters and disease (e.g., by regulating climate, floods and pests), provide a foundation for human cultures and inspire our spiritual beliefs and worldviews. These "ecosystem services" also support and maintain the essential life processes of the planet, such as primary production and nutrient cycling. Each of these supporting services is essential to human well-being, whether the services are considered at the local, regional or global level" (Secretariat of CBD, 2006).*

The characteristics and maintenance of ecosystem services are linked to the diversity of species within ecosystems and ultimately to the genetic diversity within those species.

The Millennium Ecosystem Assessment (2005) divided ecosystem services into 4 categories:

- Provisioning services are the most obvious type of ecosystem services. They include many products: food, fuel, medicine, wool, leather, materials for construction (e.g. timber, bamboo) and for other industries (natural oils, resins, tannins).
- Regulating services maintain life on earth. They include regulation of climate, prevention of flooding and soil erosion, water purification (through binding and detoxification of pollutants), regulation of air quality (including carbon storage), and regulation of pests and diseases (which help control species' populations). Chivian (2002) states that many pest species of plants (weeds), insects, rodents, bacteria and fungi, compete with humans for food or the spread of diseases. Certain animals and micro-organisms provide a service to humans by controlling naturally these biological pests.
- Cultural services are the non-material benefits people obtain from ecosystems. The beauty of the natural world is largely due to the diversity of life in its ecosystems. There is increasing evidence that our emotional well-being is enhanced when in natural environments. They inspire painters, writers, architects and musicians to create works reflecting and celebrating its beauty. Examples of services include: aesthetic enjoyment, spiritual enrichment and fulfilment and recreational activities, including eco-tourism.
- Supporting ecosystem services are those necessary for the proper functioning of ecosystems and the delivery of provisioning, regulating and cultural services. Their impact on man is not as direct as for the other services, but they are the essential for their continued production. Examples include soil formation, photosynthesis, seed dispersal, nutrient cycling (including the essential nutrients carbon, nitrogen and phosphorus), pollination and provision of habitats for flora and fauna.

PROVISIONING SERVICES	REGULATING SERVICES	CULTURAL SERVICES
Products obtained from ecosystems	Benefits obtained from environmental regulation of ecosystem processes	Nonmaterial benefits obtained from ecosystems
• Food	• cleaning air	• aesthetics
• fuel wood	• purifying water	• intellectual stimulation
• fibre	• mitigation of floods	• a sense of place
• medicines	• controlling erosion • detoxifying soils • modifying climate	
SUPPORTING SERVICES		
Services necessary for the production of all other ecosystem services		
• primary productivity • nutrient cycling • pollination		

Figure 1.3. A sampling of ecosystem services. Source: Chivian and Bernstein (2008).

Although there is no doubt as to the link between biodiversity and ecosystem services, further understanding of ecosystems will require more knowledge of biotic (living) and abiotic (non-living) controls within them, how ecological communities are structured and the forces behind species invasion and extinction (Hooper *et al.,* 2005). There is also a need to study further the social and economic constraints in ecosystem management practice. Moreover, further research, in particular long-term experimentation, is needed to understand the relationships between taxonomic diversity, functional diversity and community structure and

how they influence the properties of ecosystems and their capacity to respond to and recover from disturbances (Hooper *et al*., 2005).

1.3 The importance of biodiversity and ecosystem services for human health

According to Frumkin (2002), human health depends on all categories of ecosystem services. De Groot *et al*. (2002) distinguish four ecosystem functions relating to human health functions:

(1) direct provisioning services covering basic human needs - food, clean air and clean water;

(2) prevention of disease through biological control;

(3) provision of medical and genetic resources necessary to prevent or cure disease;

(4) maintenance of mental health through the provision of opportunities for recreational, creative and therapeutic activities.

The COHAB Initiative *(Co-Operation On Health And Biodiversity)*

The COHAB Initiative is an international work programme around human well-being and sustainable development. It aims to establish an international, inter-disciplinary framework of dialogue and partnership linking community health, international development and biodiversity conservation. Through a global network of COHAB Partners, it works towards the implementation of the United Nations Convention on Biological Diversity and the Millennium Development Goals.

The Second Conference on Health and Biodiversity (COHAB 2), held in Ireland in February 2008, examined the relationship between biodiversity and ecosystems, emerging infectious diseases and human activity. It highlighted concern for maintaining the diversity, for habitat deterioration, wildlife trade, agricultural practices and climate change (Secretariat CBD/COP9, 2008).

A recent study carried out in the framework of the UNEP financial initiative (UNEP FI, 2008) shows that biodiversity and ecosystem services have contributed to human well-being and economic development, but that this contribution is not sustainable at current levels. The rate and scale of biodiversity and ecosystem degradation is weakening significantly the ability of natural ecosystems to deliver key services, such as the regulation of infectious diseases and the provision of medicines.

Factors of degradation are linked to human activities (Vora, 2008; UNEP FI, 2008; Millennium Ecosystem Assessment, 2005):

- habitat destruction through urban and industrial development, for instance through deforestation;
- changes in agricultural land use, including intensification of livestock and crop production;
- changes in the distribution and availability of surface water, through dam construction, irrigation, and diversion of watercourses;
- pollution, particularly of water, but also of air and from solid waste;
- climate change, which is globally affecting the distribution and status of biodiversity, and the ability of ecosystems to regulate climate;
- human migration and international travel and trade;
- introduction of non-native invasive species, including accidental or intentional human introduction of pathogens.

CHAPTER 2

Biodiversity, ecosystem changes and human infectious diseases

An infectious disease is a clinically evident disease resulting from the presence of pathogenic microbial agents, including viruses, pathogenic bacteria, fungi, protozoa, multicellular parasites and aberrant proteins known as prions. These pathogens are able to cause diseases in humans, animals and/or plants. Transmission may occur through physical contact with infected individuals, (body) fluids, food, contaminated objects, inhalation or vectors (e.g. mosquitoes and ticks) (McGraw-Hill, 2005). Infectious pathologies which are transmitted through contact between individuals are known as contagious or communicable diseases (Dorland, 2004).

This literature study focuses on human infectious diseases.

2.1 Changes in biodiversity, ecosystems and human infectious diseases

The links between changes in ecosystems, biodiversity and infectious diseases are complex. They may involve socio-economic and global environmental changes (such as climate change) occurring over different scales of space and time (Foley and Ferster, 2007). There has been a tendency to categorise environmental changes into socio-economic, such as urbanization, and those that are biological, such as deforestation. However, any process affecting human health has both socio-economic and biological components that are inextricably linked and may affect the transmission cycles of infectious pathogens (Eisenberg *et al*., 2007).

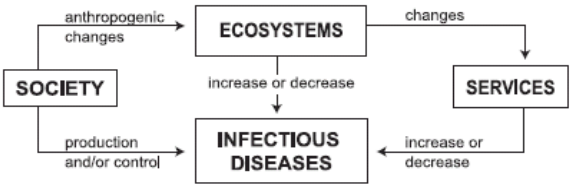


Figure 2.1. Relationships between society, ecosystem services, and human infectious diseases. Source: Millennium Ecosystem Assessment, 2005.

There are many ways in which changes in biodiversity and ecosystem services could alter the incidence of infectious diseases. Possible mechanisms under investigation are:

- increase of the abundance of a few highly efficient vector or pathogen species through loss of ecosystem balance;
- stress, which may compromise immune systems of organisms within an ecosystem;
- changes in the number of vector breeding sites or distribution of hosts;
- invasion of host niches or transfer of hosts between species;
- loss of predator species resulting in changes in host population density;
- human-induced genetic changes to disease vectors or pathogens (such as resistance to pesticides in mosquitoes or emergence of antibiotic resistant bacteria);
- contact between wild and domestic species resulting in new pathogen hosts.

Although studies have identified effects of biodiversity changes on the spread of infectious diseases, the mechanisms often remain only partially understood, Keesing and collaborators (2006) have focused future research on:

(1) describing patterns of change in disease risk with changing biodiversity;
(2) identifying the mechanisms behind observed changes in risk;
(3) proposing further mechanisms in a wide range of epidemiological models;
(4) experimentally manipulating disease systems to assess the impact of proposed mechanisms.

The relation between changes in biodiversity and the spread of infectious diseases in humans occurs at several levels, from genetic to structural diversity. The different levels of diversity and their effects are indicated in table 2.1. For example, changes in the diversity or composition of animal populations may be closely associated with the incidence of zoonotic[1] diseases such as Lyme disease or West Nile virus (Ezenwa *et al*., 2006; LoGiudice *et al*., 2003). Deforestation and habitat fragmentation or modification, and the accompanying loss of structural diversity, can lead to changes in the level of human contact with pathogens and disease vectors, such as in the case of malaria (Vittor *et al.*, 2006).

Any disturbance of an ecosystem can induce genetic changes in disease pathogens (e.g. change in pathogen virulence), changes in the population dynamics of vector or host species (abundance, diversity, composition and distribution), changes in the community (predation and competition) and changes in structural diversity (complexity, fragmentation and distribution of habitats and area-species relationships) (Pongsiri *et al*., 2009).

Table 2.1. Mechanisms linking biodiversity change and human health at different levels. Source: Pongsiri *et al*. 2009

Level of diversity	Aspect of biodiversity undergoing change	Possible mechanism leading to human health effect
Genetic	Gene frequencies within populations of pathogens or hosts	Change in pathogen virulence or host resistance
Microbial	Composition of microbial communities in the external environment or within the host	Change in pathogen exposure or virulence; change in host immune response and allergic sensitization; expansion of range through anthropogenic transport
Vector species	Abundance, diversity, composition, and geographic range of vectors	Change in host-vector contact rates; change in contact between infected vectors and humans; expansion of range through anthropogenic movement
Host species	Diversity, composition, and range of host species	Change in host-pathogen contact rates; change in competent host-vector contact rates; change in pathogen prevalence; expansion of range through anthropogenic transport
Community (interacting species including predators, competitors, etc.)	Host density and contact with pathogen; host susceptibility to infection	Change in pathogen prevalence; change in human-pathogen contact rates
Habitat structure	Structure, complexity, and diversity of vegetation	Change in vector abundance and composition; change in host composition and distribution; change in host-pathogen contact rates; change in vector-host contact rates; change in infected vector-human contact rates; change in host-human contact rates

[1] Zoonotic diseases - diseases transmissible from animals to humans. They represent more than 75% of human infectious diseases.

2.1.1 Changes in species diversity

The lifecycle of about 75% of the pathogens that cause human infectious diseases includes other organisms as vectors or hosts. Changes in the number of species living in an ecosystem, in particular changes in the relative abundance of pathogens, vectors and hosts, have major implications for the spread of human infectious diseases. Transmission cycles are generally kept in equilibrium by limits on the carrying capacity of the habitat (predation and competition for food) to support vectors and hosts and other density dependent processes. The different species involved in the life cycle of an infectious disease (predators, prey, hosts and vectors) occupy ecological niche that can prevent the invasion by a species involved in the transmission cycle of an exogenous infectious disease. The dynamic equilibrium among the diverse species in unaltered ecosystems provide a disease-regulating effect, (Millennium Ecosystems Assessment, 2005).

An increase in biodiversity may coincide with either (Chivian and Bernstein, 2008):

(1) an increased incidence of diseases, when there has been an increase in vector and/or pathogen populations,

(2) a reduction in the risk of human infection due to an increase in populations of hosts.

The relation between the different actors in disease transmission cycles is shown in figure 2.2:

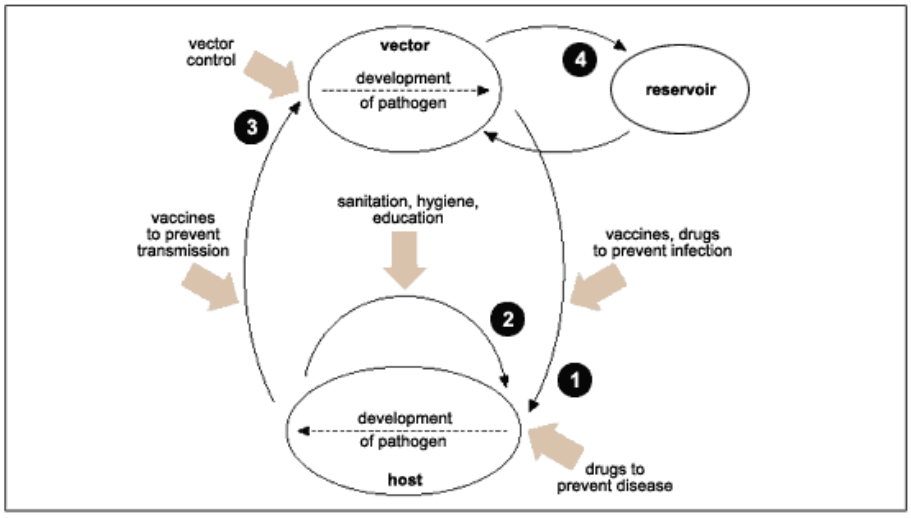


Figure 2.2. The black arrows illustrate a generalized infectious cycle; the shaded arrows indicate points where infectious diseases can be prevented. (1) A host is infected by the reservoir[2] or a vector for the pathogen. This individual may infect (2) other hosts in a population or (3) new vectors. (4) The pathogen also may cycle between the vector and a reservoir. Source: NIH, 2009.

- ***Pathogens***

The behaviour of pathogens is complex. A higher frequency may mean a higher risk of infection, but infection may also generate an immune response that protects against infectious diseases. Pathogens also mutate easily, which allows them to switch hosts and migrate to new ecological niches. This ‘‘host transfer” is more likely at the interface between

[2] A natural reservoir refers to the long-term host of a pathogen of an infectious disease, e.g. mosquitoes for malaria.

wild and agricultural communities, which have denser populations of humans, domestic animals, and crops, where the vector-host contact rate is higher. This occurs with influenza viruses. The avian influenza virus is carried by wild and domestic birds without causing illness. However, when pigs are infected, the virus can mutate into a more virulent strain (Chivian and Bernstein, 2008).

- ***Vectors***

The link between changes in species abundance and spread of infectious diseases is particularly clear and direct when speaking of vectors: higher number of vectors may result in a higher risk that people acquire a vector-borne disease. Vector diversity has the potential to affect disease dynamics in two major ways: through effects on pathogen host range and through effects on transmission rates (Power and Flecker, 2008).

This link is also very complex. In some cases a diverse vector community alone may increase the rate of disease transmission; in other cases it is the specific characteristics of the vector community (e.g. susceptibility, feeding habitats, biting behaviour) that are of key importance rather than their density or diversity (Chivian and Bernstein, 2008).

Man-made changes to the environment can set off selection processes in vector populations leading to increases in those vectors suited to the new environmental conditions. One example is the evolution of resistance of malarial mosquitoes to DDT consequent to genetic changes within the species (Millennium Ecosystems Assessment, 2005).

- ***Hosts***

The abundance of hosts influences directly density-dependent transmission (transmission rates increase with the increasing of density of infected hosts) or frequency-dependent transmission (transmission rates increase with the total proportion of the population that is infected) (Dobson, 2004). Human population density is a key factor in increasing dengue virus activity (Gubler, 1998; Kuno, 1995). The critical urban population size for sustained virus transmission is between 150,000 and 1,000,000 (Kuno, 1995; Wearing and Rohani, 2006).

High diversity of hosts often reduces the risk of infection through the “dilution effect”. According to Ezenwa *et al*. (2006) infection rates among vectors, and ultimately humans, will be lower in highly diverse host communities, where incompetent hosts[3] dilute the rates of disease transmission between vectors and highly competent hosts. The principle of the dilution effect is that increased host diversity dilutes or reduces disease incidence through (Swaddle and Calos, 2008):

- *transmission reduction*, a reduction in the probability of transmission of the disease from infected hosts to vectors,
- *encounter reduction*, a reduction in the rate of encounters between hosts and infected vectors,
- *susceptible host regulation*, a reduction in the number of susceptible hosts,
- *vector regulation*, a reduction in infected vector density, and
- *recovery increase*, a faster disease recovery rate among infected hosts.

[3] The competence of a host corresponds to its efficiency in transmitting the pathogen it harbours: hosts with a high efficiency are called “competent” hosts, while those with a low efficiency are defined as “incompetent” hosts.

Correlations between high host diversity and low rates of pathogen transmission or disease risk have been found for several zoonotic diseases, including Lyme disease (LoGiudice *et al*., 2003 and 2008), West Nile fever (Ezenwa *et al.,* 2006; Allan *et al*., 2009; Swaddle and Calos, 2008), and Puumala, Choclo and Calabazo hantaviruses[4] (Tersago *et al*., 2008; Suzán *et al*., 2009). Experimental evidence of the protective role of host diversity in disease transmission has also been gathered recently in studies of diseases of wildlife (Johnson *et al*., 2008) and freshwater plankton (Hall *et al*., 2009). In such disease systems, high species diversity within the host community either deflects pathogen transmission toward hosts that act as a sink for the pathogen (Ostfeld and Keesing, 2000b; Norman *et al*., 1999) or reduces the abundance of reservoirs, and consequently disease transmission rates (Begon, 2008). High hosts diversity reduces encounter rates between infected and susceptible hosts - the ‘‘encounter reduction’’ mode of the ‘‘dilution effect’’ Keesing *et al*., (2006).

In the same way as pathogens, vectors and hosts are embedded in a web of interactions and their populations cannot be considered in isolation. Ostfeld *et al.* (2009) showed that host communities can act as regulators of vector abundance and disease transmission. They tested the ability of nymphs[5] of the tick *Ixodes scapularis*, the main North American vector of Lyme disease, to survive while attempting to feed on six species of commonly parasitized vertebrate hosts. The model used to project tick abundance and infection prevalence when the diversity and species composition of the host community varies shows that reduction in host diversity dramatically increase the density of infected tick nymphs. Ostfeld concludes that:

“(1) some naturally-infested hosts act as ecological traps (trap species) that attract vectors but kill most of those that attempt to feed;

(2) trap species also tend to be dead-ends for the pathogen;

(3) trap species serve a potent protective role and their loss exacerbates disease risk. This leads to suspect that common life-history traits influence host suitability for both vectors and vector-borne pathogens; if so, results from the LD system should can be generalised to other vector-borne zoonoses”.

Although increased diversity of hosts can reduce transmission rates of particular diseases, the hosts can also harbour other pathogens (Pongsiri *et al*., 2009), either favouring pathogen persistence or high pathogen abundance (amplification) (Begon, 2008).

Analysing the contribution of multiple hosts to the dynamics of pathogens, Begon (2008) suggests that expected higher incidence of pathogens is not inevitable, partly because transmission between species is rarer than expected. From the study, it emerged that it may be difficult to separate a dilution effect from a density effect, both of which result in a reduction in pathogen abundance with increased host diversity. The results are summarised in figure 2.3.

[4] Hantaviruses are a recently discovered genus of viruses.

[5] A nymph is the larval form of some invertebrates, particularly insects, which resembles the adult form and undergoes gradual metamorphosis to reach the adult stage.

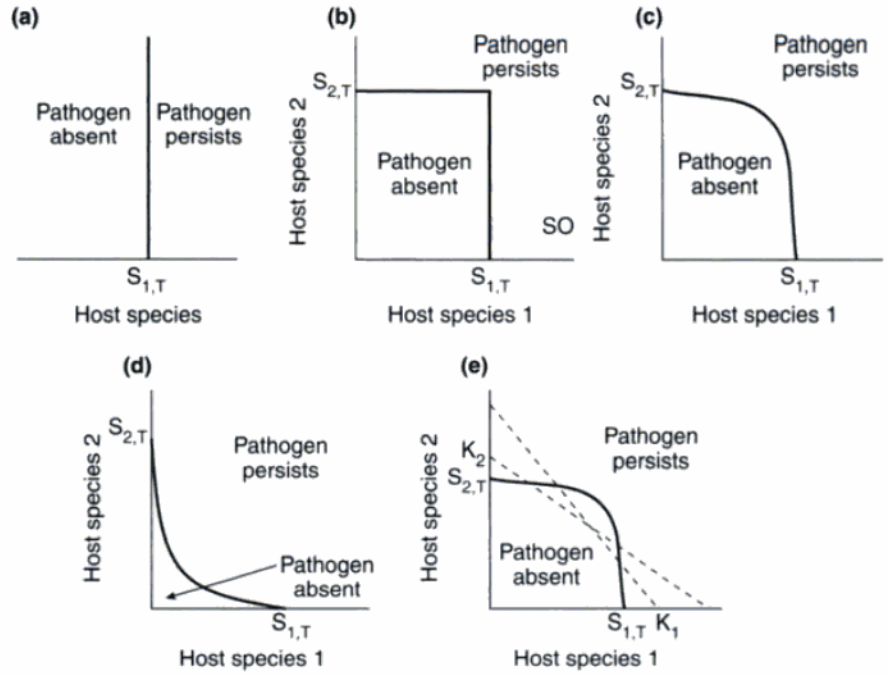


Figure 2.3. Critical threshold abundances and joint threshold curves. Source: Begon, 2008.

a) The critical threshold abundance of a single host species.

b) The joint threshold curve for two host species, when there is no interspecific (i.e. between species) transmission.

c) Similar to b, but when there is a small amount of interspecific transmission.

d) Similar to b and c, but when interspecific transmission rates exceed intraspecific ones.

e) Similar to d, but with the inclusion of Lotka-Volterra interspeciific competition zero isoclone.

S is the abundance of susceptible individuals of host species 1 or 2, $S_{1,T}$ is the threshold abundance for that species. SO represents a joint abundance typical of spillover dynamics[6].

According to Ostfeld *et al*. (2008), the following questions on the interaction between host diversity and infectious disease remain:

- How does host diversity interact with diversity in other components of the broader disease system? For instance, diversity of species that do not function as hosts for a specific pathogen might play an important role in disease dynamics if these species regulate host abundance, affect encounter rates between hosts and pathogens, or affect the nutritional or other physiological states of hosts.
- Which are the effects of host diversity per se (e.g. species richness or evenness) and which effects depend on the species composition in the host community? Host communities with the same species richness or evenness can be composed of different species or different relative abundance of the same species, with potential impacts on pathogen dynamics.
- What is the shape of the relationship between host diversity and disease risk?

[6] Pathogen spillover is the activation of disease dynamics in one host population through contact with pathogens from another host population as a result of high pathogen abundance in the latter (Power and Mitchell, 2004).

- ***Preys and predators***

The loss or extinction of predators can increase the population of a particular vector or host, leading to increased transmission of infectious disease to humans (Allan *et al*. 2003; Dobson *et al*. 2006).

One example is cited from Lake Malawi (an African Great Lake bordering Malawi, Mozambique, and Tanzania). Populations of *Bulinus* species of freshwater snails have increased due to overfishing of their natural predator *Trematocranus placodon*. *Bulinus* snails are intermediate hosts of the *Schistosoma* parasitic flatworms or trematodes, agents of the human parasitic disease schistosomiasis. Humans are infected through contact in water with the free-swimming larvae of the flatworms known as cercariae which develop in freshwater snails. The decline in predator populations and consequent increase of hosts in Lake Malawi appears to have been responsible for the rise in infection with schistosomiasis The authors hypothesize that a higher density of molluscivorous fish would act as a biological control of the disease, by reducing the availability of cercariae coming from the *Bulinus* snails (Stauffer et *al*. 2006).

According to Packer *et al*. (2003), the loss of specialist predators enables diseased individuals to survive longer and increases the possibility of transmitting disease to humans.

Holt and Roy (2007) have also analyzed the prey-predator relationships of a host-pathogen system. Using simple models, they show that in some circumstances predation can actually increase the equilibrium prevalence of infection in a host, where prevalence is defined as the fraction of the host population that is infected. Their results show that there is no general rule governing shifts in infection levels with shifts in predation pressure. The results highlight the importance of understanding of the dynamics of non-regulatory pathogens in reservoir populations and the dynamics of individuals that develop acquired immunity. This research only beginning and needs to be further developed.

- ***Allochthonous[7] species***

There are clear links between biodiversity, and human infectious diseases, through the spread of invasive species and pathogens (Pongsiri *et al*., 2009).

The introduction of alien species, combined with changing land use and climate, may have profound consequences for the ecosystems they colonise. Invasive species alter ecological dynamics through local or widespread extinction or reduction in populations of native species and even entire communities. This results in loss of biodiversity at many levels, from genetic variation to number of species, alterations in natural fire cycles, water quality, and biogeochemical cycles[8] (Crowl *et al*., 2008).

Large-scale global air travel and seaborne trade have removed natural geographic barriers that previously limited vector migration (Charrel and de Lamballerie, 2007; Reiter *et al*., 2006), enabling potential vectors to move great distances rapidly. This phenomenon, together with other social and environmental factors, has created new opportunities for infection. Furthermore, rapid adaptation of potential vectors and the microorganisms they carry, has facilitated re-emergence of previously eradicated diseases and emergence of new ones, for example yellow fever, dengue, malaria, and West Nile encephalitis (Lounibos, 2002).

[7] A species is allochthonous or alien when it is introduced in a place where it does not normally occurs.
[8] Also known as nutrient cycle. Pathway by which a chemical element or molecule moves through different mediums of the planet, both living (biotic) and inert (abiotic), e.g. the biosphere and atmosphere.

The voluntary or involuntary introduction of exotic species into temperate climate countries is increasing rapidly, as well as human migration, leading to increased incidence of viral infections and parasitic diseases outside of their natural distribution areas (Semenza and Menne, 2009). Recent examples are the wider occurrence of *Aedes* mosquitoes (which carry dengue fever and yellow fever) and outbreaks of Chykungunya (Indian Ocean Islands and Italy) and West Nile viruses (USA and Europe). This demonstrates that arboviruses represent a real threat in temperate climate developed countries. If the spread of such vector-borne diseases requires only a human host reservoir and a single widely found vector (e.g. the mosquito *Aedes albopictus*), globalization[9] of many vector-borne diseases (VBDs) is just matter of time.

Introduction of alien species into ecosystems often results in transmission of new diseases to vulnerable wildlife species and ultimately to humans.

The importation of European cattle has resulted in infection of endangered gorilla populations in central Africa with measles and polio and infection of lion, buffalo and other key wildlife species across Southern Africa with bovine tuberculosis. The emergence of these introduced diseases in wildlife can be a risk to human health through direct transmission to humans. Reinfection of livestock from humans can also occur, making it difficult to eradicate diseases and leading to loss of agricultural productivity and reduced food security and safety. Bovine tuberculosis has been shown to account for nearly 30% of diagnosed extra-pulmonary tuberculosis in humans in Tanzania (Kazwala *et al*., 2006).

Two limiting factors to the spread of vector-borne diseases (VBD) are the absence of the viruses that may transmit them and the impossibility to survive the winter season. If these two factors change they may result in outbreaks, as occurred in Greece in 1927-1928: a very mild winter, combined with the accidental introduction (probably by commercial sailing vessels) of the dengue virus together with its *Aedes* mosquito vector , which unusually survived, lead to a serious outbreak of dengue fever (Copanaris, 1928).

Uncertainties remain on the interactions of invasive alien species, disease vectors and pathogens with other agents of ecosystem change. Recent reviews on invasive alien species and (mainly non-human diseases) have focused on modelling spatial spread, species interactions, genetic evolution and ecosystem processes for policy purposes (Crowl *et al*., 2008).

Wildlife trade

More than 136,000 live mammals, 243,000 live birds, 5.9 million live reptiles and amphibians, and 222 million live tropical fish are estimated to be traded globally every year (United States Fish and Wildlife Service). Transport and trade in wildlife is now widely cited as a major threat to biodiversity homogenizing distinct flora and fauna, through introduction of invasive species and parasites and depletion of wild populations. International trade in wildlife may also play a significant role in the emergence and spread of human infectious diseases (Daszak *et al*., 2007), such as SARS, highly pathogenic avian influenza, West Nile virus, Ebola Reston virus, HIV-2 and monkey pox (Secretariat CBD/COP9, 2008; Daszak *et al*., 2007; Pavlin *et al*., 2009). A growing concern for emergence of new diseases in developed countries is the illegal importation of bushmeat[10] products from high-risk areas into major airport hubs (Swift *et al*., 2007).

[9] In medical entomology, globalization refers to the spread of vector-borne diseases outside their endemic areas.
[10] Meat of terrestrial wild animals hunted in the humid tropics of the Americas, Asia and Africa.

2.2.2 Changes in habitat structural diversity

Deterioration in the structure of habitats through disturbance represents the main threat to biodiversity. Human activities such as deforestation, water resource management, urbanization and agriculture may lead to habitat deterioration.

Modifications to natural ecosystems may result in either increased spread of infections if vectors and reservoirs find better conditions in the newly created habitats, or the disappearance of pathogens if the new conditions are detrimental to them (Millennium Ecosystem Assessment, 2005).

- ***Deforestation and reforestation***

The effects of deforestation on infectious diseases is a subject of considerable study. Deforestation destroys natural boundaries that protect humans from exposure to new diseases (Kazwala *et al*., 2006). Biodiversity loss in forest fragments may increase zoonotic and anthroponotic[11] pathogen exchange by forcing species into atypical ecological interactions that facilitate transmission of diseases. New ecological niches may be created favouring proliferation of vectors and their parasites (Molyneux, 2003).

Clearing forests alters the main elements of local ecosystems, such as microclimate, soil, and aquatic conditions, and most significantly, the ecology of local flora and fauna, including human disease vectors.

The vectors of some of the most important vector-borne diseases and the pathogens they transmit originate from forest areas (Patz *et al.*, 1996 and 2000). Mosquitoes and sand flies are the forest vector species most sensitive to ecological changes: their density and distribution are dramatically influenced even by small changes in environmental conditions, such as temperature, humidity and the availability of suitable breeding sites. Changes in mosquito ecology and human activity in deforested regions influence the transmission of mosquito-borne diseases such as malaria, Japanese encephalitis, and filariasis (Yasouka and Levins, 2007).

Increased occurrence of malaria has been related to deforestation in Africa, Asia, and Latin America (Harrus and Baneth, 2005). Studies have reported that the spread and biting-rate of the mosquito *Anopheles darlingi*, the main malaria vector in the Amazon region of Peru, were significantly higher in newly deforested areas than on sites with little habitat alteration, independent of vector population density (Tadei *et al*., 1998; Vittor *et al*., 2006).

Deforestation also favours contact between man and insect vectors and animal reservoirs of diseases originally confined to forests, such as with the bats carrying lyssavirus and Nipah virus (Halpin *et al*., 2007).

Primates are large-bodied, conspicuous animals with complex social systems and diverse habitat requirements and play a key role in forests as predators, prey and seed dispersers (Onderdonk and Chapman 2000). Their study may help better understand the connection between biodiversity and infectious diseases. Primates have emerged as important disease reservoirs in the increased risk of zoonotic disease transmission, not only because of their physiological similarity to man but also because of their response to changing biological diversity and habitat disturbance (Chapman *et al*. 2005).

[11] An anthroponotic disease, or anthroponosis, is an infectious disease in which thea disease causing agent carried by humans is transferred to animals on which it may cause the same or a different disease.

The EcoHealth Project (Goldberg, 2006), aimed at improving understanding of how reduction in biodiversity alters risk of infectious disease transmission in the Kibale National Park in Uganda. It demonstrated that forest fragmentation and consequent loss of primate biodiversity was the primary cause of the spread of some human infectious diseases. In particular, forest fragmentation leads to a reduction in primates from 12 to 3 species, coincident with changes in primate density and behaviour. These changes have in turn led to an increase in a broad variety of directly transmitted and water-borne pathogens in the remaining primates (e.g. strongyle and rhabditoid nematodes, the protozoas *Giardia* and *Cryptosporidium* and various species of pathogenic enterobacteria).

Epidemiological surveys of domestic animals living near forest fragments have identified cattle, goats, and sheep as reservoirs and vectors of infection between man and other primates. Spatial analyses suggest that the link between biodiversity loss and disease transmission between humans and primates is determined by human behaviour, primate behaviour and hydrology. The principles of the model are:

(1) human activity (driven by socio-economic and cultural factors) causes forest fragmentation and decline in plant biodiversity;
(2) primate biodiversity declines rapidly in response to these changes and the remaining primates experience dramatic demographic and behavioural changes;
(3) alterations in primate demography and behaviour "force" primates into atypical ecological interactions, including those with humans and livestock;
(4) these atypical ecological interactions lead to increased disease transmission risk;
(5) these processes are most pronounced in low altitude forest fragments, where primate population densities and human encroachment rates are high, and hydrological processes create physical reservoirs for environmentally persistent pathogens.

Although increased occurrence of infectious diseases is more often associated with deforestation, the opposite is true in the case of Lyme disease, where reforestation is the culprit. In the USA, reversion of farmland to small patches of forest has provided ideal habitats for deer, natural reservoirs of Lyme disease bacteria, carried by deer ticks. The increase in the reservoir and vector populations resulted in the increasing transmission of Lyme disease to humans (Barbour and Fish, 1993).

- ***Modifications of aquatic ecosystems***

Water-related infectious diseases can be grouped into two categories:

1. Water-borne infectious diseases, such as diarrhoea, due to poor sanitation, inadequate hygiene, ingestion of and contact with unsafe water (WHO, 2008) and
2. water-associated diseases, which require water to propagate their vectors (WHO, 2008). Examples include malaria, dengue fever and schistosomiasis.

Habitat requirements of aquatic vectors are specific to the species and include a whole range of types and sizes of water bodies (lakes, lagoons, rivers, ditches, culverts, sewers, marshlands, bogs) and objects which collect water (containers such as pots, tyres, leaves and tree stumps) (Battermann *et al*., 2009). Modification of an aquatic ecosystem may alter the local ecology so as to cause the spread of infections, particularly VBDs (Saker *et al*., 2004).

There are many illustrations in the literature relating to water management projects that have contributed to vector and parasite proliferation (Tilman *et al.*, 2001; Lindblade *et al.*, 2000; Keiser *et al.*, 2005a and b). Artificial water bodies, such as dammed lakes, drainage and

irrigation canals, ponds for rainwater collection and paddy (rice) fields, may easily become breeding sites for mosquitoes (Chivian and Bernstein, 2008; Patz and Kovats, 2002 o Patz *et al.*, 2005). Small, isolated pools at the sides of large water courses which run dry during the dry season, or poorly maintained channels, with slow-moving water, encourage proliferation of mosquito larvae (Molyneux, 2003).

A recent example of "adverse effects" related to an agricultural irrigation project in the desert region of Thar (Northern India). The construction of a net of irrigation canals lead to re-emergence of the protist *Plasmodium falciparum* (the micro-organism parasite which causes malaria) by increasing the abundance of the indigenous vector and allowing the establishment of new species of mosquitoes (Tyagi, 2004).

- ***Changes in agro-ecosystems***

The growing demand for food has lead to further conversion of natural ecosystems into agricultural ones, without consideration that this may favour transmission of VBDs (Tilman *et al*., 2001).

Irrigation can lead to the spread of malaria and conversely land reclamation can reduce the spread. Following World War II, there was an intense programme of eradication of *Anopheles labranchiae* and *An. superpictus*, the main Italian vectors of *Plasmodium falciparum*, in Tuscany. The programme included spraying with the pesticide DDT and reclamation of wetlands. The draining of these wetlands removed the habitats of the *Anopheles* mosquitoes. Recent introduction of rice cultivation in the same area, requiring the creation of temporary ponds, has favoured re-emergence of malaria (Baldari *et al*., 1998).

As livestock can act as vectors and reservoirs for human infectious diseases, change in their management can increase populations of pathogens (Patz *et al.*, 2000). When grazing extends into recently altered natural habitats, livestock may contribute to the emergence of VBDs by facilitating the exchange of pathogens from non-human reservoirs to humans (Chivian and Bernstein, 2008; Patz *et al.*, 2000). The transmission of Japanese encephalitis, for instance, is increasing in parts of South-East Asia and the Western Pacific, due to the expansion of irrigated agriculture and pig farming (especially rice paddies that provide new breeding sites for mosquito vectors in combination with pigs, the most important reservoir of the virus) (Chatterjee, 2005; Keiser *et al.*, 2005a).

The risks to human health posed by intensive factory farming have been highlighted for years. A large-scale industrial farm is a perfect breeding ground for influenza viruses. The high numbers of animals on industrial farms facilitate the rapid transmission and mixing of viruses and has been correlated with prevalence of infectious agents (Wuethrich, 2003; Gilchrist *et al*., 2007; Fablet, 2009). Data collected by the Thai government during the 2004 avian influenza outbreak show that the probability of outbreaks was significantly higher in large-scale poultry farms than in small free-range flocks (Graham *et al*., 2008).

These issues are also of concern in cropping systems where the increasing tendency towards monoculture increases the risk of epidemics of plant pathogens. Intermixing of maize and vegetable crops in Africa has led to contamination of vegetable crops with noxious species of the fungus *Fusarium*, resulting in systemic infection of persons with weakened immune systems, such as sufferers of HIV. Furthermore, it has been shown that conversion of native grasslands of Argentina and Venezuela into cropland has favoured rodents which are natural reservoirs of viruses which cause hemorrhagic fevers (Secretariat CBD/COP9, 2008).

Climate change

The relation between climate, environment and VBDs varies regionally and remains a subject of debate (Sutherst, 2004; Patz *et al*., 2000; Patz *et al*., 2005). However, many experts maintain that the impacts from changes in temperature and precipitation patterns on biodiversity are likely to result in a significant increase in emergence of VBDs such as malaria.

There is additional concern that many wild tropical species have advanced into more temperate zones (Parmesan and Yohe, 2003) and that the global distribution of key human pathogens and VBDs has followed suit (Guernier *et al*., 2004; Greer *et al*., 2008). Thus advancement of traditionally tropical microbial species into temperate zones is expected. In concrete terms, disease transmission is directly affected by shifts in a vector's geographic range, increase in reproductive and biting rates and shortening of pathogen incubation periods (Patz *et al*., 1996).

Research indicates, for instance, increased presence and duration of bacteria that cause cholera in oysters in the gulf of Mexico due to warmer water temperatures (Shapiro *et al*. 1998) and a projected increase in the global presence of dengue-carrying mosquitoes from 35% to 50-60% by 2085 (Secretariat CBD/COP9, 2008).

Global warming can work in different ways in different rainfall scenarios. Combined with increased precipitation, it may lead to higher mosquito populations through increasing the number of breeding sites and lengthening the lifespan of adult females. This phenomenon has been observed in the extension of the geographical distribution of malaria, dengue and leishmaniasis to higher altitudes and latitudes (Sutherst, 2004; Patz and Kovats, 2002; Patz *et al.*, 2005; Hay *et al.*, 2002). Conversely a rise in temperature coupled with a reduction in rainfall could shorten the length of the disease transmission season (Harrus and Baneth, 2005; Patz *et al.*, 2000).

Various effects of changing climate on VBDs in temperate areas of the Northern hemisphere have been observed (Semenza and Menne, 2009), such as the northward spread to Italy the sand fly *Phlebotomus perniciosus* (Rossi *et al*., 2007), the principle vector of visceral leishmaniasis.

- ***Urbanization***

Human settlements are man-made ecosystems that present many challenges to public health (Harrus and Baneth, 2005; Chivian and Bernstein, 2008; UNFPA, 2007). In developing countries, rapid, unplanned growth of human settlements has frequently led to overcrowding, poor housing and inadequate sanitation (notably inadequate waste removal and unsafe drinking water), the main reasons for the spread of some VBDs in urban environments (Saker *et al*., 2004).

Stagnant water in man-made containers facilitates the reproduction of mosquito vectors which colonise new, densely populated areas: this is particularly a problem for dengue and yellow fever (Sutherst, 2004). A variety of habitats, such as clay caves or rainwater collection ponds, on the edges of many large cities in Africa, where malaria transmission is still present, may harbour larvae of *Anopheles sp.* mosquitoes (Byrne, 2006). VBDs may flourish coincident with rapid urbanization when settlements are close to the natural environment of potential vectors. This has occurred in the case of neighbouring forests, where exposure to forest mosquito vector species, such as yellow fever and malaria forest disease (Chivian and Bernstein, 2008; Sutherst, 2004; Patz *et al*., 2000).

Recent outbreaks of visceral leishmaniasis – mostly a rural disease - in several Brazilian cities are related to urbanization, due to massive population movementy from rural areas to cities (Cohen and Powderly, 2004; Jeronimo *et al*., 1994). Epidemics of some forms of cutaneous leishmaniasis have occurred in densely populated cities of central and Western Asia (Ashford, 2000).

- ***Soil alteration***

Changes in land use can disrupt the critical roles that soil micro-organisms play as biological control agents to moderate outbreaks of diseases. Disturbances to soil impact ecosystem functioning, alter biodiversity and appear to be associated with the loss of ecosystem services, including control of pathogen-predator outbreaks. Although consideration of soil organisms as agents of human disease is generally limited to tropical countries, it is a global issue. Information on the biotic and/or abiotic triggers that drive the incidence of soil organism-related diseases is fragmented and disciplinary. Understanding the relationships between soil, biodiversity, and links to human diseases is a new interdisciplinary challenge (Wall, 2006).

Recommendations of the Second Conference on Health and Biodiversity (2008) regarding emerging infectious diseases

- Improving the potential for human well-being is of common understanding and concern to different cultural communities. They should exchange and learn from each other;
- failure to manage the interactions between man, livestock and wildlife may lead to emergence or re-emergence and further spread of diseases;
- there is need for more research and understanding of the role of biodiversity in controlling infectious diseases;
- although more research and robust evidence is needed, there is enough evidence as to the crucial role of biodiversity in disease control;
- there is need to refine existing models of ecosystem management and emerging diseases;
- there is need to address the relatively low levels of participation of local communities in programmes that integrate biodiversity conservation and disease control;
- there is need to integrate the issues of biodiversity and emerging diseases into existing educational curricula.

2.2 The human infectious diseases relevant in the analysis of the impact of changes in biodiversity and ecosystems

Direct links between changes in biodiversity and ecosystems and spread of infectious diseases have been demonstrated only for only a few diseases. This literature review focuses on human infectious diseases, and in particular zoonoses, vector-borne diseases (VBD) and avian flu, because, as pointed out by the Millennium Ecosystem Assessment (2005):

- these diseases are especially ecologically sensitive, i.e. environmental conditions affect both the infectious pathogens and the insects and other intermediate hosts that transmit them;
- many such infections are directly linked to certain natural ecosystem types (such as forests and wetlands);
- VBDs are major killers, causing approximately 1.4 million deaths per year and, due to the increasing impact of biodiversity changes, may be expected to represent highest proportionate future disease burden. Avian 'flu could represent a risk.

Zoonosis and vector-borne diseases

A zoonosis is an infectious disease that can be transmitted from vertebrate animals to humans, in some instances by a vector. The diseases commonly known as VBDs are those transmitted to humans or other animals by an arthropod. Globally named as Arthropod Borne Diseases, these VBDs are specifically named with the name of the family they belong to (i.e. mosquito-borne diseases, tick-borne diseases, etc.). Arthropods are a huge systematic *phylum* in the systemic classification of animals. They include the *classes* arachnids (which include the *order* Acarina, ticks) and insects (including the *order* Diptera, which covers mosquitoes and sand flies). Within the huge *phylum* arthropods, only a handful of species are of medical importance due to their capacity as vectors of disease. A vector is able to transmit pathogens which have carried out at least one cycle of development and reproduction (sexuate and/or schizogonic[12]) within the vector species before it becomes infective. Most of these diseases are caused by viruses, bacteria, plasmodes and filariae.

The epidemiology of a vector-borne zoonotic disease involves at least three organisms: the invertebrate vector, the pathogen and the human host. One or more wild or domestic animals may also be involved as reservoirs of the pathogen (Acha and Szyfres, 2003).

The nine zoonoses in the analysis (see table 2.2) have been selected according to the following characteristics:

- direct impact of biodiversity or ecosystem changes on their spread (Vora, 2008);
- present incidence and "weight" or impact on human health (VBDs affect over 700 million people every year);
- occurrence of outbreaks of the disease for the first time in areas outside their historical distribution zones (emerging diseases), or reappearance in formerly endemic areas where the disease was considered eradicated or under control (re-emerging diseases).

[12] Asexual reproduction thorough multiple division.

Table 2.2. Relevant infectious diseases selected.

DISEASE	BIODIVERSITY/ ECOSYSTEM CHANGE	PATHOGEN	VECTORS	RESERVOIRS	No ESTIMATED CASES/YEAR	ORIGINAL ENDEMIC AREAS
Malaria	Deforestation, water changes	*Plasmodium* spp.	Mosquitoes (*Anopheles* spp)	Humans[13]	350-500 millions	All continents with the exception of Europe
Yellow fever	Deforestation, invasion of alien species	Alphaviruses Flavivirus	Mosquitoes *Aedes* spp. (*Stegomya* subg.)	Humans[14]	200,000	South-East Asia, and West Africa
Dengue and dengue hemorrhagic fever	Urbanisation, deforestation, invasion of alien species	Flavivirus	Mosquitoes *Aedes* spp. (*Stegomya* subg.)	Humans[2]	50 millions	Central-South America, Asia, Africa
Chikungunya fever	Water changes, invasion of alien species	Alphavirus	Mosquitoes *Aedes* spp. (*Stegomya* subg.)	Humans[2]	Very variable	Continental areas and Islands of the Indian Ocean
West Nile fever	Pathogens, vectors and hosts changes	Flavivirus	Mosquitoes (*Culex* spp.)	Birds	Very variable	Africa and South America
Leishmaniasis	Deforestation, agricultural development	*Leishmania* spp	Sand flies (Phlebotominae)	Dogs, rodents Humans	600.000	South Europe, Africa, Asia Middle East South America Indian subcontinent
Tick-borne encephalitis	Sylviculture, water management	Flavivirus	*Ixodes* spp.	Wild mammals	10-12,000	European countries
Lyme disease	Depletion of predators, deforestation	*Borrelia* spp.	*Ixodes* spp.	Deers, small rodents	Undetermined	North hemisphere countries
Avian flu	Disappearance of wetland, Pathogen, vector and host diversity	Influenza A viruses	Poultry	Wild waterfowl	Undetermined	Asia

It should be stressed that the complexity of the relationships between the environment and zoonoses, and the still incomplete knowledge of their epidemiologic cycle, make difficult predictions of the impact of changes (Patz *et al*., 1996). For example, one would think that eradication or dramatic reduction of a vector population would lead to the disappearance of a VBD. Eradication has not been achieved, even if it still is the basis of VBD control programmes. Nevertheless, as the fight against VBDs continues, research on alternative ways of control has been focused on the influence of climate change, biodiversity, other environmental changes and human activities on the spread of a VBD.

[13] With the exceptions of rare cases due to monkeys- parasite plasmodia.
[14] These arboviruses originated from forest areas as parasite of monkeys but, at present, almost the totality of cases are due to transmitted human to human by Anopheline mosquitoes.

2.2.1 Malaria

Etiology:
Malaria represents the most important and widespread VBD caused by the protist genus *Plasmodium*. There are over 200 species of *Plasmodium* which infect vertebrates so far identified and new species continue to be described (Perkins and Austin, 2008; Chavatte *et al*., 2007). Only five species infect humans:
- *Plasmodium falciparum*, accounting for more of the 80% of global malaria cases per year and responsible for the malignant form of tertian malaria;
- *Plasmodium vivax* and *Plasmodium ovale*, both responsible of benign forms of tertian malaria;
- *Plasmodium malariae,* the agent of the quartan form of the disease;
- *Plasmodium kwnolesi* is a zoonosis that causes malaria in macaques but can also infect humans (Singh *et al*., 2004 and 2008).

Transmission:
Plasmodia have a complex life cycle that involves both an arthropod (mosquito) and a vertebrate (humans). Plasmodia, in the invasive form of sporozoites, are transmitted to humans by the bite of an infected female *Anopheles* mosquito during the blood meal.

Impact:
Malaria is an illness with a high disease burden in the developing world and a low disease burden in developed nations.

Tab. 2.2. Impact of malaria worldwide in 2008. Source: WHO, 2009b and Roll Back Malaria, 2008

	Cases	Deaths	Countries	Population at risk
Malaria	243 million	863,000	109	3.3 billion

At present, malaria ranks third among the major infectious diseases in causing deaths but is expected to become the number one infectious killer disease in tropical and sub-tropical areas, where the *Anopheles* mosquitos find ideal breeding and living conditions. WHO forecasts a 16% growth in malaria cases annually (2008).

Distribution:
Most cases and deaths are in sub-Saharan Africa. However, Asia, Latin America, the Middle East and parts of Europe are also affected (WHO, 2009a).

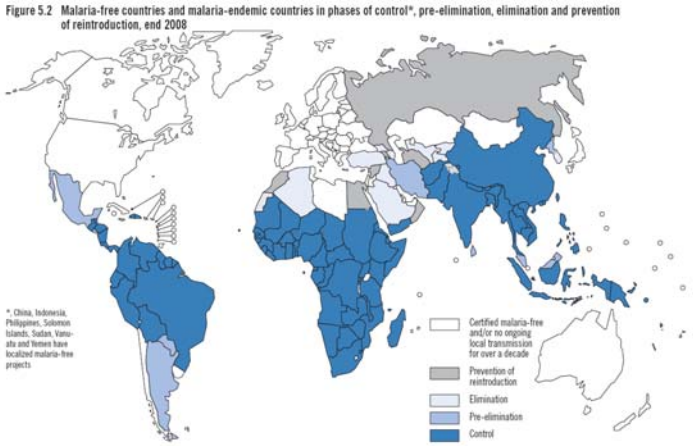


Figure 2.5. Distribution of malaria in the world. Source: World Health Organization, 2009.

Europe:
Recent reports show a re-emergence of malaria and it could occur in Europe (Rogers and Randolph, 2000). All European countries West of the Ural and Caucasus mountains were officially declared free of malaria in 1975. Up the 1980s, malaria was an almost forgotten disease in the EURO/WHO region[15], but has recently dramatically re-emerged in former USSR countries East of the Caucasus as a result of political and economic instability, massive population movements and changes in land use, coincident with the dissolution of the Soviet Union. Recent occurrence of introduced species of *Anopheles* mosquito vectors has caused great concern for the possible re-emergence of malaria in Western Europe (Pomares-Estran *et al*., 2009; Sabatinelli and Jorgensen, 2001).

Research to assess the real risk of malaria reappearance in Europe has been implemented in many countries where the disease was previously endemic (Romi *et al*., 2001). For example the EDEN project assesses the risk in Mediterranean countries basin in the light of the man-induced environmental changes. Results so far published conclude that the changes in the ecology of potential mosquito vectors present a negligible risk of malaria reintroduction in Europe, essentially due to the absence of pathogens. Despite the presence of some *Anopheles* vector populations in isolated areas (such as the Camargue wetland (France) and rice fields in Tuscany (Italy), occurrence of the disease agent *Plasmodium vivax* is possible but improbable. Endemic outbreaks are excluded because of the good socio-economic and health conditions (Ponçon *et al*., 2007; Linard *et al*., 2009; Capinha *et al*., 2009). Nevertheless, the nearly 15,000 annual cases of imported malaria in Europe deserve continuous surveillance.

For this reason - under the Roll Back Malaria EURO programme set up in 1971 - member countries of the WHO/EURO are asked to report numbers of laboratory confirmed cases of malaria registered. The database http://cisid.who.dk/mal includes five epidemiological indicators:

- the total number of malaria cases,
- the number of endemic malaria cases,
- the number of imported cases of malaria,
- the number of cases with *Plasmodium falciparum,*
- the number of deaths.

Malaria and changes in biodiversity

The effects of climate change on the presence and incidence of the disease have been studied in depth, both in endemic and non-endemic areas, Other man-induced factors - in particular deforestation and changes in aquatic ecosystems - require further study.

- *Deforestation*

In Africa, Asia, and Latin America, new infection occurs with the advance of forest clearance and the establishment of agriculture and urban development. Associated habitat alteration and fragmentation increases the risk of malaria transmission through effects on mosquito survival rates, density and distribution (Pongsiri *et al*., 2009; Yasuoka and Levins, 2007).

[15] This refers to the 51 countries belonging to the WHO/EURO region, an area including Europe, Anatolia, the Caucasus (Georgia, Armenia, Azerbaijan), Siberia, and central Asia (Kazakhstan, Kyrgyzstan, Tajikistan, Uzbekistan). The area includes the north Eurasian and Mediterranean malaria epidemiological areas.

Substitution of forest by mining and farming has created new habitats for *Anopheles darlingi* mosquitoes, leading to malaria epidemics in South America. Notably, the biting rate of *An. darlingi* increases in deforested areas (Vittor *et al*., 2006). Recent studies reveal that it is new settlements that are most exposed to risk of infection. A malariometric[16] survey carried out in a new settlement in Acre, Brazil, shows that malaria related morbidity is closely associated with forest clearance and farming, but decreases after five years (Silva-Nunes *et al.,* 2008).

In South-East Asia, the species *Anopheles dirus, An. minimus and An. balabacensis* have been affected in different ways by forest clearance with different impacts on malaria incidence. Similar events also occurred in West Africa, where the effects of the deforestation modified distributions and dynamics of local *Anopheles gambiae* populations (Molyneux and Birley, 1993).

More recently, Vittor *et al.* (2009) claimed that deforestation in the Amazon basin changes the epidemiology of malaria by contributing to a change in *Anopheles* species composition and abundance, due to change in breeding site availability. In addition to changes in shade, vegetation, and water bodies, settlers often create artificial bodies of water, such as fish farms and wells, and introduce new animal species. The authors concluded that deforestation and associated ecological alterations are conducive to *An. darlingi* larval presence, and thereby increase malaria risk.

Deforestation may create ecological niches favouring proliferation of vectors and parasites by raising surface-water availability, creating new breeding sites for some *Anopheles* mosquitoes (Pongsiri *et al*., 2009; Vora, 2008). For example, pools of water in deforested areas tend to have lower salinity and acidity than pools in forests and may be more conducive to the development of larvae of *Anopheles* species, particularly *An. darlingi*.

Deforestation can also affect microclimates. Greater exposure to sunlight raises water temperatures and changes community dynamics of larval habitats, increasing the survival of larval mosquitoes (Tuno *et al*., 2005). A warmer microclimate can cause mosquitoes to digest blood meals more quickly, leading them to feed and lay eggs more often, resulting in higher rates of vector development and reproduction (Afrane *et al*., 2006). Higher temperatures also affect the malaria parasite itself, reducing its development time and so making mosquitoes infectious more quickly (Pongsiri *et al*., 2009).

Yasuoka and Levins (2007) aimed to clarify the mechanisms linking deforestation, the ecology of *Anopheles* mosquitoes and malaria epidemiology. Different deforestation projects were reviewed in terms of their impact on mosquito density and malaria incidence. It was not niche width but increased sun which led to increased density of. mosquitoes. The study showed that land-use changes can have multiple impacts on disease transmission. The risk of malaria can rise dependent on the arrival of opportunistic vectors, adaptation of vectors to newly created niches and immigration of non-immune people (Yasuoka and Levins, 2007; Pongsiri *et al*., 2009). Pattanayak and Yasuoka (2008) found that, introducing behavioural variables (prevention, prophylaxis and medical care) the correlation between deforestation and malaria diffusion is four times as large as in standard models.

In South-East Asian and South American countries forests often are the most important centres of malaria infection (Incardona *et al.*, 2007; Erhart *et al.*, 2005; Povoa *et al.*, 2003; Singh *et al.*, 2003). Forest malaria is the result of ready availability of water and presence of large areas of virgin forest. These conditions also encourage settled populations to practice

[16] Malariometrics is the determination of the level of malarial infectious in an area or population.

the so called "slash and burn" cultivation inside the forest and rice cultivation on the edges of forests. As a consequence, humans live close to mosquito species which breed in or nearby the forest, some of which are highly anthrophilic[17] malaria vectors, such as *Anopheles dirus* and *An. minimus*.

Environment of crops such as cassava and sugar-cane, which require little water and provide little shade, are unfavourable for *Anopheles* mosquitoes, especially for those species which require shade. In Thailand, the conversion of forest to cassava or sugarcane cultivation eliminated shady breeding habitats for the main vector species, *An. dirus*, yet created extensive breeding grounds for *An. minimus*, which prefers sun. Both vectors are highly efficient for malaria transmission, but *An. dirus* is more abundant during the wet *season* compared with the dry and hot seasons, while *An minimus* is present all year round. Consequently, there was a rise in malaria transmission among resettled cultivators who were at risk during the whole year (Prothero, 1999; Pattanayak and Yasuoka, 2008).

- *Modifications in aquatic ecosystems*

Malaria is a water-related vector-borne disease. According to Rejmánková *et al*. (2006), aquatic ecosystems are essential to the presence and abundance of mosquito larvae and, consequently, to the number of adults capable of transmitting malaria. Aquatic plants provide protection from predators and, together with nearby trees and shrubs, produce detritus that support the bacteria on which mosquito larvae feed. A change in one or more constituents of an ecosystem will have an impact on the mosquito population and may lead to the replacement of one species with another. Silting up of water bodies, uncontrolled aquatic weed growth, slow water flow or creation of stagnant pools are examples of changes that affect mosquito population dynamic. In case a less efficient vector of malaria replaces a more efficient one, there could be a reduction of malaria risk, and when there is the opposite replacement, malaria transmission could increase.

Rejmánková *et al*., (2006) documented two processes leading to changes in abundance of malaria vectors in Belize:

- change in the composition of freshwater plant communities due to change in availability of nutrients;
- habitat selection by female mosquitoes. Some species of mosquito, such as *An. albimanus* and *An. vestitipennis,* are strongly habitat-specific and female responds rapidly to any modification of their “home” habitat.

A growing number of new malaria cases has been observed in connection with new irrigation and drainage schemes or hydro-electric dams (Lautze *et al.,* 2007; Keiser *et al*., 2005b). New open water surfaces in the form of canals, ponds and artificial lakes, have created new breeding sites for mosquitoes (Fritsch, 1997).

One of the methods used in the malaria control programmes is “source reduction”, eliminating habitats for larvae by draining and filling water bodies, or avoiding the creation of mosquito breeding sites. It was applied successfully against many *Anopheles* species in malaria endemic countries until the mid-20th century. A review of field studies in Africa conducted during the past 15 years (Walker and Lynch, 2007), suggests that targeting larvae, particularly in man-made habitats, can significantly reduce malaria transmission. This approach is especially suitable for urban areas where larval habitats are limited and

[17] Preferring humans to other animals.

particularly effective when combined with adulticidal measures such as indoor residual spraying and use of insecticide-treated bed nets.

Use of irrigation in agriculture, in particular for rice growing, can increase the presence of *Anopheles* larvae on a massive scale. It is particularly evident in areas where malaria is hypo- or meso-endemic (i.e. with low rates of transmission) due to the particularly vigorous mosquito vectors concerned. Vector efficiency was the subject of a study on rice field mosquitoes, *Anopheles funestus* (anthrophilic) and *An. Arabiensis* (zoophilic[18]), which was carried out in central Kenya. Although *An. arabiensis* comprises nearly all of the population (98% of the total sample), the infection rate of *An. arabiensis* was unexpectedly three times higher (Muturi *et al*., 2008). The results confirm the thesis that a good, efficient vector does not need a high population density to transmit malaria.

[18] Preferring animals, but also (in this case) may feed on humans.

2.2.2 Mosquito-borne arbovirosis

Despite centuries of control efforts, mosquito-borne diseases (MBD) and in particular mosquito-borne arbovirosis, are flourishing worldwide (Takken and Knols, 2007; Pialoux *et al.*, 2007; Rezza *et al.*, 2007). The vectors of arboviruses (arthropod-borne viruses) belong mainly to the sub-family *Culicinae*. Particular relevance deserve the arboviruses belonging to the genus *Flavivirus* (family Flaviviridae) (Gould and Solomon, 2008), some of whom being in expansion out of their natural range, are becoming a major threat for non endemic countries (Takken and Knols, 2007; Pialoux *et al.*, 2007; Rezza *et al.*, 2007).

Among this group, four are considered as most important human MBD due to flaviviruses:

1) Yellow fever (YE), which has epidemiological similarities to dengue, under control in the mid-20th century, it is once again increasing, especially with sudden epidemics in densely populated urban areas, despite the existence of experienced vaccines.2) Dengue (DEN) and its most severe form, dengue haemorrhagic fever (DHF), has expanded its range over the past several decades, following its principal vector, *Aedes aegypti*, back into regions from which it was eliminated in the mid-20th century and causing widespread epidemics of hemorrhagic fever (Rogers *et al*., 2006).
3) the Chikungunya (CHIK) virus (genus *Phlebovirus*), has spread out of its natural range, for the first time in 2006, causing in the successive years severe outbreaks.
4) West Nile virus (WNV) has become endemic throughout the Americas in the past 10 years and more recently has reached Europe, involving for the first time human cases. It is soon going to become endemic, at least in some SE country (Balanca *et al.*, 2009).

Mosquito-borne arbovirosis and changes in biodiversity

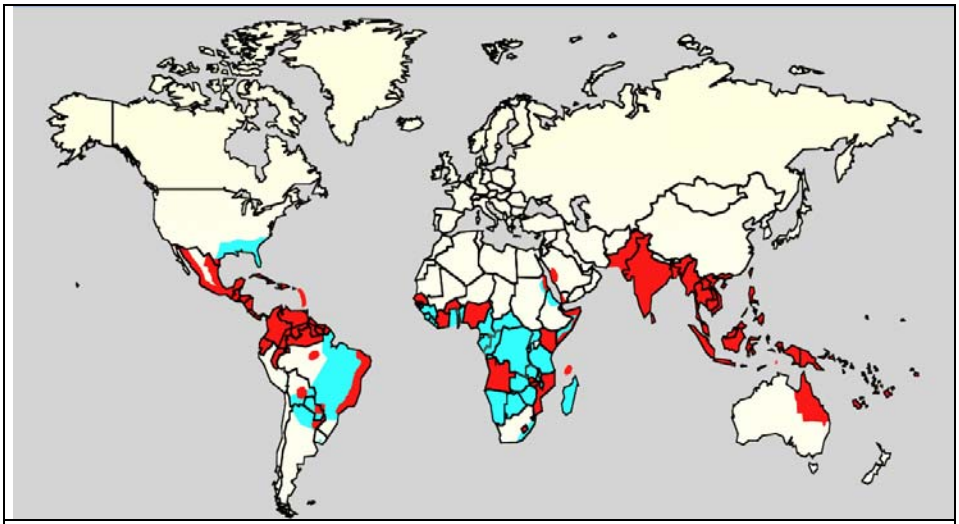
The importance that these MBD may have on human health is strictly related to the kind of environment and to the biological characteristics of their specific vectors. Some MBD are strictly dependent on specific local conditions (vector species, peculiar habitat, specific reservoir, or recipient host), that may make the spread of the diseases out of their original endemic range difficult and improbable (but not impossible) to occur. While other MBD, transmitted by vector species particularly able to adapt to different climatic and environmental conditions, may spread, causing epidemic events in areas where the disease was never experienced before. Environmental factors and human activities, which enhance population densities of vector mosquitoes (heavy rains followed by floods, irrigation, higher than usual temperature, or formation of ecologic niches that enable mass breeding of mosquitoes) could increase the incidence of all the selected mosquito-borne arbovirosis.

- *Allochthonous species*

The occurrence of outbreaks of “tropical” mosquito-borne arbovirosis in countries with a temperate climate emphasises that the globalisation of vectors is an ongoing reality. Studies on the involvement of introduction of allochthounous species (vectors of the diseases) in the spread of mosquito-borne arbovirosis have been carried out on YF, DEN and CHIK.

Ae. aegytpi, the principal vector of YF, DEN and CHIK viruses, originated from Africa. Between the end of the 18th and the first half of the 20th centuries it was very common in the Mediterranean basin, being transported by commercial sailing vessels (Gubler, 1998). At that time, sporadic dengue (DEN) and yellow fever (YF) outbreaks occurred in the Mediterranean area, remaining however confined to the site of entry, usually harbour cities. In the majority of

cases these outbreaks ceased spontaneously at the beginning of the autumn, because this species was unable to survive the low winter temperatures of temperate regions. After World War II, *Ae aegypti* disappeared from the Mediterranean basin, but in the past 50 years it was reintroduced together with its pathogens, when the use of locked containers was introduced in the sealing trade of goods and the commercial transportation by aircraft became common. The widespread trade of goods potentially carriers of *Ae. aegytpi* viable eggs, coupled with the incoming global rise in the mean temperature, are increasing the geographic spread of *Ae. aegytpi* and the geographic overlap of viruses it carries, and therefore the risk of introduction (or reintroduction) and spread of the vector even to the temperate hemisphere regions. The introduction and spread of *Aedes aegypti* to yellow fever free areas close to those of endemy is an on going event (North and Central America, the Caribbean, the Middle East, Asia, Australia and Oceania).



Areas infested with *Aedes aegypti*.

Areas with *Aedes aegypti* and recent epidemic dengue fever.

Figure 2.6. Map showing the distribution of dengue fever in the world, as of 2006. Source Clark, 2007.

The risk of introducing the vector into the temperate regions is even more significant for the most invasive mosquito in the world, *Aedes albopictus*, the secondary vector of YF, DEN and CHIK viruses. Up to the 20th century the *Ae. albopictus* natural range extended from South China to most of the Indian Ocean islands, including the tropical and subtropical regions of South-East Asia. Since the early 1900's the species has gradually expanded its range from the Western Pacific and South-East Asia to Africa, the Middle East, North and South America, and Europe. This spread has occurred largely due to the international trade of used tires, in which mosquito eggs have been laid, together with the great ability of the mosquito to adapt to different environmental and climatic conditions. The capacity to breed in many manmade containers, to maintain viable eggs for months in the used tires and to survive the low temperatures throughout an egg diapause induced by a short photoperiod, allowed the species to establish in temperate zones. An example of that is the first-ever reported outbreak of CHIK virus in a temperate country that occurred in Italy during the summer of 2007. Today, *Ae. albopictus* is widespread in Italy and has been detected in other European countries: an updated distribution and risk map for its possible further establishment in Europe have been recently published by ECDC (2009).

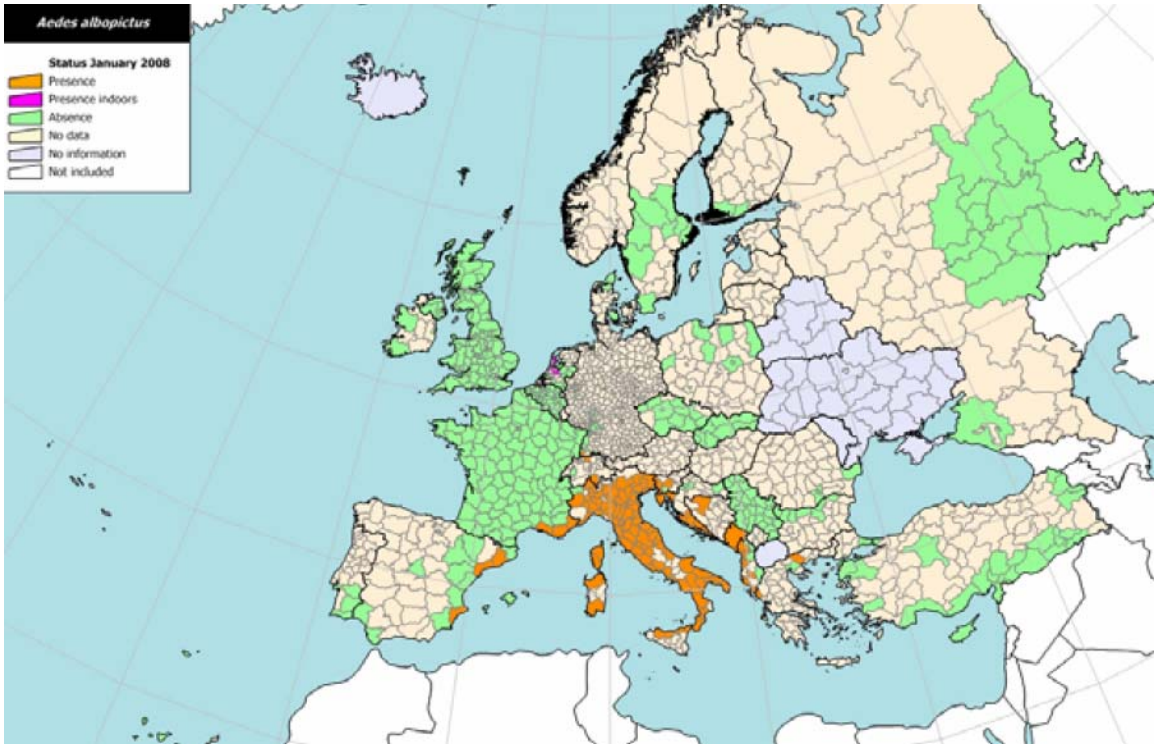


Figure 2.7. Current distribution of *Aedes albopictus* in Europe (2008). Source: ECDC, 2009.

- *Deforestation*

Deforestation in tropical and subtropical countries may affect (in different ways) the four diseases transmitted by mosquitoes. The major factor that plays a role in these forest diseases is the changes induced by human activities to the habitat of the mosquito vectors (*Aedes* and *Culex* spp.).

Current evidence suggests a common forest origin of the YE, DEN and CHIK viruses, maintained in a primitive enzootic transmission cycle involving canopy-dwelling *Aedes* mosquitoes and lower primates in the rain forests of Asia and Africa. Moreover, as these viruses do not regularly move out of the forest to urban areas, an epidemic transmission cycle may occur in rural villages, where the human population is small. Introduced viruses quickly infect the majority of susceptible individuals in these areas, and increasing herd immunity causes the virus to disappear from the population. A number of *Aedes* (*Stegomyia*) spp. may act as a vector in these situations, depending on the geographic area, including *Ae. aegypti*, *Ae. albopictus*, and *Ae. polynesiensis* and other members of the *Ae. scutellaris* group.

WNV is apparently the only zoonosis out of the four described above, probably originating from a single enzootic (forest) cycle, that adapted to a second epizootic cycle, with involvement of vertebrate dead-end hosts, when humans extended their activity close to the forest vector(s) and part of these became anthropophilic.

Through the process of clearing forests and subsequent agricultural development, deforestation alters the main elements of local ecosystems, such as microclimate, soil, and aquatic conditions, and most significantly, the ecology of local flora and fauna, including mosquitoes, which are vectors of human diseases. Of all the forest species that transmit diseases to humans, mosquitoes (together with sand flies) are among the most sensitive to environmental changes: their survival, density, and distribution are dramatically influenced

even by small changes in environmental conditions, such as temperature, humidity, and the availability of suitable breeding sites.

Deforestation not only affects the local climate, but also implies a number of forest-related activities, such as mining and logging, producing increased intrusion of people into forested areas, and thus, increased exposure to mosquito vectors of arboviruses. In the case of yellow fever, felling trees may simply increase transmission by bringing the treetop-dwelling mosquitos down closer to human contact (Vainio and Cutt, 1998).

- *Urbanisation*

Cases of people that contract arbovirosis directly in the forest are becoming less frequent, while dramatic epidemics of YF, DEN or CHIK are occurring in overcrowded urban settlements, where there is a greater vector/human contact rate due to a greater human density and a greater vector density. Urban settlements display a large variety of small man-made containers, filled mainly by rain water, which have replaced the natural breeding sites within the forest (i.e. broken bamboos, three holes, leaf axils of bromeliaceae plant). This is due to the fact that the two most competent mosquito vectors, *Aedes aegypti* and *Ae. albopictus*, are becoming specific urban "container breeding" mosquitoes which transmit "human to human" a disease that was born as a zoonosis.

Similarly, urban areas can become centrally involved in WNV transmission when urban landscapes provide breeding sites for mosquito populations and a contact of humans with domestic birds (Tsai *et al*., 1998; Brown *et al*., 2009).

Yellow fever

Etiology:

Yellow fever is a viral haemorrhagic fever caused by a virus of the *Flavivirus* genus of the Flaviviridae family.

Transmission:

Transmission occurs via the bite of an infected mosquito, primarily *Aedes* or *Haemagogus* spp. (South America only). Mosquitoes also act as an important reservoir of YF since they may remain infected throughout their lives. There are three types of transmission cycle:

- *Sylvatic cycle*: it occurs in tropical rainforests where monkeys, infected by sylvatic mosquitoes (i.e. they breed in the jungle), pass the virus onto other mosquitoes that feed on them; these mosquitoes in turn bite and infect humans entering the forest. This produces sporadic cases, the majority of which are often young men working in the forest e.g. logging.
- *Intermediate cycle*: mosquitoes infect both monkey and human hosts and increased contact between man and infected mosquito leads to disease. This cycle of yellow fever transmission occurs in humid or semi-humid savannahs of Africa, and can produce small-scale epidemics in rural villages. It is the most common type of outbreak seen in recent decades in Africa.
- *Urban cycle*: domestic mosquitoes (a forest species that has adopted the human domestic environment, breeding around houses), most notably *Aedes aegypti*, carry the virus from person to person. This mosquito is also the principal urban vector of dengue and chikungunya viruses. "Urban yellow fever" results in large explosive epidemics when travellers from rural areas introduce the virus into areas with high human population density. These outbreaks tend to spread outwards from one source to cover a wide area.

Impact:
Despite the availability of a safe and effective vaccine, yellow fever remains a disease of major public health importance. Under control in the mid-20th century, YF is now increasing, especially with sudden epidemics in densely populated urban areas. The vast majority of cases and deaths take place in sub-Saharan Africa, where case fatality rates for reported cases are in the order of 15 to 50%.

Table 2.4. Impact of Yellow Fever. Source: WHO, 2009d.

	Cases/year	Deaths/year	Countries	Population at risk
Yellow fever	200,000	30,000	45	900 million

Distribution:
The disease is endemic in tropical regions of Africa and South America.

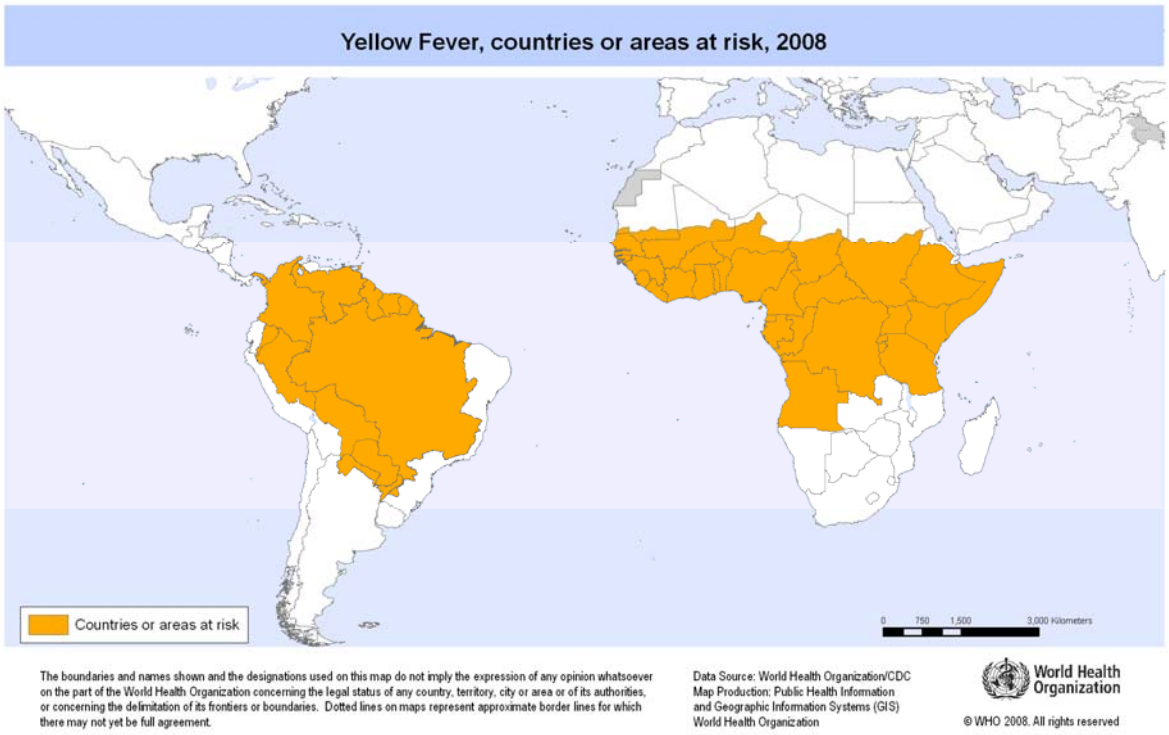


Figure 2.8. Yellow Fever distribution map. Source: WHO, 2009e

Yellow fever and changes in biodiversity

Please refer to the previous section “Mosquito-borne arbovirosis and changes in biodiversity”.

Dengue

Etiology:
Dengue fever (DEN) is an acute febrile illness caused by four closely related arboviruses (DEN-V 1-4). DEN-Vs are quite recent infectious agents of humans, probably originating from closely related simian viruses within the last millennium.

Transmission:
Viruses are transmitted to humans by the bite from an infected *Aedes* mosquito, in particular by *Aedes aegypti* that represents the main vector across all the endemic areas (Gubler, 1998 and 2006), or more rarely by *Aedes albopictus* mosquito.

Impact:
DF is the most frequent infectious disease encountered in developing countries after malaria. Today 40% of the world's population live in areas where there is a risk of dengue transmission and an additional 120 million people travel annually to affected areas.

Table 2.5. Impact of Dengue and dengue hemorrhagic fever. Source: WHO, 2009f.

	Cases/year	Deaths/year	Countries	Population at risk
Dengue and dengue hemorrhagic fever	100 million	25,000	100	2.5 billion

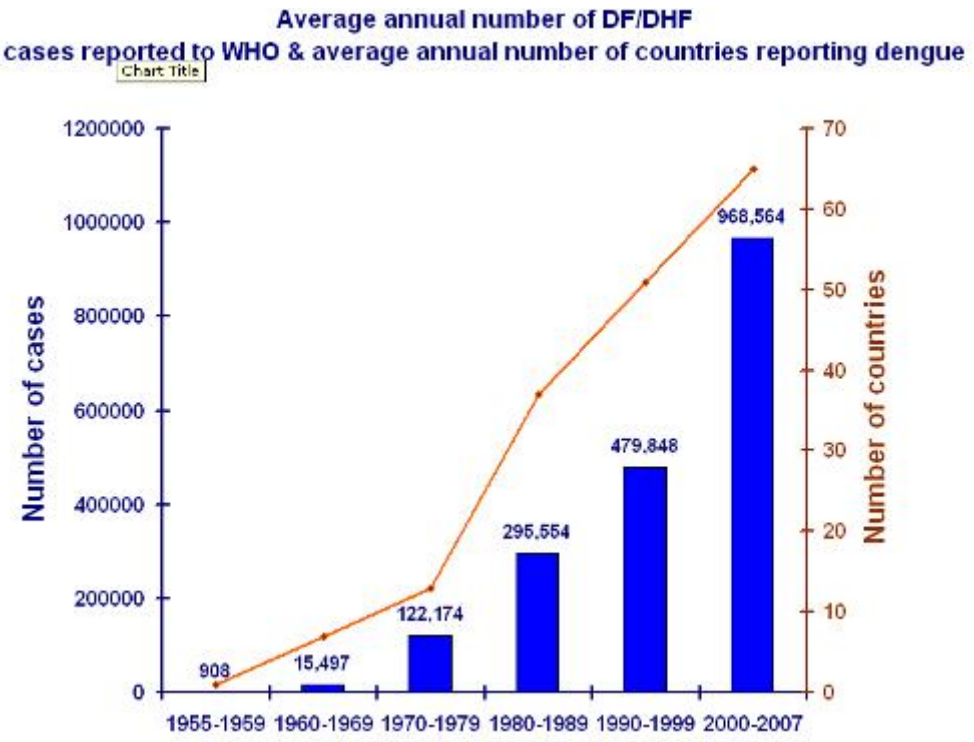


Figure 2.9. Dengue: annual reported cases and countries. Source: WHO, 2009f.

Distribution:
Dengue occurs in tropical and sub-tropical areas of the world and it is endemic in Asia, the Pacific, the Americas, Africa and the Caribbean. Dengue is the most rapidly spreading vector-borne disease.

Dengue and changes in biodiversity

Please refer to the previous section “Mosquito-borne arbovirosis and changes in biodiversity”.

Chikungunya fever

Etiology:
Chikungunya virus (CHIKV) is an arthropod-borne virus of the genus *Alphavirus*.

Transmission:
Chikungunya is generally spread through bites from *Aedes* mosquitoes species. *Aedes aegypti* (the yellow fever mosquito), a household container breeder and aggressive daytime biter which is attracted to humans, is the primary vector of CHIKV to humans. *Aedes albopictus* (the Asian tiger mosquito) has also played a role in human transmission in Asia, Africa, and Europe. Various forest-dwelling mosquito species in Africa have been found to be infected with the virus. The main virus reservoirs are monkeys, but other species can also be affected, including humans.

Impact:
There are no estimates at global level. Almost two million cases were reported in India and 266,000 cases in the Reunion Island (38% of population) in 2006 and more cases have been reported in 2007.

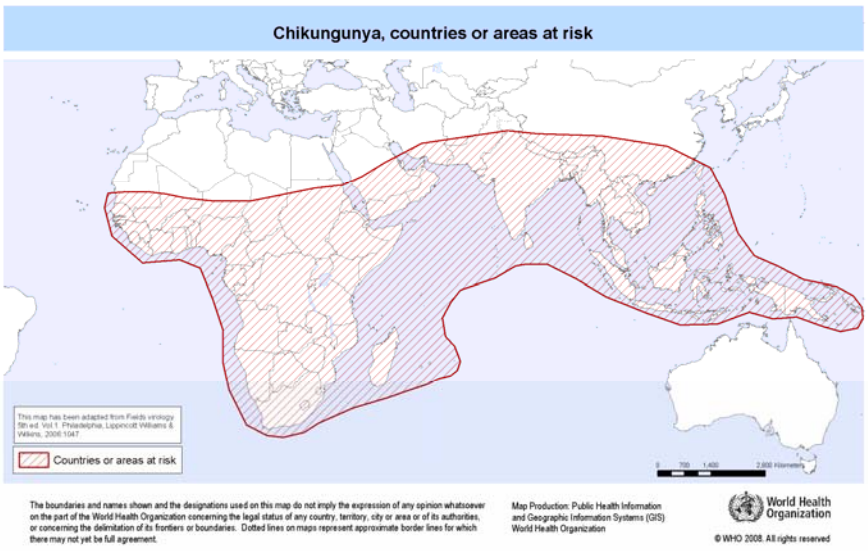


Figure 2.10. Chikungunya Distribution and Global Map. Source: WHO, 2009e.

Distribution:
Chikungunya occurs in Africa, South -Eeast Asia and Europe.

Europe:
In Europe, *Ae. albopictus* was recorded in Albania in 1979 where it was introduced probably from China, and in Italy in 1990 (Romi *et al*., 2008). Starting from the early 2000’s, *Ae. albopictus* has been detected in other European countries. Outbreaks of Chikungunya fever, carried by *Ae. albopictus,* have occurred in 2007 in Italy.

Chikungunya and changes in biodiversity

Chikungunya fever, as all the mosquito-borne diseases, can be affected by changes in the structural diversity of ecosystems and can spread thanks to the introduction of its main vectors, *Ae. aegypti* and *Ae. albopictus* in different geographical areas. In addition, studies exist on the influence of pathogen diversity on the spread of this disease.

- *Changes in pathogen diversity*

Chikungunya is generally spread through bites from *Ae. aegypti,* but a recent research has suggested that Chikungunya virus strains in the 2005-2006 Reunion Island (in the Indian Ocean) outbreak incurred a mutation that facilitated transmission by *Ae. albopictus*. Concurrent studies in Texas confirmed definitively that enhanced chikungunya virus infection of *Ae. albopictus* was caused by a point mutation of the pathogen. Analysis on the CHIK virus that caused the outbreak in 2007 in Italy showed that the strain was similar to those detected on the Indian subcontinent and contained the same mutation found in a variant in the Indian Ocean islands. The hypothesis that this variant has high vector competence (i.e. virus-vector fitness) seems to be confirmed by both the successful introduction and rapid spread of the infection from one infected human host and by the further occurrence of other smaller clusters in different localities in the same province, yet located several kilometres from the two villages initially affected. This example highlights the role shifting vector populations may play in the emergence of vector-borne diseases (Power, 2009; Tsetsarkin and Higgs, 2009).

West Nile fever

Etiology:

West Nile Fever is a zoonosis due to a mosquito-borne flavivirus belonging to the Japanese encephalitis complex, maintained in natural cycles by birds and mosquitoes.

Transmission:

WNV is maintained in nature by two separated epidemiological cycles (Hubálek and Halouzka, 1999; Higgs *et al*., 2004):

1. Enzootic cycle (or wild cycle): an indigenous competent ornithophilic[19] mosquito vector becomes infected biting an infected migratory bird (Rappole *et al.,* 2000) and after a few days is able to infect, by biting, the main hosts (migratory or indigenous birds that act also as a reservoir). Ornithophilic mosquitoes belonging to the species *Culex univittatus*, *Cx. tarsalis*, *Cx. pipiens*, *Cx. modestus* are commonly considered as the principal vectors of West Nile virus (Hubalek and Halouzka, 1999).
   Characteristic environments where this wild cycle commonly occurs are wetlands, river deltas and flooded plains that migratory birds chose for nesting, coming in touch with the potential mosquito vectors breeding in the same area.

2. Epizootic cycle (or urban cycle): a second mosquito species, more generalist in the choice of the host (i.e. feeding on both humans and birds), becomes infected biting an indigenous or domestic bird (such as white storks, pigeons, chicken, house sparrows) and in a few days is able to infect humans (Campbell *et al*., 2002), which are accidental dead-end hosts. The vector species mainly involved in the West Nile virus transmission to humans are *Culex pipiens* or its vicariant species *Cx. quinquefasciatus* (Toma *et al*., 2008; Fonseca *et al*., 2004).

[19] Bird-feeding species.

This cycle occurs in urban areas when human activities make available a number of breeding sites for mosquito populations development.

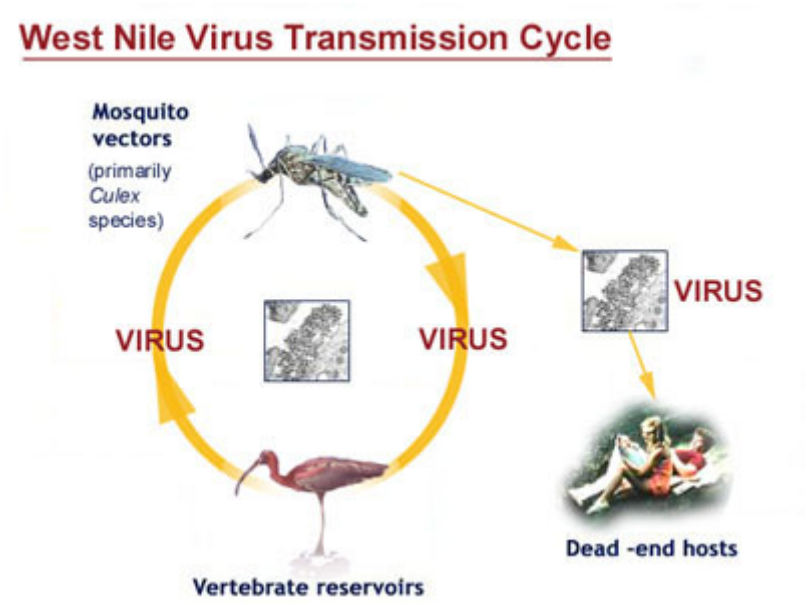


Figure 2.11. West Nile Virus transmission cycle. Source: CDC, 2004.

Wild and domestic birds are the main reservoirs that may amplify the virus spread by migratory birds, but a wide range of other animals may also harbour the infection.

Impact:
There are not estimates at global level. During the two past decades the disease has emerged or re-emerged with different severity in various foci out of its natural geographic range (Hayes *et al*., 2005; Murgue *et al*., 2001). In only four years from its arrival in North America in 1999 it spread across the US from New York to California, and from Canada (Pepperell *et al*. 2003) to Mexico and the Caribbean (Blitvich, 2008), causing 6,857 severe human cases and 654 fatalities in the US.

Distribution:
Originally distributed in Africa, the Middle East and Eurasia, WNV has dramatically expanded its geographic range in the past ten years becoming endemic throughout the Americas (Gould and Fikrig, 2004). More recently it has reached Europe, involving for the first time human cases. It is soon going to become endemic, at least in some SE country (Balanca *et al*., 2009). A subtype of the West Nile virus (called Kunjin virus, or KUNV) is also found in parts of Australia.

Europe:
In Europe, an increasing number of humans has become infected with the severe form of the disease. Recent outbreaks of WNV causing human encephalitis have occurred in the Mediterranean basin, in particular in Algeria in 1994 (Murgue *et al*., 2001), in Romania, (Bucarest), in 1996-2000, with 393 human cases and 13 deaths (Tsai *et al*., 1998), in the Czech Republic in 1997 (Murgue *et al.,* 2001), and in Volgograd, Russia, in 1999, with over 480 estimated cases and 40 deaths (Lvow *et al.,* 2000). Italy, because of its peculiar geographic position, as a bridge between Europe and Africa, seems to be particularly exposed to the introduction of exotic MBD. After the first isolated outbreak occurred in 1998 in central Italy (Autorino *et al*., 2002, Romi *et al*., 2004), the disease has reappeared in 2008

and 2009 with several, scattered foci of equine encephalitis and the first human cases (Barzon *et al*., 2009).

The source of these outbreaks is often located near wetlands, which are breeding and nesting grounds for many species of birds and mosquitoes, although urban areas can also become involved in transmission when urban landscapes provide breeding sites for mosquito populations.

West Nile fever and changes in biodiversity

Well-documented studies link the changes in incidence of West Nile fever with the following changes in species diversity.

- *Changes in vector diversity*

The competence of the mosquito vector and the avian host seems to be determinant in the efficiency of West Nile virus transmission.

Two main hypotheses on the competence of the vectors have been formulated (Bernard *et al.,* 2001). In both hypotheses the species with a broad range of hosts could be *Cx. pipiens*:

1) In the first hypothesis the enzootic cycle[20] is sustained by one or more mosquito species, mainly ornytophilic, which transfer WNV from migratory to indigenous birds, allowing the dissemination and amplification of the virus. Different species, with a broader range of hosts, and then also anthropophagic, will act as a “bridge” vector, between infected birds and horses/humans.
2) In the second hypothesis, a single species able to bite birds as well as mammals may acts as both enzootic and epizootic[21] vector.

According to the most recent literature, the findings of Italian inquiries indicate a reasonable involvement of *Cx. pipiens* as a main WNV vector both in the enzootic as well in the epizootic cycles. The existence of at least two different biological forms with different characteristics, due to the adaptation to different ecosystems (Vinogradova, 2000), namely *Cx. pipiens pipiens* (the original one, rural, mainly ornithophilic) and *Cx. molestus* (the urban form, mainly anthropophilic) are currently accepted (Vinogradova, 2000; Vinogradova and Shaikevich, 2007; Weitzel *et al.*, 2009; Bahnck and Fonseca, 2006; Kent *et al*., 2007). Nevertheless the possibility of the existence of hybrid forms and their role in the transmission of the WNF vector still need to be deeply investigated.

Transmission of WNV to people might be facilitated when at least two species of mosquito are involved in spreading the virus among hosts. Bird-feeding mosquitoes, such as *Culex tarsalis*, are effective at transmitting WNV among birds, but because these mosquitoes are unlikely to bite people, other mosquitoes are necessary for the disease to be transmitted to humans. One such species, *Culex pipiens*, bites both birds and people and so is capable of transmitting the WNV from birds to people. Recent studies indicate that *Cx. pipiens* can also transmit the infection between people. However, since *Cx. pipiens* mosquitoes bite birds infrequently, a separate vector (e.g. *Cx. tarsalis*) that maintains the disease in bird populations increases the chances that people will become infected (Chivian and Bernstein, 2008).

[20] An infection is said to be "enzootic" in a population when the infection is maintained in the population without the need for external inputs.

[21] Epizootic is an epidemic outbreak of disease in an animal population, often with the implication that it may extend to humans.

- *Changes in pathogen diversity*

Since its introduction to North America in 1999, a novel WNV genotype has been identified that has been demonstrated to disseminate more rapidly and with greater efficiency at elevated temperatures than the originally introduced strain, indicating the potential importance of temperature as a selective criteria for the emergence of WNV genotypes with increased vectorial capacity. Even prior to the North American introduction, a mutation associated with increased replication in avian hosts, identified to be under adaptive evolutionary pressure, has been identified, indicating that adaptation for increased replication within vertebrate hosts could play a role in increased transmission efficiency. Although stable in its evolutionary structure, WNV has demonstrated the capacity for rapidly adapting to both vertebrate hosts and invertebrate vectors and will likely continue to exploit new ecological niches as it adapts to novel transmission foci (Aaron, 2009).

- *Changes in host diversity*

The transmission of WNV is influenced by the heterogeneity in the host community. Recent work provide evidence that host diversity is linked to WNV ecology in the United States. For example, Ezenwa and colleagues (2006) documented a negative association between the number of non-passerine bird species (mainly wading birds) and WNV infection prevalence in *Culex* mosquitoes across a series of field sites in a single Louisiana county; the same trend was also apparent on a larger scale for human disease incidence across the State. Similarly, Allan and colleagues (2009) found that bird diversity was negatively correlated with WNV infection in vectors at a regional scale in St. Louis, Missouri, and with human disease incidence at a national level across the United States (Pongsiri *et al*., 2009).

The mechanisms underlying potential dilution effects in WNV transmission remain to be clarified. The relative role of species richness versus species composition is particularly important in the face of increasing habitat loss and land-use change, since these forces contribute not only to a reduction in numbers of species (Foley *et al*., 2005) but also potentially favour generalist species that act as amplification hosts. High transmission among birds in an urban environment could be the result of a decline in overall bird diversity or greater densities of highly efficient WNV hosts in peridomestic settings. Thus, in low-diversity communities, species identity is likely to play a key role in disease transmission (Pongsiri *et al*., 2009).

WNV virulence in birds seems to be critical in establishing elevated viremias[22] necessary to efficiently infect blood feeding *Culex* mosquitoes (Reisen *et al*., 2005), so that the bird's competence (i.e. the ability of an infected host to acquire, maintain, and transmit virus to a biting mosquito) seems of crucial importance in WNV transmission.
Moreover, it seems that *Culex* vectors prefer to feed on some bird species rather than others. Recent field studies revealed that *Cx. pipiens* becomes infected from feeding on just a few species of birds, suggesting that the dynamics of WNV transmission are influenced strongly by a few key super spreader bird species that function both as primary blood hosts of the vector mosquitoes (in particular *Culex pipiens*) and as reservoir-competent virus hosts. It has been hypothesized that human cases result from a shift in mosquito feeding from these key bird species to humans after abundance of the key birds species decreases (Hamer *et al.*, 2009).

In a paper published in 2008 by Ostfeld on the dilution effect for WNF, the author raises a hypothesis that mosquitoes occurring in areas of low avian diversity should have a high

[22] Viremia is a medical condition where viruses enter the bloodstream and hence have access to the rest of the body.

probability of encountering a competent reservoir for WNV, and therefore a high probability of acquiring infection during blood meals. In contrast, mosquitoes occurring in areas of high avian diversity should have a higher probability of taking a blood meal from one of the many species that are less competent or incompetent as reservoirs for WNV. Consequently, the author concludes that counties in the USA with high avian diversity should have a low human incidence of WNV disease, whereas those with low avian diversity should have a high WNV incidence.

- *Modifications of aquatic ecosystems*

The role of land-use change in altering WNV transmission is one of the research topics in the last few years. Ezenwa *et al*. 2007 investigated the relationships between mosquito vectors, hosts (birds) and land cover in an area of the Gulf Coast of Louisiana. They found that infection rates in *Culex* mosquitoes were negatively correlated with wetland area and that wetland area was positively correlated with non-amplifying bird hosts. This suggests that preserving large wetland areas, and by extension, intact wetland bird communities, may represent a valuable ecosystem-based approach for controlling WNV outbreaks.

Future research on the complex causal links between land-use change, species diversity and composition, and host-vector interactions, will be essential for understanding associations between biodiversity and disease risk. A recent study of WNV ecology in the Chicago area found no evidence of an association between avian diversity and WNV prevalence in either mosquitoes vectors or birds (Loss *et al*., 2009), suggesting that interactions among anthropogenic, biotic, and abiotic factors may drive regional variability in the dynamics of this disease (Pongsiri *et al*., 2009).

2.2.3 Leishmaniasis

Etiology:
Leishmaniasis are a group of vector-borne diseases characterized by diverse and complex epidemiological cycles (Desjeux, 1992). Cutaneous and the visceral leishmaniasis are the main forms of this disease that affect humans. Leishmaniasis are caused by parasitic protozoa of the genus *Leishmania*. Only two *Leishmania* species are causal agent of anthroponotic (human to human transmitted) infections: *Leishmania donovani* responsible for visceral leishmaniasis, in Indian subcontinent and East Africa, and *L. tropica*, which his responsible for cutaneous leishmaniasis (Consuelo *et al.*, 2009; Chappuis *et al.*, 2007).

Transmission:
Anthropophilic females of several species of sand fly, belonging to genus *Phlebotomus* and *Lutzomya* (in the American continent) are the proven vectors responsible for transmission of the disease to humans (Killick-Kendrick, 1990). Most of the Leishmaniasis are zoonotic infections, maintained in nature by rodents and canids as reservoir host. The characteristics of both the human host and the parasite species influence the clinical disease manifestations,which range from asymptomatic exposure to cutaneous and mucocutaneous lesions, to a serious visceral disease affecting the hemopoietic organs[23] (Chappuis *et al.*, 2007).

Impact:
Leishmaniasis are considered a tropical affliction that constitutes one of the six entities on the World Health Organization tropical disease research list of most important diseases. An estimated 12 million people are presently infected worldwide (WHO, 2009c). However, there is a gross underreporting of the cases from endemic regions, and there has been a progressive increase in the cases of leishmaniasis being reported from the newer areas.

Table 2.6. Impact of Leishmaniasis worldwide. Source: WHO, 2009c.

	Cases	Deaths	Countries	Population at risk
Leishmaniasis	2 Million	80,000	88	350 Million

Distribution:
It is endemic in 88 countries in tropical and temperate regions: in Southern Europe, Central and South America, Africa, the Middle East, and South Asia. Seventy-two of these countries are developing nations.

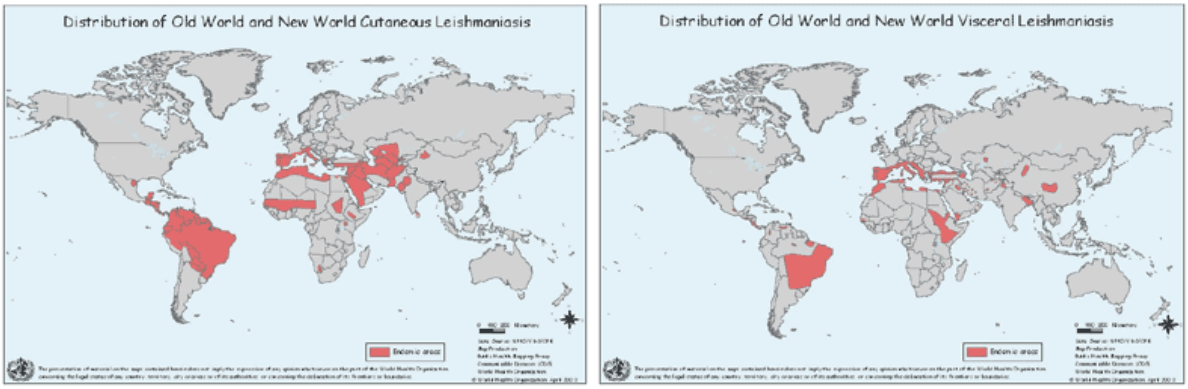


Figure 2.12. Source: Distribution of cutaneous and visceral leishmaniasis. WHO, 2009c.

[23] Blood-forming organs.

Europe:
Leishmaniasis is the only tropical vector-borne disease that has been endemic to Southern Europe for decades, with more than 700 autochthonous human cases reported each year (3,950 considering also cases from Turkey). Among the VBD endemic in Europe, Leishmaniasis plays certainly a major role, because their diffusion and "weight" on public health.

Leishmaniasis endemic to the Mediterranean region is a zoonosis due to *Leishmania infantum*, and transmitted from dogs to humans by the bite of phlebotomine sandflies (*Diptera: Psychodidae*) belonging to the genus *Phlebotomus* (Maroli *et al.*, 2008). Dogs represent the most common reservoir, but probably other domestic and wild mammals (cats, foxes) may play a secondary role.

In Southern Europe, zoonotic visceral leishmaniasis caused by *Leishmania infantum* used to be considered a rural disease, but it is becoming more prevalent in urban areas. Outbreaks in urban/periurban settings are associated with the urbanization of natural zoonotic foci. The presence of a high number of stray dogs in urban/periurban settlements may contribute to the spread and increase of new infections (WHO/TDR, 2008).

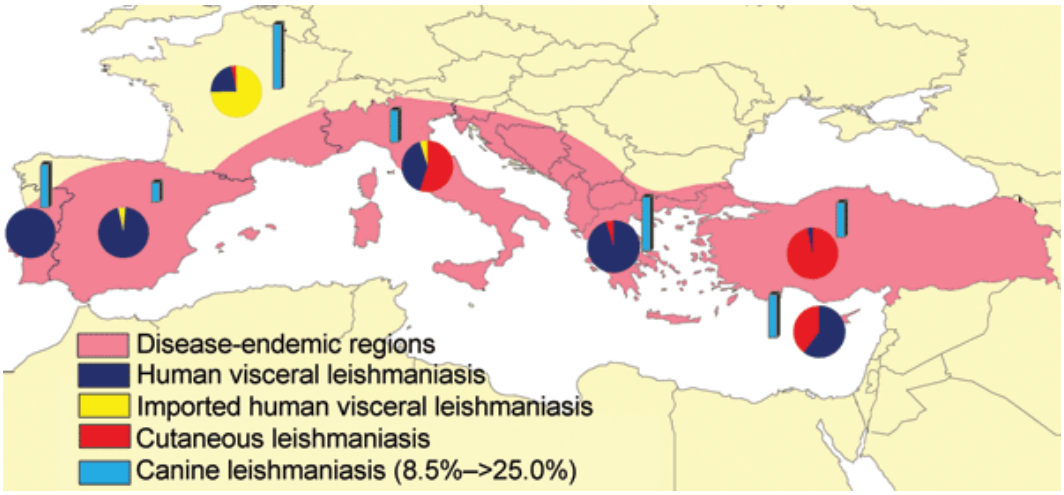


Figure 2.13. Leishmaniasis in Southern Europe. Distribution of the endemic disease; relative proportion of autochthonous (visceral, cutaneous) and imported human cases and seroprevalence in dogs. Source: Dujardin *et al.*, 2008.

Autochthonous leishmaniasis appears not to be any longer limited to the Mediterranean region. It has spread northward, as shown by recent reports (Maroli *et al.*, 2008). Its transmission is likely to be affected by climate changes, especially in temperate zones where increased temperatures may allow shortening larval development and extension of the breeding season of the indigenous phlebotomine species, or the establishment of new species in places where low temperatures have hitherto prevented their over-wintering ability. The northward spread of Leishmaniasis from the Southern Mediterranean areas to continental Europe has been proposed as a likely scenario associated with current global warming (Killick-Kendrick, 1990), and data from recent studies indicate that both could be in progress in Northern continental Italy as well as in countries of continental Europe, where sporadic autochthonous cases of human and canine disease have been recorded for the first time at latitudes higher than Italy, namely in Germany (Bogdan *et al.,* 2001) and the Netherlands (Diaz-Espineira and Slappendel, 1997).

Even though leishmaniasis is essentially associated with *Leishmania infantum,* two other forms of the disease are present in the Mediterranean basin: *L. major* and *L. tropica,* etiological agents of two forms of cutaneous leismaniasis, respectively zoonotic and anthroponotic. The possible spread of these two leishmaniases in Southern Europe cannot be ignored, even if this event appears to be highly improbable, because of the complex biological and ecological relationships among parasite, vectors and reservoirs that contribute to maintain endemic this forms of Leishmaniasis in North Africa and the Middle East.

LEISH MED *Monitoring risk factors of spreading of Leishmaniasis around the Mediterranean Basin* (P6-2002-INCO-MPC-1)

This FP6 project had the objective of creating a multidisciplinary network linking European and South--/East Mediterranean partners in order to document the main risk factors involved in the spread of leishmaniasis around the Mediterranean and to promote transborder control strategies.

Leishmaniasis is endemic in all Southern countries of Europe, but evidences exist on the possibility of its spread in Northern Europe. Using the Mediterranean region as a model, a net of collaborative scientists, the project aimed to launch the bases for integrated and transborder surveillance and control of leishmaniasis. A first objective of LEISHMED is to bridge the gap between research, surveillance and control, monitoring risk factors for the spread of leishmaniasis around the Mediterranean basin.

Leishmaniasis and changes in biodiversity

The leishmaniasis are related to ecosystem changes such as deforestation, modification of water ecosystems and urbanization, but also to migration of non-immune people to endemic areas (WHO, 2009c).

- *Deforestation*

Forest leishmaniasis are maintained in nature by a complete wild cycle, being the vector, the parasite and the host/reservoirs all present in the forest.

Chaves *et al.* (2008) state that populations living inside or close to fragmented forests intermixed with crops where the overall biodiversity of the landscape is reduced, could have a higher risk of infection with *Leishmania* sp. when compared with those where agricultural practices and crops allow the maintenance of biodiversity. Changes in biodiversity due to deforestation are probably of importance to American cutaneous leishmaniasis (ACL) since the major reservoirs of *Leishmania* species are small mammals, including marsupials, rodents and sloths. Forest fragmentation has been shown to increase densities of these species, because in small and isolated habitat fragments, large predators are lost first, leading to major changes in inter-specific interactions that lead to the dominance of rodents, including possible *Leishmania* spp. reservoirs (Chaves *et al.,* 2008; Davis *et al*., 2005).

Widespread deforestation has frequently led to a domestication of transmission throughout Latin America, increasing the peri- and intra-domiciliary transmission. As the forest close to settlements is progressively disappearing, transmission is moving from sylvatic to peri-domestic areas (Desjeux, 2001; WHO, 2002). In Brazil, for example, the occupation of new areas on the outskirts of the primary forest brought many people into contact with the zoonotic cycle of *L. (V). guyanensis*. As sylvatic reservoirs (mammals) and vectors (*Lutzomya umbratilis*) maintain the *L. guyanensis* cycle in the remnants of the forest, a

correlation between the transmission to humans and the proximity of the forest has been clearly established (Barrett and Senra, 1989).

The ability of zoophilic vectors to adapt to human blood as an alternative source of food and to become associated with human dwellings (peridomestic behaviour) has influenced the distribution of leishmaniasis in South America. Certain species of sandflies (*Lutzomyia intermedia, Lu. longipalpis, Lu. whitmani*), which were originally zoophilic and sylvatic, have adapted to feeding on humans in peridomestic and even periurban situations. The changes in behaviour of reservoir hosts and the ability of pathogens to adapt to new reservoir hosts in the newly created habitats also influence the patterns of the disease (Walsh *et al.*, 1993).

- *Modification of aquatic ecosystems*

The building of dams with corresponding new irrigation schemes and new crops, has frequently provoked a sharp change in the reproduction patterns of the animal reservoirs (gerbils). For example, following the construction of a large dam in Tunisia, a large area was planted with *Atriplex*, a well-known food plant for sheep. Unfortunately, *Atriplex* is also a plant of the Chenopodiacae family, the sole source of food for *P. obesus*, the main reservoir for cutaneous leishmaniasis in this area. Consequently, there was a sudden and exponential increase of the gerbil population followed by an epidemic of cutaneous leishmaniasis (Ben Ammar *et al.*, 1984; Ben Ismail *et al.*, 1989). A similar situation occurred in Syria, where the geographical extension of irrigated areas near the Euphrates River led to increase in the animal reservoirs (*Nesokia indica*) population, followed by an epidemic of cutaneous leishmaniasis in the city and neighbouring villages (Desjeux, 2001).

- *Changes in agro-ecosystems*

Changes in landscape quality are likely to affect composition of the arthropod vector community. In Costa Rica, sand fly species richness is greater in traditional, shaded coffee agro ecosystems than in those that are intensified and unshaded. More generally, traditional coffee production supports similar biodiversity as undisturbed forests (Alexander *et al*., 2001). During the last two decades, most Colombian coffee growers have changed from the traditional system of cultivation, where the crop is grown under different species of shade trees, to an intensified system where it is grown at high densities in full sunlight. According to Alexander *et al*. (2009), this change may affect transmission of *Leishmania* spp. to humans in several ways, probably resulting from reduced human–vector contact. The responses of residents of traditional and intensified coffee plantations to the leishmanin skin test were compared to ascertain whether intensification has indeed affected Leishmania transmission. Although prevalence of infection was significantly higher ($P \leq 0.01$) among residents of traditional plantations (26.8%) than among those of intensified ones (13.2%), no significant difference could be demonstrated with respect to incidence of infection at the time of the study.

- *Urbanization*

One of the major risk factors for leishmaniasis, especially in anthroponotic foci, is the worldwide phenomenon of urbanization, closely related to the sharp increase in migration.

In Southern Europe, visceral leishmaniasis was initially purely rural but is increasingly spreading to suburbs. Significant foci are located on the outskirts of cities where dogs are present and small gardens encourage the presence of sandfly vectors (*P. perniciosus* and *P. ariasi*). Climatic changes in the future could further modify the geographical distribution (Desjeux, 2001).

Between 1989 and 1994 cases of American cutaneous leishmaniasis in South-Western Asian countries were associated with seasonal migrations from villages to cities in

coincidence with the transmission season of sandflies, which find ideal conditions to breed and lay eggs in the abundant cow dung, commonly dried in the streets and sold as fuel for cooking. Also American visceral leishmaniasis has been correlated with an increase in the cattle population in the suburbs of the cities. The presence of organic matter, such as cow dung, provides opportunities for sandfly breeding sites. Moreover, the numerous ponds and the high sub-soil water level keep the soil moist and the level of humidity high: this factor encourages the survival of *P. argentipes*, the proven sandfly vector of *Lu. donovani* in India and Nepal (Thakur, 2000; Desjeux, 2001).

Urbanization and vector domestication are currently proposed as factors that contributed to the recent increase of American cutaneous leishmaniasis. Nevertheless, a recent survey, carried out in 5 urban areas of Argentina, located in a ACL hyper-endemic area, showed that the potential vectors (*Lutzomyia neivai, Lutzomyia migonei, Lutzomyia cortelezzii* and *Lutzomyia shannoni*) are still strictly related to their original forest environment and that ACL transmission occurs in the neighbourhood, on the fringe of the cities only (Solomon *et al*., 2008).

Leishmania mexicana, L. amazonensis, L. braziliensis, L panamensis, L. peruviana and *L. guyanensis* are the major species that cause New World cutaneous leishmaniasis. Approximately 62,000 cases occur primarily in Brazil, Colombia, Paraguay, Venezuela, Panama, Ecuador, and Peru where urbanization near Lutzomyia sandfly breeding sites has led to an increase in the number of cases. In North-Eastern Brazil, visceral leishmaniasis (*L. chagasi*) has become an important infection in the favelas and urban centres. In these impoverished urban and periurban settings, the cracked walls and damp earth floors, together with an absence of sanitation and inadequate garbage collection, combine to create sandfly breeding sites. With the exception of Brazil, surveillance systems in Latin America have been limited in their capacity to assess the true burden of visceral leishmaniasis.

Cross-border movement is also a major risk factor that frequently contributes to urbanization of leishmaniasis (WHO, 2002).

2.2.4 Tick-borne diseases

Ticks (Acari: Ixodidae) are ectoparasites[24] of animals and humans, that heavily impact global health by transmitting a wide variety of pathogens to vertebrates, including viruses, bacteria, protozoa and helminthes. Almost all tick-borne diseases (TBD) are zoonoses that primarily affect animals, but may also cause severe diseases in humans. Tick-borne pathogens are believed to be responsible for more than 100,000 cases/year of illness in humans throughout the world. Ticks are considered to be second worldwide to mosquitoes as vectors of human diseases, but they rank first as vectors of pathogens of domestic and wild animals diseases.

Fifteen TBD, eleven of which in Europe, due to bacterial pathogens have been described throughout the world. The commonest TBD affecting humans is Lyme disease, while as emerging human diseases the tick-borne encephalitis (TBE) and the Crimean-Congo fever should be considered. The most advanced studies on TBD are focused on these emerging diseases and, in particular, on the factors that play a role in the recognition of new TBD, on infection and development of pathogens in both tick and vertebrate hosts that are mediated by molecular mechanisms at the tick-pathogen interface. While information on these molecular interactions that facilitate pathogen infection, development and transmission is limited, a comprehensive understanding of the tick-pathogen interface would be fundamental toward development of new measures for control of both tick infestations and tick-borne pathogens. These mechanisms, involving traits of both pathogens, include the evolution of common and species-specific characteristics. The molecular characterization of the tick-pathogen interface is rapidly advancing and providing new tools for the development of vaccine and novel control strategies against tick and the pathogens they transmit.

Each tick species has preferred environmental conditions and biotopes that determine their geographic distribution and, consequently, the areas of risk for TBD. As the other VBD, TBD are strongly influenced by climate and ecological changes. The significant increase of cases of Lyme disease and tick-borne encephalitis in the endemic countries and the Northward spread to new areas, recorded in Europe over the past decade, may be related to a multifactor system of causes: climate changes, political, socio-economic and behavioural changes in the human population, and environmental transformations, due to human activities (Randolph, 2007 and 2008).

According to several authors there is a connection between vertebrate diversity and the risk of human exposure to tick-borne diseases. Vertebrates serve as natural reservoirs of pathogen that are transmitted to humans by blood-feeding arthropod vectors. Both the infection prevalence and the abundance of the tick vector are critical to determining human exposure rates.

[24] An ectoparasite is a parasite that lives on or in the skin but not within the body.

Lyme disease

Etiology:
Lyme disease (LD) is a relatively new vector-borne diseases. It was first recognized in 1975 in Lyme, Connecticut, and some years more were needed (1982) before discovering that a causative agent was a bacteria, *Borrelia burgdorferi* (spirochetes) transmitted by the bite of a tick from the genus *Ixodes*.

Transmission:
The *Ixodes* tick goes through a 2-year life cycle that is composed of three stages of development: larva, nymph, and adult. Tick larvae acquire the spirochete via blood meal from an infected host, particularly the white-footed mouse. Both the nymph and female adult may infect humans. It is estimated that from 10 to 50 percent of ticks in endemic areas carry the disease. Ticks are most likely to transmit *Borrelia burgdorferi* while they are in the nymphal stage. The vectors competent to transmit *B. burgdorferi* to humans belong to different species of Ixodiadae ticks, according to their geographical distribution. In the North-Eastern and Midwestern US the main vector is the deer tick *Ixodes dammini (scapularis),* while in the Western United States it is due to *Ixodes pacificus*, in Europe to *Ixodes ricinus,* and in Asia to *Ixodes persulcatus*. Rodents and other small mammals are the natural hosts of the larval and nymphal stages.

Impact:
There are no figures at global scales.

Table 2.7. Impact of Lyme disease in Europe and in the US. Source: WHO/Europe, 2006 and LDF, 2010.

	Cases/year Europe	Cases USA (1980-Feb. 2010)	Countries
Lyme disease	85,000	381,552	15

The number of cases is underreported mainly due to the difficulty to diagnose the initial stages of the Lyme disease. The reporting system may account for only 36 percent of the actual cases.

Distribution:
The Lyme disease occurs in temperate regions of Europe, Asia and North America but significant risk of infection with *Borrelia burgdorferi* is found in only a number of states of the U.S.

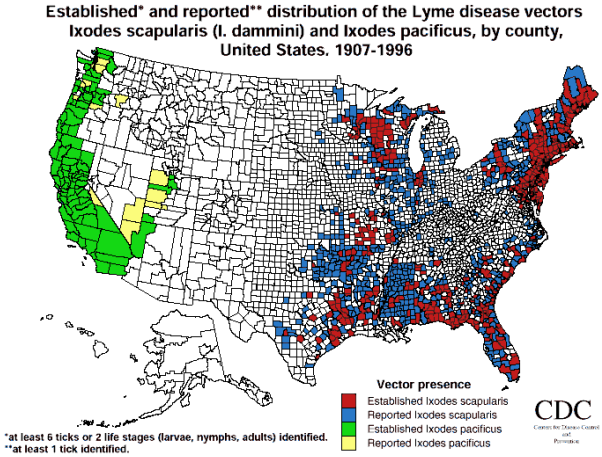


Figure 2.14. Distribution of the Lyme disease vectors in the US from 1907 to 1996. Source: Dennis *et al*., 1998.

Europe:
LD has become established in Europe in the 1980's. It is found mostly in the Central and Eastern countries of the continent, where its range of endemy overlaps with that of TBE, according to the distribution of their common vector *Ixodes ricinus*, a tick strictly related to wooded areas, where climate is temperate and the relative humidity is constantly high (Šumilo *et al.,* 2008).

Lyme disease and changes in biodiversity

The major part of the literature studies on Lyme disease has been carried out in the US, where it is the most common vector-borne disease. Current literature underlines the relation between deforestation (changes in structural diversity) and changes in species diversity and spread of Lyme disease.

- *Changes in vector diversity*

The Lyme disease is transmitted in California by two species of ticks *Ixodes spinipalpis* and *I. pacificus.* The first species maintains the infection cycle of the bacterium *Borrelia burgdorferi* within rodent reservoirs, but it rarely bites people. The tick *I. pacificus* transmits the infectious from rodents to humans. Therefore the presence of both tick species increases the risk that people will become infected with Lyme (Chivian and Bernstein, 2008).

- *Changes in pathogen diversity*

A high degree of genetic diversity occurs within local populations of the bacterium *Borrelia burgdorferi*: in Eastern US 15 different strains of the bacterium can coexist in stable populations. Only four of them cause Lyme disease in humans. A speculative hypothesis, still under investigation, exists on the protective role of these bacterial diversity, based on the assumption that prior exposure to one of the eleven strains that does not cause the Lyme disease results in an enhancement of the individual immuno-response to the four strains that cause illness (Chivian and Bernstein, 2008).

- *Changes in host diversity*

When high biodiversity of host vertebrates exist in areas where the Lyme disease is present, the risk of getting it is lessened.

One reason for this is that some of the vertebrates that are bitten by infected ticks are "dead-end" hosts[25] or are not competent for the transmission of the bacterium. This effectively decreases the disease agent and makes it less likely for an infected tick to transmit the disease to a human (Keesing *et al*., 2009). Host species can differ dramatically in their quality as a reservoir, that is, in their probability of infecting a feeding vector with a specific pathogen (Ostfeld and Keesing, 2000a). Host species might also differ substantially in their quality as a host, here defined as the probability that a vector attempting a blood meal from that host successfully feeds and survives. Some host species of the *Ixodes scapularis* (e.g. opossums, squirrels) that are abundantly parasitized in nature kill 83–96% of the ticks that attempt to attach and feed, while other species are more permissive of tick feeding. Given natural tick burdens on these hosts, Keesing *et al*. (2009) show that some hosts can kill thousands of ticks per hectare. These results indicate that the abundance of tick vectors can be regulated by the identity of the hosts upon which these vectors feed.

[25] Animals poorly able or incapable of passing on the bacteria and continuing the disease cycle.

Another reason is that the *Ixodes* ticks feed from a variety of host species that differ dramatically in their reservoir competence[26]. Vertebrate communities with high species diversity will contain a greater proportion of incompetent reservoir hosts that deflect vector meals away from the most competent reservoirs (for instance the white-footed mice, *Peromyscus leucopus*), thereby reducing infection prevalence and disease risk. Incorporating the likelihood that the abundance of competent reservoirs is reduced in more diverse communities, owing to the presence of predators and competitors, reinforces the impact of the dilution effect (whereby the presence of vertebrate hosts with a low capacity to infect feeding vectors - incompetent reservoirs - dilute the effect of highly competent reservoirs) on the density of infected vectors (Ostfeld and Keesing, 2000b). Therefore, knowledge of the species composition of these communities, beyond simple measures of species richness or evenness, strongly enhances the ability to predict risk, because the presence of a diverse assemblage of vertebrates can dilute the impact of the principal reservoir of *Borrelia burgdorferi*, thereby reducing the disease risk to humans (Ostfeld and Keesing, 2000b).

Some common tick hosts serve not only to dilute the effects of the most competent reservoirs, but also to maintain the spirochete in the community under conditions of low mouse density, the so called “rescue effect” (LoGiudice *et al*., 2003). When vectors acquire disease agents efficiently from many hosts, infection prevalence of ticks may increase with increasing diversity hosts. A positive correlation between per capita Lyme disease cases and species richness of ground-dwelling birds supported this hypothesis (Ostfeld and Keesing, 2000a).

The reservoir competence of hosts within vertebrate communities and the degree of specialization by ticks on particular hosts strongly influence the relationship between species diversity and the risk of exposure to the many vector-borne diseases that affect humans. In most of North America, the vector of Lyme disease is the blacklegged tick, *Ixodes scapularis*, and the primary reservoirs for B*. burgdorferi* are white-footed mice (*Peromyscus leucopus*), Eastern chipmunks (*Tamias striatus*), short-tailed shrews (*Blarina brevicauda*), and masked shrews (*Sorex cinereus*). Blacklegged ticks feeding on these species have a higher probability of becoming infected with the bacterium than do ticks feeding on any other host species. White-footed mice, Eastern chipmunks and short-tailed shrews are highly resilient, widespread species that are abundant in degraded and fragmented habitats, and can dominate low-diversity vertebrate communities. Communities with higher mammal and bird diversity contain these species, but also contain many other species that are poor reservoirs for the Lyme disease spirochete. Ostfeld (2009) demonstrated that ticks occurring in forests supporting high vertebrate diversity would have lower infection prevalence than would ticks occurring in low-diversity habitats where mice, chipmunks, and shrews dominate. In addition, he demonstrated that they would be more abundant in low-diversity habitats. Ostfeld concludes that high vertebrate diversity is negatively correlated with human risk of exposure to Lyme disease.

According to Pongsiri and collaborators (2009), the mechanisms that underlie the negative correlation between species diversity and Lyme disease risk or incidence require clarification. These include interactions between hosts and ticks, between hosts and pathogen, and among different host species.

- *Deforestation*

Forest destruction and fragmentation in the United States recently have been shown to reduce mammalian species diversity and to elevate population densities of white-footed mice (*Peromyscus leucopus*), one of the principal natural reservoirs of the Lyme bacterium. One

[26] The probability of transmitting the infection from host to vector.

potential consequence of reduced species diversity and high mouse density in small fragments is an increase in human exposure to Lyme disease. Allan and collaborators (2003) demonstrated that small forest patches within Lyme disease endemic zones (2 ha) have a higher abundance and infection prevalence of *I. scapularis* ticks, which is the primary risk factor for Lyme disease, than larger patches (2-8 ha). They found a significant linear decline in nymphal infection prevalence and a significant exponential decline in nymphal density with increasing patch area. The consequence was a dramatic increase in the density of infected nymphs, and therefore in Lyme disease risk, with decreasing forest patch size. They did not observe, however, a similar relationship between the density of larval ticks and patch size. These results suggest that by influencing the community composition of vertebrate hosts for disease-bearing vectors, habitat fragmentation can influence human health.

Tick-borne encephalitis

Etiology:
The agent of the tick-borne encephalitis (TBE) is the TBE virus (TBEV), a flavivirus that is transmitted to humans by the bite of a tick. There are two subtypes of TBEV: Eastern and Western, which show slight differences in the structure of the viral proteins. The virus subtype determines the clinical course of the disease. The Eastern variant has proven to be more virulent and to lead more often to severe illness.

Transmission:
Eight species of ticks have been identified that can transmit TBEV. The chief vectors *are Ixodes ricinus* in Europe and the Western part of the Russian Federation, and *Ixodes persulcatus* in the Eastern part of the Russian Federation. Occasionally, transmission also can occur through consumption of raw milk from an infected cow, goat or sheep. Rodent populations (voles and field mice) are the main hosts and reservoirs of the virus. Transmission of the disease is seasonal and occurs in spring and summer, particularly in rural areas, where two seasonal peaks of the disease are typically seen, one in June–July and the other in September–October, corresponding to two waves of feeding of tick larvae and nymphae.

Impact:
A rise in incidence of TBE has been observed in recent decades in some regions, presumably linked to global warming.

Table 2.8. Impact of tick-borne encephalitis in Europe and in the world from 1990 to 2007. Source: Süss, 2008.

	Cases world	Cases Europe	Countries
Tick-borne encephalitis	157,584	50,486	19

Fifteen of the endemic countries for TBE are European.

Distribution:
Tick-borne encephalitis is a serious acute central nervous system infection, which may result in death or long-term neurological sequelae in about half of the patients. TBE is endemic in Europe (from North-Eastern France to Russia eastward and from Scandinavia to Italy, Greece and Crimea Southward) and in North-Eastern regions of Asia, with some extensions to North Japan.

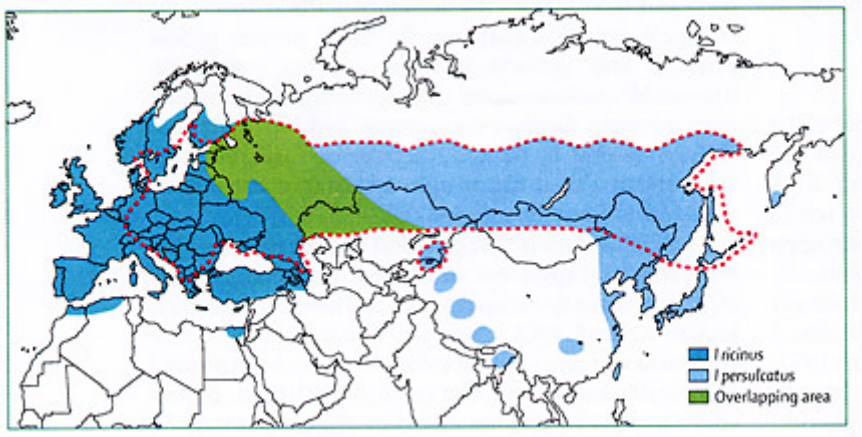


Figure 2.15. Map showing the range of *Ixodes ricinus* and *Ixodes persulcatus*, the vectors of tick-borne encephalitis. The border of known TBE endemicity is defined by the red dotted line. Source: Lindquist and Vapalati, 2008.

Tick-borne encephalitis and changes in biodiversity

Current literature underlines the strict interrelation between deforestation (changes in structural diversity), changes in species diversity and spread of tick-borne encephalitis. In particular, the results of the FP6 EDEN project show that forest structure and roe deer abundance can be used to predict tick-borne encephalitis risk in Italy.

- *Deforestation and changes in vector/host diversity*

The European subtype of the TBE virus is most often transmitted to humans by adults and nymphs of the ticks *Ixodes ricinus* and *I. persulcatus* which acquire the infection while feeding as nymphs and larvae on forest-dwelling rodents, especially the yellow-necked mouse (*Apodemus flavicollis*), which is widespread throughout the continent. Changes in forest cover are likely to affect the occurrence of tick vectors and competent vertebrate hosts (*Apodemus* spp.). The presence of wild ungulate species, such as red deer (*Cervus elaphus*) and roe deer (*Capreolus capreolus*), has also been shown to be essential in maintaining and amplifying tick populations and, consequently, the TBE virus (Rizzoli *et al*., 2001; Rosà *et al*., 2007; Carpi *et al*., 2008). Ungulates are dilution or non-competent hosts (i.e. they act as tick hosts, but are not responsible for virus transmission between ticks); however, since adult ticks usually take their final blood meal from deer, many studies have focussed on the effect of deer exclusion on the disruption of the tick-host cycle, which may result in a decrease or increase in transmission risk depending on the size of the exclosure (Perkins *et al*., 2006).

Rizzoli *et al*. (2009) analysed the effect of a larger-scale increase in deer abundance in combination with changes in forest structure, resulting from changes in wildlife and forest management, on TBE incidence in humans in Northern Italy. They demonstrated that substantial changes in vegetation structure that improve habitat suitability for the main TBE reservoir hosts (small mammals), as well as an increase in roe deer abundance due to changes in land and wildlife management practices, are likely to be among the most crucial factors affecting the circulation potential of Western TBE virus and, consequently, the risk of TBE emergence in humans in Western Europe.

2.2.5 Avian influenza

Etiology:
Avian influenza is a zoonotic viral disease caused by influenza A viruses subtypes adapted to birds (ECDC, 2005). Only four of the hundreds influenza A viruses are known to have caused human infection: H5N1, H7N3, H7N7, and H9N2 (WHO, 2006), but only subtypes H5 and H7 have been shown to be responsible for highly pathogenic phenotypes (Alexander, 2000; Yen *et al.*, 2008).

Transmission:
Members of the orders Anseriformes (ducks, geese and swans) and Charadriiformes (gulls and shorebirds) may constitute the natural reservoir of all influenza A viruses (STFAIWB, 2008a; Stallknecht and Brown, 2007; Widjaja *et al.*, 2004; Kamps *et al.*, 2006).
In human infection the likely portal of virus entry is via the respiratory tract, the gastrointestinal tract, or the conjunctiva. Three different routes of transmission have been identified, according to the sources of infection (Peiris *et al.*, 2007):

- Bird-to-human transmission: through close contact with infected poultry, or consumption of uncooked poultry products. It is the predominant means of human infection, although the exact mode and sites of virus acquisition are not completely understood.
- Environment-to-human transmission: through contact with contaminated water, surfaces and objects; according to the current knowledge it is considered to be possible.
- Human-to-human transmission: through close contact with respiratory secretions and all bodily fluids, including feces. It is limited and nonsustained and has probably occurred during very close, unprotected contact with a severely ill patient (Ungchusak *et al.*, 2005; Blanchard, 2008).

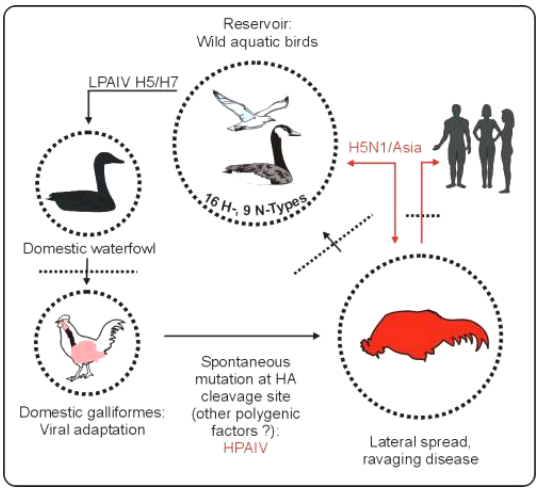


Figure 2.16. Scheme of avian influenza pathogenesis and epidemiology. LPAIV - low pathogenic avian influenza virus; HPAIV - highly pathogenic avian influenza virus; HA - haemagglutinin protein; dotted lines with arrows represent species barriers. Source: Kamps *et al.*, 2006.

Impact and distribution:
From 2003 until 30 December 2009, the avian flu caused by the virus H5N1 has been confirmed in domestic poultry and/or wild birds in 61 countries throughout Asia, Africa and Europe and in 467 confirmed human cases in 15 countries, with 282 deaths, and an overall mortality rate of 60% (Van Kerkhove, 2009; WHO, 2009g, FAO, 2009).

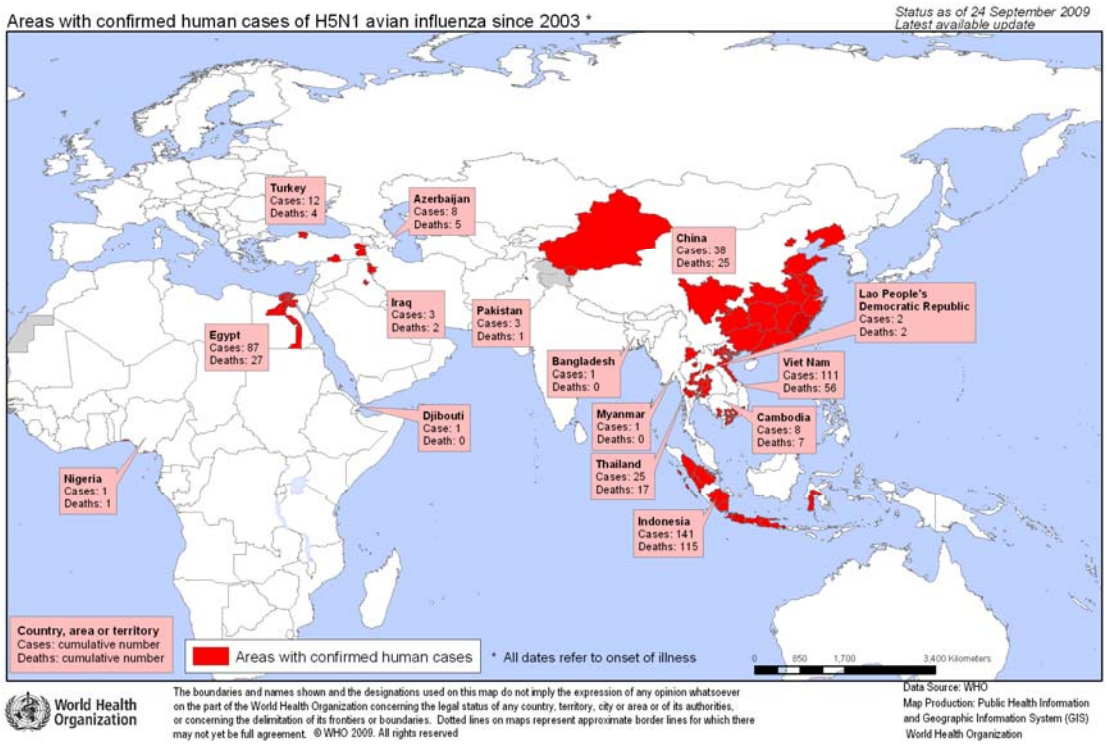


Figure 2.17. Impact and distribution of avian flu worldwide from 2003 to 2009. Source: WHO, 2009g.

Avian influenza and changes in biodiversity

The underlying causes of the emerging, persistence and spread of H5N1 are rooted in the changes of pathogen diversity, host diversity, disappearance and degradation of wetlands, in the deterioration of landscape along wild bird migration routes, as well as in the cultural practices involved in poultry production and marketing (Rapport, 2006; Sims and Narrod, 2008).

- *Changes in pathogen diversity*

The avian influenza viruses are divided on the basis of their impact on poultry into those of high and low pathogenicity avian influenza (hence HPAI and LPAI), mostly on the basis of their biological characteristics. LPAI viruses are generally of lower virulence, but these viruses can serve as progenitors to HPAI viruses, while HPAI are highly virulent, and mortality rates in infected flocks often approach 100% (CIDRAP, 2010; STFAIWB, 2008a).

Wild aquatic birds are the natural reservoir of LPAI viruses (Hinshaw and Webster, 1982; Webster *et al.*, 1992; Stallknecht and Brown, 2007; STFAIWB, 2008a), which co-exist in almost perfect balance (Webster *et al.*, 1992; Alexander, 2000; Kamps *et al.*, 2006; USGS, 2005). When low pathogenic avian influenza virus (LPAIV) strains are transmitted from avian reservoir hosts to highly susceptible poultry species such as chickens and turkeys (i.e. a trans-species transmission step), viruses can mutate, adapting to their new hosts, into highly pathogenic viruses form (HPAIV) (STFAIWB, 2008a; WHO, 2006). Therefore, factors influencing the emergence of HPAI in domestic poultry include host adaptation, husbandry practices, and the intensified poultry industry (Yen *et al.*, 2008).

Avian influenza viruses are highly species-specific and only on rare occasions cross the species barrier to infect other species (WHO, 2005). However, the highly pathogenic avian

influenza virus H5N1 of Asian lineage, not only has the capacity to jump the barriers to trans-species transmission, but also 'traversed interclass barriers' (Perkins and Swayne, 2003) when transmitted from birds to mammals (Yen *et al.*, 2008). Since 1997, when this virus caused a major and severe outbreak of disease among birds in South-East and East Asia, and was directly transmitted to humans (ECDC, 2005) (Claas *et al.*, 1998; Webster *et al.*, 2006; Thiry *et al.* 2007), it evolved into a flu virus strain that:

1. gained enzootic[27] status in poultry throughout South-East Asia,
2. infected more species than any previously known flu virus strain expanding its host range (wild migrating birds, humans, pigs, horses, cats, dogs, seals, camels, whales) and geographic spread,
3. was deadlier than any previously known influenza virus strain, and
4. continues to evolve and to increase its genetic and antigenic diversity, becoming both more widespread and more deadly (Webster *et al.*, 2006; Alexander, 2008).

In order to cause a pandemic, H5N1 viruses will have to acquire the ability to transmit efficiently and in a sustainable way from person to person (Subbarao and Luke, 2007). The concern is that if the H5N1 virus, which shows a significant ongoing evolution, mutates or recombines with other well-adapted (human) strains of influenza A viruses, through dual infections in humans and other mammals, it may acquire the abilities to spread from person-to-person efficiently (USGS, 2005; WHO, 2006). Some animals (e.g. pigs, swine) can be infected with both human and avian influenza viruses and may serve as “mixing vessels”, i.e. as intermediate hosts where genetic material is exchanged between species-specific viruses, creating new reassortant virus strains adapted, and thus easily transmissible, to humans (Cotruvo *et al.*, 2004; FSRIO, 2006; Morse, 2004). Genetic reassortant strains of human and animal influenza viruses have been detected in swine and in humans, and these novel strains have the potential to cause pandemics (Olsen *et al.*, 2002). Thus, the role of such animals, susceptible to human and avian influenza viruses, migratory birds, and water may be an important dynamic to consider in the transmission of HPAI A(H5N1) (Cotruvo *et al.*, 2004).

The combination of high concentrations of poultry, in association with dense populations of humans and other mammals (e.g. swine), provides the potentially lethal mixing vessel which facilitates the genetic recombination that is the prerequisite for newly emerging diseases (Rapport, 2006). The interplay between agriculture, animal (domestic and wild) health, human health, ecosystem health, and socio-cultural factors has been important in the emergence and spread of the virus (STFAIWB, 2008a; Rapport, 2006).

- *Changes in host diversity*

Influenza A virus H5N1 can infect different hosts, from wild birds to poultry. The species diversity may play an important role in the pathogenicity of influenza viruses since while the H5N1 HPAI viruses are 100% lethal to chickens and gallinaceous poultry, they often cause asymptomatic infection in some species of domestic and wild ducks. Although it is not clear how HPAIV H5N1 virus first originated (Sims and Narrod, 2008), it is clear that it benefits from a community of potential host species, rather than a single species, so as to persist, spread and evolve, selecting, through cross-infection, new forms better adapted to propagation (Tibayrenc, 2007).

An emerging consensus on the cause of spread of H5N1 appears to be that both poultry trade and wild birds migration are involved in a complex interaction over time and space: the spread in some regions and timeframes is primarily driven by migratory birds, while in others it is driven by trade routes, and in still others, by a combination of the two (Rapport, 2006).

[27] Enzootic means endemic for non-human population.

However, many uncertainties remain that need to be explored about the role of migratory waterbirds (STFAIWB, 2008b; OIE, 2007; BirdLife International, 2007; UNEP, 2006;):

- Prevalence of H5N1 in various wild bird populations and identification of higher risk species i.e. those with high susceptibility to H5N1 and which have a relatively higher risk of spreading it;
- Effects of the virus on wild birds and how efficiently they can spread it to other wild birds or to domestic poultry, especially over long distances;
- Ecology of H5N1 in the environment to improve understanding of host- or strain-specific pathogenicity, extent or length of viral shedding of H5N1, and the routes of transmission between wild birds;
- Behaviour and ecology of those migratory and non-migratory bird species living in close association with man, which might act as a 'bridge' for the transmission of HPAI between waterbirds and poultry.

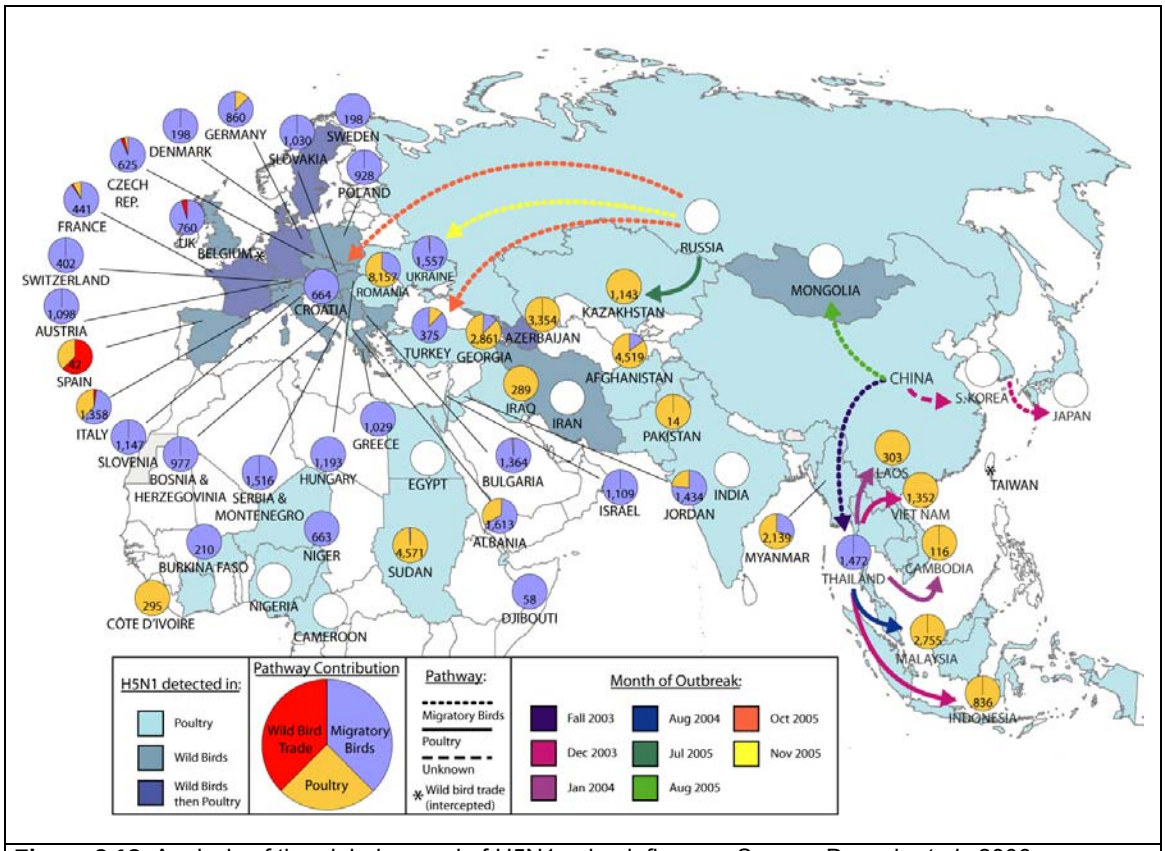


Figure 2.18. Analysis of the global spread of H5N1 avian influenza. Source: Daszak *et al.*, 2006.
Circles represent analyses of the most likely pathway for each spreading event of H5N1 avian influenza since 1998 to 2005. The color-coding denotes the proportion of contribution to the pathway by Migratory birds (blue), poultry trade (yellow) and the trade in wild birds (red). Empty circles represent unresolved spreading events. The analysis demonstrates that spread within Asia was largely due to the poultry trade, and spread to and throughout Europe and Africa was largely due to migratory birds.

- *Modifications in aquatic ecosystems*

As the natural hosts of LPAI H5N1 virus are wild waterbirds, it is not surprising that wetlands play a major role in the natural epidemiology of avian influenza (STFAIWB, 2010a).

As well as the waterbird hosts, these wetlands are probably a permanent reservoir of LPAI H5N1 virus (Rogers *et al.*, 2004; Smith *et al.*, 2004). Indeed, in some wetlands used as staging grounds by large numbers of migratory ducks, avian influenza viral particles can be

readily isolated from lake water (Hinshaw *et al*., 1980; STFAIWB, 2010b). LPAI H5N1 virus survives longer in colder water (Lu *et al*., 2003; Stallknecht *et al*. 1990), and it is strongly suggested to survive over winter in frozen lakes in Arctic and sub-Arctic breeding areas. Therefore, in wetlands LPAI H5N1 virus is a natural part of the ecosystem (STFAIWB, 2010b).

Wetlands in turn influence the movement, social behaviour and migration patterns of waterbird species (Avian Influenza technical Task Force FAO, 2005). Wetland habitats worldwide continue to decline, owing to agricultural expansion and urban development. This process led to substantial loss of natural wetlands or to alteration of the remaining ones, converted to intensive rice farms or paddy fields or other forms of agriculture or human settlement. Under these conditions, migrating wild birds are forced to concentrate in fewer, smaller and altered wet area, often associated with agricultural farms. Such situations inevitably results in “mixing” between wild migratory species and domestic flocks, providing ideal conduits for Asian lineage H5N1 to move from migrating wild birds into domestic flocks, or vice versa, and thus more opportunities for the emergence of new strains.

Moreover, intensive poultry rearing units located in wetlands along major wild bird flyway zones (a common practice in animal husbandry, particularly in countries in South-East Asia) disperse wastewater highly concentrated and contaminated (with also poultry faeces), in wetlands used by wild birds, compromising water quality and allowing wildlife elsewhere to pick up H5N1.

CHAPTER 3
The socio-economic impacts of the changes in incidence of infectious diseases

3.1 The global disease burden

In recent years there has been growing interest in the surveillance and control of infectious diseases, as well as in their importance as a problem in economic development. There is evidence that endemic human infectious diseases and re-emerging infectious diseases are critical in the persistence of poverty. The vector-borne diseases considered in this survey imply wide social and economic costs and prevent economic development, perpetuating the poverty trap.

These diseases, which are often clustered in the same geographical regions with profound economic, social and political consequences, demonstrate the urgency of defining efficient criteria for assessing and ranking global health priorities. The criteria should enable measurement of the total incidence of a disease (for instance, burden of illness, control costs, cost-benefit analysis of prevention campaigns etc) and cost-efficiency of prevention and treatment.

In 1992 the World Bank commissioned the first Global Burden of Disease (GBD) study to provide a general assessment of the burden of more than 100 diseases and injuries and 10 major risk factors for eight regions of the world. Analyses were also made of the cost-effectiveness of interventions in different populations of countries at different stages of development (Murray and Lopez, 1996).

The 2004 GBD update report provided a framework for cost-effectiveness and priority setting analyses carried out within the Disease Control Priorities Project (DCPP) “to review, generate, and disseminate information that contributes to the scientific evidence base for improving population health in developing countries” (Lopez *et al.,* 2006).

3.2 Health, income and economic growth

Although the GBD studies have provided a conceptual and methodological base for managing health care and prevention resources, they are neither sufficient nor sufficiently coherent to estimate the impact of population health on income. There are different mechanisms through which health can affect income and economic growth (see figure 3.1 below).

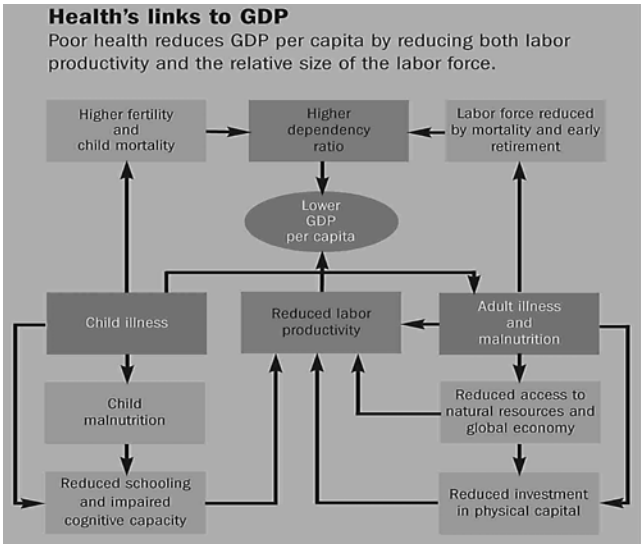


Figure 3.1. Factors linking health and aggregate income. Source: Breman *et al.,* 2004.

Poor health affects the quality of human capital by reducing available labour and working time. The standard of health is a determinant of a household's cash economy.

3.2.1 Health and growth

There is no dispute as to the effects of populations health on economic growth. Basic economic intuition, supported by empirical evidence, suggests that a good level of health in a society matters for economic growth: higher life expectancy induces large savings and higher investment in education (both of which facilitate capital accumulation) while healthier individuals are more productive. Nonetheless quantification of the relationship between health and economic growth is very controversial.

As an example consider the different conclusions of Acemoglu and Johnson (2007) Lorentzen *et al.* (2008) and Aghion *et al.* (2010).

Acemoglu and Johnson (2007) investigated the relationship between life expectancy and economic growth in 75 countries all around the world (Western Europe, Oceania, the Americas, and Asia) from 1940 to 2000. They found only a small positive effect of life expectancy on *total* GDP over the first 40 years. This effect grew somewhat over the next 20 years, but GDP per capita did not rise in that period because of the increase in population (Acemoglu and Johnson, 2007).

Different conclusions are drawn by Lorentzen *et al.* (2008) who examined, using regression analysis, the effect of child and adult mortality rates on per capita GDP over the period 1960-2000. They found a strong effect of mortality rates on income growth. In particular, that adult mortality alone can account for all of the shortfall in growth in Africa over the 1960-2000 period.

In a recent paper, Aghion *et al*. (2010) consider health as a particular form of human capital and combine the approaches of Acemoglu and Johnson (2007) and Lorentzen *et al.* (2008) to analyse the relationship between health and growth. They investigate the relationship between health and growth across OECD countries, using cross-country panel regressions, and "find a significant and positive impact of health on growth between 1940 and 1980, even

though this relationship tends to weaken over the contemporary period, say from 1960 onwards".

Similar conclusions are found in Swift (2010), who examined the relationship between health and GDP for 13 OECD countries, for two periods: 1820 to 2001 and 1921 to 2001. He concludes that " the relationships have a significant influence on both total GDP and GDP per capita in most of the countries estimated, with 1% increase in life expectancy resulting in an average 6% increase in total GDP in the long run, and 5% increase in GDP capita".

"For low-income countries, a given increment in income tends to be associated with a larger gain in life expectancy. Far from becoming dissociated from income, mortality may have become more responsive to it in low-income countries where economic-demographic interrelations are most critical for economic prospects" (Preston, 1975). Preston showed the existence of a relationship between per capita income and health status, as measured by life expectancy, and more recent data reported by the World Bank confirm this strong connection (fig.3.2).

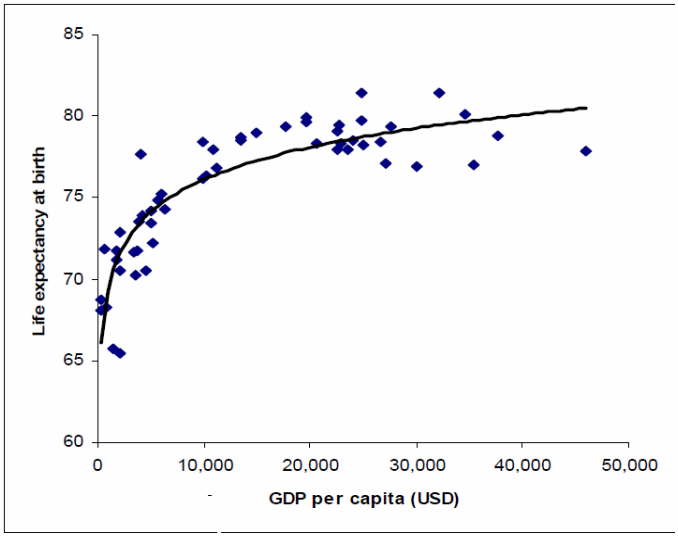


Figure 3.2. The Preston Curve 2001. Source: Jack and Lewis 2009.

In this perspective, Bond *et al.* (2009) coupled simple infectious disease and economic development models to produce a model of infectious disease that tends towards a "poverty trap". They consider the combined causal effects of health on poverty and poverty on health (positive feedback) and using a general single disease susceptible–infected–susceptible (SIS) model, in which individuals can be serially re-infected over the course of their lifetime. This is typical for an infectious disease such as malaria. The model produces both a high productivity/low disease regime and a low productivity/high disease regime. A community can be pushed into or out of the poverty trap as a consequence of cumulative infections. Due to absence of appropriate data for making empirical tests, Bond *et al.* use per capita income and the total infectious disease burden as measured in disability-adjusted life years (DALY) for all countries in the world and find that "the correlation between income and infectious diseases is strongly negative and highly non-linear, which could be considered suggestive of the positive feedback described above" (Fig. 3.3). Furthermore they find that "the coefficient estimates of non-linear functions for income and disease burden are all negative, supporting the hypothesis that the disease burden lowers per capita income, whereas poverty is an underlying cause of disease" (Fig. 3.4).

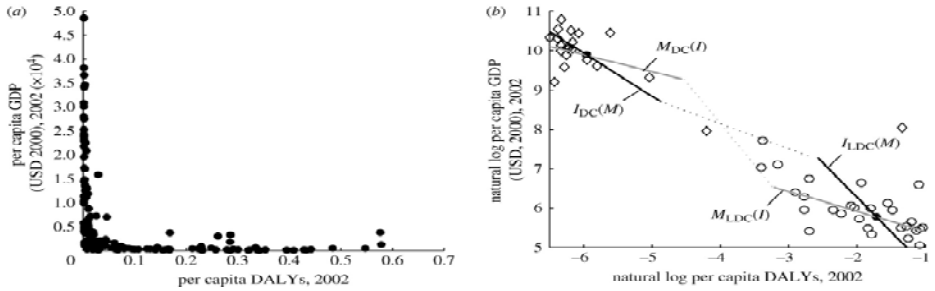


Figure 3.3. Disease burden and income.
(*a*) The correlation between per capita GDP (USD, 2000) in 2002 and the infectious disease burden (DALYs) in 2002 over 170 countries in the world is negative and highly nonlinear.

(*b*) The natural log of the per capita DALYs and GDP are presented for least developed countries (LDCs, open circles) and developed countries (DCs, open diamonds) with the filled circles representing the average values for the LDCs and DCs. The slopes of the estimated effect of income on disease burden, $I_{DC}(M)$ and $I_{LDC}(M)$, and of disease burden on income, $M_{DC}(I)$ and $M_{LDC}(I)$, are represented by the solid lines. If the estimates of the stable equilibria are part of a continuous system, then there is an unstable equilibrium in between, represented by the dotted lines. Sources: Lopez *et al.* 2006.

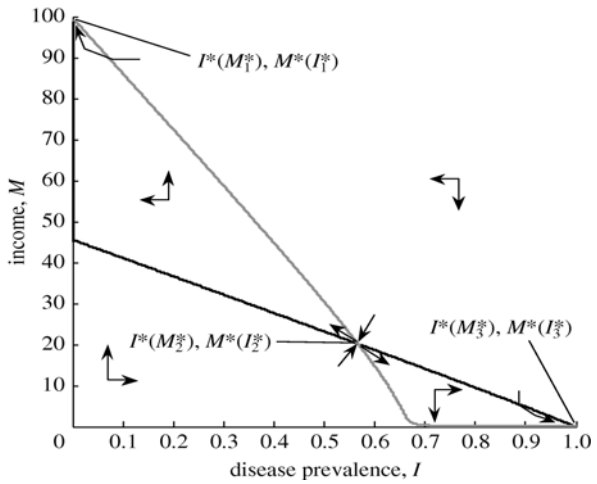


Figure 3.4. Feedback between economics and the ecology of infectious diseases forms a poverty trap. The prevalence of infectious diseases, $I^*(M)$ (black line), falls as per capita income rises, while per capita income, $M^*(I)$ (grey line), falls as disease prevalence, I, rises. The disease and income functions are in equilibrium where these two curves intersect at ($I^*(M^*)$, $M^*(I^*)$). Two of these equilibria ($I^*(M^*_1)$, $M^*(I^*_1)$ and $I^*(M^*_3)$, $M^*(I^*_3)$) are stable, and one ($I^*(M^*_2)$, $M^*(I^*_2)$) is unstable. The poverty trap is the basin of attraction around ($I^*(M^*_3)$, $M^*(I^*_3)$). α = 0.06; $\bar{\beta}$ = 40; $\bar{\mu}$ = 0.01; v = 0.02; $\bar{h}$ = 90; δ = 5; ϱ = 0.003; τ = 0.15; ϕ = 15; κ = 30. Source: Bond *et al.*, 2009.

3.2.2 Two different approaches

The relationship between the health of populations and economic growth has been evaluated using two different approaches: extrapolation from microeconomic studies and direct estimation using macroeconomic data.

In **microeconomic** studies, *life expectancy* is the main health criterion. Microeconomic studies examine individual and household investments in health and their effects on household income. In microeconomic studies, there is the advantage that impacts of health on other variables, such as productivity, education and learning, appear to be clear, but it is difficult to give a general conclusion for the population at large because of trade-off effects.

Shastry and Weil (2003) derive a production function model of aggregate output using microeconomic estimates of economic return to health. They assume a positive stable relation between average height and adult mortality. Using estimates of the relations between height and worker productivity and wages from microeconomic studies they estimate the effect of health improvements - represented as lower adult mortality rates - on aggregate economic output.[28]

One of the robust results of improvement of health status on productivity and income reported in microeconomic studies is the effects of interventions in early childhood on the cycle of poverty, morbidity and early mortality.

In 2007 Weil defined a microeconomic framework in which “estimates of the effect of variation in health inputs on individual wages can be used to generate estimates of how differences in health, as measured by observable outcomes, contribute to differences in national income”.

Macroeconomic models estimate directly the effect of a population’s health on economic growth. Three main classes of macroeconomic models have been used to estimate the impacts of infectious diseases:

(1) **Empirical growth models** analyse health and economic growth in a cross-section of countries. In general, growth regressions show that initial levels of population health are a significant predictor of future economic growth (Bloom *et al.,* 2004 provide a survey of this literature). Bhargava *et al.* (2001) argue that the effect of health on economic growth is greater in developing countries than in developed countries. However, “although population health measures are highly predictive of future economic growth, there is debate about how to interpret the link. The health effect could be interpreted as the macroeconomic counterpart of the worker productivity effect found in individuals” (Bloom and Canning, 2008). The effects of the disease on economic growth are derived by adding the variable ‘disease’ to a standard growth equation and “by distinguishing direct effect on total factor productivity and indirect effects of the disease on growth operating through lower growth elasticity of human and physical investment” (Bloom and Canning, 2008).

    There are however problems in the observed correlation between health and income: “simple correlations of public health and economic outcomes are unlikely to measure the

[28] An increase of income as a consequence of the improvement of an individual health rank could be matched by reduction in the income of other people with no impact on aggregate income; if workers use relatively fixed factors of production (i.e. land), an increase in the supply of labour, induced by health improvements, could result in a reduction of the average output per worker (Acemoglu and Robinson, 2008).

causal effect, since public health is endogenous. Indeed, it is likely a normal good" (Bleackley, 2007) and "the causal effect of malaria on poverty cannot readily be isolated from the effect of poverty on malaria.

Endogeneity[29] and omitted-variable biases are common problems in cross-section and panel data analysis and the methodological response is to use instrumental variables as proxy for indicator for health status, such as geography (Gallup and Sachs, 2001), malaria ecology and institutional quality (Sachs, 2003). Lorentzen *et al.* (2008) use seventeen instruments (a malaria ecology index, twelve climate variables and four geographic features of countries) for the average child and adult mortality rates. Crucially, there is no consensus among researchers on these instrumental variables.

(2) **Macro-econometric models** are used to replicate, simulate and forecast the main mechanisms of a regional, national or international economic system, focussing on the relation between infectious diseases and relevant variables, such as human capital and labour productivity. Authors usually include epidemiological data in micro-based macroeconomic structural econometric models to define different disease scenarios (Keogh-Brown *et al.*, 2009; Oxford Economics, 2005). These models, static or dynamic, evaluate the consequences of vector-borne diseases in a framework based on the notion of disease burden and cost-effectiveness analysis. Their results depend on assumptions, definitions and structure, insofar as they are very sensitive to parameters (i.e. clinical attack rate or case fatality ratio), statistics considered (i.e. previous outbreaks) and assumed economic consequences (i.e. labour productivity or general effect on human capital).[30] As a consequence these models can be only considered approximations that provide broader insights but not numbers.

(3) **Computational general equilibrium models** have the following main characteristics: multiple interacting agents (for instance households and firms), multiple markets (two or more sectors), behaviour derived from inter-temporal optimization processes and estimation of the value of behavioural parameters. They use numerical methods or algorithms to define optimal solutions. In recent years, economists have combined dynamic epidemiology and economics and introduced mitigating policies and treatments for vector-borne diseases in numerical optimization models (Gersovitz and Hammer, 2005).

Alternatively, they have used dynamic general equilibrium models (ADAGE) to investigate how climate change, environmental degradation and health affect macroeconomic output and economic welfare (Pattanayak *et al.,* 2009). Economic epidemiological models are inherently complicated because of the several state variables and value assumptions for many of the parameters, as a consequence they cannot predict the future, but they can shed light on important economic relationships and test the robustness of alternative policies. Although many aspects of the relation between vector-borne diseases, environmental change and GDP cannot yet be quantified, analyses provide interesting qualitative results (Philipson, 2000). In particular they show the prevailing positive elasticity of prevention – i.e. household preventive actions are positively related to the incidence of the disease in the population - and the critical role of externalities. Examples of the latter are the improper use of artemisinin (an expensive

[29] 'Endogeneity' arises when the factors that are supposed to affect a particular outcome, depend themselves on that outcome. For example, in a political election, the effect of campaign spending on the chances of electoral success cannot easily be estimated since the level of campaign spending depends itself on the perceived chance of success.

[30] In the first case it is considered the effect of a VBD on actual labour productivity, in the latter effects of childhood exposition on adult outcome are also considered.

anti-malarial drug), combination treatments, or insufficient use of insecticide-treated nets in the control of infectious diseases.

3.3 Economic impacts of infectious diseases relevant in the analysis of the impact of changes in biodiversity

Historical and current data appear to indicate that human infectious diseases have long-term consequences on the economic performance of low-income countries through their impact on human resources, income distribution and wealth, education and productivity. Prevention and treatment of pandemic outbreaks also represent a significant cost for developed countries.

As shown in the previous chapter, a key factor driving the emergence and spread of a several vector-borne diseases is the change in wildlife population dynamics in ecosystems. However, the authors of this review have not found studies that specifically assess the costs of the increased incidence of infectious diseases in relation with biodiversity and ecosystem change. The analysis of the impacts of biodiversity loss and ecosystem degradation on the spread of infectious diseases is still a recent field of research and their economic implications have not been much investigated as yet.

Combining a literature review and statistical analyses, to give one example, Yasuoka and Levins (2007) attempted to clarify the mechanisms linking deforestation and agricultural development with mosquito ecology and malaria. They reported that “mechanisms linking deforestation and agricultural development with mosquito ecology and malaria epidemiology are extremely complex. The results of the statistical analyses showed that deforestation and agricultural development are favourable for sun-loving species, allowing them to increase in or invade deforested areas where water bodies became exposed to sunlight. Contrary to expectations, niche width was not associated with density change of a species” (Yasouka and Levins, 2007). The authors could not predict with precision the impact on a local disease vector of changes to an ecosystem, because of the complexity not only of the relationship between (in this case) mosquito density, biting frequency and vector capacity, but also between of the behaviour of the different pathogen species.

A few recent studies (e.g. Pattanayak and Yasuoka 2008; Asenso-Okyere *et al*., 2009) analyse the relationship between ecosystem or land use changes, infectious diseases, and income. They identify some critical aspects of this complex relationship: positive elasticity of households demand for prevention with respect to prevalence of an infectious disease, the role of negative externalities in implementing public campaigns of disease control, the negative correlation between malaria risk and change in forest cover.

3.3.1 Different approaches in evaluating the burden of diseases

The literature considers two key aspects of the economic cost of infectious diseases: the direct costs of expenditure on prevention and treatment and the indirect costs of the loss of productive working time of the labour force through morbidity and mortality.

The most frequent approach toward evaluating the economic burden of a disease is the Cost-of-Illness (COI). The COI measures the economic burden of a disease by taking into account direct and indirect costs associated with the illness (opportunity cost of resources consumed and lost for the disease). Direct costs are direct medical costs associated with

medical diagnosis, treatment, and follow-up care, and non-medical costs. Direct medical costs include doctors' visits, hospitalisation, and pharmaceuticals. Direct non-medical costs include transport costs to health care providers, relocation expenses, and costs of making changes to one's diet, house, car, or related items. Indirect costs measure the value of resources lost due to a particular illness; they include opportunity cost items, that is *the value of the foregone opportunity to use in a different way those resources that are used or lost due to illness.* Indirect costs include morbidity due to absenteeism, losses associated with illness and mortality.

Measures of the socio-economic impacts of infectious diseases

Cost of Illness (**COI**) measures the economic burden of a disease by taking into account direct and indirect costs associated with the illness (opportunity cost of resources consumed and lost for the disease). COI includes direct private medical costs (expenditure on prevention, diagnosis, treatment etc) and direct non-private medical costs (expenditure on prevention, treatment, vector control, health facilities, education etc). Indirect costs encompass productivity losses associated with VBD, the value of lost workdays for each person with the disease, etc: "The standard formula for the COI method of calculating the cost of a disease is COI = Private Medical Costs + Non- Private Medical Costs + Foregone Income + Pain and Suffering" (Malaney *et al.,* 2005).

Quality-Adjusted Life Year (**QALY**) is a measure of years of life lived (gained) adjusted for quality of life using health state preferences for health ranging between 0 (equivalent to death) and 1 (full health). Introduced by Zeckhauser and Shepard (1976) and widely used in economic evaluations, QALYs were developed for the assessment of the cost-effectiveness of interventions in health economics.

Disability-Adjusted Life Year (**DALY**) is a time-based measure which combine years of life lost due to premature mortality with the equivalent number of years lived with illness or disability: "one DALY can be thought of as one lost year of 'healthy' life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability. DALYs for a disease or health condition are calculated as the sum of the *Years of Life Lost* (*YLL*) due to premature mortality in the population and the *Years Lost due to Disability* (*YLD*) for incident cases of the health condition" (WHO 2009a). DALYs measure health loss in populations against a normative standard, whereas QALYs (the measure favoured by WHO) are usually used to quantify health gains for interventions. Even if for cost-effectiveness analyses, the mechanics of estimating DALYs averted and QALYs gained are virtually identical, "the critical difference between the DALY and QALY measures is in the measurement of utility weights for the QALY and disability weights for the DALY. Utility weights are typically elicited from general population samples or groups of patients, and do not always match the specific disease and physical activity states used in modelling cost-effectiveness of interventions. Utility weights also lack consistency across many different diseases" (Cobiac *et al.,* 2009).

Theoretically, the COI approach also includes intangible costs such as the costs of pain and suffering. However, those are often omitted because of the difficulty in their assessment. An approach that is better designed to access these and other less tangible costs is the stated preference approach, , which determines, through household surveys, the willingness-to-pay (WTP) of a household for avoiding the disease. the Contingent Valuation method (CV), a survey-based economic technique for the valuation of non market resources, has been used mostly in the last decade to evaluate the economic costs induced by infectious diseases. Citizens are being asked in direct surveys how much they would be willing to pay to avoid infection by disease (in particular through vaccination) (Asenso-Okyere, 1997). It is worth noting that, despite methodological progress and increasing consensus on the conditions of their use, contingent valuation methods remain controversial.

Estimates of WTP differ from those of the more conventional Cost of Illness (COI) method, which is likely to underestimate the benefits of prevention programmes. Households' willingness to pay a percentage of their annual income for a vaccine can be considered as a good indicator of the economic cost of an infectious disease. As an example, Cropper *et al*. (2000) compare different versions of COI, both standard COI and a larger version that also includes the value of lost leisure time, for households with WTP for prevention. Since the purchase of malaria vaccine would prevent future illness, COI may be considered as the expected (future) illness cost. Thus in this review we consider the cost of a vaccination programme as the minimum cost necessary to avoid a disease and its induced costs.

There are also measures that combine mortality and morbidity in a single indicator and allow quantifying the overall burden of an infectious disease. Among them are disability-adjusted life years (DALYs), the measure favoured by the World Health Organization, and the alternative quality-adjusted life year (QALY), both measure used in cost-effectiveness analyses. DALY is a measure of health loss in populations, adjusted for disability against a normative standard. QALY captures in a single metric two dimensions of medical outcomes: the degree of improvement in health, and the duration of the improvement, including any increase in life expectancy.

"QALYs gained and DALYs averted through an intervention are calculated in very similar ways, and the main differences relate to the interpretation of the weights. Whereas the disability weights in the DALY quantify loss of health, the corresponding QALY weights are often interpreted in terms of well-being, quality of life, or utility" (World Bank, 2006).

Many papers reviewed in this survey evaluate VBD comparing the negative and positive consequences of alternative projects and interventions. Two closely related evaluative techniques, *cost-effectiveness analysis* (CEA) and *cost-benefit analysis* (CBA), are used. Both CEA and CBA require analysts to identify, measure, and compare all of the relevant costs and consequences of alternatives. CEA distinguishes between the *direct costs* (drugs, staff time, equipment, transport, out-of-pocket expenses)**,** *indirect* or *productivity costs* associated with the intervention, and *intangible costs* (pain; suffering; adverse effects). CEA requires *cost-effectiveness-ratios* (CERs) to be calculated for each programme and placed in rank order. The CER is simply the sum of all benefits divided by the sum of all costs. The aim of CEA is to maximise the level of benefits – in this case health effects – relative to the level of resources available: in CBA the benefits are expressed in monetary terms, while in the *cost utility analysis* (CUA) benefits are evaluated in QALY or DALY.

In some papers the social burden of VBD is considered, even though it is poorly analysed and described and difficult to quantify. It has been suggested that the *socio-economic status* (SES) influences the distribution of the burden of VBD, but in developing countries SES measures are very challenging. Since data about personal or household income or expenditure are very partial and their collection is often prohibitive, SES is often evaluated by proxies, such as: ownership of assets, education, occupation, location (urban or rural) and gender.

In a survey on social burden evaluations, Worral *et al.* (2003) conclude that "the studies do not describe adequately their methods, assumptions or the basis for choosing their particular method of SES measurement. Some studies use arbitrary categories such as low, medium and high without describing how they were developed. Furthermore, there is sometimes difficulty in interpreting the range of poverty (for example from 'poor' to 'least poor'), if no information is provided to contextualise the study area within the broader country situation. This problem also makes it virtually impossible to make comparisons across country studies.

A clear conclusion from the inconsistent methodology employed is that equity has neither been a focus of the interventions nor of the literature, but rather has often been examined as a secondary variable not requiring the same degree of methodological rigour as the epidemiological variables which form studies' primary focus. In summary, the standard of SES measurement in the studies reviewed is generally poor or inadequately described. There is a lack of common methodology that makes comparison across studies impossible. These limitations should be borne in mind in drawing insights from the literature. In order to improve the quality and reliability of results and facilitate comparison across studies and countries there is an urgent need for consensus on standards for measuring SES".

Measures used to assess the comparative impact of alternative policies

Cost-Effectiveness Ratio (**CER**) is the core measure of Cost-Effectiveness Analyses (CEA) and it is used to assess the comparative impact of expenditures on alternative interventions. "The CEA involves estimating the net, or incremental, costs and effects of an intervention – its costs and health outcomes compared with some alternative, which might be the cure that would be given if the intervention were not used at all, or a different intensity of intervention. The Cost-Effectiveness Ratio (CER), which compares two alternatives, is calculated as the difference in costs between the alternatives (net cost) divided by the difference in health outcomes (net effectiveness)" (Gold *et al.,* 1996). It is worth noting that "when choosing how to spend a fixed health budget, the procedure is to first rank all possible interventions in terms of their cost-effectiveness, begin implementing the most cost-effective intervention until the disease burden is eliminated, then continue down the list adopting gradually less cost-effective interventions until the budget is exhausted. This process assumes that the CER is invariant to the scale of intervention: if ratios vary with scale, then efficiency may require switching to the next-best intervention before the first burden is eliminated. However, because the benefits in CEA are measured in terms of health outcomes (usually DALYs or QALY), it is not possible to compare the benefits of investing in health with other uses of these funds (for example, education or infrastructure development)" (Hanson, 2004).

Cost-Benefit Analysis (**CBA**) was extensively used after the launch of the Global Malaria Eradication Programme (1955). CBA was considered the most appropriate method to obtain the allocation efficiency of a health programme or strategy, since it induces a direct comparison, in monetary terms, of all its costs and benefits. The assessment of the programme effects is summarized in the *Benefit Cost Ratio* (BCR) that can be compared to define an order of efficiency on alternative health programmes. In the '80s CBA fell into disuse up to some recent studies (i.e. Mills and Shillcutt, 2004).

3.3.2 Malaria

Malaria is commonly considered as a disease of poverty. At the global level, malaria incidence is concentrated in the world's poorest countries, with 90% of malaria deaths occurring in Sub-Saharan Africa.

A recent review at a micro level (Worrall *et al.*, 2005) has shown that evidence on the distribution of malaria and incidence of malaria in poor and less-poor population groups is mixed and contradictory. Most studies using assets as a proxy for *Socio-Economic Status* (SES) have failed to establish a clear relationship between asset ownership and the incidence of febrile episodes (as a proxy for malaria). The most extensive study, using *Demographic Health Survey* (DHS) data, found no difference at the household level in incidence of fever between the poor and less-poor, but significant differences were seen at more aggregate levels (Goodman *et al.,* 2008).

The burden of malaria is summarized in quite different measures: DALY or QALY, microeconomic impacts and macroeconomic effects, but all of them put in evidence that this burden is unsustainable for developing countries, particularly for Africa, that carries more than 90% of the burden, followed by South-East Asia with almost 9%: "Malaria deaths are responsible for almost 3% of the world's DALYs (> 10% in Africa), not counting the considerable and imprecisely quantified burden due to morbidity and disability. Despite advances in understanding malaria ecology, and development of interventions, more than 50% of the world's population is exposed to malaria. This is an increase of close to 10% over the past decade" (Breman *et al.,* 2004).

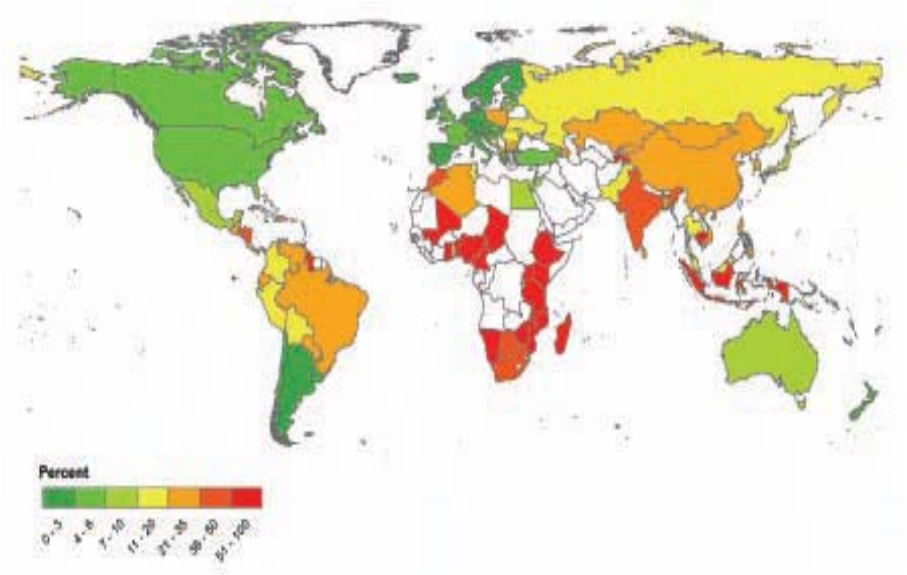


Figure 3.5. Predicted future impact of malaria. Source: World Economic Forum, 2006.

Malaria costs Africa more than USD 12 billion a year, which is about 3% of the total GDP of the region (WHO-AFRO, 2004) and it may considerably retard economic development: an African family may spend up to 25% of income on malaria prevention and control (Russell 2004). Moreover, "in some countries with a heavy malaria burden, the disease may account for as much as 40% of public health expenditure, 30-50% of inpatient admissions, and up to 50% of outpatient visits" (WHO, 2009b).

- *Microeconomic studies*

Microeconomic studies provide national estimates assessing the cost of malaria accrued by productive unit and aggregating these estimates across households or firms. A common method of estimation employed in many studies has been to sum the direct costs of expenditure on prevention and treatment and the indirect costs of productive labour time lost. COI, WTP, and production-function methods for microeconomic analysis provide a broad range of estimates for the economic costs of malaria.

Crucially, each of these methods of analysis focuses only on certain costs of the illness. "In 1919, Carter estimated that malaria cost the United States US$ 100 million (in 1917 dollars). Since then, many area-specific studies ranging from South and South-East Asia to Latin America and Africa have attempted to assess the costs imposed by the disease on both households and systems of public health. The results of these studies show considerable variation, in part due to variations in methodology, but also, no doubt, because the burden caused by malarial morbidity and mortality is highly dependent on the endemicity of the disease and the species of parasite involved…. The standard approach used by economists to evaluate the microeconomic burden of a disease is the Cost of Illness (COI) methodology" (Malaney, 2003).

The majority of studies attempting to evaluate the burden of malaria on households have used the human capital approach. In one of the earlier studies of costs of malaria in West Pakistan, Khan (1966) estimated that 4.2 million persons (2.5 million of workers) are concerned and considering an average annual loss of 13 Pakistan rupee and a medical expenditure of 2.5 Pakistan rupee per capita he calculated an annual burden cost of malaria of 81 million of Pakistan rupee (0.75% of gross national product - GNP).

In 1991, Shepard *et al.* conducted four case studies (Rwanda, Solenzo medical district of Burkina Faso, Mayo-Kebbi district, Chad, and Brazzaville, Congo) to illustrate the diversity in the kinds of data which can be used (aggregate national health statistics versus household surveys) and in locations (urban versus rural). They estimated costs for the recent past and concluded that: for Sub-Saharan Africa, a case of malaria costs $9.84 (in 1987 USD) - $1.83 in direct costs and $ 8.01 in indirect costs (the average value of goods and services produced per day in Africa was $0.82, this cost is equivalent to 12 days of output) and a total cost of 0.8 billion USD (0.6% of regional GDP). In Burkina Faso, the cost per case averaged 5.96 USD, in Chad the cost was estimated at 0.6 USD per capita, or five days of individual production, and, in Congo, the cost was estimated to be 0.74 USD or less than one day of individual production. Finally, in Rwanda they estimated the cost at 2.88 USD (or 3.5 days of production) per capita - 0.63 USD per capita represents the direct cost of treatment and 2.25 USD represents the indirect costs, thus the total cost was estimated at 1% of GDP.

In a recent study, Chuma *et al.* (2006) explore the link between malaria, poverty and vulnerability at the micro-level in the Kilifi district (Kenya). They find that "mean direct cost burdens were 7.1% and 5.9% of total household expenditure in the wet and dry seasons respectively. The case study data revealed no clear relationship between cost burdens and vulnerability status at the end of the year".

Uguru *et al.* (2009) undertook a study in four malaria endemic villages in the Enugu state, South-East Nigeria. They collected data using interviewer-administered questionnaires and an asset-based index to categorize the households into SES quartiles: least poor; poor; very poor; and most poor. They found that "all the SES quartiles had equal exposure to malaria".

The pattern of health seeking for all the SES groups was almost similar, but in one of the villages, the most poor, very poor and poor significantly used the services of patent medicine

vendors and the least poor visited hospitals. The cost of treating malaria was similar across the SES quartiles. The average expenditure to treat an episode of malaria ranged from as low as 131 Naira ($1.09) to as high as 348 Naira ($2.9), while the transportation expenditure to receive treatment ranged from 26 Naira to 46 Naira (both less than $1). The level of expenditure to prevent malaria was low in the four villages, with less than 5% owning untreated nets and 10.4% with insecticide treated nets".

Cropper *et al.* (2000) measure the monetary value households place on preventing malaria in Tigray, Ethiopia, by comparing the private costs of illness with the willingness to pay (WTP) for prevention. They estimate a household demand function for a hypothetical malaria vaccine and calculate WTP to prevent malaria. They indicate that the value of preventing malaria with vaccines is about 36 USD per household per year (15 % of imputed annual household income), that is three times as much as what could be suggested by a COI evaluation, and obtain similar results for insecticide-treated bed nets. The demand for vaccines appears to be price inelastic, or insensitive to price variations, which means that vaccination practices should be subsidised.

In a survey, Asante *et al.* (2004) estimate the economic burden of malaria at macro and micro levels by using three approaches. They estimate the gross domestic product of Ghana by a production function; assess the total COI by using direct, indirect and institutional costs of malaria care and evaluate the WTP for malaria care with the contingent valuation method through a household survey. They find that "the estimation of the production function revealed a negative correlation of 0.367 between economic growth and malaria incidence, with a coefficient of –0.41. This means that the impact of malaria on economic growth in real GDP is negative and that a percentage increase in malaria morbidity rate will result in a decrease in growth in real GDP by 0.41%. The results from the COI approach indicate that a single episode of malaria costs the household US$15.79. The total COI due to malaria in Ghana in 2002 was estimated at per capita average cost of US$2.63 or US$13.51 per household".

- *Macroeconomic studies*

There are a few macroeconomic studies on the economic effect of malaria. Only in the last decade a rebirth of studies has been observed that use malaria as an explanatory variable in economic growth models, most of them showing a significant relationship between GDP growth and the infectious disease.

Macroeconomic analyses indicate that malaria inhibits long-term growth and development to a degree that was previously unimagined. "A comparison of income in malarial and non-malarial countries shows that the average 1995 purchasing-power parity GDP in malarial countries was US$ 1,526 compared with US$ 8,268 in countries without intensive malaria - more than a fivefold difference. Malarial countries are not only poorer than non-malarial countries; they also appear to have lower rates of economic growth" (Sachs and Brundtland, 2002).[31] In a report to the World Health Organization Sachs and Brundtland explain the correlation between better health and higher economic growth and how gain in growth of per capita income is a result of improved health.

In 1967, Barlow published *The Economic Effect of Malaria Eradication* that shows the economic effect on per capita income in the long run of malaria eradication in Ceylon. In his

[31] A complete characterization of the limits of GDP as an indicator of economic performance and social progress, including the problems with its measurement is in 'The Report by the Commission on the Measurement of Economic Performance and Social Progress (Stiglitz *et al.,* 2009).

seminal paper, Barlow distinguished some main classes of economic consequences related to malaria eradication on: population size, labour inputs, capital input and output.

- **Effects on population size**: “other things being equal, a rise in the rate of population growth will reduce per capita income. There is evidence that malaria eradication produces this result both by lowering death rates and by raising birth rates. The fall in death rates occurs, not only because of a reduction in deaths directly attributable to malaria, but also because the population acquires a greater resistance to other diseases. The rise in birth rates which has often been observed to follow eradication can probably be explained by the fact that pregnant women attacked by malaria are more liable to suffer miscarriages”.
- **Effects on labour inputs**: “other things being equal, a rise in the quantity or quality of labour inputs will cause per capita income to rise. Eradication can affect labour inputs by reducing mortality, morbidity, and debility.
- **Effects on capital inputs**: “other things being equal, the higher the rate of capital formation, the more rapid will be the growth of per capita income in the future. We must therefore examine the effects of disease eradication on the division of total expenditures between consumption goods and capital goods in both the private and public sectors”.
- **Effects on capital output**: “the level of output depends not only on the quantity and quality of human and nonhuman inputs but also on the manner in which those inputs are combined. It is possible for eradication to increase output by inducing a change in input combinations”.

In a model of the entire economy, Barlow estimated the effect of malaria eradication on Ceylonese per capita income during the thirty-year period following the successful campaign of 1947 and shown that “eradication has numerous positive and negative effects on income per equivalent consumer. These effects do not occur all at once but in a staggered fashion, and the model therefore involves several lags… On the positive side it is shown that there are some strong effects occurring in the first year after eradication. The lags in the negative effects can be best seen by following the career of the first cohort of "eradication babies"; that is, those babies who would not be alive one year after the eradication campaign if the campaign had not occurred…Thus in the short run, malaria eradication in Ceylon proved economically beneficial. Eradication makes an immediate contribution to output by increasing the quantity and quality of labour inputs, primarily through reductions in morbidity and debility, and secondarily through reductions in mortality… The negative influences of eradication gather strength as time progresses [and] are seen to lie in the rapid increase in the population of children resulting from the marked changes in infant mortality and birth rates. A final set of simulations will therefore be performed on the assumption that these disadvantages were avoided in Ceylon through the adoption in 1947 of a twin programme of malaria eradication and birth control. It seems likely that the twin programme would have made a dramatic contribution to the growth of per capita income” (Barlow 1967)**.**

Some studies use malaria as an explanatory variable in economic growth models in the style of Barro (1991) by means of cross-countries regression analysis models, showing a relevant relationship between malaria and GDP dynamic.

In a seminal study, Gallup and Sachs (2001) show that “cross-country regressions for the 1965–1990 period confirm the relationship between malaria and economic growth. Taking into account initial poverty, economic policy, tropical location, and life expectancy, among other factors, countries with intensive malaria grew 1.3% less per person per year, and a 10% reduction in malaria was associated with 0.3% higher growth. Controlling for many other tropical diseases does not change the correlation of malaria with economic growth, and these diseases are not themselves significantly negatively correlated with economic growth.

A second independent measure of malaria has a slightly higher correlation with economic growth in the 1980–1996 period" (Gallup and Sachs, 2001).

McCarthy *et al.* (2000) obtain a similar estimation of economic growth for the period 1983-1998. In a cross-section growth framework, they find "that for many countries the growth cost of malaria is pronounced. Even disregarding the tails of the distribution, the estimated growth reduction due to malaria exceeds 0.25 percent per year for about a quarter of the sample" (McCarthy *et al.,* 2000). Interestingly the countries located in Sub-Saharan Africa have an estimated average annual growth reduction of 0.55 percent. Considering the economic and non economic benefits of reducing malaria, McCarthy *et al.* report that "substantial reductions can be obtained by fairly simple, low cost measures such as pre-packaging complete treatments, better education regarding the need to complete treatment cycles, better availability of second- and third-line drugs in areas with building resistance against currently used drugs, and the widespread use of bed nets".

Raut (2004) models the equilibrium dynamics of malaria and aggregate income growth in a discrete time framework. Raut describes the disease dynamic and defines a malaria endemic equilibrium, then analyzes the interaction between malaria and growth in human and physical capital. Raut defines two stable steady-state equilibria: the malaria-endemic equilibrium and the malaria free-equilibrium. He analyses the two long-run balanced growth rates of per capita income. Crucially the growth rate in the first case is smaller than the growth rate at the malaria free-equilibrium. As a matter of fact, "without government and foreign aid, the malaria disease prone tropical countries will be stuck in malaria endemic equilibrium with low or negative growth in labor productivity and per capita income as compared to the malaria-free tropical countries".

Goenka and Lin (2009) study an endogenous economic growth model where there is a prevalence of infectious diseases. In their model, human capital accumulation induces economic growth through learning by doing (Lucas, 1988). The dynamics of the spread of infectious diseases, which depends on the ratio of health and physical capital, is modelled explicitly. They prove that the disease affects the effectiveness of human capital accumulation adversely and hence, the long run growth rate crucially depends on the proportion of healthy population. The results highlight that endemic diseases even if they do not lead to mortality, can have long run effects.

With respect to the effect of a reduction in the malaria burden, following the recent approach of converting CER to monetary values by applying WTP value to health gains, Mills and Shillcutt (2004) "drew on the cost-effectiveness literature to estimate the costs and averted DALYs of high coverage of a package of malaria control measures, and then calculated the BCRs (Benefit Cost Ratios) by assuming a year of life gained is worth one per capita income" (Mills *et al.,* 2008). Mills and Shillcut apply the relationship between malaria and economic growth to estimate the increased annual economic growth rate associated with a 50% reduction in the malaria burden (the Abuja target 2005), and then calculate the BCR by comparing the gain in national income to the costs of high levels of coverage of a package of malaria control measures. They conclude that BCRs of 4.7 and 1.9 indicate the malaria control as an efficient investment[32].

[32] In a review Barlow and Grobar (1986) and Mills (1987) estimate the costs per year of lives saved and cost-benefit ratios can be calculated for malaria control efforts in several countries. It was reported a very large variability in resulting discounted QALYs, indeed thee costs per case prevented ranged from $1.30 to $260 (in 1987 dollars) and the benefit-cost ratios from 2.4 to 146; that is, the monetary benefits are between 2.4 and 146 times as high as the costs.

New analyses that evaluate eradication campaigns by comparing their costs to those of ongoing control show a per capita cost of several USD, in particular "the Commission on Macroeconomics and Health (2001) estimated the costs of achieving 70% coverage of interventions for the prevention and treatment of malaria in all countries with GNP per capita of less than $1,200 in 1999 USD (a total of 83 countries, not all of which were malaria affected). Total annual costs (in 2002 USD) of prevention and treatment of adults were $3,535 m – 5,267 m, or $0.74–1.1 per capita of the total population, plus a share of the $9,414 –11,987 m ($1.97–2.50 per capita) cost of treatment of childhood diseases including malaria.

Kiszewski *et al.* (2007) similarly estimated the total costs of scaling-up a set of malaria control measures in the 81 countries most heavily affected by *Plasmodium falciparum* malaria. They included both service and programme strengthening costs, and 100% coverage targets. Total annual costs of fully scaled up services were $4,468 – 5,660 m (in 2006 USD), or $2.35–2.98 per capita of populations in falciparum-affected areas.

Finally, the Roll Back Malaria (RBM) Global Action Plan (2008) estimates "$6 bn annually for implementation costs of 80% coverage in 107 countries covering 3.2 bn people at risk of *P. falciparum* and *P. vivax* malaria ($1.88 pc). RBM's Global Malaria Action Plan estimated the costs of country implementation of malaria control and elimination strategies to be $5.3 and 6.2 billion ($2008) in 2009 and 2010, respectively, and $5.1 bn per year from 2011 to 2020, for 109 countries and 3.3 bn people at risk, suggesting roughly $1.55 per person" (Mills *et al.,* 2008).

In a recent study, Bleakley (2009) evaluates to what extent eradication campaigns determine an improvement in health and income. He examines the malaria control campaigns in Southern US (1920) and Brazil, Columbia, and Mexico (1955) by using micro-data to construct cohort-level panels. He finds that "cohort born after eradication campaigns had a higher income (and literacy) than adults than the preceding generation. This is true both in absolute terms and when measured relative to comparable cohorts in low-malaria areas". Bleakley emphasises the very negative effect of early-life exposure to the disease on lifetime income," in the US with the highest levels of malaria, cohorts born after the anti-malaria campaign earned 15 percent more than the previous generation….in Latin America cross-cohort changes in income are about 27-35 percent higher in areas with more malaria before the DDT campaign". Crucially, Bleakley shows that the estimated income gain from eradication is coherent with the Abuja Declaration (2005) which states that the income in Africa would be 37% higher today, but for the influence of malaria since 1960.

Cutler and others (2007) examine the impact of a malaria eradication programme across Indian States during the 1950s. They find that the programme increased literacy and primary school completion rates by 10%, accounting for about half the observed gains over the period spanning the intervention in malarial regions. Barreca (2007), Hong (2007), and Lucas (2007) find significant effects of either exposure to malaria or its eradication on a variety of economic outcomes such as schooling, literacy, labour force participation, and wealth.

In conclusion, the literature reviewed in this survey shows a significant difference between the microeconomic, or 'bottom-up' approach and the macroeconomic, or 'top-down' approach for assessing the economic burden of malaria. Even though there is a general agreement on the significance of the economic burden of malaria, estimates diverge as a consequence of different methodological approaches. Microeconomic studies providing national estimates assessing the cost of malaria ranged from 0,41% to 1% of the annual per capita GDP, while macroeconomic estimates indicate that the impact of malaria could account for a reduction up to 50% of the annual GDP.

Divergence between microeconomic estimations and macroeconomic evaluations may be induced by the fact that in the former results are derived in a *partial equilibrium condition*, and in the latter in a *general equilibrium condition*. In a general equilibrium framework, if other production factors (land, capital) do not adjust (they are *inelastic* or *sluggish*) to health changes and population growth, there are dilution effects, crowding effects etc. that reduce the GDP per capita.

3.3.3 Yellow fever

Yellow fever caused major epidemics from the 17th to the 20th centuries and was effectively controlled in the Americas by the *Aedes aegypti* elimination programme in the 1950s and 1960s. In West Africa it virtually disappeared as a result of mass vaccination campaigns carried out between 1940 and 1953. But in the mid-1980s epidemic yellow fever resurged in West Africa because of the failure to continue mass vaccination campaigns.

The vast majority of cases and deaths takes place in Sub-Saharan Africa, where case fatality rates for reported cases are in the order of 15 to 50%, and South and Central America. Yellow fever potentially concerns 538 million persons living in the countries at risk of contagion (20% in urban areas) and visitors. It affects an estimated 200,000 persons annually, causing an estimated 30,000 deaths and since the 1980s epidemics in Africa affect predominantly children under the age of 15 years.

The resurgence of epidemics, which attests the failure to control yellow fever, seems to arise from a misapplication of public health strategies and insufficient political commitment by governments in endemic areas to control the disease. Given difficulty in eradication, reduction of the burden of yellow fever is possible through outbreak prevention (immunization campaigns and vaccination of travellers in endemic areas) and control (surveillance and case management). As a consequence, the yellow fever vaccine has been introduced into routine infant immunization programmes in 19 of the 23 (83%) high-risk African countries endemic for yellow fever. In fact, “reduction of the human disease burden is achievable through routine childhood vaccination in endemic countries, with low cost for the benefits obtained” (Monath, 2001). The cost of the immunization programmes implemented by the yellow fever vaccine can be considered as a proxy of the cost of the disease.

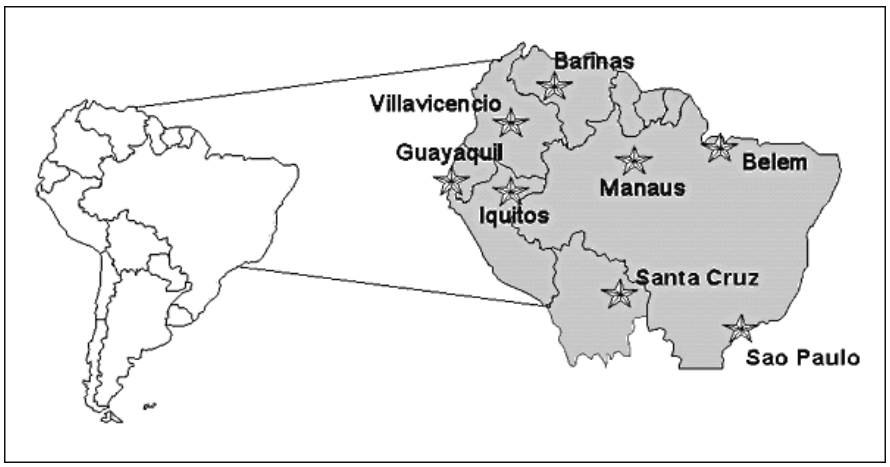


Figure 3.6. Major urban centers of South America recently infested with *Aedes aegypti* and at high risk for imported yellow fever. Source: Gubler 1999.

In 1993 Monath and Nasidi published a cost-effectiveness analysis of preventive yellow fever vaccination versus emergency mass vaccination campaigns. They evaluated the effects of including yellow fever 17D vaccine in the Expanded Programme of Immunization (EPI) on the immune status of population in Nigeria. According to Monath and Nasidi “using assumptions based on data from other African countries, the cost of adding the yellow fever vaccine to the existing EPI was estimated at +0.65 per fully immunized child, whereas the cost of emergency vaccination in the face of an epidemic was estimated at +7.84/person….In large epidemics, such as that occurring over successive years (1986-1991) in Nigeria, cost-effectiveness of the EPI exceeded that of emergency control”.

Despite the clear indication of the potential risk on the disease, yellow fever it is not widely recognised as an endemic problem in Africa. As a consequence, at the best of our knowledge, the actual disease burden from this endemic infection has not been estimated.

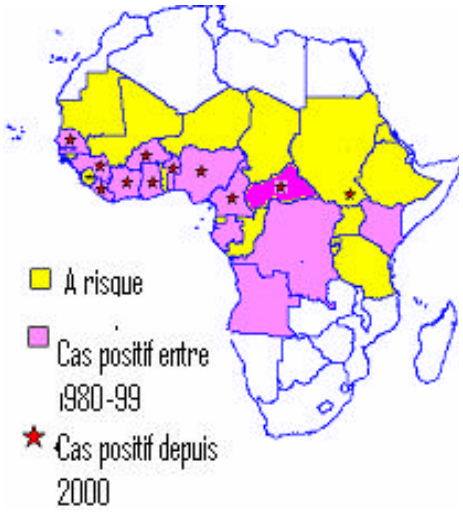


Figure 3.7. Countries at Risk in Africa Source: Hoekstra, 2008

In a study to quantify the cost of childhood immunization against yellow fever in Cameroon, Waters *et al.* (2004) concluded "that costs per fully immunized child varied from US$ 2.19 to US$ 26.59 (not adjusted for inflation) in a range of low-income and middle-income countries. The relatively low rates of immunization coverage in Cameroon, and the strong influence of the household's socio-economic status - particularly the mother's level of education - on immunization rates suggest that the effectiveness of the Cameroon programme could be increased by promoting immunization and directing such programmes towards households with limited resources".

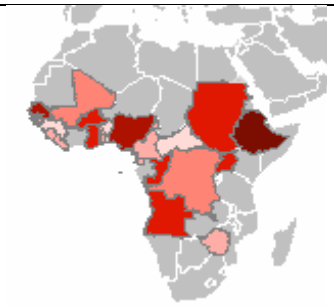
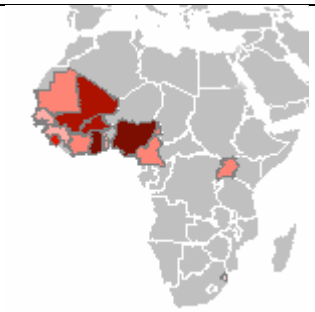
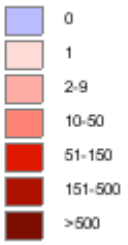
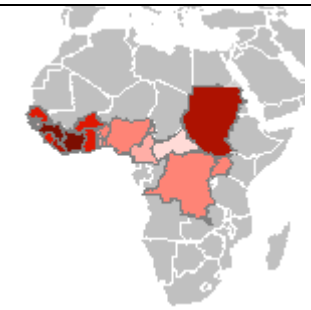
1950-1974	1975-1987	cases per year
		
49 cases per yea Epidemic in Ethiopia 100 000 cases and 30000 deaths	568 cases per year Nigeria and Ghana Epidemics	
1988-1999	2000-2004	
		
483 cases per year Nigeria and Ghana Epidemic	505 cases per year Epidemic in West Africa, Sierra Leone, Ivory Coast, Liberia, Guinea	

Figure 3.8. Epidemic trends in Africa: 1950-2004. Source: Hoekstra, 2008.

3.3.4 Dengue

Dengue fever is a rapidly growing public health problem in tropical and sub-tropical countries. Dengue fever and dengue hemorrhagic fever are considered diseases of poverty endemic in the tropical belt. However, recently temperate latitudes have become more suitable for dengue transmission.

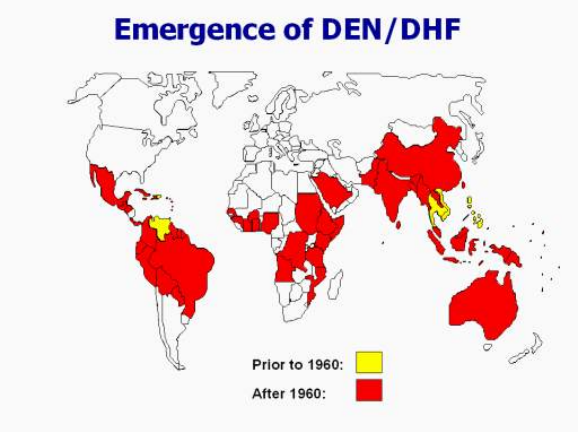


Figure 3.9. Distribution of dengue before and after 1960. Source: WHO, 2009c.

Despite the growing worldwide burden of dengue fever, the global economic impact of the illness is poorly documented. A recent World Bank-sponsored study on the global burden of the disease estimated that 750,000 DALYs are lost each year worldwide due to dengue hemorrhagic fever. There are no estimates for DALYs lost due to classic dengue. Literature mainly reports local or regional analyses of socio-economic costs of dengue fever.

Suaya *et al.* (2009), using a common protocol, present the first multi-country estimates of the direct and indirect costs of dengue cases in eight American and Asian countries. “We conducted prospective studies of the cost of dengue in five countries in the Americas (Brazil, El Salvador, Guatemala, Panama, and Venezuela) and three countries in Asia (Cambodia, Malaysia, and Thailand). All studies followed the same core protocol with interviews and medical record reviews. The study populations were patients treated in ambulatory and hospital settings with a clinical diagnosis of dengue. Most studies were performed in 2005. Costs are in 2005 International Dollars (I$). We studied 1,695 patients (48% paediatrics and 52% adult); none died. The average illness lasted 11.9 days for ambulatory patients and 11.0 days for hospitalised patients. Among hospitalised patients, students lost 5.6 days of school, whereas those working lost 9.9 work days per average dengue episode. Overall mean costs were I$ 514 and I$ 1,394 for an ambulatory and hospitalised case, respectively. With an annual average of 574,000 cases reported, the aggregate annual economic cost of dengue for the eight study countries is at least I$ 587 million”. The authors comment their result by suggesting that “our estimate of the eight-country cost of dengue illness is conservative. Official reports substantially underestimate the true number of cases and highlight the need for expansion factors to adjust for this underreporting. Previous research indicates expansion factors from 1.6 to 3.2 for hospitalised dengue from 10 to 27 for ambulatory dengue, 11 and 6 for all dengue cases. As a preliminary illustration, an overall expansion factor of 3 would suggest a cost of dengue illness in these eight countries averaging I$ 1.8 billion per year, but ranging from I$ 1.3 to I$ 2.3 billion. With expansion factors of 2 or 6, the eight-country costs would range from I$1.2 to I$3.6 billion…. Furthermore, these estimates also exclude the substantial costs associated with dengue surveillance and vector control programmes. For example, Brazil’s budget for vector control in 1997 was US$0.6 billion, equivalent to I$1.2

billion in 2005 prices. Panama, with a population of only 3.2 million people, spent US$5.0 million, equivalent to I$7.9 million in 2005. Mass larviciding[33] efforts against the dengue vector *Aedes Aegypti* in two urban areas of Cambodia with a population of 2.9 million people between 2001 through 2005 had an annual average gross cost of US$ 568,000 in 2005 US$, or US$ 0.20 (I$ 1.31) per person covered". [34]

In a study on the impact of symptomatic dengue fever infection on the families of patients hospitalised at the Kamphaeng Phet Provincial Hospital with laboratory-confirmed dengue, Clark *et al.* (2005) calculate the DALYs lost for fatal and non-fatal cases of dengue using population level data for Thailand, observing that "when we accounted for the direct cost of hospitalisation, indirect costs due to loss of productivity, and the average number of persons infected per family, we observed a financial loss of approximately US$61 per family, which is more than the average monthly income in Thailand. The DALYs were calculated using selected results from a family level survey, and resulted in an estimated 427 DALYs/million population in 2001".

A recent study reports that since 1879, dengue has manifested itself in epidemic form in Australia. Canyon (2008) finds that "the average time lost through illness in 1992-93 Charters Towers epidemic was calculated to be 10.5 days. Using the total number of infected people, the result is 19,477,500 man-days being lost in total or 177,068 days per annum. With each day valued at AU$ 96, according to an average income of AU$ 35,000, the annual cost since the introduction of dengue is almost AU$ 17 million in current terms. However, epidemics are much smaller these days, infection rates have changed and the average wage has risen to AU$ 45,000, so it is only appropriate that the current situation should be separated from the past. Prior to 1990, the cost of work lost in today's dollars is close to two billion dollars. In the last 18 years alone, 32,000 infections with 336,000 lost days have equated to AU$ 41.3 million or AU$ 2.3 million per annum in lost time alone".

The Indian Institute of Management Ahmedabad (IIMA) calculates the likely economic impact of dengue and chikungunya, both of them transmitted by *Aedes* mosquitoes. The preliminary estimates indicate a considerable economic burden. For India as a whole, the studies evaluate an immediate COI of US$ 1.5 billion (range 0,6-3,5bn), that is US$1,6 per capita with respect to US$5,3 in Malaysia and US$ 6,2 in Panama. IIMA estimates that a severe outbreak could determine a 4% decline in tourism from non endemic countries, namely at least US$ 8 million for Gujarat (the focus Indian state with 56 million of inhabitants), US$ 65 million for Malaysia, and US$ 363 million for Thailand (Mavalankar *et al.* 2009a and 2009b).

In a seminal study on Latin America, Torres and Castro (2007) estimated that "the number of DALYs per case lost to any form of the disease in Venezuela in endemic periods as 0.012 and 36.83 for non-lethal and lethal cases, respectively. Estimates of total direct and indirect costs from the 1977 epidemic in Puerto Rico range from US$ 6.1 million to US$ 15.6 million (approximately US$ 26 to US$ 31 per symptomatic case). The 1981 epidemic in Cuba, with a total of 344,203 reported cases, cost some US$ 103 million (approximately US$ 299 per reported case). The overall economic impact of the 1994 dengue epidemic in Nicaragua, which resulted in an estimated 60,916 cases of classic dengue and DHF, was calculated at US$ 2.7 million (approximately US$ 44 per case). Since the cost of hospitalising dengue patients in Nicaragua is very high (US$ 130 per day for a hospital bed), the disease clearly

[33] Larviciding efforts is the use of pesticides to control specific species of insects.

[34] To standardize the cost figures from the eight different countries, the authors made use of the *International Dollar* (I$) - a hypothetical unit of currency that has the same purchasing power that the US dollar had in the United States in 2005. The ratio of the international dollar to the US dollar, based on the rate of the exchange, varies in this study from 1.3 to 3.0 depending on the purchasing power of the dollar in the individual countries.

exacts a large economic burden. In fact, the cost of medical care accounted for 64% of the overall cost of that epidemic…. Based on the experience in Puerto Rico, using DALYs as a means of assessing dengue's economic impact, the disease was found to cause the loss of an average of 658 DALYs per year per million inhabitants….When comparing the impact of dengue versus other diseases in terms of DALYs, the majority of its impact is clearly borne by patients with classic dengue fever lasting approximately five days. Since most families in the region have a relatively low income (US$ 10,000/year), it is logical to assume that the largest share of the dengue burden is borne by those in the lower socioeconomic strata. Such people can ill afford the five or more days of productivity lost from dengue". Crucially, even if data on cost-efficiency and cost-benefit analysis of dengue control programmes in Latin America do not exist, Torres and Castro find that "the cost per DALY averted by the Venezuelan programme during endemic periods was comparatively low (US$ 122) as compared to other mosquito-borne diseases such as yellow fever (US$ 396), leishmaniasis (US$ 1,893), or malaria (US$ 1,915). Meanwhile, the cost-benefit ratio of the dengue control programme was also positive (US$ 0.46 invested per dollar saved)".

Lim *et al.* (2009) consider the costs of dengue and chikungunya in Malaysia and find that "the immediate cost of dengue to Malaysia to be in the range of US$ 88- US$ 215 million (mean US$ 133 million) per annum. Fortunately, chikungunya is not yet a major problem and its estimated immediate cost is only an additional US$ 1.2 million. However, it is an emerging threat and could cost Malaysia an additional US$ 134 million if its epidemic activity reaches the recent levels of dengue. While the impact on tourism is traditionally not included in cost of illness studies, it could reach an additional US$ 171 million if there were a major outbreak of dengue or chikungunya in Malaysia".

Borja and Lorenzo (2009) consider the economic burden of dengue fever in the Philippines, where the disease has an incidence of 19.8/100,000 and a case fatality of 1 to 4%. They estimate that "approximately 18,074 (21.96/100,000) DALYs are lost per year due to dengue indicating that its health impact in the Philippines is more akin to the South-East Asian Region (23.92/100,000) than to the Western Pacific Region B (8.39/100,000)....The dengue morbidity cost per patient which is the sum of the cost of diagnosis (Php 2,531), cost of treatment (Php 1,223) and estimated income loss of patients and watchers (Php 357), amounts to Php 4,123 (US$ 85.36). The national morbidity cost is Php 447.6 million".

3.3.5 Chikungunya fever

Scarcely considered up to 2006, the Chikungunya fever has spread out of its natural range, for the first time, giving rise to a large epidemic that involved most of the islands of the Indian Ocean, some countries of the Indian subcontinent, South-East Asia (in 2006-07), and an outbreak in Europe (2007).

Despite the high prevalence of chikungunya infection, there have been few attempts to quantify the impact on poverty and the socio-economic profile on the spread of the disease or morbidity experienced.

Kumar *et al.* (2007) investigate the relation between poverty and infection using a cross-sectional, hospital-based study of 3541 consenting patients from three states in South India with clinically confirmed chikungunya during the epidemic in 2006. The study reveals that "80% of chikungunya-affected patients were below the poverty line according to the World Bank's definition of income level of less than US$ 1per person per day (the calculated average family size was 4.5). Almost two thirds of infections occurred in the most productive age group of 15-45 years, and many (62%) patients experienced morbidity related to their infection for more than 15 days. One quarter (27.5%) suffered for more than 1 month….Infection was significantly more common in lower income groups across all age groups". Authors suggest that "poverty is an important determinant of chikungunya infection and, further, that….illness in individuals from poor backgrounds can have serious consequences, such as reduced productivity at the individual and community level, malnutrition, other infections, socioeconomic instability and exacerbation of poverty".

In 2009, two studies shed light on the economic effects of chikungunya in India.

Gopalan and Das examine the household economic impact of an outbreak of chikungunya in terms of health-care expenditure and income foregone due to loss of productive time in Orissa, India. They conduct a community-based cross-sectional survey (150 persons) in Kural village in Nayagarth. Gopalan and Das find that "the median out-of-pocket health care expenditure was US$ 84, of which the proportion of cost of diagnosis was the highest (US$ 77). One hundred and forty nine respondents incurred cost of care more than 10% of their monthly household income (catastrophic health expenditure). The median catastrophic health care expenditure was 37%. The respondents depended more on private health care providers (49%) and 31% of them accessed care from both public and private health care providers. The median work days lost was 35 with a consequent loss of income of US$ 75". Crucially, Gopalan and Das (2009) put in evidence a large loss in productivity (number of work hours lost along with loss earnings per day) after the acute phase of the illness, "the median work hours lost during the acute phase of illness was 29.1 with a consequent loss of median income of US$ 5.02. After the acute phase 21 days were lost. Out of the total respondents, 42% lost 37 days. About 29% of respondents lost 22 days. The remaining 21% lost 68 days. The median daily work hours before the illness were nine hours and it reduced to six hours due to illness". In conclusion, the chikungunya outbreak induces unforeseen catastrophic health care expenditure that reinforces the poverty-disease relationship.

Seyler *et al.* publish a seminal paper in which they estimate the burden and cost of chikungunya in the village of Mallela, Andhra Pradesh (India), and collect information on the demography, signs, symptoms, healthcare utilization and expenditure associated with the disease. Seyler *et al*. (2009) estimate the burden of chikungunya using DALYs and the economic costs of the disease by considering direct and indirect costs in Mallela village, and then they project estimations to the district of Kadapa and Andra Pradesh using coherent and consistent data. They find that "each chikungunya case in Mallela village led to an average

burden of 0.027 DALYs. Overall, the chikungunya burden in Mallela was 6.6 DALYs. The acute phase of the disease accounted for 6.5 DALYs (97% of the total)" (Seyler *et al.,* 2009, 3). Projection indicates that the estimated burden of chikungunya in Kadapa district was 160 DALYs and 257,034 cases and 6,600 DALYs in the state of Andra Pradesh. The estimated total economic cost of chikungunya in "Mallela village was US$9,100 (US$ 37.50 per case). It was higher in males (US$ 43.90 per case) than in females (US$ 32.90 per case), and for patients over 15 years of age (US$ 37.90 per case) compared with others (US$ 33.0 per case). The cost of chikungunya was also higher among adult females reporting a regular income (US$ 41.60 per case)" (Seyler *et al.,* 2009). The estimated total economic cost of the disease in the district and State are respectively US$ 290,000 and US$ 12,400,000".
Not surprisingly this seminal study emphasises that even if chikungunya may have a moderate burden on the population as a whole, it always induces very high and often out-of-pocket costs.

3.3.6 West Nile fever

First identified in the 1930s in Africa (Smithburn *et al*.,1940), up to the early 1990s, West Nile fever was considered mainly a disease of wildlife. But during the two past decades the disease has emerged or re-emerged with different severity in various foci out of its natural geographic range, in particular in Europe and in the US (Hayes *et al.*, 2005; Murgue *et al*., 2000).

Regarding the direct economic cost of West Nile fever, Zohrabian *et al.* (2004) find that "in 2002, a total of 4,156 West Nile Fever cases were reported in the United States; 329 were in Louisiana. To estimate the economic impact of the 2002 West Nile Virus epidemic in Louisiana, we collected data from hospitals, a patient questionnaire, and public offices. Hospital charges were converted to economic costs by using Medicare cost-to-charge ratios. The estimated cost of the Louisiana epidemic was US$ 20.1 million from June 2002 to February 2003, including a US$ 10.9 million cost of illness (US$ 4.4 million medical and US$ 6.5 million non-medical costs) and a US$ 9.2 million cost of public health response. These data indicate a substantial short-term cost of the West Nile fever disease epidemic in Louisiana".

Even if currently there is no human vaccine for prevention and no specific treatment for West Nile fever[35], Zohrabian *et al.* (2006) also evaluate a universal vaccination programme to prevent the disease, coming to the conclusion that "universal vaccination programme to prevent West Nile fever disease would be unlikely to result in societal monetary savings unless the incidence of the disease increases substantially over what has been seen in the past 6 years, or the cost of vaccination were < $12 per person vaccinated. The risk for West Nile fever infection, probability of symptomatic illness after infection, and cost of vaccine appeared to have the greatest influence on the cost-effectiveness outcome. Within the range of possible values used in our model, variations in vaccine effectiveness, cost of West Nile fever illness, and probabilities of various health outcomes did not lead to considerable change in the cost-effectiveness".

The authors show that "through simulations and sensitivity analysis that incorporated uncertainties regarding future transmission patterns of West Nile Fever and costs of health outcomes, we estimated that the range of values for the cost per case of West Nile Fever illness prevented by vaccination was US$ 20,000 – US$ 59,000 (mean US$ 36,000).

Cost-effectiveness was most sensitive to changes in the risk for infection, probability of symptomatic illness, and vaccination cost. Analysis indicated that universal vaccination against West Nile Fever disease would be unlikely to result in societal monetary savings unless disease incidence increases substantially" (Zohrabian *et al.,* 2006).

[35] In 2008 Biotech Inc announced notification by US FDA that it may proceed to initiate a 24 patient safety study in health human volunteers with its recombinant, subunit West Nile vaccine in Hawaii.

3.3.7 Leishmaniasis

Leishmaniasis is a neglected disease mainly embedded in poverty.
The overall disease burden has been estimated at 2,090,000 DALYs (1,249,000 in men and 840,000 in women).

Leishmaniasis contributes significantly to the propagation of poverty, because treatment is expensive and hence either unaffordable or it imposes a substantial economic burden, including loss of wages. Treatment-cycle costs range from US$ 30 to US$ 150 depending of type of medicine, but in the case of relapse medicines are more toxic and expensive, in this case costs increase from US$ 60 to US$1,500, for medicine without side effects (WHO 2006). In 2006 WHO declared that “no well-defined model for cost-effective control exists …The core problem is access to treatment, as the cost of admission to hospital has to be added to the cost of the medicine”.

A recent assessment in India of the cost and cost-efficiency of interventions, comparing the total cost of treatment (medicine plus hospital stay) with results (cure, relapse, treatment failure, or interruption), showed that the overall figure for successful treatment varied considerably, from US$ 175 to US$ 1,613. For 100,000 new cases each year in Bihar State, the cost of treating those patients would amount to some US$ 11 million.

Facing a possible new epidemic outbreak, WHO (2006) observes that “active case detection in health centres has proved to be cheaper than passive detection: US$ 25/per case and US$ 145/per case, respectively. The cost of preventing one death is US$ 131 by active case detection and US$ 200 by passive case detection - in other words, passive case detection implies the unforeseen death of some patients, hence a greater disease burden….In cost effectiveness terms, the cost of each DALY saved amounted to US$ 18.40, making treatment a measure of high return on investment”.

There are some studies on the global and local economic burden of leishmaniasis. Rijal *et al*. (2006) evaluate the economic burden of visceral leishmaniasis in Nepal, and find that the disease affects persons from the lowest socio-economic strata of the community. They evaluate the economic costs of the disease by a survey administered to households in a cluster and find that “15.0% of the residents had suffered from visceral leishmaniasis … Average total costs incurred per episode of visceral Leishmaniasis were above the median annual per capita income, and six of the seven affected households either had to sell part of their livestock or to take a loan to cover the costs. Direct costs consisted of 53% of the total cost, with 75% of this cost incurred before the patients actually received any treatment for visceral leishmaniasis”.

Sharma *et al.* (2006) study the household economic impact and identify household strategies to cover the costs of visceral leishmaniasis care in rural Bangladesh. The authors interviewed 113 patients from 87 households in two villages and found that “patients paid a median of 7 visits to six different providers before beginning visceral leishmaniasis treatment…. While health care, including anti-leishmaniasis drug therapy, is officially available free of charge at government facilities, 79% of patients reported making informal payments for provider access, diagnostics and drug administration; only 14% of patients received their full drug course from this source. For the 58% of patients who purchased the full treatment course, drug cost constituted 34% of direct expenditure”. The study puts in evidence that “The median direct expenditure for care for a visceral leishmaniasis patient was US$ 87, or 81% of the median annual per capita income…. The median income lost was US$40 (range US$1- US$616). The illness had permanent repercussions for some households. The median total cost for one visceral leishmaniasis patient, including direct and

indirect costs, was US$ 126 or 1.2 times the median annual per capita income". In addition they found that "households employed multiple coping strategies to cover expenditures, most commonly sale or rental of assets (62%) and taking out loans (64%)".

In 2008 Bern *at al.* published a study on leishmaniasis which emphasized that even if the disease occurs globally, it has disproportionate impact in some areas, namely Horn of Africa, South Asia and Brazil (visceral leishmaniasis), and Latin America, Central Asia, and South Western Asia (cutaneous leishmaniasis). The authors estimate the burden of the disease and find that for visceral leishmaniasis "the cost of caring for a patient with kala-azar in South Asia (US$ 80–US$ 120) approaches or surpasses the annual per capita income, and substantial additional income is lost by patients and family members unable to work"; for the cutaneous leishmaniasis "in Guatemala the cost of treatment is about US$ 250, beyond the means of most rural inhabitants. The disease also causes a major financial burden on public health systems. Treatment is provided free of charge by the governments of Colombia, where the cost of pentavalent antimony is approximately US$ 345 per person cured, and in Brazil, which has spent the equivalent of US$ 2.5 million to treat 35,000 persons with antimonial drugs, and an additional US$ 500,000 to treat 95 persons with liposomal amphotericin".

Reithinger (2008) supports conclusions in the study of Bern *et al.,* (2008) but contests that the disability weight for visceral leishmaniasis and cutaneous leishmaniasis is 0.243 and 0.023, respectively and asks for a new approach and methods to obtain up-to-date information on the leishmaniasis' burden of disease.

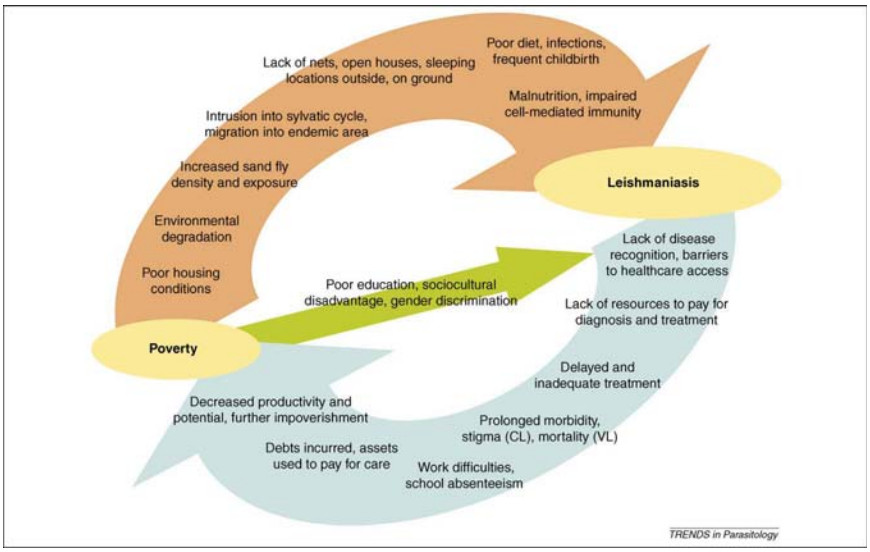


Figure 3.10. Poverty and leishmaniasis interaction. Source: Alvar *et al.,* 2006.

Studying the relationship between leishmaniasis and poverty, Alvar *et al.* (2006) conclude that "poverty and leishmaniasis together create a mutually reinforcing cycle. Compared with diseases such as malaria, diarrhoeal or pneumonia, the cost of leishmaniasis treatment is high ($ 30 to $ 1,500 for drug costs alone), and leishmaniasis is therefore an even more important contributor to poverty for affected families. In French Guyana, the cost of CL care was estimated to total 0.13% of the yearly budget of the territory, and 0.43% of its annual social security budget. In Nepal, the median total healthcare cost for one kala-azar patient was equivalent to the yearly median per capita income in the study population…. Households covered these costs by using up their meagre savings, liquidating assets such as livestock and land, and taking out high-interest loans. A case of leishmaniasis also causes substantial

loss of household income, both through the inability of affected wage-earners to perform physical labour, and because it is often impossible for a child or woman to obtain care unless accompanied by the male head of household…. Burdensome healthcare expenditures and coping strategies have long term consequences for households, leading to further impoverishment".

Crucially for the scope of this research, that is the relationship between biodiversity loss and re-emergence of infectious diseases, Chaves *et al*. (2008) find that "American cutaneous leishmaniasis tended to afflict socially marginal populations more heavily, which is common to other infectious diseases, and has been historically documented in public health studies particularly at small spatial scales…. Social marginalization also can explain patterns of American cutaneous leishmaniasis at larger geographical scales. When this influence is taken into account, risk of infection is diminished among those living close to forests, an unexpected pattern in light of previous studies on the role of this habitat type. The pathway by which social marginalization promotes transmission of *Leishmania* in this context probably is linked to a major environmental problem affecting the tropics: destruction of forests and associated biodiversity".

3.3.8 Lyme disease

Generally, studies of economic impact of Lyme disease are not based on data collected from the field, but induced by assumptions; as a consequence estimated costs are not fully reliable.

The US Centers for Disease Control and Prevention (CDC) estimates that Lyme Disease patients spend on average US$ 8,172 on direct costs, indirect medical costs, non medical costs and productivity losses. Assuming that only a part between 10 to 20 percent of physician-diagnosed cases of Lyme disease is reported to state authorities in high endemic areas, estimation of the total number of Lyme disease cases in 2006 varies from 200,000 to 400,000 and estimated total cost is from US$ 160 to US$ 320 million.

In 1999, Maes *et al.,* conducted a study on COI of Lyme disease in the US. “Using an annual mean incidence of 4.73 cases of Lyme disease per 100,000 populations the decision analysis model yielded an expected national expenditure (direct and indirect costs) of US$ 2.5 billion (1996 dollars) over 5 years for therapeutic interventions to prevent 55,626 cases of Lyme Disease sequelae.” They concluded their study suggesting the development of vaccination strategies for specific target groups.

In a recent paper Zhang *et al.* (2006) combine data from medical records with results from a patient survey to approximate (extrapolation) the annual economic impact of Lyme disease nationwide. They considered direct medical costs of Lyme disease diagnosis and treatment, indirect medical costs, non-medical costs (transportation, babysitting, etc) and productivity losses. The authors found that “the annual total direct medical cost of Lyme disease cases on Maryland Eastern Shore was US$ 1,455,081; 490 cases were in the clinically defined early or late stage of Lyme disease. Total indirect medical costs, non-medical costs, and productivity losses were US$ 436,949; 84 cases were clinically defined early- or late stage Lyme disease. Therefore, in general, a Lyme disease patient (clinically defined early or late stage) costs US$ 2,970 in direct medical costs plus US$ 5,202 in indirect medical costs, non-medical costs, and productivity losses. In 2002, CDC reported 23,763 Lyme disease cases. Hence, the estimated nationwide annual economic impact of Lyme disease and relevant complaints was almost US$ 203 million (in 2002 dollars). However, since Lyme disease cases reported on the basis of the surveillance case definition are believed to be underreported, this nationwide estimate is likely to be low”.

In 1998, the Food and Drug Administration approved a recombinant outer-surface protein A (rOspA) Lyme disease vaccine (LYMErix, SmithKline Beecham Biologicals) for persons between 15 and 70 years of age. The vaccine is effective and its use should be part of cost effectiveness assessment or similar evaluation. There are different studies on this problem and they converge in valuating the probability of contracting Lyme disease as the most important factor in determining the economic benefit of vaccination. Meltzer *et al.* (1999) find that “assuming a 0.80 probability of diagnosing and treating early Lyme disease, a 0.005 probability of contracting Lyme disease, and a vaccination cost of US$ 50 per year, the mean cost of vaccination per case averted was US$ 4,466. When we increased the probability of contracting Lyme disease to 0.03 and the cost of vaccination to US$ 100 per year, the mean net savings per case averted was US$ 3,377. Since few communities have average annual incidences of Lyme disease >0.005, economic benefits will be greatest when vaccination is used on the basis of individual risk, specifically, in persons whose probability of contracting Lyme disease is >0.01”.

This conclusion is confirmed by Shadick *et al.* (2001). They developed a decision-analytic model to evaluate the cost-effectiveness of vaccination compared with no vaccination in

individual living in endemic areas. They found that “vaccinating 10,000 residents living in endemic areas with a probability of Lyme disease per season of 0.01 averted 202 cases of Lyme disease during a 10-year period. The additional cost per QALY gained compared with no vaccination was US$ 62,300. Vaccination cost US$ 12,600/QALY gained for endemic areas with an attack rate of 2.5% per season, and US$ 145,200/QALY gained for an attack rate of 0.5%. Vaccinating individuals over an accelerated 2-month vaccination schedule improved the cost-effectiveness to US$ 53,700/QALY gained. If a yearly booster shot is required for persisting efficacy, the marginal cost-effectiveness ratio increases to US$ 72,700/QALY. The cost-effectiveness of vaccination was most sensitive to the Lyme disease treatment efficacy and assumptions about the persistence of vaccination effect. Vaccination against Lyme disease appears to be economically attractive only for individuals who have a seasonal probability of *Borrelia burgdorferi* infection of greater than 1%”.

3.3.9 Tick-borne encephalitis

The morbidity associated with tick-borne encephalitis is considerable. During the last 30 years, a continuous increase in TBE morbidity – 400% from 1974 to 2003 – was observed in Europe (Süss, 2008).

In Europe and Russia, tick-borne encephalitis (TBE) is the most important flavivirus infection of the central nervous system. The total annual number of cases is estimated to be up to 10,000 in Russia and about 3,000 in European countries. The virus prevalence in ticks as well as the prevalence of infected ticks within the risk areas can vary. Countries with high risk areas are Russia, Latvia, Lithuania and Estonia. TBE is also a significant issue in Germany, the Czech Republic, Poland, Switzerland, Sweden, Finland, Slovakia, Hungary and Slovenia.

Since there is an effective vaccine against TBD, only the cost-effectiveness of vaccination programmes is considered, at the best of our knowledge.

Donoso Mantke *et al.* (2008) observe that "while Lyme disease, another tick transmitted disease of similar epidemiological importance in Europe, can be treated with antibiotics, no specific treatment for tick-borne encephalitis is available to date and the administration of tick-borne encephalitis immunoglobulin for a passive post-exposure prophylaxis is highly questionable and not recommended anymore, for example in Germany. Due to the fact that tick-borne encephalitis causes high costs for health care systems (intensive care in hospitals, possible long-lasting cognitive and neuropsychiatric sequelae etc.) tick-borne encephalitis vaccination should be recommended and reimbursed for residents of and travellers to tick-borne encephalitis endemic areas, who are at risk of tick bites".

Desjeux *et al.* (2005) report the cost benefit analysis of tick-borne virus vaccination among French troops in the Balkans. They assess the economic impact of a three injection vaccination programme against tick-borne encephalitis for all French military personnel in the Balkans versus no vaccination during a period from 2004 to 2014. The authors state that previous studies had shown that the vaccine against tick-borne encephalitis is generally considered effective and well tolerated. Vaccination costs included vaccine acquisition and administration and side effects. Indirect costs, namely the costs associated with absence from work and compensation for serious adverse effects, are included in evaluation.

Assuming the price year is 2004, a discount rate of 5% and an inflation rate of 1% the authors found that "total vaccine programme costs were EUR 10.05 million and total costs averted were EUR 4.37 million. The main categories of costs averted were those related to hospitalisation and rehabilitation, medical evacuation flight and disability pension pay. Thus, the extra costs of vaccination were EUR 5.68 million. The ratio of costs incurred and saved was EUR 2.30. The break-even point (when the vaccine programme costs are equal to the cost savings) was a seroconversion rate of 1,936 per 100,000 person years, i.e. 280 tick-borne encephalitis cases for the period considered. The sensitivity analysis showed that in the favourable scenario the extra costs were EUR 2.86 million (break-even seroconversion rate: 1,206), while in the unfavourable scenario they were EUR 17.63 million (break-even seroconversion rate: 6,343). If the vaccine was applied to the whole army, then the extra costs of vaccination would be EUR 25.7 million (break-even seroconversion rate: 6,971). The incidence of disease had a large impact on the estimated costs. However, in no case did vaccination lead to cost savings".

3.3.10 Avian influenza

There are many studies (global, regional, continental) on the economic effects of a possible avian flu pandemic. Conjectures about the possible human and economic cost of an influenza pandemic are fraught with uncertainty. Even though there is uncertainty about the nature of such pandemic and its economic fallout, all the studies agree in considering economic consequences catastrophic.

A conservative estimate of the general economic damage induced by a pandemic of avian flu disease only in Asia sets the total cost at US$ 282 billion and the World Bank has estimated that a pandemic could cost the world economy between US$ 800 billion and US$ 2 trillion, depending on the virulence of the virus.

Potential mortality from an avian flu pandemic is also very uncertain and epidemiologic models produce estimates from 2 million to 360 million deaths.[36] According to a recent study based on a quantitative analysis of vital registry data from the 1918-1920 Spanish flu pandemic "Extrapolation of 1918-20 mortality rates to the worldwide population of 2004 indicates that an estimated 62 million people (10^{th}- 90th percentile range 51 million - 81 million) would be killed by a similar influenza pandemic; 96% (95% CI 95-98) of these deaths would occur in the developing world. If this mortality was concentrated in a single year, it would increase global mortality by 114%....This analysis of the empirical record of the 1918-20 pandemic provides a plausible upper bound on pandemic mortality. Most deaths will occur in poor countries- i.e., in societies whose scarce health resources are already stretched by existing health priorities" (Murray *et al.,* 2006).

In 1999, Meltzer *et al.* provided a range of scenario estimates based on the gross attack rate from 15% to 35% (percentage of clinical influenza illness cases per population) of the pandemic flu. They found that "without large-scale immunization, the estimates of the total economic impact in the United States of an influenza pandemic ranged from $ 71.3 billion (gross attack rate of 15%) to $ 166.5 billion (gross attack rate of 35%). At any given attack rate, loss of life accounted for approximately 83% of all economic losses. Outpatients, persons ill but not seeking medical care, and inpatients accounted for approximately 8%, 6%, and 3%, respectively, of all economic losses".

The Oxford Economics (OE) in the Commentary on Avian Flu (2005) taking the model of Metzler *et al*. (1999) estimates a global cost of pandemic influenza ranging from US$ 8 billion to US$ 24 billion (excluding deaths). Using OE-SARS reaction function, the Oxford Economics considers a rough estimate of the costs of a fairly serious outbreak of pandemic flu from a minimum of 1% of global GDP in the first year (almost US$ 400 billion) to a maximum of 4%-5% of global GDP (US$ 1,500-2,000 billion) plus the impact of the death rate in the long term (0.5% of GDP loss per 1% of population lost per year).

McKibbin and Sidorenko (2006) evaluate the consequences of an outbreak on the global economy through a range of scenarios using the Asian Pacific G-Cubed (APG-Cubed) model which consists of 20 countries with six sectors of production and consumption. The scenarios have a historical character since they refer to the US during the past outbreaks, namely: the mild scenario is defined with respect to Hong Kong flu (1968-1989), the moderate scenario refers to Asian flu (1957), the severe scenario refers to Spanish flu (1918-1919) and the ultra scenario is similar to Spanish flu but without anomalously high elderly survival rate. They

[36] The economic value of the human life can be measured by the so-called *value of statistical life* (VSL), which is the relevant parameter for the valuation of accidents. VSL recommended for policy decisions in Europe and North America, is in the range of 1 to 5 million of Euros.

conclude that “even mild pandemic has significant consequences for global economic output. Global consequences are very impressive: “the mild scenario is estimated to cost the world 1.4 million lives and the global economy close to 0.8% of GDP (US$ 330 billion in lost economic output)…A massive global economy slowdown occurs in the ultra scenario with 142.2 million people killed and some economics, particularly in the developing world, shrinking by over 50% in 2006. The loss to global GDP is US$ 4.4 trillion or 12.6%” (McKibbin and Sidorenko, 2006).

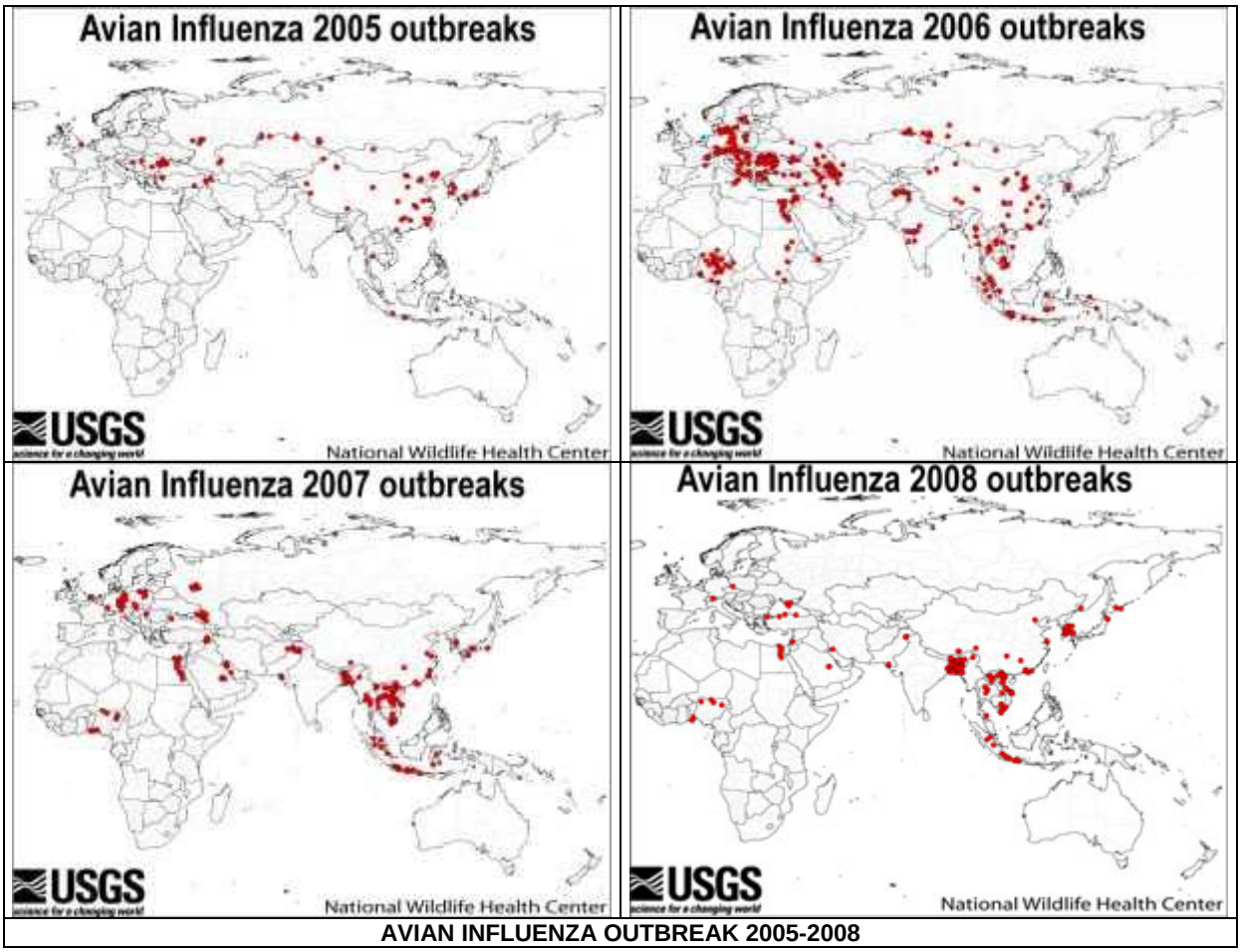


Figure 3.11. Avian influenza outbreak 2005 – 2008. Source: USGS, 2010.

Burns *et al.* (2008) evaluate the economic consequence in term of GNP decrease of avian influenza and find that “the impact ranges from 4.4 percent in Latin America and the Caribbean to 2.6 percent in the East Asia and Pacific region, mainly reflecting the relative importance and labour intensity of tourism and other services in each region. In this scenario of a moderately severe pandemic, the total cost to the global economy would be slightly more than US$ 2 trillion. In the case of a more severe pandemic, however, such as one causing a 4.8 percent drop in economic activity, the total cost to the world economy is estimated to be about US$ 3.13 trillion”.

In an assessment of the possible macroeconomic effects of a pandemic flu in US, the Congressional Budget Office of US (CBO) observes that a pandemic involving a highly virulent flu strain (such as the one that caused the pandemic in 1918) could produce a short-run impact on the worldwide economy similar in depth and duration to that of an average post-war recession in the United States (CBO, 2006).

Jonung and Roeger (2006) estimate the macroeconomic effects of a pandemic flu in Europe in 2006, using a quarterly macroeconomic model and adopting the severe scenario of CBO. They assume a morbidity rate of 30% and a mortality rate of 2.5% per cent; moreover they consider on average 3 weeks off work due to illness per worker. “Applying these figures on sickness and mortality rates to the EU-25 suggests that about 150 million Europeans will become sick for three weeks and 2.5 per cent of those, in other words 0.75% of the total population, will die” (Jonung and Roeger, 2006). On these assumptions, they estimate that “the epidemic breaks out in the first quarter of 2006, and combining the supply and demand effect….a drop in EU GDP growth in 2006 of 1.6 percentage points according to our calculations….Instead of growing at 2.1 per cent in 2006, as projected in DG ECFIN’s autumn 2005 forecast, the EU-25 economy would grow by only 0.5 per cent. In absolute terms, the output loss in 2006 would amount to about 180 billion Euros” (Jonung and Roeger, 2006).

Keogh-Brown *et al.* (2009) apply the UK macroeconomic model COMPACT to epidemiological data on previous UK influenza pandemics, that last one quarter, to cover different disease scenarios.[37] They find that “the economic impact of a repeat of the 1957 or 1968 pandemics would be short-lived, constituting a loss of 3.35% and 0.58% of GDP in the first pandemic quarter and year respectively. A more severe scenario (with more than 1% of the population dying) could yield impacts of 21% and 4.5% respectively… mild disease scenario then shows first quarter/first year reductions in GDP of 9.5%/2.5%, compared to severe scenario reductions of 29.5%/6%”. Severity of a scenario is defined with respect to Clinical Attack Rate (CAR), from 35% of the 1957 and 1968 influenza pandemics (base-case) to 50%, and Case Fatality Rate (CFR), from 0.04%, base-case, to 2,5, Spanish Flu. School closure and prophylactic absenteeism induce fall in labour supply, Keogh-Brown *et al.* find that “the addition of one week of prophylactic absenteeism is similar to the impact of increasing the CAR to 50%”. Interestingly, the authors show that influenza pandemics not only induce inflation effects but also produce precautionary changes in consumption patterns that amplify the economic consequences of the outbreak. Assuming a per capita GDP of £ 21,200 (2006 UK GDP) Keogh-Brown *et al.,* calculate that “the economic impacts for the base scenario, high CFR, high CAR, and severe scenarios equate to per capita effects of £ 47, £ 218, £ 226, and £ 329 respectively for the first year. To illustrate the impact of prophylactic absenteeism for one week and four weeks, the base cost to GDP per capita of £ 47 would increase to £89 and £225 respectively, whilst for four week-school closures the cost would be £123. Finally, the cost to GDP per capita in the severe disease scenario would be £ 437, and if a quarter of school closure were combined with four weeks of prophylactic absenteeism the cost would be £ 934. Impacts for the consumption shocks in terms of GDP per capita would be £ 534 for the base scenario and £ 1,283 for the severe”.

[37] COMPACT is a quarterly macroeconomic model of the UK; it is a micro-founded macroeconomic structural econometric model.

CHAPTER 4
Medicines from biodiversity

"Despite the remarkable progress in synthetic and organic chemistry, human efforts have scarcely been able to document, let alone duplicate, the plethora of bioactive molecules produced by life on earth. It is therefore not surprising that human cultures throughout the world rely on biodiversity as a source of medicines" (Cox, 2009).

Human medicines are subdivided into traditional and modern medicines. The latter is also referred to as modern, Western or allopathic medicine.

4.1 Traditional medicines

The World Health Organisation defines traditional medicine (TM) as "diverse health practices, approaches, knowledge and belief incorporating plant and animal and/or mineral-based medicines, spiritual therapies, manual techniques and exercise applied singularly or in combination to maintain well-being, as well to treat, diagnose or prevent illness" (Patwardhan, 2005). When adopted by non-native populations traditional medicine is often known as alternative or complementary medicine (CAM).

Traditional medicine is characterised by centuries of experience of the healing powers of the earth's natural systems and includes the use of substances derived from plants and animals and the purifying qualities of the air, water and landscape (Alvez and Rosa, 2007). The dominant traditional medicines are the Chinese and the Ayurveda (meaning literally the science of life) of the Indian subcontinent. Traditional knowledge from the East has been guarded and passed on to the west by the Arabs and Persians while the monasteries in Western Europe preserved traditional knowledge (such as that of the druids) through the Dark Ages (Gupta *et al*., 2005).

The use of natural products as medicines goes back to the dawn of civilization when humans learned to use plants and plant products as remedies for various illnesses. Knowledge of herbal medicine has been documented from the civilizations of Mesopotamia (2900 B.C.), Egypt (1500 B.C.), China (1100 B.C.), India (1000 B.C.), Greece (300 B.C.) and Rome (100 A.D.), and from religious texts such as the Bible. Herbal medicine has been an important component of healthcare all over the world through the ages.

Herbal treatments that contain parts of plants or plant derivatives as active ingredients are the most popular form of traditional medicine. In current day China herbal therapy is an essential part of internal medicine. One classic example is the use of reishi and shiitake mushrooms, which are currently under intense study by ethnobotanists and medical researchers, for immune system enhancement (Dharmananda, 1996; China National Corporation, 1995).

Traditional medicine is widely used and growing in importance on all continents. It is used by up to 80% of the population in Asia and Africa and 40% in China for regular health care (Hostesttmann *et al*., 2002; WHO, 2000 and 2008).

In the developed world, the use of herbal medicine declined in the 20th century coincidentally with advances in medical science that resulted in wide-scale introduction of synthetic

pharmaceutical products. However, there has recently been a revival in the use of plant-based products in the treatment of diseases (Esimone *et al*., 2009). Complementary medicine[38] in general is becoming more and more popular in many developed countries, having being used at least once by 48% of the population in Australia, 70% in Canada, 38% in Belgium and 75% in France (Foster *et al*., 2000; WHO, 2002). The use of herbal medicines in the USA increased from 2% of the population in 1990 to 37% in 2000 (WWF 2000).

Modern medicine is now beginning to adopt herbal products following scientific validation, such as ispaghula, garlic, ginseng, ginger, ginkgo, St. John's wort, and saw palmetto. This trend is likely to continue due to the high cost of developing and patenting chemical drugs (Gilani and Rahman, 2005). This interest is reflected in investment by the pharmaceutical industry - in 2006, Novartis invested US$ 100 million in the construction of an integrated research and development centre for traditional medicine in Shanghai (Cortes-Maramba, 2009).

4.2 Modern medicine

Modern medicine developed from ancient Greek and Roman medicines, later spreading to the rest of Europe and the Americas (Azaizeh *et al*., 2008). It began to develop rapidly only in the 19th century after Pasteur, Koch, Ehrlich and Semmelweis proved the relation between germs and diseases. Other invaluable developments were the use of disinfection and inoculation; the introduction of anaesthetics in surgery and better public health and sanitary measures (Walton *et al*., 1986).

The discovery and commercial production of antibiotics gave medicine a big impetus in the 1930s. Further progress came with the preventive use of vaccination following increased understanding of immune mechanisms, treating hormone-based diseases through development of endocrinology, and better understanding of nutrition and the role of vitamins. The discovery of the chemical structure of deoxyribonucleic acid (DNA) by Crick and Watson in 1953 laid the basis for molecular genetics and the consequent revolution in modern medicine (Walton *et al*., 1986).

During the development of modern medicine, traditional medical practices have generally been rejected as unscientific. Hence, scientific literature in the west relating to natural products has largely remained in the academic realms of chemistry, pharmacognosy[39], ethnobotany and anthropology.

Investigation of plant chemistry is credited to classical plant physiologists, biochemists and organic chemists. Through their work we now understand the chemical validity of several traditional herbal remedies. Some examples are:

- the antihypertensive and tranquilizer alkaloid reserpine from *Rawolfia serpentina* (snakeroot) (Ayurvedic or ancient Indian medicine);
- the cardiotonic glycoside digitoxin from *Digitalis purpurea* (ancient Greek medicine);
- stimulants from Chinese Ginseng *Panax ginseng* (ancient Chinese medicine) and American Ginseng *Panax quinquefolium* (native American medicine);

[38] CAM includes medication therapies, such as herbal medicines, and non-medication therapies, such as acupuncture, manual therapies and spiritual therapies.
[39] Pharmacognosy is the study of medicines derived from natural sources.

- the antimalarial and antipyretic (fever reducing) alkaloid quinine from the bark of *Cinchona officinalis* or *Cinchona ledgeriana* (traditional South American medicine).

Indeed, entire plant families such as Acanthaceae and Asclepiadaceae are described in ancient Indian, Chinese or Greek medical literature (Gupta *et al*., 2005). Active compounds extracted from many species have already been commercially patented (see examples in Fig. 4.1).

Species	Patent number and owner	Use and benefit-sharing
Forskolin (*Coleus forskohlii*)	US 4,724,238; EP 0265,810; IN 162,171; IN 147,030; IN 143,875 held by Hoechst (DE)	Traditionally used in medicine throughout Africa, India and Brazil. Patent applies to the use of Forskolin's anti-inflammatory and analgesic properties.
Yellow yam (*Dioscorea dumetorum*)	US 5,019,580 held by Shaman Pharmaceuticals and M. Iwu	Used in West African traditional medicine to treat diabetes. Patent applies to the use of dioscoretine to treat diabetes
Monellin from serendipity berries (*Dioscoreophyllum cumminisii*)	US 3,998,798; JP 5,070,494 held by University of Pennsylvania (USA) and Kirin Brewery Ltd (Japan)	Used for centuries by West Africans to sweeten food and drink
Harungana vismia	US 5,837,255 held by Shaman Pharmaceuticals Inc. (USA)	History of traditional medicinal use in a variety of African countries. Product targeted towards the treatment of hypoglycemia and diabetes.
Mesembryanthemaceae family, including *Sceletium tortuosum*	WO 9,746,234 held by Farmac Nederland B V (NL) and South African nationals	Traditionally used by communities in Southern Africa as an inebriant and sedative. Patent grants a monopoly on the use of mesembrin and related compounds in the treatment of mental disorders.
Brazzein ("J'oublie") (*Pentadiplandra brazzeana*)	US 5,527,555; US 5,326,580; US 5,346,998; US 5,741,537 held by the University of Wisconsin (USA)	Plant originates from Gabon, where it has long been used as a sweetener. Patent applies to the protein compound providing the sweetness, the Brazzein gene and transgenic organisms expressing the gene. This will eliminate the need for it to be collected or grown commercially in West Africa. Prodigene is introducing the gene in maize. There are plans for benefit sharing with West African people who discovered and nurtured the resource.
Pygeum (*Prunus Africana*)	US 3,856,946; FR 2,605,886 held by Debat Lab (France)	The tree is native to African montane forests, with a broad range of distribution. Traditionally used for carving and to some extent for medicinal purposes. Its use for the treatment of prostate disorders has resulted in sales of some US $150 million per year, but also serious overexploitation in many areas.
Thaumatin from (*Thaumatococcus daniellii*)	US 4,011,206 US 5,464,770 held by Tate & Lyle (UK) and Xoma Corp (USA)	Plant originates in West Africa, and researchers at the University of Ife in Nigeria first identified its potential as a sweetener. The gene has since been cloned and used as a sweetener for confectionery. People from whose lands the plant was obtained received no compensation.
Fungus (*Eupenicillium shearii*)	US 5,492,902 held by the U.S. Dept of Agriculture; the University of Iowa Research Foundation; and Biotechnology Research and Development (USA)	Fungus is derived from soils of Côte d'Ivoire. Intended use is as an insecticide.

Figure 4.1. Major patents on African biodiversity.

The loss of traditional medical knowledge could have an impact on the development of modern medicine (Alvez and Rosa, 2005). Aspirin, atropine, ephedrine, digoxin, morphine, quinine, reserpine and tubocurarine are examples of drugs originally discovered through the study of traditional cures and folk knowledge of indigenous people (Gilani and Rahman, 2005). Traditional medicine can offer a holistic approach to drug design and myriad targets for scientific analysis (Patwardhan, 2009).

4.3 The dependence of traditional and modern medicines on biodiversity

Natural products are an important – and have been the main, or even the only source of drugs for most of human history - source of new drugs (Barnes and Gallagher, 2007). Some examples are antibiotics (mainly from micro-organisms), painkillers (e.g. from cone snails), anticancer drugs (e.g. taxolo from plants, bryostatin from a marine bryozoa) and drugs against infection (e.g. plant derived quinine and artemisin against malaria).

Between 50,000 and 70,000 plant species are known to be used in traditional and modern medicine worldwide (see table 4.1).

Table 4.1. Use of medicinal plant species world-wide (Schippmann *et al*., 2003).

COUNTRY	TOTAL PLANT SPECIES	PLANT SPECIES USED IN MEDICINE	Share of medical to total species %
China	26 092	4 941	18.9
India	15 000	3 000	20.0
Indonesia	22 500	1 000	4.4
Malaysia	15 500	1 200	7.7
Nepal	6 973	700	10.0
Pakistan	4 950	300	6.1
Philippines	8 931	850	9.5
Sri Lanka	3 314	550	16.6
Thailand	11 625	1 800	15.5
USA	21 641	2 564	11.8
Viet Nam	10 500	1 800	17.1
Average	**13 366**	**1 700**	**12.5**
World	**422 000**	**52 885**	

Most medicinal plants originate from the wild, and harvest in countries like India and China amounts to 90% and 80% of their medicinal plants respectively (Correa, 2002). A similar situation exists in Africa (Lettington, 2000).

About 3,000 medicinal plants species are traded (Leaman, 2009). China and India account together for 63% of exports (aromatic plants included) in volume terms and Europe and the USA together take 44% of imports (see Table 4.2).

Table 4.2. The 12 leading countries of import and export of medicinal and aromatic plants. Sources: Schippmann *et al*., 2003.

COUNTRY OF IMPORT	VOLUME [TONNES]	VALUE [1 000 US$]	COUNTRY OF EXPORT	VOLUME [TONNES]	VALUE [1 000 US$]
China (excl. Hong Kong)	73 650	314 000	China (excl. Hong Kong)	139 750	298 650
Japan	56 750	146 650	India	36 750	57 400
USA	56 000	133 350	Germany	15 050	72 400
Germany	45 850	113 900	USA	11 950	114 450
Rep. Korea	31 400	52 550	Chile	11 850	29 100
France	20 800	50 400	Egypt	11 350	13 700
China	12 400	41 750	Singapore	11 250	59 850
Italy	11 450	42 250	Mexico	10 600	10 050
Pakistan	11 350	11 850	Bulgaria	10 150	14 850
Spain	8 600	27 450	Pakistan	8 100	5 300
UK	7 600	25 550	Albania	7 350	14 050
Singapore	6 550	55 500	Marocco	7 250	13 200
Total	342 550	1 015 200	Total	281 550	643 200

According to Bhat (1998), information relating to medicinal plants can be found in documents and databases designed for a wide range of disciplines. The bulk of information on medicinal plants is geared to identifying new plants containing bioactive compounds or isolating and characterising active compounds from plants already used in herbal therapy in some part of the world. Databases with more than 20,000 traditional Chinese herbal formulae are available to scientists worldwide.

Very little information relates to the therapeutic use of these plants in the traditional medicine where they were identified. For example, substantial information on plants used in traditional Chinese, Ayurvedic, and Western herbal medicine has been generated from screening programmes but the same databases contain virtually no information on how these plants are already used in a specific traditional medicine (Bhat, 1998).

IUCN's Medicinal Plant Specialist Group is compiling a data bank based on published pharmacopoeias[40] and other sources that document plants used in various systems of medicine throughout history.

Regarding zootherapy, wild and domestic animals and their by-products (e.g. hooves, skin, bones, feathers and tusks) form important ingredients in the preparation of some curative, protective and preventive medicine worldwide (Adeola, 1992). Despite their importance, there are few studies on the therapeutic use of animal products as compared to plants (Alvez and Rosa, 2005). They are geographically restricted and relate only to particular traditional medicines. One study shows that at least 165 reptile species are used in traditional folk medicine around the world. Some reptile species are also used as sources of drugs for modern medical science. Fifty-three per cent of the reptiles recorded are on lists of endangered species (Alves *et al*., 2008).

[40] Pharmacopoeias is a book containing directions for the identification of samples and the preparation of compound medicines.

4.3.1 The use of natural products in traditional medicine

Ayurvedic and traditional Chinese medicine have relatively well organized databases with exhaustive descriptions of botanical material available for use in the preparation of medicines (Patwardhan, 2009).

Chinese medicine uses about 6,000 plant and animal species and over 100 minerals. About 1,500 medicines are derived from animal sources (China National Corporation,1995)

Rather than being prescribed individually, herbs are combined in mixes adapted to the needs of individual patients. A herbal formula can contain from 3 to 25 species. Many animal tissues are also used in traditional Chinese medicine, including as tiger bones, antelope, buffalo or rhino horns, deer antlers, testicles and penises of dogs, bear or snake bile, frogs, bees, toads, geckos and earthworms. They may be combined with medicinal herbs (Dharmananda, 1996).

In **India**, some 2,500 plants are used in traditional medicinal (Kala *et al*., 2006; Anyinam, 1995). Minerals - including sulphur, arsenic, lead, copper sulphate and gold – are also used. Between 15 and 20 percent of Ayurvedic medicine is based on animal-derived substances (Unnikrishnan, 1998). In various parts of India, approximately 270 medicines are produced from 109 animal species, using products such as milk, bones and gallstones. The largest number of animal products (50 from 42 species) has been reported for the treatment of respiratory problems, followed by those for treatment of rheumatic and other pain (34 products from 32 species) and gastric problems (26 products from 22 species). Products from mammals predominate (44 species), followed by birds (18), reptiles (12), fish (9), amphibians (2) and invertebrates (24 species). Seventy-six of sourced species are included in the IUCN red data list and 36 in the CITES lists (appendices I, II, and III[41]) (Mahawar and Jaroli, 2008).

In **Pakistan**, thirty-one animal-based compounds comprise 9% of all listed compounds in traditional medicinal (Sam and Mahdihassan, 1984).

Gollin (1997) reports on the traditional medicine system of the Kenyah Dayaks of **Borneo**, who use 200 species of plants and 6 species of animals in the preparation of medicines and poisons.

Animal-based remedies constitute an integral part of **Brazilian** traditional medicine. Products from at least 250 animal species (178 vertebrates and 72 invertebrates) are used as remedies in traditional medicine in the North-East of Brazil (Alvez, 2009). The species represent 10 taxonomic orders and 141 families. The largest groups are fishes (58), mammals (47) and reptiles (37). The most widely treated conditions are asthma, rheumatism and sore throats. Many animal-based medicines are used for the treatment of multiple ailments in humans and also in veterinary medicine.

[41] The traditional medicine trade has been disastrous for many species of wildlife. Even highly endangered species continue to be exploited to supply this large market, the most difficult in the world to control. Even threats of international sanctions, strict national laws and the listing of most of the species involved in CITES Appendix I have not stopped it. In many cases, enforcement is impossible because products of endangered animals are sold in forms difficult to detect by customs' officials, e.g. powder made from ground bones. According to Nilsson (2005), the majority of potions sold in this trade have substitutes from non-animal sources, and many of these natural products do not cure the diseases they claim to.

Barrett (1995) found 154 plant species used medicinally in the city of Bluefields and surrounding countryside in **Nicaragua.** Widening the field of survey brought the total to more than 200 medicinal plants.

Laird and Wynberg (1997) report 3000 species of higher plants used as medicines in **South Africa**, of which 300 are in common use (Colfer *et al*., 2006).

Traditional medicine is mainly based on compounds extracted from immobile organisms, in particular plants, due to the easy access to the organism and to the possibility to re-find it in the same place. Moreover, these organisms produce the most active compounds because chemical molecules mediate their relationships with the external environment (i.e. defence from a predator): these are effective already at very low concentrations and in some cases they are toxic at higher doses. There are only a few examples of mobile organisms used in traditional medicine, coming mainly from the Chinese medicine. Among them there are for example hooded pithoui from the bird *Pitohui dichrous* and the gall bladder from the Asian bear (Cox, 2009).

4.3.2 The use of natural products in modern medicine

According to Berdy (2005), more than one million natural compounds have been discovered so far. Among them, 50-60% are produced by plants (alkaloids, flavonoids, terpenoids, steroids and carbohydrates) and 5% are of microbial origin. Of all reported natural products, 20-25% show pharmaceutical activity (Demain and Sanchez, 2009). Practically, all the ecosystems on the Earth have been explored for pharmaceutical purposes.

- *Terrestrial sources*

Interest in investigating **natural plant materia**l as a source of drugs waned in the late 1970's and early 1980's with advances in molecular biology, genetic engineering and computational chemistry. The development and use of robotics in the 1990's – which enabled high-throughput random screening of large numbers of samples - coupled with the continual need to discover new drugs, gave renewed interest to the chemistry and pharmacology of natural plant material (Baum, 1996; Borman, 1996).

Despite the relatively small number of species so far exploited as compared to existing biodiversity, drugs derived from plants are very important in terms of numbers of patients treated. Patwardhan (2009) reports that 25% of all prescriptions dispensed from community pharmacies in the USA between 1959 and 1973 contained one or more herbal ingredients. Grifo and Rosenthal (1997) state that 57% of all prescriptions in the USA in 1993 included at least one major active natural compound (or synthetic compound patterned after a natural substance).

According to Lange (2004), "*the goals of using plants as sources of therapeutic agents are:*

a) to isolate bioactive compounds for direct use as drugs, e.g., digoxin, digitoxin, morphine, reserpine, taxol, vinblastine, vincristine;

b) to produce bioactive compounds of novel or known structures as lead compounds for semisynthesis to produce patentable entities of higher activity and/or lower toxicity;

c) to use agents as pharmacologic tools, e.g., lysergic acid diethylamide, mescaline, yohimbine;

d) *to use the whole plant or part of it as a herbal remedy".*

Animal products have also been methodically tested by pharmaceutical companies as sources of drugs (Kunin and Lawton, 1996) and there are a significant number of drugs from animal sources. Of the 252 essential chemicals that have been selected by the World Health Organization, 8.7% are derived from animals (compared to 11.1% from plants) (Marques, 1997). Of the 150 prescription drugs used in the USA, 27 are of animal origin (WRI, 2000).

Drugs are also produced naturally from **micro-organisms** (Cragg and Newman, 2002; Hallock and Cragg, 2003). They are favoured for their biochemical diversity and are found not only in areas with high species diversity, but also in extreme environments or ecological niches (Lange, 2004). Of the 22,500 biologically active compounds so far obtained from micro-organisms, 45 percent are produced by actinomycetes, 38 percent by fungi and 17 percent by unicellular bacteria (Berdy, 2005; Sivaramkrishna and Mahajan, 2009). Examples are antibiotics such as streptomycin from the soil bacteria of the genus *Streptomyces* spp. and penicillin from the fungus *Penicillium* spp.. Several of today's most promising candidate drugs against cancer - such as ecteinascidin, halichondrin, bryostatin and the epothiolones - are synthetically modified products of micro-organisms (Cragg and Newman, 2002; Hallock and Cragg, 2003).

- *Marine sources*

Most current medicines come from terrestrial organisms. However, their effectiveness is decreasing as bacteria and viruses become more resistant to them. The last 10 years have seen a surge of interest in **marine organisms**. Although marine life chemistry is new to natural product chemists, already approximately 20 marine natural products are undergoing clinical trial.

Considering that 34 of the 36 phyla of the planet's biodiversity is found in oceans (compared to only 17 on land), it is likely that most future medicines will come from marine organisms which live in extremely hostile environments and in a perpetual state of 'chemical warfare', producing potent toxins and a number of novel compounds that work in a similar way to existing anti-cancer agents (Laird *et al.*, 2006), such as bacteria found on *Bugula neritina*, a bryozoan. Research into the ecology of marine natural products has shown that many of the compounds function as chemical weapons and have evolved into highly potent inhibitors of physiological processes of the prey, predators or competitors of the marine organisms that use them. Organisms already tested belong to all of the marine phyla : examples are cone snails (*Conus* sp.), sponges (e.g. *Verongia aerophoba*), corals (e.g. *Sarcodictyon roseum*) ascidians/tunicates (e.g. *Didemnum cuculiferum, Polysyncraton lithostrotum, Aplidium albicans*), bryozoans (e.g. *Bugula neritina*), the sea slug *Elysia rufescens* and its green algal diet *Bryopsis* sp., dogfish shark (*Squalus acanthias*) (Haefner, 2003).

- *Natural compounds in the pharmaceutical industry*

Over 50% of modern drugs include bioactive[42] compounds extracted from plants and animals, or synthetic imitations of these drugs (Grifo *et al*., 1997). They include antibiotics, anti-inflammatory drugs, painkillers, drugs for treatments of ovarian cancer, breast cancer, leukemia and malaria and nutritional supplements (Alonso *et al*., 2004). Almost every type of drug has a structure derived from a natural compound (Grifo *et al*., 1997).

A recent study shows that over 66% of the new chemical entities (excluding vaccines) brought onto the market between 1981 and 2006 have their origins in nature. Newman and Cragg (2007) classify new chemical entities according to figure 4.2.

[42] Bioactive refers to a substance which has an effect on or causes a response from living tissue.

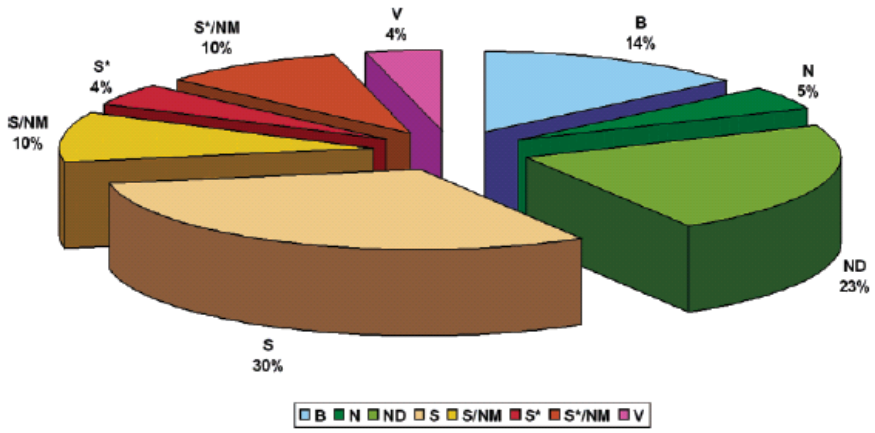


Figure 4.2. Classification by source of the 1,184 new chemical entities approved between 1981 and 2006. Source: Newman and Cragg, 2007.
B = Biological; N = Natural product; ND = Derived from a natural product (usually a semi-synthetic modification); S = Totally synthetic drug, often found by random screening, modification of an existing agent; S* = Made by total synthesis, but with pharmacophore[43] from a natural product; V = Vaccine; NM = Natural product mimic.

For drugs used in the treatment of cancer, the authors show that of the 155 new small molecules used since the 1940s, only 27% are synthetic (class "S") and as many as 47% are either natural products or directly derived from them. The influence of natural product structures is also quite marked for groups of drugs for other uses, particularly for drugs against infections. A significant number of these drugs are produced by microbes or microbial interactions between a host and microbe. The authors consider that this area of natural product research should be expanded significantly (Newman and Cragg, 2007 and 2003; Cragg *et al*., 1997).

The importance of natural products for modern medicine emerges clearly using the three criteria of assessment defined by Chin *et al*. (2006):

1) the rate of introduction of new compounds with wide structural diversity, including their use as templates for synthesis;
2) the number of diseases treated or prevented by these substances;
3) their frequency of use in the treatment of diseases, measured by the a) number and/or b) economic value of prescriptions, from which the extent of preference and/or effectiveness of drugs can be estimated indirectly.

The recent study of Newmann and Cragg (2007) satisfies the first criterion, showing that a large portion of the new pharmaceutical entities is nature-derived (see above).

Regarding the treatment of diseases, Newmann and Cragg (2003) found that 87% of all human diseases were treated by natural or nature drugs between 1981 and 2002. These include antibacterial, anticancer, anticoagulant, anti-parasitic and immunosuppressant drugs.

Elements relevant to the third point emerge, for instance, from:
a. a study by Grifo and colleagues (1997), according to which 84 (27 from animals, 34 from plants, 17 fungus, 6 microbes and 2 from marine organisms) of a representative 150 prescription drugs in the United States fell into the category of natural products and

[43] Pharmacophore is a molecular framework that carries the essential features responsible for a drug's biological activity.

related drugs. They were prescribed predominantly as anti-allergy/pulmonary/respiratory agents, analgesics, cardiovascular drugs, and for infectious diseases. And

b. another study of Butler (2004), who found that natural products or related substances accounted for 40%, 24%, and 26% of the top 35 worldwide ethical drug sales in 2000, 2001, and 2002 respectively. Of these natural product-based drugs, paclitaxel (ranked as number 25 in sales), a plant-derived anticancer drug, had sales of US$ 1.6 billion in 2000. Sales of plant-derived cancer chemotherapeutic drugs were responsible for approximately one third of total anticancer drug sales worldwide in 2002, valued at just under US$ 3 billion dollars. They include the taxanes (paclitaxel and docetaxel), and the camptothecin derivatives (irinotecan and topotecan) (Thayer, 2003; Oberlies and Kroll, 2004).

4.4 The potential importance of undiscovered species for medicines

Biodiversity reduction has direct effects on the potential development of new medicines through the reduction in supply of raw materials for drug discovery and biotechnology and drug templates (Alvez and Rosa, 2007; Chivian, 2002). Despite progress in technology it is still not possible to synthesize all natural molecular structures (Cox, 2009). Scientists estimate that biodiversity loss reduces potential new medicines by three each year (Center for Biodiversity Conservation, 2004). The transformation of ecosystems through human economic activities and consequent threat to many plant and animal species poses problems for the future of traditional and modern medicine.

For instance, forest degradation in the Brazilian Amazon basin since the 1980s has diminished the availability of some widely used medicinal plant species (Shanley and Luz, 2003). Considering that medicinal products collected from forests are often the only remedies available to people in the developing world (Elisabetsky and Wannamacher, 1993), degradation of forests may mean not only a loss of potential drugs for the developed world but also the erosion of the sole health care option for many in the developing world (Shanley and Luz, 2003).

There are an estimated 250,000 (and possibly as many as 500,000) species of **higher plants** (angiosperms and gymnosperms) on the planet. Only about 6% have been screened for bioactive compounds, and a reported 15% have been evaluated phytochemically (Fabricant and Farnswort, 2001). Many forest plants which may possess many more useful compounds remain unscreened (Colfer *et al*., 2006).

Estimates of **fungal species** vary from 65,000 to 250,000 species, with some even up to 10 million species). Only a small proportion have been cultured in the laboratory. Considering their large number, the potential use of fungal species in drug development is extremely important (Demain and Zhang, 2007).

Micro-organisms show the highest level of biodiversity of all species. It is estimated that less than 1% of all microbial flora has been investigated to date, and that this is an overestimate, since micro-organisms have barely been studied in most environments. The diversity of micro-organisms is substantial: in one cubic centimetre of soil more than 1,000 different species are found, although less than 5% of these can be cultured using current techniques. Surface water of oceans contains an average 500,000 micro-organisms per millilitre and 10 to 100 times greater numbers have been reported in deep oceans (Chivian, 2002 and Chivian and Bernstein, 2008). Many of their products can be marketed without any chemical modifications, evidence of the remarkable ability of micro-organisms to produce small molecules required for drugs (Farnet and Zazopoulos, 2007). It is estimated that more

than 500 bioactive compounds products in micro-organisms were discovered annually up to 1997 (Demain and Zhang, 2007). These data emphasize the importance of the potential from micro-organisms for drugs in medicine.

Marine life provides an exceptional reservoir of bioactive compounds, many of which show structural and chemical features not found in terrestrial life (Carté, 1996). The sea is indeed far richer in biodiversity than land and would have been the better place to start to look for developing natural pharmaceutical products (Kijjoa and Sawangwong, 2004). Up to 1995 researchers had identified approximately 7,000 marine natural products, 25% of which from algae, 33% from sponges, 18% from coelenterates (sea whips, sea fans and soft corals), and 24% from species of other invertebrate phyla. The latter include ascidians or tunicates, opisthobranch molluscs (such as nudibranchs and sea hares), echinoderms (such as starfish and sea cucumbers) and bryozoans (animal mosses). Drugs derived from marine organisms are increasing at roughly 10 per cent annually. Researchers are concentrating their efforts on phyla that depend on a chemical defence mechanism (Faulkner, 1995). A decline in marine biodiversity could lead to loss of species containing potential wonder drugs (Hilchey, 2003).

Marine cone snails are an example of a rich and unique source of basic compounds for drug production. The venoms they produce contain a cocktail of up to 100 different toxins, considered excellent candidates for drugs for the treatment of neurological diseases. With over 500 living species of cone snail, each having up to 100 toxins, there are possibly more than 50,000 new molecules available for with drug development. Furthermore, turrid snails, relatives of the cone snails, possess similar venoms, but are much more numerous (over 10,000 known species). This could mean a million compounds with potential pharmacological value (Bassler and Olivera, 2009).

Although covering only 6% of the land area of the earth, **tropical rainforests** contain at least half of the world's species. While 25% of modern drugs are derived from tropical rainforest species, less than 5% have been studied for their pharmaceutical potential. There is a high possibility of more drug discovery, but also a great loss of potential if rainforests continue to be felled around the globe, their biodiversity reduced and species yet to be studied lost (McDonald, 2009).

A single tropical forest plant species can contain over 1,000 different chemical compounds. The explanation is that they have had to survive intense competition for nutrients and light and have also had to develop an extraordinary array of defences, most of them chemical, to protect themselves from viral diseases, fungal pathogens, insects and other animal predators. The combination of the high biodiversity of the environment and rich chemical diversity of individual plants means that tropical forest plants are perhaps the most valuable source of new bioactive compounds (Rainforest facts, 2009). Mendelson and Balick (1995) estimate that higher plants in the world's tropical forests contain about 375 potential drugs of which only 48 have already been discovered. Adding the pool of biodiversity of animals and micro-organisms increases significantly the importance of tropical forests for medicine. Some scientists have predicted that unless significant measures are taken worldwide, ten percent of tropical forests will be left intact by 2030, and a further ten percent in a degraded condition (Nielsen, 2006; Wilson, 2002). Hundreds of thousands of species could be lost definitively, together many possible cures for life-threatening diseases (Wilson, 2002).

4.4.1 Prospecting biodiversity for new drugs

Biodiversity prospecting or '**bioprospecting**' is the search for living organisms that can be used in commercially, including that as drugs for medicine. It can be carried out randomly, through the screening of all living organisms in a specific area, or in a focused manner, through the study of local traditional medicine.

Ethnopharmacology is a multi-disciplinary approach to drug discovery involving the observation, description, and experimental investigation of indigenous drugs and their biological activity. It involves botany, chemistry, biochemistry, pharmacology, anthropology, archaeology, history, and linguistics. According to the literature, Ethnopharmacology can contribute more than random screening to increase our knowledge of the enormous potential of natural products (Fabricant and Farnsworth, 2001).

The **Convention on Biological Diversity**, signed by more than 150 nations at the Earth Summit in June 1992, affirms States' sovereign rights over their own biological resources and encourages the equitable sharing of the benefits arising from the utilization of genetic resources. The Convention provides a broad framework for the manner in which bioprospecting activities should take place. In particular, it highlights how the conservation of biological diversity depends not only on the sustainable use of those resources but also on the equitable sharing of benefits which result from that use. Unless the benefits generated are equitably shared among the different stakeholders, source countries will find little incentive to conserve their biological diversity (Guérin-McManus *et al*., 1998).

In connection with CBD about 100 countries have introduced or are developing appropriate national legislation and other policy measures on bioprospecting. National legislation is also being drafted to cover issues of access and benefit sharing relating to the use of genetic resources that originate outside the country in question. The Norwegian government, for example, is proposing such legislation to cover the use in Norway of genetic material originating elsewhere.

Complementing developments on national and international policy, a range of codes of ethics, research agreements, statements and declarations, and corporate and institutional policies have been developed by indigenous peoples, researchers, professional associations, and companies, marking a significant shift in the ethical context for bioprospecting partnerships.

Benefit sharing and the creation of partnership within diverse bioprospecting industries can however be both complex and time consuming. The protection of the rights of indigenous communities and source contries has often created tensions, with the investment sector concerned with altered levels of return and profitability.

The CBD, that until now has left parties a great deal of discretion, is now engaged in providing further clarifications through the definition of legally binding rules addressing issues such as access, benefit sharing, and traditional knowledge. A meeting of the CBD held in Cali, Colombia, in March 2010, produced a draft protocol on new international rules on access and benefit sharing (ABS) to be proposed for adoption October 2010.

4.5 The existing and future value of medicines derived from nature

Environmental economists assign several types of values to ecosystem services. The principal types are:

Use values

- **direct use value** attributed to direct utilisation of ecosystem services (such as harvesting of medicinal products);
- **indirect use value** derived from regulation services provided by ecosystems (such as regulation of air or water quality, or regulation of infectious diseases);
- **option value** attributed to preserving the possibility to use ecosystem services in the future, i.e. the willingness to pay to conserve the option of making use of biodiversity for which no current use is made (Pearce, 2001).

Non-use values

- **Existence** reflects the value attached by individuals to simply knowing that biodiversity continues to exist.
- **Bequest value** refers to the value attached to the fact that biodiversity or certain ecosystem services will be preserved for future generations.

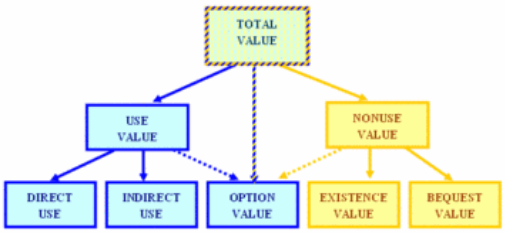


Figure 4.3. Components of the Total Economic Value applied to ecosystem services.

Regarding medicines, existing literature shows that economic evaluation of natural genetic material as source of medicines can be made through the estimation of the use values, and in particular of the direct use and option values. Option values are critically dependent upon future research and use of raw materials in the medical drugs sector (Pearce and Puroshothaman, 1995).

Estimating the option value biodiversity for medicines in Europe

In a study on the economic value of Mediterranean forests, Croitoru and McGinley (2008) have estimated the option value of biodiversity for potential pharmaceutical products in Turkey, based on the rent capture technique[44]. They estimated the potential rent which might be generated, based on the number of species at risk, the number of drugs using plant species and the number of hectares likely to provide medicinal plants. The authors find an average value of € 6 per hectare, equivalent to 12% of the total economic value of the forests. This value is likely to be higher in areas of high biodiversity, such as protected areas, where more genetic resources are likely to be found (Merlo and Croitoru, 2005).

The main parameters taken into account in the estimations are listed below. The choice of each parameter can influence substantially the resulting economic value. There is ongoing debate amongst economists as to which parameters are the “most reliable”.

[44] The rent-capture approach estimates the option value as a function of the number of species at risk, the number of drugs based on plant species and the number of hectares likely to support medicinal plants.

- *Probability of success of pharmaceutical research*
  The development of a drug, from the initial collection of natural samples to the marketing of an approved product, takes between ten and twenty years.
  The probability of a species giving rise to a successful drug ranges considerably, from the most optimistic estimate of 1 in 1,000 to the most pessimistic of 1 in 40,000. A typical estimate is 1 in 10,000 (Costello and Ward, 2006)

- *The value of drugs*
  The valuation method for successful drugs is critical for the total estimate. The valuation based on life-saving properties gives the highest values, using the value of a 'statistical life' of US$ 4 million (Pearce *et al*., 1992). Market values of plant-based drugs give lower values, and actual traded prices of plant material give the lowest values of all. The price of drugs reflects, of course, much more than the cost of the plant genetic material.

- *Royalty rate*
  Royalty benefits are derived directly from the development of a drug. Estimations of the value of royalties take into consideration the type of patent claims granted, potential product sales, current level of development and potential costs of subsequent research and development, the marketing position of the pharmaceutical company, competition from related market products, and the contribution of ethnobotanical knowledge (Guérin-MacManus *et al*., 1998). According to Pearce and Puroshothaman (1992), existing royalties are in the range of 5-20% of the value of the drug to the drug company.

- *Potential revenue that could be generated from pharmaceutical prospecting of natural resources if a new drug is discovered.*
  The potential contribution of an unknown species to the development of a new drug can be interpreted as the value of preserving a particular species. The net return from the new drug is calculated as gross revenue less the costs of prospecting and development. The value of the species is estimated as the species success rate multiplied by the net return to biotic samples adjusted for the number of samples per species that are screened.

- *Number of species and redundancy*
  The number of species should include both known and undiscovered species. Redundancy or substitutability can occur between species, i.e. the same useful compound might be found in more than one species or compounds from different species might have the same curative properties. Redundancy may have implications for the value of conserving one additional untested species or additional unit of land. If there is already a high level of biodiversity then the marginal value of one extra species will be low and even zero, once a discovery is made.

Table 4.3. Example of an estimation carried out in the Knuckles Forest (Sri Lanka). Source Pushpakumara *et al*., 2002.

Basis of estimate	(1) Number of plants (Nr)	(2) Probability of success of research (p)	(3) Royalty (r)	(4) Rate of appropriation (a)	(5) Market value of plant based drugs (v/n) US $/yr	(6) Forest area (A) Ha.	(7) Potential revenue (Vmp(L)) Rs/ha/yr	(8) Potential revenue (Vmp(L)) US$/ha/yr	(9) PPR/AGR %
1. Global biodiversity : Pearce and Moran's upper bound value	60000	0.001	0.05	1	7.0	1000000000	1596	21	3.793858
2. Global biodiversity : Pearce and Moran's lower bound value	60000	0.0001	0.05	0.1	0.39	1000000000	0.8892	0.0117	0.002114
3. Knuckles : on average values of Pearce and Moran's p and V/n	85	0.0005	0.05	0.1	3.695	16000	3729.641	49.07422	8.865743
4. Knuckles : on Pearce and Moran's upper value of p	85	0.001	0.05	0.1	3.695	16000	7459.281	98.14844	17.73149
5. Knuckles p : based on patents on medicinal plants of Sri Lanka	85	0.008	0.05	0.1	3.695	16000	59674.25	785.1875	141.8519
6. Knuckles p : that break evens the revenue generated from agriculture (Rs 34800 /ha/yr)	85	0.006	0.05	0.1	3.695	16000	44755.69	588.8906	106.3889
7. Knuckles at maximum r of 15%	85	0.0005	0.15	0.1	3.695	16000	11188.92	147.2227	26.59723
8. Knuckles a : that break even the revenue generated from agriculture	85	0.0005	0.05	1	3.695	16000	37296.41	490.7422	88.65743

4.5.1 Value of nature for commercial drugs

Literature assessing the value of biodiversity as a source of new pharmaceutical products began to be published in the mid 1980s. A commonly used approach in estimating the gross value of wild genetic material is to draw on the pharmaceutical industry's previous experience with medicines derived from plants. This type of valuation assumes that the "pharmaceutical" value of biodiversity depends on the level of "willingness to pay (WTP)" price that "bioprospectors" would be willing to offer for a unit of habitat[45] (OECD, 2004). The "price" determined in such bioprospection markets depends on various demand and supply factors (Pearce *et al*., 2006):

- Current technological developments: the use of synthetic and combinatorial chemistry and biotechnology using human genes may reduce reliance on natural organisms whilst advances in genetics may have the opposite effect.
- Technological change is increasing the ability to further exploit existing collections of seeds, reducing the need for access to new genetic resources.
- Search processes are becoming very selective, favouring research areas with already existing information, so reducing the general demand for access to new areas.
- Growing demand for "natural" products requires direct access to genetic material.
- Legal and institutional difficulties in securing access deters bioprospectors.
- The supply of genetic material is so vast that, at best, bioprospectors can be expected to "demand" only a tiny fraction of what is available., Thus most natural areas (and biodiversity) will very unlikely benefit from bioprospecting.
- International patent law still discriminates against worldwide protection for natural materials.

[45] According to Pearce *et al*. (2006), the WTP for a specific genetic resource is a concept which is difficult to identify. For this reason, authors tend to translate this value in the WTP for land which is subject to the risk of conversion. Even though it is not always appropriate to express values in respect of land, nonetheless, expressing values in 'per hectare' terms has become the convention in this kind of analysis and it serves to focus on the underlying choice problem, namely which land use to choose among the available options (Pearce and Puroshothaman, 1992).

There are two distinct views about the economic value of genetic material with potential pharmaceutical use. The first argues that it is huge, and the second suggests that it is very modest, certainly when converted to value per unit of land area (Secretariat of the CBD, 2001).

Studies by Principe (1991) and Farnsworth and Soejarto (1985) suggest relatively high valuations. Estimates of low economic value are obtained by Aylward (1993), Simpson *et al*. (1994, 1996) and Simpson and Craft (1996). These estimates are based mostly on simulations of what drug companies are willing to pay for plant genetic material. Rausser and Small (1998a, 1998b, 2000) argue that methods used in studies arriving at only very small economic values for plant genetic material are flawed, and that when due allowance is made for the competitive structure of the pharmaceutical industry, resulting values are significant. However these arguments are controversial (OECD, 2001).

The results of both sets of studies are summarised in table 4.4. The reasons for the wide variation in estimates are ascribed to differences in methods, context and scope, as explained by OECD (2001):

- Many studies compute the total value of plant genetic material, i.e. they compute a total market value of a drug by multiplying the sale price of the drug by the quantity sold. Dividing total values by the number of drugs gives an average value per drug. However several authors have pointed out that averages are misleading and that it is the marginal value, i.e. the value attached to one extra unit of genetic material, that should be used (Simpson *et al*., 1994; Simpson and Craft, 1996).
- Some studies refer to the total market value of a drug to the plant material. This is legitimate if and only if there are no substitutes for that material, but Aylward *et al.* (1993) point out that this is not the case. Substitutes exist in the form of synthetic alternatives to plants and syntheses of drugs from plant material. The same applies to studies that attempt to allocate health benefits of drugs to the basic plant genetic material alone (Principe, 1991; Pearce and Puroshothaman, 1995).
- Most studies only consider the private value of the drugs derived from plant material, i.e. the value to drug companies or the value to the public through payments in the market place. A more relevant value, however, is the social value of the drugs, e.g. in terms of lives saved or illness avoided, less the costs of developing the drug. Principe (1991), Pearce and Puroshothaman (1995) and Simpson and Craft (1996) have attempted social valuations.
- Early studies rely on US prescription data was heavily influenced by the success of only a few drugs.
- Markedly different estimates of economic value arise when the competitive structure of the drugs industry is taken into account (Rausser and Small, 1998a and 1998b).
- Valuation procedures vary not only according to whether the value is ‘private’ (WTP of drug companies) or social (value of health benefits), but also according to the focus of the valuation. In the early studies the focus was on the value of the drug. In a study by Ruitenbeek (1989), the focus is on the value of the research discovery, represented by the renewal fee for patenting the resulting compound. Aylward *et al.* (1993) note that patent renewal fees impart a downward bias to estimates since they are small relative to other costs of research and development. Pearce and Puroshothaman (1995) and Reid *et al*. (1993) adopted a royalty approach, i.e. looking at what a ‘prospecting’ company would pay to a host country for the rights to prospect for plant genetic material.

Table 4.4. Estimates of the medicinal value of plants, at 2001 US dollar values (for reasons stated in the comments, the figures from different studies are not comparable). Elaboration from Gundimeda *et al*., 2006.

Study	Value	Comment
Farnsworth and Soejarto (1985)	US$ 2.6 million per year per single untested plant species, USA	40 successful plants out of 5,000 tested entails 1 success per 125 tested plants. Total value of plant based drugs (US$ 298 million) divided by 125 gives value of untested species. Average value.
Principe (1991)	US$ 0.5 million per year per untested plant species, OECD wide	Based on Farnsworth and Soejarto but with modified probability of success in deriving a drug from a plant test. OECD total value of US$ 600 million (1980 US$) x 1 in 2000 probability of success = US$ 300,000 per untested drug = US$ 510,000 per untested drug 1998 prices. Average value.
McAllister (1991)	US$ 10,355 per untested tree species, Canada, per annum	3 in 100 Canadian trees estimated to have marketable medicinal properties. Value of untested species = annual global value of a drug = US$ 250,000 x 0.03 = US$ 7500 in 1990 prices. Average value (low value due to low assumed value of successful drug)
Principe (1991)	US$ 31 million per untested species, OECD, per annum	US$ 37.5 bn annual value per successful species divided by 1 in 2000 probability of success = US$ 18.8 billion per untested species, or US$ 28.4 billion in 1998 prices. Value based on value of statistical life saved of US$ 8 million (1984 prices).
Ruitenbeek (1989)	US$ 207 per untested species per annum	Assumed 10 research discoveries in Cameroonian rainforest each with patent value of US$ 7,500 pa. Divided by 500 species = US$ 150 or US$ 190 in 1998 prices. Use of patent values as measure of value.
Pearce and Puroshothaman (1995)	US$ 810 to US$ 1.45 million per untested species, OECD, per annum.	Uses Principe and Farnsworth data. Lower value is private value and upper is social value based on VOSL of US$ 7 million.
Reid *et al*. (1993)	US$ 4 to US$ 5,014 per untested species per annum, hypothetical deal (annuities at 5% over 20 years)	Royalty of 3% assumed, 1 in 10 000 success rate.
Artuso (1997)	Present value of US$ 944 per sample extract in terms of private WTP; US$ 10,790 per extract in social terms	Detailed analysis of cash flows associated with sampling 25,000 extracts. Average value
Mendelsohn and Balick (1995)	Net revenue to drug companies = US$ 3.0 to 4.5 billion from rights of access to all tropical forests. Around US$ 1 per hectare.	Average value based on likely discoveries and their market value.
Simpson *et al*. (1994, 1996)	WTP of US$ 0.02 to US$ 2.5 per hectare of 'hotspot' land.	See Pearce *et al*. (1999)
Simpson and Craft (1996)	WTP of US$ 31.6 to US$ 3,148 per hectare of hotspot' land.	See Pearce *et al*. (1999)
Rausser and Small (1998a)	WTP of US$ 0 to US$ 10,000 per hectare of 'hotspot' land.	See Pearce *et al*. (1999)

4.5.2 Value of biodiversity for traditional medicine

According to Colfer *et al.* (2006), the economic value of traditional medicines is considerable but difficult to estimate. Evaluation methods include estimates of the value of plants in international and local markets.

Estimates carried out in the United States using the first method show that about $ 75 billion worth of pharmaceuticals of natural origin are sold each year (Kaimowitz, 2005) and that annual reported imports of medicinal and aromatic plants for pharmaceutical use averaged over US$ one billion annually during the 1990s (Rao *et al*., 2004).

Herbal treatments are highly lucrative in the international marketplace. Annual revenues in Western Europe reached US$ 5 billion in 2003 and 2004, while in Brazil they amounted to US$ 160 million in 2007 (WHO, 2008). In China, the production of traditional plant remedies is worth about US$ 571 million annually (Akerele, 1991) and sales of products totalled US$ 14 billion in 2005 (WHO, 2008).

In many parts of the world expenditure on traditional and complementary medicine is significant and growing rapidly. In Malaysia, an estimated US$ 500 million is spent annually on this type of health care, compared to about US$ 300 million on modern medicine. In the USA, total over the counter (non-prescription) CAM expenditure was estimated at US$ 2,700 million. In Australia, Canada and the United Kingdom, annual CAM expenditure is estimated at US$ 80 million, US$ 2,400 million and US$ 2,300 million respectively (Foster *et al*., 2000; WHO, 2002).

Balick and Mendelsohn (1992) have tried to value native medicinal plants collected by local people from a forest in Belize. They estimated a net return of $ 726 per hectare for 30-year rotation and $ 3,327 for 50-year rotation forests.

Traditional and complementary medicine in Europe (De Smet, 2005; Cortes-Maramba, 2009).

Prescribed herbal medicines

Germany (2003):
US$ 283 million in reimbursements for prescribed ginkgo, St. John's wort, mistletoe, saw palmetto, ivy, hawthorn, stinging nettle root, mystol, phytosterolsand cucurbita

France (2002):
Health insurance schemes paid $ 91 million in partial reimbursements for ginkgo, saw palmetto, and pygewen prescriptions with a total value of $ 196 million.

Sales of over-the-counter (non-prescription) herbal medicines (2003)

Total: US$ 4.960 million European Market, of which:

Germany:	$ 2.060 million	Belgium:	$ 127 million
France:	$ 1.130 million	Switzerland:	$ 93 million
Italy:	$ 543 million	Austria:	$ 88 million
Poland:	$ 252 million	The Netherlands:	$ 81 million
United Kingdom:	$ 211 million	Czech Republic:	$ 76 million
Spain:	$ 170 million		

The remaining $ 132 million sales were divided among Portugal, Hungary, Ireland, Slovakia, Finland and Norway

CONCLUSIONS

The links between biodiversity, ecosystem functioning and the spread of infectious diseases are complex and knowledge is still fragmentary. However, there are indications that the current decline in biodiversity and the widespread changes in ecosystems may generate increased risks of spread of several major human diseases. Maintaining biodiversity could also allow us to continue to obtain and develop medicines from natural products.

At present, a number human vector-borne diseases are returning to areas where they had been previously eradicated, and are on the increase in endemic areas as well as emerging in new countries. The serious health and economic impact of infectious diseases is expected to continue and even increase in the near future.

Better understanding of the links between changes in biodiversity, epidemiology of infectious diseases and availability of natural resources for medicines would be necessary for administrators to make informed decisions regarding the management of biodiversity concerning human health risks and to reduce the incidence of infectious diseases in humans.

Human infectious diseases

Infectious diseases prevention and treatment and biodiversity conservation decisions are generally considered separately, despite the links.
Although several studies indicate that changes in biodiversity affect the rate of transmission of infectious diseases to humans, the connections between infectious diseases and biodiversity are poorly understood and have only been partially studied and documented. Part of the reason is that the relation between the relevant components within ecosystems is still unclear. For example, the consequences of changes in a host or vector to the spread of an infectious disease are often still unknown. This shortfall in information makes estimates of future incidence of infectious diseases due to changes in biodiversity very difficult.

A health care strategy for a vector-borne disease must take into account its biology and ecology, the possible range of adverse effects, the risks and the costs and benefits of protective actions, in decision making.
Data connecting the socio-economic impact of changes in biodiversity and ecosystem services on human infectious diseases are very scarce. They are also difficult to compare, since they measure disease burden in different ways. Moreover, studies are generally at local level and do not allow comparison of results between developing and developed countries. As a consequence, it is still not possible to put a value on the loss of an infectious disease regulation “service” provided by an ecosystem.
However, studies analysing the relation between infectious diseases and incomes do propose public actions to combat infectious diseases which take into account development of immunity, disease ecology, changes in ecosystems and management of diseases.

Since the publication of the Millennium Ecosystem Assessment in 2005, there has been an increasing attention to the links between biodiversity and transmission of infectious diseases.
In recent years, and in particular during 2009, there have been numerous studies on the link between biodiversity changes and the spread of infectious diseases, an indication that this is becoming a “hot” topic of research.

Further interdisciplinary research (combining ecology, biology, epidemiology, pharmacology, medicine, social sciences and economics) is needed in order to better understand:

- the role of biodiversity in the emergence, spread and transmission of infectious diseases;
- the relations between man-made changes in ecosystems, biodiversity and transmission of infectious diseases to humans, including their economic impact;
- the value of biodiversity in protecting against infectious diseases.

Development of an integrated approach requires agreement on common terms and definitions.

The main topics to be investigated should include:

Ecosystem service	***Research topic***
REGULATION OF INFECTIOUS DISEASES	• Characterization of the factors that contribute to biodiversity change;
	• Identification of the mechanisms which enable ecosystems to regulate the spread of infectious diseases;
	• Epidemiological study of disease life cycles, including biological features of pathogens, vectors and hosts, their population dynamics and species interactions;
	• Evaluation of environmental factors affecting host and vector populations, including effects of human activities;
	• Identification of the biological mechanisms of disease transmission to humans and the processes of infection and spread of infectious diseases;
	• Identification of factors linking human stressors, changes in biodiversity and disease transmission;
	• Monitoring of vector populations in space and time, and how they are affected locally by human activities;
	• Risk analysis of intentional and accidental introduction of non-indigenous species and species mixing related to epidemiology;
	• Development of tools to forecast risks and spread of diseases;
	• Development of models to map biodiversity change and emerging infectious diseases in order to predict disease occurrence;
	• Development of environment-based strategies against emergence of infectious diseases;
	• Identification of data necessary for the economic evaluation of biodiversity as it relates to infectious diseases;
	• Identification of human behaviours affecting biodiversity and health and of the strategies promoting human behaviours to protect the environment and human health;
	• Estimation of the values of changes in relevant health and ecological endpoints.

Medicines

Biodiversity provides an essential source of medicines, and will continue to do so in the future. With the development of new techniques in combinatorial chemistry (the rapid synthesis of drugs using large numbers of different but structurally related molecules) and chemical modification in the development of new drugs, one would expect a decline in the interest in natural products as a chemical source for medicines.

However, the same techniques also facilitate the screening of natural products and consequently revive the search for basic chemical material in organisms which have never been used in traditional medicine. Thus, maintenance of biodiversity will be important in preserving a source of raw material for new drugs. Of particular interest are marine ecosystems and microorganisms.
Although there is no doubt as to the current reliance of traditional and modern medicines on biodiversity, only recently have scientists and economists combined forces to quantify biodiversity as a provider of medicines.

Further research is needed to evaluate biodiversity as a source of natural products for health care.

Investigation should include (Biodiversity and Health Symposium, 2006):

Ecosystem service	***Research topic***
PROVISION OF MEDICINES	• Methodologies to better integrate and quantify drug discovery, biodiversity and conservation;
	• Socio-economic assessments of volumes and values of harvested medicinal plants for optimizing opportunities in market supply and demand;
	• Identification of threatened ecosystems, habitats and species of interest for medicines (especially in dry and semi-arid regions);
	• Evaluation of the potential social and biological impact of marketing and trade (local, regional, and international) on the resource-base and people's livelihoods;
	• Identification of appropriate mechanisms to improve and ensure equity in access to, and benefit from, medicinal plant resources;
	• Identification of key considerations in/for integrating traditional medicine and use of medicinal plants in public health care sector;
	• Identification of mechanisms to resolve potential conflicts between local level access and benefit sharing priorities and national/international interests;
	• Analysis of challenges for policy development, policy harmonization and implementation;
	• Identification of opportunities for processing, quality development and marketing of medicinal plant materials by local communities.

ABBREVIATIONS AND ACRONYMS

ACL	American cutaneous leishmaniasis
APG-Cubed	The Asian Pacific G-Cubed (Global General Equilibrium Growth Model)
CAM	Complementary Medicine
CAR	Clinical attack rate
CBD	Convention on Biological Diversity
CBD/COP9	Convention on Biological Diversity/The ninth meeting of the Conference of the Parties
CBO	Congressional Budget Office of United States of America
CDC	Centers for Disease Control and Prevention
CFR	Case Fatality Rate
CHIK	Chikungunya (genus Phlebovirus)
CHIKV	Chikungunya virus
COI	Cost of Illness
COMPACT	It is a micro-founded macroeconomic structural econometric model
DDT	Dichlorodiphenyltrichloroethane
DEN	Dengue
DG ECFIN	Directorate General for Economic and Financial Affairs
DHF	Dengue haemorrhagic fever
DNA	Deoxyribonucleic Acid
ECDC	European Centre for Disease Prevention and Control
EFPIA	European Federation of Pharmaceutical Industries and Association
FAO	Food and Agricultural Organization
GBD	Global Burden of Disease
GDP	Gross Domestic Product
H1N1	Swine flu

H5N1	Avian flu
HIV-2	Human Immunodeficiency Virus Type 2
HPAI	High pathogenic avian influenza
HPAIV	Highly pathogenic viruses form
IUCN	International Union for Conservation of Nature
LD	Lyme disease
LPAI	Low pathogenic avian influenza
LPAIV	Low pathogenic avian influenza virus
MDB	Mosquito-borne diseases
NIH	National Institutes of Health
OE	Oxford Economics
OECD	Organisation for Economic Co-operation and Development
SAR	Secondary attach rate
SARS	Severe Acute Respiratory Syndrome
STFAIWB	Scientific Task Force on Avian Influenza and Wild Birds
TBE	Tick-Borne Encephalitis
TEV	Total Economic Value
TM	Traditional Medicine
TBEV	Tick-Borne Encephalitis virus
UNFPA	United Nations Population Fund
VBD	Vector-Borne Diseases
WHO	World Health Organization
WHO/EURO	World Health Organization/Regional Office for Europe
WNV	West Nile virus
WTP	Willingness to pay
YE	Yellow fever

APPENDIX

Tables with costs of the relevant infectious diseases using different measures

MALARIA	
Authors	Chuma *et al.*
Year	2006
Country	KENYA
Focus	Relationship Malaria and Poverty (micro-level)
Measure	Cost of Illness (COI)
Results	Mean direct cost burdens were 7.1% and 5.9% of total household expenditure in the wet and dry seasons respectively
Authors	Cropper *et al.*
Year	2000
Country	TIGRAY, ETHIOPIA
Focus	Monetary Value of Preventing Malaria
Measure	Willingness To Pay (WTP)
Results	The value of preventing malaria with vaccines is about US$ 36 per household per year (15% of imputed annual household income). The vaccine demand is price inelastic.
Authors	Asante *et al.*
Year	2004
Country	GHANA
Focus	Economic Burden of Malaria at Macro and Micro Levels
Measures	Cost of Illness (COI) and Willingness To Pay (WTP)
Results	The estimation of the production function revealed a negative correlation of 0.367 between economic growth and malaria incidence, with a coefficient of –0.41. A single episode of malaria costs the household US$ 15.79.
Authors	Sachs and Brundtland
Year	2002
Country	CROSS-COUNTRY
Focus	Relationship Malaria and Economic Growth
Measure	Purchasing-Power Parity GDP
Results	The average 1995 Purchasing-Power Parity GDP in malarial countries was US$ 1,526 compared with US$ 8,268 in countries without intensive malaria. Malarial countries are not only poorer than non-malarial countries; they also appear to have lower rates of economic growth.
Authors	Gallup and Sachs
Year	2000
Country	CROSS-COUNTRY
Focus	Relationship Malaria and Economic Growth
Measure	Cost of Illness (COI)
Results	Countries with intensive malaria grew 1.3% less per person per year, and a 10% reduction in malaria was associated with 0.3% higher growth (regression for both the 1965–1990 and the 1980–1996 period)
Authors	McCarthy *et al.*
Year	2000
Country	CROSS-COUNTRY
Focus	Relationship Malaria and Economic Growth
Measure	Cost-Benefit Analysis (CBA)
Results	The estimated growth reduction due to malaria exceeds 0.25% per year for about a quarter of the sample. In Sub-Saharan Africa the estimated average annual growth reduction is 0.5%.
Authors	Mills and Shillcutt

MALARIA	
Year	2004
Country	CROSS-COUNTRY
Focus	Reduction in Malaria Burden
Measures	Cost-Effectiveness Ratio (CER)
Results	Calculation of the BCR by comparing the gain in national income to the costs of high levels of coverage of a package of malaria control measures: BCRs of 4.7 and 1.9 indicate the malaria control as an efficient investment.
Authors	Bleakley
Year	2009
Country	Southern US, Brazil, Columbia, and Mexico
Focus	Impact of Eradication Campaigns
Measure	Cost-Benefit Analysis (CBA)
Results	Cohorts born after eradication campaigns had a higher income (and literacy) as adults than the preceding generation. In the US states with the highest levels of malaria, cohorts born after the anti-malaria campaign earned 15% more than the previous generation. In Latin America cross-cohort changes in income are about 27%-35% higher in areas with more malaria before the DDT campaign.

YELLOW FEVER	
Authors	Monath and Nasidi
Year	1993
Country	NIGERIA
Focus	Preventive Yellow Fever Vaccination
Measure	Cost-Effectiveness Ratio (CER)
Results	The cost of adding yellow fever vaccine to the existing EPI was estimated as +0.65 per fully immunized child, whereas the cost of emergency vaccination in the face of an epidemic was estimated as +7.84/person. In large epidemics, cost-effectiveness of the EPI exceeded that of emergency control.
Authors	Silva *et al.*
Year	2003
Country	TIGRAY, ETHIOPIA
Focus	Microeconomic Evaluation of the Costs
Measure	Cost Effectiveness
Results	The addition of yellow fever antigen brought down the campaign mean cost by 0.11 euro and it allowed economies of scales. Direct unit costs per administered dose were higher when people were vaccinated through the outreach strategy (0.35 euro) than when fixed and mobile strategies were used (0.318 and 0.323 euro, respectively). Costs related to transportation and staff were proportionally higher for the outreach strategy; direct unit costs per administered dose were higher when vaccinations were done in rural areas (0.32 euro) than when done in urban areas (0.31 euro). Direct unit costs increased when the size of target communities decreased.
Authors	Waters *et al.*
Year	2004
Country	CAMEROON
Focus	Quantification of the Cost of Childhood Immunization
Measure	Cost Effectiveness
Results	Costs per fully immunized child varied from US$ 2.19 to US$ 26.59 (not adjusted for inflation) in a range of low-income and middle-income countries.

DENGUE	
Authors	Suaya *et al.*
Year	2009
Country	BRAZIL, EL SALVADOR, GUATEMALA, PANAMA, VENEZUELA, AND CAMBODIA, MALAYSIA, AND THAILAND
Focus	Estimation of the Direct and Indirect costs
Measure	Cost of Illness (COI) in International Dollar (I$)
Results	Overall mean costs were I$ 514 and I$ 1,394 for an ambulatory and hospitalised case, respectively. The aggregate annual economic cost of dengue is at least I$ 587 million (Conservative estimation). Official reports underestimate the true number of cases and highlight the need for expansion factors to adjust for this underreporting: an overall expansion factor of 3 would suggest a cost of dengue illness in these eight countries averaging I$ 1.8 billion per year, but ranging from I$ 1.3 to I$ 2.3 billion; with expansion factors of 2 or 6, the eight-country costs would range from I$ 1.2 to I$ 3.6 billion.
Authors	Clark *et al.*
Year	2005
Country	THAILAND
Focus	Impact of symptomatic dengue fever infection on the families of patients hospitalised
Measure	Disability-Adjusted Life Year (DALY)
Results	The direct cost of hospitalisation, indirect costs due to loss of productivity, and the average number of persons infected per family induce a financial loss of US$61 per family, which is more than the average monthly income
Authors	Mavalankar *et al.*
Year	2009
Country	INDIA, MALAYSIA, THAILAND
Focus	Economic Impact
Measure	Cost of Illness (COI)
Results	For India there is an immediate COI of US$ 1.5 billion (range 0,6-3,5bn) that is US$1,6 per capita with respect to US$5,3 in Malaysia and US$ 6,2 in Panama. A severe outbreak could determine a 4% decline in tourism from non endemic countries, namely at least US$ 8 million for Gujarat (the focus Indian state with 56 million of inhabitants), US$ 65 million for Malaysia, and US$ 363 million for Thailand.
Authors	Torres and Castro
Year	2007
Country	Latin America
Focus	Direct and Indirect Cost and Effectiveness of Control Programme
Measure	Disability-Adjusted Life Year (DALY) and Cost-Effectiveness Ratio (CER)
Results	Total direct and indirect costs in Puerto Rico (1977) range from US$ 6.1 million to US$ 15.6 million; in Cuba (1981), US$103 million; in Nicaragua (1994) US$ 2.7 million. In Nicaragua, the cost of medical care accounted for 64% of the overall cost. The disease was found to cause the loss of an average of 658 DALYs per year per million inhabitants. The cost per DALY in Venezuela was comparatively low (US$ 122) as compared to other mosquito-borne diseases such as yellow fever (US$ 396), leishmaniasis (US$ 1,893), or malaria (US$ 1,915). The cost-benefit ratio of the dengue control programme was also positive: US$ 0.46 invested per dollar saved.
Authors	Lim *et al.*
Year	2009
Country	MALAYSIA
Focus	Economic Impact
Measure	Cost of Illness (COI)
Results	The immediate cost is in the range of US$ 88-215 million (mean US$ 133 million) per annum. Chikungunya is not yet a major problem and its estimated immediate cost is only an additional US$ 1.2 million. The impact on tourism is traditionally not included in cost of illness studies, it could reach an additional US$ 171 million if there were a major outbreak of dengue or chikungunya.

DENGUE	
Authors	Borja and Lorenzo
Year	2009
Country	PHILIPPINES
Focus	Economic Burden
Measure	Disability-Adjusted Life Year (DALY)
Results	Approximately 18,074 DALYs are lost per year (incidence of 21.96/100,000). The dengue morbidity cost per patient ,223) and estimated income loss of patients and watchers (Php 357) is Php 4,123 (US$ 85.36). The national morbidity cost is Php 447.6 million.

CHIKUNGUNYA FEVER	
Authors	Gopalan and Das
Year	2009
Country	ORISSA (INDIA)
Focus	Household economic impact
Measure	Cost Of Illness (COI)
Results	The median out-of-pocket health care expenditure was US$ 84, of which the proportion of cost of diagnosis was the highest (US$ 77). The median catastrophic health care expenditure was 37%; the median work days lost was 35 with a consequent loss of income of US$ 75 (the median work hours lost during the acute phase of illness was 29.1 with a consequent loss of median income of US$ 5.02, after the acute phase 21 days were lost); the median daily work hours before the illness were nine hours and it reduced to six hours due to illness. Chikungunya outbreak induces unforeseen catastrophic health care expenditure that reinforces the poverty-disease relationship
Authors	Seylor *et al.*
Year	2009
Country	ANDHRA PRADESH (INDIA)
Focus	Economic Burden and Direct and Indirect Costs
Measure	Disability-Adjusted Life Year (DALY)
Results	Each case led to an average burden of 0.027 DALYs. Overall the burden in Mallela village was 6.6 DALYs; the estimated burden in Kadapa district was 160 DALYs and 257,034 cases and 6,600 DALYs in the state of Andra Pradesh. The estimated total economic cost in Mallela village was US$9,100 (US$ 37.50 per case), higher in males than in females, and for patients over 15 years of age compared with others. The cost was also higher among adult females reporting a regular income (US$ 41.60 per case). The estimated total economic cost of the disease in district and state are respectively US$ 290,000 and US$ 12,400,000.

WEST NILE FEVER	
Authors	Zohrabian *et al.*
Year	2004, 2006
Country	LOUISIANA, UNITED STATES OF AMERICA
Focus	Economic impact and evaluation of a vaccination programme
Measure	Cost of Illness (COI)
Results	The estimated cost of the epidemic was US$ 20.1 million from June 2002 to February 2003, including a US$ 10.9 million cost of illness (US$ 4.4 million medical and US$ 6.5 million non-medical costs) and a US$ 9.2 million cost of public health response. The range of values for the cost per case prevented by vaccination was US$ 20,000 – US$ 59,000 (mean US$ 36,000).
Authors	Custer *et al.*
Year	2005
Country	UNITED STATES OF AMERICA
Focus	Economic Impact
Measure	Quality-Adjusted Life Year (QALY)
Results	The cost effectiveness of annual, national mini-pool testing was 483,000 dollars/QALY. The cost effectiveness of annual, national individual donation testing was 897,000 dollars/QALY. The cost effectiveness of targeted individual donation testing in an area experiencing an outbreak coupled with mini-pool testing elsewhere was 520,000 dollars/QALY. The 95% range of results from probabilistic sensitivity analysis for targeted individual donation testing was 256,000 dollars to 1,044,000 dollars/QALY.

LEISHMANIASIS	
Authors	Rijal *et al.*
Year	2006
Country	NEPAL
Focus	Economic Burden
Measure	Cost of Illness (COI)
Results	The disease affects persons from the lowest socio-economic strata; households either had to sell part of their livestock or to take a loan to cover the costs. Direct costs consisted of 53% of the total cost; 75% of cost incurred before any treatment.
Authors	Bern *at al.*, Reithinger
Year	2008
Country	HORN OF AFRICA, SOUTH ASIA, BRAZIL, LATIN AMERICA, CENTRAL ASIA, AND SOUTH WESTERN ASIA
Focus	Comparison of Impact
Measure	Cost of Illness (COI)
Results	In South Asia (US$ 80–US$ 120) approaches or surpasses the annual per capita income. In Guatemala the cost of treatment is about US$ 250, beyond the means of most rural inhabitants. The disease causes a major financial burden on public health systems: in Colombia US$ 345 per person cured, and in Brazil US$ 2.5 million to treat 35,000 persons

LYME DISEASE	
Authors	Maes *et al.*
Year	1999
Country	UNITED STATES OF AMERICA
Focus	Economic Impact
Measure	Cost of Illness (COI)
Results	Annual mean incidence of 4.73 cases per 100,000 populations; an expected national expenditure (direct and indirect costs) of US$ 2.5 billion (1996 dollars). Over 5 years for therapeutic interventions to prevent 55,626 cases
Authors	Zhang *et al.*
Year	2006
Country	UNITED STATES OF AMERICA
Focus	Economic Impact
Measure	Cost of Illness (COI)
Results	The annual total direct medical cost of Lyme disease cases on Maryland Eastern Shore was US$ 1,455,081. Total indirect medical costs, non-medical costs, and productivity losses were US$ 436,949. A patient (clinically defined early or late stage) costs US$ 2,970 in direct medical costs plus US$ 5,202 in indirect medical costs, non-medical costs, and productivity losses. The estimated nationwide annual economic impact of Lyme disease and relevant complaints was almost US$ 203 million (in 2002 dollars).
Authors	Hsia *et al.*
Year	2002
Country	UNITED STATES OF AMERICA
Focus	Cost Effectiveness of Vaccination
Measure	Cost-Effectiveness Ratio (CER)
Results	At the average national incidence the disease (0.0067%), the incremental cost effectiveness of vaccination was US$ 1,600,000 per case averted. For populations with an annual disease incidence of 1%, the incremental cost effectiveness was US$ 9,900 per case averted.

TICK-BORNE ENCEPHALITIS	
Authors	Desjeux *et al.*
Year	2005
Country	BALKANS
Focus	Cost Benefit of Vaccination
Measure	Cost-Benefit Analysis (CBA)
Results	Total vaccine programme costs were EUR 10.05 million and total costs averted were EUR 4.37 million; the main categories of costs were those related to hospitalisation and rehabilitation, medical evacuation flight and disability pension pay: the extra costs of vaccination were EUR 5.68 million; the break-even point was a seroconversion rate of 1,936 per 100,000 person years. In the favourable scenario the extra costs were EUR 2.86 million (break-even seroconversion rate: 1,206), while in the unfavourable scenario they were EUR 17.63 million (break-even seroconversion rate: 6,343). If the vaccine was applied to the whole army, then the extra costs of vaccination would be EUR 25.7 million (break-even seroconversion rate: 6,971); the incidence of disease had a large impact on the estimated costs; in no case did vaccination lead to cost savings.

AVIAN INFLUENZA	
Authors	Oxford Economic (OE)
Year	2005
Country	WORLDWIDE
Focus	Global Cost
Measure	OE-SARS Reaction Function
Results	Cost ranging from US$ 8 billion to US$ 24 billion (excluding deaths). A rough estimate of the costs of a fairly serious outbreak of pandemic flu goes from a minimum of 1% of global GDP in the first year (almost US$ 400 billion) to a maximum of 4%-5% of global GDP (US$ 1,500-2,000 billion) plus the impact of death rate in long term (0.5% of GDP loss per 1% of population lost per year).
Authors	McKibbin and Sidorenko
Year	2006
Country	WORLDWIDE
Focus	Global Cost
Measure	Asian Pacific G-Cubed (APG-Cubed) Model
Results	The scenarios have historic character since they refer to the US during the past outbreaks, namely: mild scenario is defined with respect to Hong Kong flu (1968-1989), moderate scenario refers to Asian flu (1957), severe scenario refers to Spanish flu (1918-1919) and ultra scenario is similar to Spanish flu but without anomalously high elderly survival rate. Even mild pandemic has significant consequences for global economic output: the mild scenario is estimated to cost the world 1.4 million lives and the global economy close to 0.8% of GDP (US$ 330 billion in lost economic output), while a massive global economy slowdown occurs in the ultra scenario with 142.2 million people killed and some economics, particularly in the developing world, shrinking by over 50%; the loss to global GDP is US$ 4.4 trillion.
Authors	Burns *et al.*
Year	2008
Country	WORLDWIDE
Focus	Economic Consequence in GNP Decrease
Measure	Cost of Illness (COI)
Results	The impact ranges from 4.4% in Latin America and the Caribbean to 2.6% in the East Asia and Pacific region. The total cost to the global economy would be slightly more than US$ 2 trillion, in the case of a more severe pandemic, however, such as one causing a 4.8% drop in economic activity, the total cost to the world economy is estimated to be about US$ 3.13 trillion.
Authors	Jonung and Roeger
Year	2006
Country	EUROPE
Focus	Macroeconomic Effects
Measure	Quarterly Macroeconomic Model
Results	With a morbidity rate of 30%, a mortality rate of 2.5%, 3 weeks off work due to illness per worker, about 150 million Europeans will become sick for three weeks and 2.5% of those, in other words 0.75% of the total population, will die. The epidemic breaks out in the first quarter of the year, and combining the supply and demand effect; a drop in EU GDP growth of 1.6%; the EU-25 economy would grow by only 0.5%; the output loss would amount to about 180 billion Euros.

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