CHAPTER 32

Fundamentals, Domains, and Diffusion of Disease Emergence: Tools and Strategies for a New Paradigm

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FOREWORD

In this chapter, we will focus on establishing the origin of infectious diseases. Taken that disease is an entity strictly dependent on human thought, it will not deal with the origin of a parasite *sensu lato* but with its intrinsic pathogenicity; it will not be about the animal’s role in the natural cycle of a parasite but about the origin of their role as host, reservoir or vector of a pathogen and how humans, as individuals or societies, witness, face, and understand a disease when it appears in our bodies, or spreads through a community.

The cognitive approach to infectious disease is studied to enable better understanding of fundamentals of disease emergence mechanisms and definition of borders around domain expansion.

The concept of “Disease Emergence” constitutes in itself the epicenter of this study, which will not be focused on an object—a disease-centered approach—but a systemic approach to disease, among other diseases, in a given environment and time scale. It will not be purely a study of epidemiology, spatial or descriptive, but a wide integrative approach centered on the understanding of all mechanisms of
emergence and encompassing them from molecular to global level. We present scientific thought about the nature of infectious disease not only in nature but also in the collective consciousness with as final goal the understanding of the rise and fall of plagues threatening all biological life forms on earth.

In order to present the entire concept of disease emergence, its understanding and offensive strategies to counterattack germs, we will therefore discuss the following aspects:

• Concepts and the “domino effect” of disease emergence: Understanding the mechanisms involved from the index cases to a pandemic;
• Strategies to address the challenge, and tools to investigate: Tools and methods developed to study the dynamics of the emergence;
• Some explanations and solutions that are shared by several exemplary diseases: Diseases with a profile of generic evolution applicable to a common nosology and diseases with emergence and single diffusion dynamics.

32.1 FROM NOSOLOGY TO CONCEPT

From “emerging diseases” to “fundamentals of disease emergence”: Two propositions, succeeding each other, show during the past two decades, an evolution of thought which went from the nosological, objective view point of “emerging diseases” to a more conceptual and subjective approach that included factors and mechanisms of emergence as “fundamentals of disease emergence.” Later on, spatial and social dimensions were added with the term “domains of emergence.” A new more exhaustive way of thinking evolved, with a temporal dimension, which necessitated a multidisciplinary approach.

32.1.1 Emerging Diseases

32.1.1.1 Change in awareness The scientific community decided in the late 1980s to forge a new semiological concept encompassing arboviruses, that is, vector-borne transmitted diseases, such as hemorrhagic fevers and other apparently new diseases.  

1In French “territoires d’émergence” a term for designing a specific domain with borders of natural, human, biological origin where the event of emergence happened.

2Charles Nicolle 1866–1936 (Nobel prize of Medicine, 1928): Doctor, biologist, born in 1866 in Rouen (France), died in Tunis in 1936 in Tunis (Tunisia). Doctor of the hospitals of Rouen, Director of the Pasteur Institute of Tunis (1902–1936), discovered the role of the louse in the exanthematic transmission of typhus (1909) “the pathocenosis, a new historical, epidemiologic and clinical approach to diseases.”

32.1.1.2 An old concept However, the phenomenon of disease emergence was understood much earlier by scientists paving the way to a more general concept focusing on the life and death of diseases and their epidemic occurrences.

In fact the concept preexisted and was clearly expressed by Charles Nicolle,2 director of the Institute Pasteur de Tunis, in 1920 when he gave a talk at the university entitled “Life and death of Infectious Diseases” presenting the idea of an intrinsic one dynamic approach for infectious diseases and moreover a sense of the rare, but no less important, vanishing diseases.

Charles Nicolle developed in his book “Le Destin des maladies infectieuses” [50] his vision on the “Naissance, vie et mort des maladies infectieuses.” Later, in the 1970s, Max Germain and his colleagues [18] described the concept of “zone of emergence of Yellow Fever” in west and central Africa, pointing out the necessity of a convergence of several factors (i.e., primate herd immunity, seasonal vector activity) to allow the emergence of the disease in a given environment (i.e., the sub-Sudanese phytogeographic domain). Since then, both concepts of emerging diseases and disease emergence were used as a practical approach to focus attention and research on new pathogens and disease evolution in a changing world.

Over time, the concept of emerging diseases appeared gradually within the medical scientific community during the late 1980s when viral hemorrhagic fevers (e.g., Lassa fever, Ebola fever) or other surprisingly severe syndromes (e.g., Lyme disease, Legionella diseases) were identified and large and sudden epidemics were witnessed (e.g., HIV). It was only in 1987 that Joshua Lederberg, Robert B. Shope, and Mary Wilson formally coined the term of emerging and reemerging diseases. Responding to political demand they addressed the issue of new infectious diseases around for the last 30 years. What was truth or artifact? What measures should be taken? [38]

Since then, national and international meetings periodically arise, books, publications, journals are produced, university and institutional departments and laboratories are formed with teams of specialists that focus on emerging diseases with the objective of preventing or forecasting epidemics. But, after deploying scientific potential, mostly to fulfill political and public demand, the main scientific objective lies in understanding the emergence of new pathogens, new diseases, and their reemergence in virgin populations or domains after a long epidemic silence.

In the 1990’s, most of the researchers in arbovirology already involved in the study of deadly hemorrhagic fever of viral origin joined the current movement in medicine by focusing their study field on the emerging diseases. At the same time, WHO created a special force on emerging diseases, at the Centre for Disease Control and Prevention (CDC) in Atlanta (Georgia, USA); the “special pathogens branch” became the cradle of the emerging disease team, and also, several laboratories across the world were fully or partially oriented on such research.

As for a research unit example, our IRD team named “fundamentals and domains of disease emergence” as developed in 1997 the first “Research Centre for Emerging Diseases,”
hosted by Mahidol University in Thailand. At the beginning of the twenty-first century, we merged human and social sciences, computer sciences, and specialized biomedicine. Health geography, health information systems, and health ecology have been combined, thus adopting a transdisciplinary approach toward understanding the emergence of diseases. Today, above all concepts, health security, biosecurity, and its corollary biodefense appears as a most important concept showing the dependence between social and environmental factors underlying the fundamentals of disease emergence.

32.1.2 Understanding the Fundamentals of Emergence

In this chapter the phenomenon of disease emergence is tackled from three angles, as a multidisciplinary approach is required, it focuses on

- the old framework of the emergent diseases;
- the historical concept of pathocenosis which deals with emergence in time and space;
- health ecology as opposed to traditional epidemiology, which is generally restrained to a more linear disease analysis.

32.1.2.1 Emerging diseases have specific timeframe

All diseases one day emerge, either in the biosphere or in the collective conscience, but the reactions are the same: to fight, control, and contain them. The concept of emergence in its present meaning makes it possible to focus research on factors of emergence, to fight and protect against disease, and using emergence indicators, to prevent and control them. The emergent, new viral diseases (new virus, new syndrome), reemerging (nonimmune populations or interepidemic silence), or expanding (due to infected hosts and vectors traveling to unaffected areas), are complex and result from host–vector–virus interactions in often cryptic natural cycles, for which the environment plays a major role.

Diseases are generally regrouped into nosological frameworks to develop comprehensive studies (e.g., arbovirosis, viral encephalitis, water-borne diseases). The EID concept was chosen to help identify common risk factors, diffusion agents, and mechanisms of increasing or changing pathogenicity. Prevalent EID and later ED were categorized and a typology defined regarding risk and indicators of risk, as for example, risk of natural origin, risk associated with human behavior, and risk linked to environment.
<table>
<thead>
<tr>
<th>Year of Emergence</th>
<th>Emerging Disease</th>
<th>Pathogenic Agent</th>
<th>Place and Domain of Emergence</th>
<th>Factors of Emergence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1958</td>
<td>Argentine hemorrhagic fever (AHF)</td>
<td>Junin virus (arenavirus)</td>
<td>Argentina; Pampa, corn fields</td>
<td>Changes in agricultural practices of corn harvest (maize mechanical harvesting)</td>
</tr>
<tr>
<td>1981</td>
<td>Acute immuno-deficiency syndrome (AIDS)</td>
<td>Human immunodeficiency virus HIV (HIV 1 and 2; retroviruses)</td>
<td>USA; urban communities</td>
<td>Yet not entirely understood origin of the virus introduction; sexual contact with or exposure to blood or tissues of an infected person.</td>
</tr>
<tr>
<td>1959</td>
<td>Bolivian hemorrhagic fever (BHF)</td>
<td>Machupo virus (arenavirus)</td>
<td>Bolivia; Beni Province, in house</td>
<td>Population increase of infected rats gathering for food</td>
</tr>
<tr>
<td>1986</td>
<td>Bovine spongiform encephalopathy (BSE) in cows</td>
<td>BSE agent (prion)</td>
<td>Great Britain; cattle rising aera</td>
<td>Feeding cattle with products containing prion infected sheep tissue</td>
</tr>
<tr>
<td>2005</td>
<td>Chikungunya arthritus</td>
<td>Chikungunya virus (alphavirus)</td>
<td>Indian Ocean Islands</td>
<td>Introduction of the virus in the Islands (Comore, Reunion) by a yet to be discover mean (plane, wind?</td>
</tr>
<tr>
<td>1996</td>
<td>Creutzfeld Jacob disease</td>
<td>CJD agent (prion)</td>
<td>Great Britain</td>
<td>Emergence of a BSE variant</td>
</tr>
<tr>
<td>1983</td>
<td>Crimean-Congo hemorrhagic fever</td>
<td>CCHF virus</td>
<td>West Africa Sahel – Senegal river basin</td>
<td>Ecological changes favoring increased human exposure to ticks on sheep and small wild animals</td>
</tr>
<tr>
<td>1953</td>
<td>Dengue hemorrhagic fever (DHF)</td>
<td>Dengue virus 1,2,3,4</td>
<td>Philippines, Thailand (1956)</td>
<td>Increasing human population density in cities and favoring vector breeding sites (water storage) (Aedes aegypti)</td>
</tr>
<tr>
<td>1976</td>
<td>Ebola hemorrhagic fever</td>
<td>Ebola virus types Zaire and Sudan</td>
<td>Zaire and Sudan</td>
<td>Congolese rains forest penetratoin by humans</td>
</tr>
<tr>
<td>1976</td>
<td>Hemorrhagic fever with renal syndrome (HFRS)</td>
<td>Hantaan virus (Hantavirus)</td>
<td>Korea</td>
<td>Exposure of military US troops to rodent infected habitat during the armed conflict in Korea</td>
</tr>
<tr>
<td>1993</td>
<td>Hantavirus pulmonary syndrome (HPS)</td>
<td>Sin Nombre Virus (Hantavirus)</td>
<td>USA, “Four corners” area</td>
<td>Human invasion of virus ecologic niche by rice field agriculture; close contact with the infected rodent natural reservoir; inhalation of aerosolized rodent urine and feces</td>
</tr>
</tbody>
</table>

**TABLE 32.1. Domains and Emergence Conditions of Some Recent Exemplary Human Diseases**
<table>
<thead>
<tr>
<th>Year</th>
<th>Disease</th>
<th>Virus/Agent</th>
<th>Location/Details</th>
<th>Mode of Transmission or Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989, 1890, 1918, 1957, 1968</td>
<td>Influenza pandemic</td>
<td>Influenza A virus (Paramyxovirus)</td>
<td>Russia, India, USA, China, Hong Kong</td>
<td>Airborne (crowed, enclosed spaces)</td>
</tr>
<tr>
<td>1997</td>
<td>Japanese encephalitis</td>
<td>JE virus (flavivirus)</td>
<td>Australia, North Queensland Tip</td>
<td>Concurrent large epidemic and epizootic in Indonesia</td>
</tr>
<tr>
<td>1997</td>
<td>Japanese encephalitis</td>
<td>JE virus (flavivirus)</td>
<td>Japan</td>
<td>Bite of an infective mosquito</td>
</tr>
<tr>
<td>1969</td>
<td>Lassa fever</td>
<td>Lassa virus (arenavirus)</td>
<td>Nigeria; rural area</td>
<td>Rat vector reservoir pullulation in houses</td>
</tr>
<tr>
<td>1956</td>
<td>Marburg disease</td>
<td>Marburg virus (filovirus)</td>
<td>Germany; monkey experimental laboratories</td>
<td>Preparing monkey cell kidney for medical research; direct contact with infected tissue</td>
</tr>
<tr>
<td>1961</td>
<td>Oropuche fever</td>
<td>Oropouche virus (Bunyavirus)</td>
<td>Brazil Amazonia, Cacao plantations</td>
<td>Developing and incising agriculture</td>
</tr>
<tr>
<td>1987</td>
<td>Rift Valley fever (RVF)</td>
<td>RVF virus (bunyavirus)</td>
<td>Mauritania, cattle rising area</td>
<td>Dramatic increase of mosquito vector breeding sites by filling a new dam; weather (rainfall) and cattle migration guided by artificial water holes</td>
</tr>
<tr>
<td>1957 and 1986</td>
<td>Seoul infection</td>
<td>Seoul virus (hantavirus)</td>
<td>Korea, USA harbors</td>
<td>Increasing population of urban rats</td>
</tr>
<tr>
<td>2003</td>
<td>Severe acute respiratory syndrome (SARS)</td>
<td>SARS Coronavirus</td>
<td>South Province of China</td>
<td>Eating practices of infected wild animals (virerrids)</td>
</tr>
<tr>
<td>17th and 18th centuries</td>
<td>Smallpox</td>
<td>Smallpox virus (poxvirus)</td>
<td>North American colonies</td>
<td>A new virus arrive with infected European traveling to the Americas</td>
</tr>
<tr>
<td>1965</td>
<td>Yellow fever</td>
<td>Yellow fever virus (flavivirus)</td>
<td>Nigeria</td>
<td>Reintroduced from sylvan source by viremic travellers; lack of immunization camping</td>
</tr>
<tr>
<td>1968</td>
<td>Viral Gastroenteritis</td>
<td>Norwalk &amp; -like virus (Norovirus)</td>
<td>USA</td>
<td>Increased recognition</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Year of Emergence</th>
<th>Emerging Disease</th>
<th>Pathogenic Agent</th>
<th>Place and Domain of Emergence</th>
<th>Main Probable Factor</th>
<th>Secondary Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975</td>
<td>Babesiosis fever (malarialike infection)</td>
<td>Babesia microti</td>
<td>USA; Long Island, New York</td>
<td>Reforestation; deer population (<em>Babesia</em> tick vector host) increases, increasing outdoor recreational activity</td>
<td>Bite of an infected <em>Ixodes</em> tick feeding on mice and deers</td>
</tr>
<tr>
<td>1980</td>
<td>Campylobacter gastroenteritis</td>
<td>Campylobacter jejuni</td>
<td>Sweden</td>
<td>Ingestion of contaminated food, water, or milk; fecal–oral spread from infected person or animal</td>
<td>Increased recognition consumption of uncooked poultry</td>
</tr>
<tr>
<td>1986</td>
<td>Human monocytic erlichiosis</td>
<td>Ehrlichia chaffeensis</td>
<td>USA</td>
<td>Unknown; tick is suspected vector</td>
<td>Increased recognition; possibly increase in host and vector populations</td>
</tr>
<tr>
<td>1996</td>
<td>Hemorrhagic colitis</td>
<td><em>Escherichia coli</em> O157:H7</td>
<td>USA</td>
<td>Ingestion of contaminated food, undercooked beef and raw milk</td>
<td>Likely due to the development of a new pathogen</td>
</tr>
<tr>
<td>1976</td>
<td>Legionnaires’ disease</td>
<td>Legionella pneumophila</td>
<td>USA, Pennsylvania</td>
<td>Air-cooling systems, water supplies</td>
<td>Recognition in an epidemic situation</td>
</tr>
<tr>
<td>1975</td>
<td>Lyme disease</td>
<td>Borrelia burgdorferi</td>
<td>USA, Lyme Connecticut</td>
<td>Bite of infective <em>Ixodes</em> tick (deer ticks)</td>
<td>Increase in deer and human populations in wooded areas</td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976</td>
<td>Malaria</td>
<td><em>Plasmodium</em></td>
<td>92 Countries of Africa</td>
<td>Global eradication policy abandoned, economics, growing interchange of populations</td>
<td>Drug and insecticide resistance, political unrest, lack of public health, human behavior, poverty</td>
</tr>
<tr>
<td>1960</td>
<td>Anisakiasis: acute localized enteritis</td>
<td>Anisakis marina A. simplex</td>
<td>Netherland</td>
<td>Increasing consumption of crude fish</td>
<td>Recognized in Japan since 1955</td>
</tr>
<tr>
<td>1970</td>
<td>Gnathostomiasis</td>
<td>Gnathostoma spinigerum, G. hispidum</td>
<td>South America</td>
<td>Increasing consumption of crude fish (sashimi or “ceviche”); endemic in Asia</td>
<td>Undercooked fish or poultry, drinking water with infected Cyclops</td>
</tr>
<tr>
<td>1994</td>
<td>Acute pneumocystis pneumonia</td>
<td>Pneumocystis carinii</td>
<td>USA, Europe</td>
<td>Immunosuppressed patients, HIV infected patients CD4+ cell count</td>
<td>Unknown; possibly reactivation of latent infection</td>
</tr>
</tbody>
</table>
Disease is a human concept all “new” diseases will one day emerge in a given population and environment. This table cannot therefore be exhaustive, the diseases selected were chosen for their exemplary nature and belonging to a particular period of time, population or original geography with complex, or rare transmission.

The concept of emerging diseases was developed in order to adopt a specific strategy of control and prevention in response to the sudden appearance of unedited pathogens and diseases during the last century, the rapid propagation of such diseases at a regional or global level, and the challenge for public health officers to counteract such a growing threat in ever changing environments and societies.

In the context of emergent diseases, new diseases or emergence of the diseases, several remarkable works have been written, which deal with infection risk at all levels [12, 38, 47, 56, 59].

The emergent and or new viral diseases (new virus, new syndrome), reemergent (nonimmune population or inter epidemic silence), or expanding (from hosts and infected vectors traveling) are among the most important and represent two-thirds of the present complex. There are the results of host–vector–virus interactions in natural cycles often cryptic for which the environment plays a major role. They are generally transmissible zoonosis, often by a vector and, frequently infections of exceptional gravity (encephalitis, hemorrhagic fever) or of exacerbated epidemic kind (AIDS, SARS, influenza). The dynamic of these diseases are subject to constantly changing, human environments and genomic plasticity of evolving viruses.

32.1.2.2 Toward the historical concept of pathocenosis

The concept of pathocenosis is presented like an element structuring disease emergence clearly identified as a temporal (emergence sensu stricto) and spatial (the territory of the disease) phenomenon. The term pathocenosis, created by Mirko Grmek, historian of biomedical sciences is not only a neologism, which so elegantly associates “pathology” and “biocenosis” but above all a concept to define “pathological states within a population determined in time and space.”

“However, Mr. Grmek’s idea is not limited to describing these pathological states. It (also) postulates that the frequency and distribution of each disease depends on the frequency and distribution of all the other diseases. Examples of interdependences between pathological states, whether in the case of a synergy or an antagonism, are numerous.”

The pathocenosis naturally tends to equilibrium, and is therefore particularly sensitive (observable) in a stable ecological situation. It is known that the human immune-deficiency virus (HIV) by its immune-suppressor effect will favor patient infection by Koch bacillus and tuberculosis will then become the syndrome dominating the patient. *Esherichia coli*, a commensal bacterium of the digestive tract of all humans, can, under certain conditions, changes its phenotype to increase its invasive potential, weakening intestinal epithelium, paving the way of intense replication of latent viruses such as are Rotavirus or picornaviruses becoming enteropathogen.

**PATHOCENOSES** is a state, which tends toward balance but exists in perpetual imbalance. This creates the conditions of disease emergence; rebuilding the pathocenosis toward a nonattainable balance and which with this new more or less significant imbalance will integrate or eliminate pathology.

As with pathocenosis, disease research strategy, aims to understand the disease emergence mechanisms and imposes a multidisciplinary approach; historical, epidemiological, biological, clinical, and environmental. Historians, health geographers, philologists, epidemiologists, mathematicians, or even specialists of emergent diseases find themselves in the same dynamic flow of thought, that of the concept of disease emergence like an imbalance of pathocenosis in a place, a population, and a given time. Specialists in these various disciplines met to compare and share their knowledge in a 3-day seminar at the Abbey of Ardennes in Caen in April 2005.

Thus, pathocenosis globally tends toward a balance observed in stable situations but can undergo brutal changes, which favor the emergence of new diseases or of known ones that, will reemerge after an often incompletely understood inter epidemic silence.

For any given population, one will see over time the domains of diseases, coexisting, succeeding, and gradually being replaced by others. The causes of these effects are multiple; they interact to produce a complex epidemiologic profile with a certain stability leading to a silence or an evolution before a renewed epidemic eruption when appropriate conditions are finally installed.

Lastly, Gerard Lambert, writes “(. . .) the passage of a pathocenosis dominated by infectious diseases to a pathocenosis in which the degenerative diseases (in particular cardiovascular diseases and cancer) take the ‘lion share,’ constitutes the last great rupture of the history” (. . .) and further “(. . .) the relevance with which Mirko Grmek had at the time analyzed the origins of AIDS pandemic [22] in comparison with the pathocenosis, proves the potential operational value of this concept (. . .)”.

32.1.2.3 Health ecology In a given ecosystem the emergence of infectious diseases depends on dynamics of human societies, of animal populations and also of the germ's

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4 Days of study where organized by the Workshop on the pathocenosis in collaboration with Louise L. Lambrichs and in partnership with the Institut Mémoires de l’édition contemporaine (IMEC), at the abbey of Ardennes (Caen) April 13-16, 2005.

5 Personal communication, 2005.
pathsogens, factors which are all more or less dependant on the varying environments at both micro (genetics) and macro scale (populations and land).

### 32.1.2.3.1 Structural change of human society
A rapidly growing global population changing societies, a tremendous increase of communications and exchanges of all kinds, an evolving environment under human and natural influences, and the potential globalization of any local phenomenon have characterized the past century. When it comes to health, besides the outstanding technological and fundamental progress in medical science over the past 50 years, the inequality between societies from urban to rural, from industrialized to developing countries, are a permanent challenge for health care, officers, and politicians. Health care access underlines the disparities between the two extremes; despite the efficient and thoroughly conducted immunization programs and campaigns, the cost is unbalanced between control and prevention. Medications are increasing in price, as are public health systems, which must deal with the specific challenge of unprepared populations facing the emergence of unedited diseases.

### 32.1.2.3.2 Changing societies: Transition from Rural to the Urban Society
Let us consider the factors that have influenced the infectious risk increase: This century is without precedent in terms of demographic growth, human exchanges, transport of domestic animals from one continent to another, the transformation of landscapes (deforestation, land development), and anarchistic use of modern tools (antibiotics, pesticides, new foods). Pandemics are fast and frequent, the germs and their vectors escape weapons of prevention and control, the clinical picture changes under the combined effect of emergent pathogenic agents (virus of AIDS) and the new therapeutic treatments (immune-therapy). The biodiversity of the pathogenic germs, globalization of human behavior, global warming, early alarm systems, strategies of defense are the many concepts that lead to the redefinition of health management.

### 32.1.2.3.3 Hosts, vectors, reservoirs
This trilogy, considered formerly as the dogma defining infectious diseases as a whole, is recomposed today around essential elements of modern medical thought: It is no longer the role of the individual, but his behavior and actions on the environment (including social environment); that prescribes the necessary steps to be taken for the improvement of health care.

### 32.1.2.3.4 Parasites
The parasites sensu lato are dependant on the hosts who carry them and constitute the microenvironment of their existence. These parasites will then not only be dependent on their host but also indirectly on the environment, which modulates hosts (in a broad sense, vectors, reservoirs, accidental hosts · · · ), physiology (with temperature), and behavior (with seasonality).

### 32.2 Tools and Strategies: An Integrative Approach

#### 32.2.1 Choosing the Appropriate Strategies and Identifying Corresponding Tools
Choosing the appropriate strategies and identifying corresponding tools are the main paths in order to provide answers for complex situations of disease emergence. For the understanding and hopefully prevention of diseases emergence, field observation is essential. This makes it possible to examine the phenomena behind the process of emergence. The mechanisms may be biological, at molecular level, or behavioral at an individual or population level. However, observation of exemplary situations is not sufficient, to transform emergence into equations. There are too many parameters that intervene in the emergence of a disease. An epidemic is only one of the possible outcomes of a great number of possibilities of emergence and diffusion. The reduction of risk can only be considered in temporal and spatial terms which make the system stable, but which no longer corresponds to individuals. Only an approach integrating observation, simulation, and prevention will make it possible to locate these optimum domains in terms of time and space. Observation is necessary to describe and decipher the reality and understand the phenomena, simulation to evaluate possible danger and to find areas of stability, and prevention by modifying the parameters to decrease the vulnerability of population or the probability of a situation favorable to emergence.

#### 32.2.1.1 Deterministic risk assessment
An omnipresent misguided principle in research is that of the relation of cause and effect in nature. It is implicitly accepted when one seeks to understand causes of a phenomenon by highlighting the relations, factors, and behaviors, which explain a given situation. It should make it possible, in theory, to envisage the state of a system starting with initial conditions and the rules, which govern temporal evolution. The object of the majority of sciences is to determine these primary laws and conditions.

But there exists in nature considerable number of systems (in fact the majority, if not all), which do not satisfy the principle of determinism. Very often, a state cannot be deduced from initial conditions because the relation of cause to effect cannot be quantified with sufficient precision to ensure the determinism of the system. One would need, for that, an infinite precision for all parameters of the system. The majority of systems in nature such as the climate are dynamically unstable and their exact evolution is thus impossible to envisage with certainty.

#### 32.2.1.2 Probabilistic risk assessment
Even if the value of all parameters for participants entering the system is known, (position, displacement, etc.) its evolution cannot be extrapolated with certainty but only estimated in a probabilistic approach. A deterministic approach of individuals is impossible (the exact
behavior of a mosquito or a human cannot be predicted). Therefore, it is necessary to regroup agents (domains, social or environmental characteristics, temporal factors, etc.) or objects (subsystems, domains, etc.) in larger entities which evolution can be predicted with a greater probability. We thus seek to pass from a study of a dynamically unstable system to a more stable one by changing the study focus.

It is possible to give the probability of occurrence of an influenza epidemic in a given population but it is impossible to give the probability that a certain individual will be sick at a given time. The emergence and diffusion of diseases appears to have a similar mechanism as climate, but more complex, because the laws, behavior and initial conditions of agents are less known. On the contrary, it is easier to act on the initial conditions and the behaviors (by vaccinating the population, by giving rules of hygiene, by restricting displacements, etc.).

In the face of dangers represented by disease emergence, reemergence, or diffusion, the research and practice of a therapeutic solution are all the more effective if the disease development mechanisms in the population (human or animal) are known. Afterward the risk can be evaluated to avoid situations that are highly favorable to emergence or diffusion. Given the population, it is also necessary to describe their behavior, the various states induced by these behaviors, and the phenomena and significant parameters leading to a change of state.

Describing the system, questions arise

- Is it necessary to study individuals, or populations, and which ones? Which parameters should be taken into account?
- Is there sufficient scientific knowledge to study them?
- How can the agent’s behavior and inter-relationships be described and interpreted?
- Finally, in reviewing the entire system/mechanism can a potential risk be removed?

32.2.2 The Emergence Play: Actors and Decors of a Drama

32.2.2.1 Agents and behaviors It is the risk (probability of an event) and not the actual event, which must be studied. A real medical situation is conceived only as a possible event among many others. The phenomena being studied have individuals as participants or dynamic agents causing evolution in the system. The agent’s outcome is determined by its position; the interrelations and its condition, the whole is determined by rules of behavior (probabilistic). The change of states or the rules of behavior can be strongly influenced by the medium (which is not regarded as agent—not cause leading to effect—but which can also evolve over time. Thus, the climate is in general one of the principal factors in vector behavior).

32.2.2.2 From object to population It is the existence and unique characteristics of individual agents, their behavior and interrelations, which causes disease evolution in a population. But it is not possible to describe all individuals and to envisage all behaviors, even if one knew exactly the mechanisms of disease evolution. If one considers only populations, a statistical description would be satisfactory but behavioral variations between populations would be difficult if not impossible to describe and thus to use. In particular, when behavior depends on environmental conditions the system becomes too inaccurate to reflect real life. A deterministic approach, by discipline, cannot make an accurate study of disease emergence in populations. No system of equations will be able to answer the questions, because of the element of unpredictability at all levels. The principal difficulty consists in controlling as much as possible these random components. Biological and medical science intervenes in studying the pathogenic agents at individual level. Social sciences and geography intervene in studying agents’ behavior; factors and invariants are found from regrouping agents and measuring environmental influence. The study of real situations enables us to identify and study the actors of the transmission (pathogens, vectors, hosts, humans), to make assumptions on rules (states and change of states) and behavior of actors (actions producing a change of state), to specify initial conditions, but they should not be perceived as more probable than other possible outcomes.

The rules of individual behavior, even if they are known to be uncertain, are necessary to take into account the total phenomenon: It is only on the scale of individuals that one will really be able to simulate the process to find the most significant invariants, without using arbitrary and often too simplistic regrouping.

32.2.2.3 Population or individual? It is difficult to avoid this contradiction among study scales; to preserve the study of individuals while avoiding any determinism on their level. This amounts to describing agents and their behavior in probability terms compared to actual values (in a statistical way on populations or descriptive on selected individuals).

Of course, to assign to an individual values of the population to which it belongs (according to the probabilities determined by observation) cannot be valid other than within the framework of a model or simulation aiming at highlighting invariants (with, once again, the process ensuring the statistical validity of the results obtained).

32.2.3 Requiring and Acquiring Data: From Who, to Where and How?

The observation of a real situation is fundamental to try to define agents and rules of behavior, whether they are molecular or demographic. Biology, epidemiology, entomology, geography are all essential disciplines to decipher parameters in an epidemic situation.

Who? The study objects. It is necessary to describe several levels to understand phenomena, both at individual and population level. It is necessary to describe several systems, to describe their agents, their states and their behaviors, and to find relations or inferences which make it possible for the descriptive study to enrich knowledge in other fields. It is necessary to set up procedures of stochastic simulation.
making it possible statistically to validate the inferences used between the various levels of descriptions.

*Where?* It can be useful to change the object of study, by privileging space and time rather than the individual or the population in the process of risk evaluation. The studied individual is then a spatial unit (or an aggregate of spatial units), and the objective is to evaluate the probability of this entity to be the place of disease emergence at a given time. But this is based on the supposition that at every moment the characteristics of this entity are known for its agents (pathogenic, human, vectors) and for all parameters intervening in the behavioral rules of these agents (natural environment, vicinity, domain, etc.). Here again the use of a stochastic model is necessary, because the source of information is not exhaustive and must be approached in probability terms.

*How?* In certain exemplary diseases this approach makes it possible to seek objectives and invariants, in terms of emergence and diffusion in time and space, which will make it possible to describe and hopefully avoid situations favorable to certain health situations. This systemic framework also makes it possible to focus on the problem of emergence, beyond such or such pathology (e.g., concept of rupture in balance of population’s health stability and concept of pathocenosis).

*What?* Many tools are necessary for this approach: Tools of biological and medical science to evaluate the medical, biological, and behavioral characteristics of individuals. Tools related to the information sciences, to allow definition of the various agents, and then use them in a rational way. Mathematical and statistical tools, to evaluate certain agent’s characteristics compared to the population. Tools for geography, to define and represent the real world and environment. Tools for space and temporal analysis, to manage the environment and evaluate certain agent characteristics compared to their environment. Tools for models and simulation, incorporating all characteristics of the studied system to detect temporal invariants. The geographical information systems perform an essential task of regrouping some of these functions.

### 32.2.4 Model and Simulation

A model is designed using information based on observation of a real or supposed situation. Each hypothesis will be represented by a unique model: It is formed by the definition of agents and their states, by rules of behavior (probabilistic) inducing changes of state, as well as variables resulting from random determination of states and behaviors.

Simulation makes it possible to implement the model to obtain “events” starting from initial conditions. These events are obtained in a nondeterministic way, by applying to each agent the appropriate behavior rules for each step of time. It makes it possible to describe the probability of clusters of events (in space and time), and to test the influence of change in certain parameters (public health, behavior) on these probabilities (rates of vaccinations, social behavior, etc.).

As it is impossible to deduce the state of a population from one individual, and if one does not want to remain focused on the level of populations but to go to the finer scale of individuals, it is necessary to use a process of stochastic simulation, the state of each individual being evaluated in a random way according to its place within the population or of the place he comes from (to measure the influence of environmental factors). In such a process of simulation, the inference is statistically possible if it is repeated many times (to be statistically valid, according to a confidence interval) and if it stays within a framework of non-deterministic modeling. Thus, it will be possible to seek invariants evaluate the influence of certain factors (descriptive or behavioral) on the system evolution, and draw some results on the probability of disease emergence based on these factors.

### 32.3 Emergence of Exemplary Diseases or Systems

Several diseases have been chosen because they show in a practical manner how the use of modern technologies applied to the study of emergence can produce an original
understanding of its mechanisms and also help to develop strategies of prevention or prediction of diseases not yet emerged in a population and domain and for a period of given time.

The examples, which follow, were generally selected from work in progress at the time of drafting this chapter. In addition, it is shown that the cross-disciplinary approach is at the heart of analysis, to exceed the multidisciplinary element and juxtaposition of employed disciplines and to achieve a united thought process regardless of disciplines while emphasizing one or the other, a domain according to the angle chosen for the demonstration.

### 32.3.1 Assessing the Risk of Disease Emergence in a Changing World

Indicators observed in southern cities attest longer life expectancy; decreasing child mortality and better vaccine cover than in the countryside. Even if these indices pose problems of comparison, it is evident that urban situations create major differences depending to some extent on the presence of infrastructures and public services with greater accessibility. Better access to facilities like electricity, drinking water, education, and health care are also influential as are the possibilities of adequate housing and more job offers, and so on.

As a result of demographic and health surveys, ORC Macro.

#### 32.3.1.1 Environment and the “Urban Case”

The demographic transition resulted in an increase in life expectancy, which was accompanied by a marked change in the nature of medical problems in cities, particularly the larger ones. In northern countries, an evolution of cause of death has been observed; the first stage characterized by a prevalence of deaths from infectious or parasitic origin, was superseded by deaths from cancer, metabolic diseases, or cardiovascular infections. The simple model of “epidemiologic transition,” imagined by Omran [51] no longer seems applicable to southern countries. Now South cities are also experiencing a real epidemiologic modification, characterized by the emergence of pathologies previously viewed as reserved for the North; like arterial hypertension, diabetes, the problems of mental health, traditional pathologies of incessant poverty, possibly in new forms.

### Urban pathology, for the least developed countries, thus remains dominated by the infectious and parasitic problems, with first rank given to malaria, diarrhea, malnutrition, and respiratory infections. These traditional pathologies are in direct relation to problems of poverty and associated unhealthy living conditions.

For a long time it was thought that, urbanization would end the plague which malaria inflicted due to its incompatibility with the polluted urban environment and the ecological needs of anopheles, the mosquito-vector of malaria. However, it is recognized today that urban malaria exists [25]. Several studies show that it was actually transmitted in cities where the perimeters of irrigated cultures, imprint holes for the manufacture of bricks, the foot prints of cattle which frequent the banks of these water holes, all constitute the ideal breeding ground for anopheles.

Because of less dense vector population, transmission is weaker than in the countryside, but infection is often more severe and spread worse as the city dweller’s immunity is much lower than that of villagers. In addition, transmission is unequal, depending on conditions varying from one district to another.

This is true not only for malaria but also for the schistosomiasis, which are transmitted in cities (The Dam at Aswan, Egypt) or for the African human trypanosomiasis (Sleeping sickness), which continues to prevail even in cities as was the case in the 1970’s in Bamako or Conakry, in relation to crop areas (orchards in Bamako, cash crops in Conakry) and with proximity to rural surroundings [45].

#### 32.3.1.1 Malaria in Ouagadougou (Fig. 32.3)

Ouagadougou, capital of Burkina Faso, has approximately 1,200,000 inhabitants (more than 50% of total urban population). Malaria is responsible for 30 –40% of morbidity recorded in medical centers. A domiciliary investigation made recently in Ouagadougou shows that in children from 6 months to 12 years old, the average prevalence of malaria is 21.3% with great disparities in time and space [1]. In the irregular and sparsely built-up areas of Congo, prevalence exceeds 33.2% at the end of the rainy season whereas in regular densely built districts, it is recorded as less than 11% on average without increase in rainy season. There are however,
areas where risk levels are less distinct, populations of regular zones being subjected to similar risk as those of irregular zones. The regular less densely built districts like Tanghin and the irregular densely built districts represent intermediate environments with a prevalence rate of approximately 15%. The existence of significant numbers of anthropised larval habitats explains transmission of intra urban malaria. The banks of the dams provide places where anopheles find good conditions for survival, just as the orchards around the dams or the imprint holes for the manufacture of bricks as well as the wetted ground near to the numerous wells at Ouagadougou.

These cultivation methods are frequent, even in the large cities. In Accra, capital of Ghana, 90% of vegetables on sale are produced in the city. The presence of these crops not only on

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**Fig. 32.3.** Density of urban community in Ouagadougou and malarial risk. Photo C (below) at top, left, a regular district, which overlaps an irregular one (bottom, left). On the other side of the road (on the right), the dam Boulimougou drained in April, fringed by small plots of crops for market gardening which generate a risk of malaria infection (habitats for anopheles) for the entire area's inhabitants (ONEA, 2003).
the periphery but also in the city center contributes in breaking the decreasing gradient of malaria transmission of central districts to resemble the peripheries and allows transmission in almost any season depending on the area. If this prevalence is much weaker than in villages close to the capital (prevalence of more than 60%), it is noted that people adopted very different habits from the rural areas, on average one child in three sleeps under a mosquito net in the regular districts as in the poor districts and more than three children out of four had taken an anti malaria treatment 15 days preceding the survey. If traditional pathologies due to severe poverty persist in southern cities, possibly in new forms, as previously evoked with malaria at Ouagadougou, they now share the same diseases as northern cities, for example, diabetes and populations, particularly the most vulnerable, find themselves prey to a double burden of diseases.

These changes are explained by the evolution of styles of living, eating habits, people eat more meat, more sugar while reducing their energy expenditure. Social references are also upset. Along with these factors, a growing pollution of southern cities is added without proper provision for making health care a priority. The living conditions of new immigrants are difficult when recently arrived in the capital, it is necessary for them to find work, housing and be nourished. These new life styles generate a stress, which can be at the origin of pathologies related to the way of life like diabetes, certain cancers, or arterial hypertension.

32.3.1.2 Conditions of emergence, from one pathology to another: The respiratory infections in France  
During the twentieth century, France has experienced immense changes in the field of medicine. Considerable progress was achieved, which is reflected in the evolution of mortality. In one century, life expectancy increased by 30 years for men and 34 years for women. This strong progression was accompanied by a significant shift in the cause of death, and is seen in particular, in the evolution of respiratory mortality. Mortality by respiratory infections (all types of infections included) strongly decreased over this period. The rate was divided by three for men and 7.4 for women. This strong fall is primarily due to a collapse of mortality by infectious diseases of the breathing tract. The infectious component represented indeed more than 3/4 of mortality by respiratory diseases, in 1925, tuberculosis constituted a real plague killing nearly 90,000 people each year.

To the deplorable consequences of tuberculosis other quite as significant infections concerning the breathing apparatus are added. Fault of treatment available, at the beginning of the twentieth century pneumonia, influenza and the other acute affections of the respiratory tract appeared particularly fatal. The respiratory complications of affections considered as benign today were frightening and dreaded, affecting in particular, young children, old people, or those already weakened by chronic respiratory problems. The influenza epidemics caused significant fluctuations in death rates from one year to the other. It was not until the end of the 1970’s, with the diffusion of a general-purpose vaccine, that the fluctuations from mortality by influenza start to disappear. The death rates by influenza are maintained today on a very low level.

32.3.1.2.1 The growing burden of chronic affections and tumors  
The strong fall in respiratory infections is accompanied by a strong increase in mortality by cancer of the respiratory tract throughout the period and by an increase in the chronic affections at the end of this period (from the Sixties). Death rate by upper respiratory tract cancers was thus multiplied by 23 in 50 years. This rise primarily occurred between 1930 and 1970. Even if a share of this increase can be explained by the diagnostic progress, it testifies mainly to a considerable and regular development of the male nicotinic addiction since the beginning of the century. The beginning of a decrease in nicotine consumption from 1975 resulted in a stagnation of levels since the Nineties. Minimal, even unimportant at the beginning of the century, cancers of the respiratory tract became today the first cause of male mortality by respiratory diseases. The development of female nicotinic habit, much more recent, causes a true increase in the death rates only as from the Eighties. These remain still today largely lower than the male rates. This late development saved France from a plague, which already affected the countries of northern Europe and the United States since a long time. After having touched the principal agglomerations, it extended today to all French cities. The expansion of female nicotine addiction, at least until the years 2000, makes inescapable the generalization of this phenomenon.

Risks associated with respiratory affections have shown deep upheavals during the last century. From a primarily infectious risk, French society passed in less than one century to behavior related risks. This change was accompanied by a reduction in respiratory affection mortality. Control of infectious risk was beginning to lead to the belief in the Sixties that respiratory problems were definitively solved. The diseases of respiratory tract were therefore put aside for a long time as medical priorities in France. Their development results from a late awakening as to the severe health consequences from the rise in nicotine addiction and industrialization.
In a preliminary conclusion, it is thus difficult to say that urban public health is better or worse than that of rural populations with so much intra urban disparities regional effects are significant. Concepts of epidemiologic and medical transition, which seek to give an account of this complex evolution, must also be revised because they are too normative and deterministic. It is necessary to allow for a period of reflection on general conditions of emergence and disappearance of diseases (in particular of coexistence and interactions, of exclusion) in any given environment. Geography is at the core of this initiative, by its capacity to aid in analysis of combinations of natural, social, economic, and cultural factors in a given place, to determine the different necessary levels of information and not to lose direction in a pseudo spatial epidemiology, which is unable to lend reason to its charts, or more basically to health inequalities.

32.3.2 Comprehension of Mechanisms of Emergence and Their Control

32.3.2.1. Defining proper spatial scales for dengue hemorrhagic fever According to a WHO (http://www.who.sea.org) annual report, infection with Dengue virus (DENV)—recorded for more than 100 countries—is the most widespread arboviral disease in the tropical zone, only restricted by deserts, oceans, cold, and elevated areas as its geographical borders. DenV is mainly transmitted by Aedes aegypti a mosquito breeding in small artificial containers, such as jars, flower pots, cans, tires, frequent in urban environments and by Aedes albopictus in more rural areas.

The dengue virus belongs to the family of Flaviviridae, the same as Yellow Fever virus; it exists in four forms, (serotypes), and at least two circulate simultaneously in most endemic countries. An infection by one of the four serotypes induces in the host a specific and permanent immune protection for this serotype, no durable crossed protection toward the other serotypes, but a previously infected mother transfers a temporary protection (about 6 months) to her progeny. Dengue infections range from unapparent or nonspecific fever (DF) in more than 90% of cases, to severe forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). In Thailand, the mortality is lower than 0.2%. DenV transmission exhibits a wide range of spatial and temporal variations related to the vector density, seasonal variations, differential level of herd immunity, and socio-culture parameters [35]. After several years, the spatial distribution of herd immunity in an endemic country resembles a patchwork where the propagation of each serotype will be more or less facilitated. Meanwhile, in Thailand cross-sectional serological surveys show that dengue infections mostly unapparent or undiagnosed reach more than 50% of the population (more than 90% of adults have experienced an infection by at least one serotype) and are incompletely reported; to be pertinent, epidemiological studies have to be based on records of DHF cases which account for less than 10% of the total infection but have characteristic symptoms and are generally hospitalized, and then recorded.

As neither treatment nor vaccine exists, the control of dengue fever is based on the reduction of vector populations, in particular by the community’s efforts to eliminate potential breeding sites [71]. A permanent control of transmission over a whole country is not realistic, and a major goal for public health authorities is to identify periods and areas at risk. A strategy to control the disease should target risk factors such as the high-density vectors, areas of low herd immunity, and urban environments, which favor virus propagation. This approach can be taken at different epidemiological levels, from individuals to provinces, each providing specific types of information.

Since the 1990’s, spatial studies have multiplied leading to the development of Geographical Information System (GIS), a powerful tool that stores spatial entities, and allows a wide range of analysis and included analysis in epidemiology [32]. Entities, such as houses are localized (georeferenced) thanks to their coordinates (latitude—longitude is the most common system) and characterized by attributes (e.g., house address; number of inhabitants; connection to water network; number of containers ···). In many countries, several geo-referenced databases exist with layers of information at different scales for the census, administrative limits, main roads, altitude, and type of land cover. DHF cases can be integrated in a GIS to generate incidence maps at different scales and time (e.g., seasons), or to describe the spread of an epidemic.

Daily records of hospitalization for dengue virus infection include information on patient address, date, age, and social status and on disease, severity, and treatment. The address leads to the place of habitation at the level of which one can observe clusters of cases, due to the short flying capacity of A.aegypti and the frequency of interrupted blood meals which allow a same vector to contaminate different family members. Moreover, the inhabitants, in proximity to their homes, create the majority of breeding sites for mosquitoes. At the community scale, the type of dwelling, connection to water network and water storage type are important factors for the creation of breeding sites, the number of which is estimated by classical entomological indices such as the Bréteau Index and House Index (respectively number of positive containers and number of houses with positive containers for 100 surveyed houses) used since decades and in many countries for dengue surveillance to classify villages and cities districts according to the density of positive containers. A major limitation is that larvae, on which these indices are based, face a high mortality during their development (because of competition for food, predators, drying up of containers) and different types of containers (e.g., a 0.2-L can or a 200-L jar) do not have the same probability to stay wet during the 5–6 days necessary to the full larval development; actually most of the positive breeding sites will not produce any vector. Larval indices appear then as not such an accurate way of estimating

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*From arthropod borne virus: a group of viruses that needs an hematophagous arthropod vector (mosquitoes, ticks) to infect a new vertebrate host.*
the number of vectors and the risk of transmission [8]. To improve the pertinence of entomological indices, WHO developed a multi-country study to promote a surveillance system based on the identification of the types of breeding sites producing the majority of pupae. Pupae do not eat, have a low mortality before becoming adults and surveillance based on the containers producing pupae is therefore more likely than using those with larvae to inform on the number of potential vectors and the transmission risk in a given area.

As an example, information on each house collected during an exhaustive survey of breeding sites in a village (north-east of Thailand) were stored in a GIS, including GPS localization, number, type and productivity of containers. Results showed that 40% -50% of the positive container (with larvae) had also pupae and that the production by containers storing water for domestic use accounted for 90% of pupae. These containers were found regularly distributed over all houses, but during the dry season, houses located along the main street exhibited higher densities of breeding sites with pupae whereas peripheral houses distant of more than 110 m from any other houses were not colonized by *A. aegypti*.

Dwelling distribution; potential containers with pupae during the dry season in a village of north-east Thailand. (a) Dwellings distribution in a village of northeast Thailand. The intensity of the grey is proportional to the density of habitation (number of houses in a radius of 100 m around each house), varying from 1 to 25 houses. (b) Isolines represent potential density of breeding-sites (a number of potential larval sites in a radius of 100 m around each house), varying from 1 to 45 containers. (c) Isolines represent density of pupae (number of pupae in a radius of 100 m around each house), varying from 1 to 86 pupae. The black line marks the contour of the village at 100 m from the periphery dwellings. The disappearance of the vector in isolated zones, in spite of the presence of potential breeding sites, is due to the stochastic pattern of the colonization by the females. The presence of water in containers is dependent on the activity of villagers and rainfall and is thus widely random. Each container can thus be emptied at any given moment, but with females laying their eggs one by one, in different containers, the production of adults can be maintained if the density of potential breeding sites is sufficient. In dry season the total number of water containers decreases and in isolated houses the females, whose flight is made more difficult by low air humidity, are brought to lay all their eggs in a small number of containers, whose drying out may lead to the local disappearance of the vector. At village scale the zones with higher dwelling density, share a greater number of potential breeding sites, which are unlikely to all, dry out simultaneously. According to Figure 32.1, the local disappearance of *A. aegypti* takes place when density of potential lodgings is lower than 3.5 sites/ha.

However, transmission is probably homogenous in the whole village due to movements of humans and vectors in areas with different levels of risk. These observations could help to improve the control strategy: The exclusive treatment of the most productive containers in the most dense areas of villages could reduce the production of vectors with a better cost–efficacy ratio than the exhaustive treatment of all containers in every houses. Sociological patterns in relationship to environment must be taken into account to orient villagers in strategy for elimination of potential breeding sites, as most are filled by house owners.

Higher dwelling density also favor contact between vectors and hosts, whereas the presence of administrations, temples, markets, tourist areas, and proximity of main roads increase the risk of spread or importation of virus through travelers. Once a virus is introduced in a populations, infection involves the progressive immunization of potential hosts and the probability of an infested mosquito “finding” a susceptible host is likely to decrease until the transmission stops, whereas susceptible hosts are still present in the community, according to a similar stochastic process that causes interruption of pupae production in villages. Transmission in small communities is characterized by successions of epidemic periods due to emergence
of imported viruses, followed by long interruptions. Local interventions for elimination by ULV pesticides of females can thus be effective short-term, but must be carried out at the beginning of the epidemic, with the risk of being launched when the virus has already spontaneously disappeared. The development of control and prevention strategies implies that incidence data are aggregated at a higher level. Cliff and Hagett [10] established empiric rules linking the size of host population (several tens of thousands of potential hosts are necessary to allow a sustainable endemic transmission) with waves of incidence or delay before interruption in transmission of infectious diseases and characteristics of the disease (measles, influenza). They also showed that the spread of a disease is a diffusion process dependant on the density of communities but also on distance between communities.

Information on density of human settlements and their distance from each other cannot easily be obtained from a census or map as the expected information is complex and may change rapidly: the actual limit of communities (that is not only an administrative definition or a dot on a map), number and density of dwellings in the different community sectors, distance from other communities, presence and size of roads. Another approach is based on satellite images to obtain an accurate description of the dwelling distribution. Rodgers and Randolph who delineated environments favorable for tsetse flies in Africa through information provided by the meta-analysis of the dense literature written on trypanosomiasis (sleeping sickness) during the twentieth century and the classification of vegetation provided by satellite images from Landsat and NOAA did a precursor work using remote sensing data in epidemiology [6]. Such research opened a vast field of applications. In an attempt to adapt method to epidemiological studies in urban areas, a preliminary step is the use of satellite data for the estimation of distance and densities of places where potential cases live.

A classification performed on a Landsat image used geographical coordinates of several known inhabited areas to characterize the corresponding pixels in the satellite image. A computer process using specific software is then initiated to find all pixels having same values of radiometry in the satellite image and enables the identification of all zones with (likely) same type of land use that is the inhabited areas. The result is confirmed by a comparison with the census giving a 90% correlation between the number of pixels and the number of inhabitants in each administrative entity (1 pixel = \( n \) inhabitants). For each subdistrict, we can calculate the population density by using the census associated to the satellite image (1 pixel = \( n \) inhabitants). Moreover, the distribution of “urban” pixels is not a random process but correspond to the expected urbanization structure: Beside some isolated pixels corresponding generally to farms or small hamlets, most are grouped, longitudinally (along roads) or in polygons (villages, cities).

\[ \text{Pixel: the smallest spatial unit in a satellite image, where the land use is characterized by its radiometry measured by a satellite.} \]

Figure 32.6, areas with medium density of urbanization (urban pixels) and distant from the main road, faced more epidemic events than areas with higher density of inhabitants. Development of herd immunity is a dynamic and heterogeneous process: Areas with outbreaks in 1997–1998, where relatively less affected during the precedent years, had a lower density of immunity, and therefore a higher risk to develop epidemics. After field investigations to quantify transmission (density of vectors, level of herd immunity) in specific communities, other communities presenting similar spatial characteristics can be identified on the satellite images (GIS) and epidemiologic results can (carefully) be extrapolated.

The study of spatial factors in the transmission of dengue thus highlights strong constraint, which structure transmission in large communities, mainly the density of vectors, the contagious process of transmission [2], and the density of susceptible hosts. However, in small communities, the low-flight capacity of vectors and social variability induce local heterogeneities. The females emerging in a given house will more frequently bite inhabitants of this house or nearby neighbors,

Figure 32.6. “Urban pixels” distribution and the number of epidemic months among the 103 sub districts (1997–1998 Dengue outbreak, Nakhon Pathom Province, Thailand). Darker red corresponds to an increasing number of epidemic periods by sub district. Blue spots are aggregates or “urban pixels” obtained by the classification process of a Landsat satellite image. See color plates.
but can by chance, disappear. The severely sick individuals have to go to hospital where they are relatively isolated, but the healthy virus carriers will continue to move within their community contributing to locally spread the virus [49] but also to the constitution of a high density of immune hosts. Others can also traverse long distances thus taking part in spatial expansion of the virus. As a consequence of this discrete process, the contagious transmission pattern can reach any community, despite the vector's low-flight range (a few hundred meters for A. aegypti) and that most humans are globally sedentary.

Spatial analysis of dengue transmission using modern tools and technologies provides new insights on former studies and a better understanding of disease diffusion process. In the frame of control activities, the use of GIS and satellite images will allow identification of small communities with low probability of durable transmission where the community participation for the elimination of containers is traditionally well developed and that do not need to be preventively treated as they do not participate significantly to the virus diffusion. But they will largely benefit from the treatment of cities that will reduce the number of infective carriers potentially spreading the virus.

32.3.2.2 Japanese encephalitis: changing epidemiological pattern in a changing environment
Japanese encephalitis (JE) is a mosquito transmitted viral disease (arbovirosis) due to the JE virus (JEV, Flaviviridae family). The basic selvatic cycle among birds involves ornithophilic mosquitoes and is in a large part responsible of the spatial extension of the disease during the twentieth century. The JEV is generally transmitted trough a domestic cycle to pigs by zoophilic mosquito species. Theses mosquitoes rarely bite humans whose infection is therefore accidental. Moreover, humans provide a parasitic impasse, as mosquitoes biting humans cannot be infected. Birds are resistant to the infection whereas infected pigs show high rate of abortion. The local virus transmission is closely associated with porcine farming, which has regional disparities (e.g., size of farms, feeding pattern, structure of breeding); whereas pigs trade contributes to the disease spread.

In Thailand, after epidemics in northern provinces during the 1980’s (several thousands of cases per year) the JE vaccination program was launched in 1990 and from 1997 has become part of the Expanded Program of Immunization in 28 provinces. The rare infections observed during the last decade (less than 100 per year) concerned mainly adults living or working in proximity of porcine farms, and where distributed over the whole country.

The context of transmission evolves concurrently with changes in agricultural practice. In particular huge industrial farms raising thousands of animals have replaced family farms with only a few dozen pigs. Theses farms being often located at short distance from inhabited communities create a risk of exposing nonimmunized population to the spread of the virus from areas of intense transmission among the pigs. An evaluation of this risk is necessary in order to develop preventive or reactive strategies.

The traditional cycle of transmission (during the major epidemics in the 60’s and 70’s prevailing in Thailand was due to rural mosquitoes (mainly Culex tritaeniorhynchos, C. gelidus, C. vishnui, C. fuscocephala), developing in rice plantations or ponds, and biting mainly birds and domestic animals (buffalos, pigs). The population lived near cultivated areas, generally in hamlets or small villages gathering a few dozen traditional houses built on piles, each family keeping some domestic animals within its dwellings. However, sometimes the zoophilic mosquito attracted in the village by domestic animals could feed (about 2%) on human blood and thus transmit the JEV. Epidemics generally then break out quickly among the villagers living at short distance from each other, infected pigs being at the origin of virus persistence. However, virus disappearance was also rapid following the progressive immunization of pigs (human do not allow infection of mosquitoes), preventing the establishment of an endemic transmission. Virus first arrival in the villages was largely random, due to the pig trade at the origin of the introduction of infected pigs in villages (birds could also play a role).

During last decades, rural landscape has greatly changed. The small hamlets have progressively disappeared to the profit of larger villages, where inhabitants have easier access to services, schools, health centers, electricity, and water supplies . . . In addition, agricultural practices have evolved toward greater intensification of farming. Considering factors in JEV transmission, villagers live at greater distance from rice plantations, family breeding of pigs has become rare, and transmission by rural vectors is therefore more difficult. Together with the vaccination, this has practically wiped out the disease in humans. On the contrary, the larger pig farms generally located in not densely inhabited areas for reasons of public health and safety are always in the flight path of Culex species from rice plantations.

The transmissions among pigs is very intense and after 6 months of fattening in industrial farms nearly 100% of pigs arriving at the slaughterhouse are positive in JEV antibodies. Persistence of transmission is, again, made possible by the pig trade, but at the difference of the former situation, now the fast renewal of piglets in farms, which regularly bring new susceptible hosts, allows the durable maintenance of the virus circulation. Although pigs are more numerous, the number of humans in contact is much lower than it was when family breeding was practiced; they are the owner and farm employees, who now provide the majority of the rare JEV cases since the last decade.

An alarming factor, however, is the presence in the industrial farms of Culex quinquefasciatus, the most widespread urban mosquito in tropical zone, and thus now in the large Thai villages, very anthropophilic for its blood feeding but also very opportunistic, as this species also feeds on birds or pigs. Moreover, it is a confirmed vector of JEV, in the laboratory and in natural environment. The participation of this species to the transmission cycle of pig farms, associated to its presence in villages modifies the epidemiologic background and in the frame of constant increase in human settlement could cause the virus to be transmitted to large nonimmune, nonvaccinated human populations.
In view of this threat, various studies were undertaken to characterize and delineate risk and develop answers. One objective is to highlight variations in prevailing mosquito species according to environment, from rural to industrial farm to within villages and their risk to be in contact with unprotected populations. In an experiment developed in Thailand, mosquito traps were installed in pig farms then at increasing distances until the closest villages, generally located a few kilometers away. From analysis on engorged mosquitoes, the origin of the blood meal can be identified (ELISA techniques), whether from humans, pigs, or other vertebrate. Each trap site was georeferenced by GPS technology. Satellite high-resolution photography has been carried out (Google earth®) which allowed visualization of sites and their environment and evaluation of flight distances. Moreover, starting from this photography, various layers of information can be created and used through a SIG approach.

Species feeding only on pigs or that do not flight to inhabited areas are not very likely to transmit the JEV to humans, whereas exclusively anthropophilic species have little chance of being infested. The risk is in the diversity of behaviors. From these results, strategies for preventing and controlling the disease can be elaborated such as identification of the populations in need of vaccination or antimosquito activities. It may also be possible to make modifications in the pig trade. This example shows how, modification of environment, in this case of anthropic origin, modifies the sphere in which diseases emerge and develop.

In other situations, a change can be favorable, such as the draining of marshy areas in Southern Europe, during the twentieth century, which has contributed to the disappearance of local malaria transmission. However, special awareness must prevail as the increase in intensive agriculture together with rural migration implies dramatic modifications in environment and contact between populations (pathogens, hosts, vectors) that may have significant consequences on transmission of rural diseases. Another example is that because of intense use of insecticides for crop protection many species of mosquitoes, despite being not the target of interventions, have developed resistance to chemical insecticides.

### 32.3.3 Climate-Dependent Arboviroses

#### 32.3.3.1 Dengue, aedes and climate: relationship between temperature and dengue haemorrhagic fever incidence

Dynamics variations in dengue incidence range from low incidence endemic pattern to high incidence, the epidemic pattern and generally follow the seasonal variations, and longer cycles over 2–10 years.\(^8\) Level of dengue virus transmission is a resultant of the dynamics of three interacting populations, host, virus, and vector [73]. Host dynamics beside demographic component (births, deaths, immigration) integrates the change from susceptible to infected and to immune status at a rate dependant on incidence. The virus is an obligatory intracellular organism, and its dynamics follow the number of infected hosts and vectors. The vector dynamics involve different phenomena: production of females in breeding sites, infection on infected hosts, and infection of susceptible hosts.

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\(^8\) cf C.2.1 for generalities on dengue
The part of the cycle, which takes place in the vector, is subjected to weather variations with a direct impact on the density of vectors at several levels. The eggs of \( A. aegypti \) generally laid above water can wait several months for the first rains enabling their hatching as well as the creation of durable water filled breeding sites; a high temperature accelerates larval development, but increases evaporation in the breeding sites; high humidity help flight and supports survival and dispersion of adults. Moreover, high temperatures reduces the duration of the gonotrophique cycle (GC), period between two blood meals (for digestion of blood and maturation of eggs) and allows a greater number of blood meals during the life of a female; the duration of the extrinsic cycle of multiplication of the virus in the mosquito (extrinsic incubation period, EIP) is also reduced allowing for a greater number of females to become infectious.

The three principal climatic parameters, temperature, rain, and humidity are correlated but each one has proper dynamics: In tropical zone, the rainy season which follows the hot season is generally accompanied by a reduction in temperature; humidity decreases with high temperatures. Incidence also exhibits seasonal variations. In Thailand typically, the first rains lead to a rapid increase in dengue incidence, followed by a peak in the middle of the rainy season and then a slow decrease until a minimal value during the dry, cold season. The figure shows succession of these climatic variations and incidence variations observed in the north–east of Thailand.

It is thus as a result of all climatic factors taken into account that the relation climate-transmission can be evaluated.

Complexity of those phenomena appears if we try to interpret the peak/decrease observed during the rainy season in endemic countries.

This pattern may be in large part driven by the variation in vectors number and probability to perform a complete EIP. The decrease in temperature affect different steps of the transmission potential (GC, EIP, and larval growth); heavy rains may wash up larvae and pupae from the small containers or decrease the density of food; populations of predators and pathogens of \( A. aegypti \) may stabilize at a high density level after a slow process due to the quasi-disappearance of \( A. aegypti \) during the dry season. But other factors are essential. Epidemics of infectious diseases (with no vector involved) generally follow a progression according to a bell-shaped curve: The number of cases increases in an explosive way, then reaches a threshold due to a progressive immunization of potential hosts and a low probability of the virus being transmitted to a susceptible host. The incidence then decreases quickly. The same phenomenon applies to arthropod-borne diseases and in the middle of the rainy season, after several months of intense transmission the density of susceptible hosts can have reached a threshold making further transmission difficult.

Several factors vary simultaneously and the role of temperature alone is difficult to quantify. However, constants, thresholds, and tendencies can be described.

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**Fig. 32.8.** Japanese encephalitis virus cycle of transmission in Thailand: past and present. The main JEV cycle in Thailand has evolved from a rural agricultural pattern to a village-pig raising farm environment.
Laboratory analysis showed that an increase of 10°C, within the limits compatible with vector survival, that is between 20° and 35°C, approximately divides in half the duration of the phenomenon considered: GC, EIP, and larval development.

Each year the seasonal drop in number of cases intervenes, during the rainy season, when the temperature reaches between 27° and 28.5°C, whatever the accumulated incidence since the beginning of the period of transmission, and thus independently of the level of immunity reached by the population.

In districts of northern Thailand located at an altitude higher than 600 m (Fig. 32.9b), the transmission is stopped during 4–6 months of the cold, dry season during which the rain decreases then stops. The monthly average temperature drops until falling below 21°C for 2–3 months, then rises until the first rains in May. An essential difference with the situation observed in Figure 32.9a is that virus circulation is stopped for this long cold period. As a consequence, the resumption of the transmission is delayed for several weeks after the first rains, corresponding on the one hand to the reconstitution of vector population but also for reemergence of the virus, initiated by viruses imported by travelers or transmitted by vectors resulting from eggs infected by females of the preceding generation.

On the contrary, the generalization of the water supply allows for a greater number of breeding sites to remain productive during the dry season, but it is especially the appreciable increase in minimal temperatures observed during the cold season, which makes it possible to avoid the disappearance of the virus. This illustration of a possible effect of global warming, must however be considered in the context of a country of endemic transmission of the dengue viruses. A high temperature would not be enough to allow virus transmission of the dengue in any area, even tropical: the vector must be present, and the social and cultural context, in particular the habitat, must allow a close contact between vectors and hosts.

The global warming is not the only factor likely to change the epidemiological situation, the enlargement of the area colonized by A. albopictus, is also highly challenging health authorities. The Asian tropical rural vector of dengue virus is becoming more urban, breeding in tires, which trade has largely contributed to its dispersal and over the last decennia has spread to Europe, USA, Southern America, and Africa. In these areas, the low level of herd immunity could favor the propagation of dramatic outbreaks.

32.3.3.2 The Rift Valley Fever: A climate-related arbovirosis in Senegal Zoonosis with vectorial transmission are all, more or less, dependent on the climate which can be defined or characterized by all the conditions combined such as the air or water temperatures (maximum, minimal, average), the winds (intensity, direction), the relative humidity and its daily and seasonal variations, sun, rain (intensity, mode, a number of
rainy days, total quantity and distribution), and others. These conditions have significant role in epidemiologic cycles, largely due to the vector biology. Among arbovirosis, those, which are transmitted by mosquitoes, having aquatic larval stages, represent a category of particularly climate-dependent diseases. In recent years, some have earned considerable importance: emergent in North America (West Nile virus), reemergent in West Africa (Yellow Fever), or in Southern Asia (dengue); or expanding in many countries of Africa and recently in the Arabic Peninsula (Rift Valley Fever, originating in East Africa).

To analyze relationships between environmental conditions and evolution of these diseases, we studied the fever of the Rift Valley in central Senegal, where it emerged in epidemic form in 1987. Several species of mosquitoes were found carrying the virus but two of them can be regarded as the endemic and/or epidemic vectors: *Aedes vexans arabiensis* and *Culex poicilipes*. Ferlo, a Sahelian area of approximately 60,000 km², represents a zone of extreme importance for the herds of ruminants (bovine, ovine and caprine), which can traverse hundreds of kilometres in search of fertile pastures. The appearance of these pastures is related to rains which, also fill the many temporary ponds of the area, provide water for animals, and stimulate development of sometimes extremely abundant populations of mosquitoes, able to transmit many viruses including the Rift Valley Fever to both animals and humans.

### 32.3.3.2.1 Climatic environment and viral transmission risk

Our studies relate to the ecology of these two species (73 % of the mosquitoes present) in relation to rainfall: How the rains can modify conditions of virus transmission of a mosquito to a host population? In this area of the Sahel the rain season is short (4 months), and variable from one year to another, (e.g., 2002 annual rainfall reached 299.1 mm; and 379 mm in 2003, showing a deficit of respectively 25 to 5 %

![Breeding site dynamics of Rift Valley Fever vectors](image_url)

**Fig. 32.10.** Breeding site dynamics of Rift Valley Fever vectors: evolution of cumulative rainfall and abundance variations of *A. v. arabiensis* and *C. poicilipes* females. During the rainy season of the Sahelian region of Barkedji (Ferlo, Senegal) in 2002 and 2003, mosquito-breeding sites have been explored for four periods of 10 days. Red line, Cumulative rainfall; Green circle, Relative quantities of *A. v. arabiensis* females; Brown circle, Relative quantities of *Culex poicilipes* females; Relative numbers of *A. v. arabiensis* females; Cumulative rainfall. The surface water used by cattle are mainly temporary ponds where Rift Valley Fever Virus Vectors are breeding during rainy season in the province (Ferlo, Senegal). See color plates.
from the average over the last 40 years). By studying, in parallel, the variations of adult female populations and the characteristics of the rainy season, we tried to connect these data between them and to consider the extent to which a rainy season characterized by a certain quantity of cumulated water, a number of days of rain, their duration, rate or rhythm could stimulate, or not, an endemic or epidemic transmission of the Rift Valley virus to domestic animals and humans.

32.3.3.2.2 The survival adaptations of mosquito vectors
After emergence, females, once fertilized, take a first blood meal essential to the formation of eggs which will be laid at water level of the temporary ponds, either on wet ground close to water/air interface (case of *Aedes vexans*) or on the water surface (case of *Culex* sp.). If the eggs of *Aedes* are not immersed in water (no or very weak rains), they can wait several weeks even several months, until the rains of the following year to hatch, spending the period of dryness in quiescence. On the contrary, the great majority of eggs of *Aedes*, will not be able to hatch before having undergone a certain drying period, estimated at one week approximately, which corresponds to the duration of their embryogenesis.

The eggs of *C. poecilipes* laid in a raft by the female on the surface of water cannot enter in quiescence: They hatch on finishing embryogenesis or die if the pond has previously dried out. However, the appearance of a few adult female *Culex*, shortly after first rains of the wet season, after a period of dryness lasting sometimes up to 8 months, attests to the capacity of some females to resist the dry season in shelters of particular microclimatic conditions. The adults of *Ae. vexans*, appear only the fourth or fifth day after the first rains filling the ponds. *Culex* and *Aedes* thus have two different methods to resist the adverse conditions of the dry season: In the first case by surviving through some resistant adults and in the second case surviving from the egg populations, which can be extremely dense and which are ready to hatch with the first rain. The dynamics of these two populations will therefore be quite different.

32.3.3.2.3 Rainfall and vector population dynamic
Comparison of rain diagrams with relative numbers of *Cx. poecilipes* and *Ae. vexans* females during rainy season of 2002 and 2003 will enable us to understand dynamic these two vector populations.

At the beginning of a rainy season, the number of *Culex* females is low and they require stable ponds with sufficient water level so that the species biological cycle can be established: The first females can each lay a hundred eggs in one cycle and complete a cycle in 10 days, but the establishment of stable *Culex* populations may take several weeks. On the contrary, at the beginning of the rainy season, *Aedes* are potentially extremely abundant in the form of quiescent eggs. The quantity of females will depend on the surface area of ponds flooded after the first rains, as eggs laid by the females the previous year are distributed all over the pond surface.

Evolution of *Cx. poecilipes* populations is thus related to a constant filling of the breeding sites, whereas the dynamics of *Ae. vexans*, more complex, will depend on the quantities of rainwater but also on the period separating two rains, which must exceed the duration of embryogenesis to permit the eggs hatching.

Observations made during these studies can enable us to associate a type of rainy season to the potential risk of viral transmission. The actual beginning of the rainy season seems particularly significant: If the rains are abundant from the start (as in 2003), most eggs may hatch simultaneously and the population of *Ae. vexans* will quickly be very abundant, the risks of emergence of the virus even if it is still rare will be very high. In addition, significant rainfall means that pastures develop quickly, thus encouraging the early arrival of many herds of transhumant ruminants. If, on the contrary (year 2002), the rains at the beginning of the season are weak and scattered, *Aedes* populations will remain on a low level and the risks of viral emergence will be much less.

During the next weeks, the quantity of *Aedes* female will depend on the number of eggs laid by the first females of the year; so for those which hatch, a lag between rains of at least a week is necessary, which is seldom the case. The eggs, which do not hatch, will provide stocks able to wait until next year’s rainy season. Then, the evaporation of the water of the ponds being generally higher than the rainwater input, no more egg hatching is possible. But, if as in 2002 (and a little less in 2003), significant late rains occur, the level of the ponds rise again, and a new batch of *Ae. vexans* will appear at the end of the rainy season. Herds being numerous, the risk of virus transmission from viremic animals to nonimmune animals increases and this is the traditional period of epidemics. Moreover, the risk of vertical transmission from an infected mosquito female *Aedes* to her progeny also increases, the virus can be maintained in eggs and re emerges quickly from *Aedes* the following year as soon as the rainy season begins.

The role of *C. poecilipes* appears simpler and in particular restrained to the transmission in the second half of the rainy season, the only period during which this mosquito species is abundant. The two species play then different epidemiologic roles. *Ae. vexans* has one of initiating the epidemiologic cycle and virus amplification at the beginning of year, then virus circulation at the end of the year and its persistence in environment through vertical transmission from one year to another; *C. poecilipes* contributes to the circulation and the risk of outbreak at the middle and end of the rainy season.

It can be assumed therefore that, provided that the serologic state of sedentary and transhumant herds of ruminants with respect to the virus of RVF is known, and that the rainfall records are quickly made available, it is possible to predict the risks in a rather precise way, according to the likely abundance and dynamics of the two main vector species populations.

32.3.4 Rain, Rodent, and Rice: Leptospirosis
**Epidemics in Thailand**

After 8 years of epidemics, affecting thousands of people yearly with the highest incidence in 2000 (14,285 cases), leptospirosis seems to be fading in the epidemiological records to the
satisfaction of public health officers and local communities. With a total of 1202 deaths from 1997 to 2004 mainly in the Northeast, Northern, and Southern regions, leptospirosis had become a major threat in rural villages. As an occupational disease, it has showed a specific vulnerability, as 75% of the cases are men and farmers. Prevention has been the main strategy of the Ministry of Public Health (MOPH) and its provincial and local offices to control the epidemics of leptospirosis.

32.3.4.1 Rapid emergence and decline of leptospirosis: marked patterns in space and time. Leptospirosis is a worldwide zoonosis, occurring mostly in rodents from tropical and subtropical countries, where high rainfall helps the transmission of the pathogenic bacteria, from animals to humans, directly, or through water contaminated by rodent’s urine. In Thailand, leptospirosis has shown a pattern typical of infectious disease epidemics, a rapid emergence since 1997 and decline starting in 2001. Leptospirosis is a seasonal disease, amplified in incidence during and after the rainy season, from June to October and later in the southern region.

In collaboration with the Ministry of Public Health, an active mapping was set up to produce monthly maps of leptospirosis incidence as a surveillance and control tool. Monthly cases, recorded by the MOPH from January 2000, were aggregated by month and incidences (for 100,000 population) calculated at district level, using population data.
from the National Statistical Office. Monthly rainfall, recorded by the Thai Meteorological Department in 1250 stations, is spatially interpolated over the country to calculate the average by district. All data are regularly integrated into a Geographic Information System (GIS, SavGIS®). For the whole country, a positive correlation (0.49; \( p < 0.0001 \)) between rainfall and leptospirosis incidences illustrates the action of long rainfall periods, amplifying the range of infections, by spreading the bacteria and exposing rural populations to higher risk.

Spatial and dynamic epidemiology show marked patterns with the highest incidences recorded in the north-eastern and northern regions with a near one month gap between the monsoon rainfall and the recorded cases. Some sporadic spots of high incidences are recorded later in the year in the southern region, also in relation to the longer rainy season.

32.3.4.2 From observed to real incidences: difficulties in assessing the extent of an epidemic Although retrospectively studying a disease, based on either epidemiological records or research and laboratory investigations of human or animal prevalence, recurrent difficulties lie in comparing results obtained with evolving techniques. Back before the emergence of leptospirosis, serological investigations in humans or rodents have fed research work on the identification of a growing number of Leptospira serotypes. For instance, immunofluorescent techniques used in histopathology for the visualization of Leptospira in kidney sections are specific of serotypes, expected according to the rodent species involved and the ecosystem where it was trapped. However, the spread of an unexpected serotype would lead to false negative diagnosis.

Epidemiological records show main biases related to the health system, structure and quality, to the frequentation of health services by local populations and also to the difficult diagnosis of Leptospirosis presenting symptoms similar to fevers with other etiologies, such as dengue fever or scrub typhus. Before the first large epidemics in 1997, the clinical diagnosis was not sufficiently specific and the number of cases was possibly underestimated. Screening tests on suspected patients were generalized in 2001, each provincial hospital sending blood samples to a regional laboratory. It explains in part the decrease in incidence as confirmed cases were recorded the same year, while in 2000 the high concern for leptospirosis epidemics and awareness of the health sector contributed to attribute unknown fevers to leptospirosis cases.

32.3.4.3 Investigating hazard and exposure to understand leptospirosis dynamics Higher density and diversity in species prevalence of rodents explains the higher incidences in the north-eastern region compared to very low incidences in the central plain, despite intensive rice culture.

Serological investigations of leptospirosis in rodents have shown positive cases throughout the country and have never distinguished spatial patterns of prevalence \([7, 33, 65]\). Several rodent species, although occurring throughout the country, were found positive: Bandicota indica, B. savilei, Rattus rattus, R. exulans, R. norvegicus, R. argentiventer, and R. losea. Other species were never tested in sufficient number to make any assumption relating to their noninvolvement in the transmission of leptospirosis. Not only were different serotypes of Leptospira interrogans identified in rodents, some relatively common like L. javanica, L. autumnalis, L. bataviae, and L. pyrogenes, but some other serotypes were also identified such as L. canicola, common in dogs, and L. Pomona, common in pigs and cattle, showing the proximity with domestic animals and the dynamics of bacteria, possibly infecting different vectors \([7, 26, Herbreteau et al., 2005, unpublished data]\). Therefore, the pathogenic bacteria present a low-host specificity, increasing the range of colonized habitats. Rodents inhabit most of the biotopes in Thailand, from natural biotopes, fields, gardens to houses. In the cycle of transmission, rain and standing water are a critical factor of transmission, maintaining the bacteria and also spreading them in contact with humans. Wet areas, flooded fields, and especially rice fields, are probably the main places of transmission. In order to delimit the leptospirosis risk, related to the rodent presence, tools have been developed using SavGIS® and its integrated remote Sensing module (RS) \([26]\). The basic principle of such process is to delimit the potential habitats of the main vectors of leptospirosis, which represent also the hazard in the risk assessment. The land cover is analyzed and interpreted as land use from high spatial resolution satellite images, using different vegetation indices. Such maps of the potential distribution of rodent species can help to target surveillance in risk areas and plan preventive actions.

32.3.4.4 Decline of leptospirosis: the role of prevention and public awareness Immunity is usually a major factor explaining the decline of emerging diseases. In the case of leptospirosis, it seems that serotype-specific antibodies are protective and that a patient is immune to reinfection with the same serotype. On the contrary, over 200 pathogenic serotype divided into 25 serogroups have been described. This huge diversity has also been found during serological surveys, where different serotypes were generally identified in the same areas, either in rodent vectors or in patients. So, immunity may only have played a minor role in leptospirosis decline.

Since the first epidemics, the MOPH has conducted active prevention campaigns to increase public awareness of the situations of high exposure to leptospirosis infection. They have recommended to the farmers to wear protective equipment, such as boots and gloves, as well as teaching the younger inhabitants of the danger of walking barefooted in any puddle or wet area.

Teachers taught songs about the “Rat’s urine disease” (in Thai: “rok chee nu”), and villagers were informed during plenary meetings in the courtyard of dispensaries. Thanks to

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1SavGIS® is a Geographic Information System (GIS) freeware developed by the French Development Research Institute (IRD, Marc Souris).
these efforts, leptospirosis is no more a mysterious disease for any Thai citizen. Even if working with boots in paddy can be very tricky, exposure has been reduced.

At last, easier access to health care has increased in treating fevers, allowing a better and faster treatment. If leptospirosis remains an environmental threat for farmers, a better surveillance in focused endemic areas and improved health care have contributed to its exemplary decline, at least in the epidemiological records.

### 32.3.5 New Pathogens, New Diseases: A Faunistic Approach to Reservoirs and Their Hosts

Ticks are also vectors of infectious diseases and participate in the emergence of several viruses belonging mainly to the rickettsia families (since 1991 more than 12 tick-borne rickettsial infections have been discovered). Also, ticks can transmit bacteria and protozoa.

The “Lyme disease,” a seasonal polyarthritis of New England, appears as one of the most emblematic of emerging tick-borne viral diseases from the past decade: The disease appeared in the eponymic county of Connecticut state and was associated to Ixodes tick genus and wild ungulates. *Ixodes scapularis* and *Ix. pacificus* are recognized as the vectors10 and the Virginian deer (*Odocoileus virginianus*) as a main host for adult ticks whereas rodents (*Tamias stratus* or *Peromyscus leucopus*), and, when rodents are in low density, birds (*Turdis migratorius*), or domestic dogs can be vicarious (secondary) hosts.

To date among the 869 tick species known from around the World, 53 species have been identified in Thailand, and are present in the Oriental biogeographical region. The particularly marked biodiversity known in Southeast Asia is also expressed in its number of *Acaridae* species.

Our objective in Thailand was, to produce an inventory of tick species with reference to those of medical importance. Most of Thailand has been explored and specimen collected, new species and new distribution described. Altogether using the entire literature available on the subject and our georeferenced records, a precise tick species distribution was provided. In order to obtain such degree of precision, beside a precise taxonomy, place of collection, date, and hosts were recorded. Using a Geographical Information System (GIS Savane freeware), we were able to generate maps, which will ultimately be used for risk evaluation of tick-borne transmitted diseases in Thailand.

The comprehensive approach of tick-borne diseases transmission requires knowledge of tick ecology as well as their vertebrate hosts and their seasonal geographic distribution. Even if the host–ectoparasite specificity appears determinant, it is known that for a region one virus can be transmitted not only by one tick species but also by another tick species, in another region, mostly when climatic factors are different, and that another vertebrate host will replace the former from a different biogeographical domain.

Such dynamic epidemiology will also need to take human behavior into account in order to evaluate the risk of tick-borne disease transmission to in fine propose prevention and control strategies. The table below presents the biodiversity of ticks and hosts regarding the arthropod-borne viruses transmitted by ticks and belonging to the biogeographical domain of south Asia.

The Langat virus strategies: Using the most abundant vector in the appropriate territory: The Langat virus (flavivirus) is responsible for meningo-encephalitis in humans, with a rodent reservoir of virus in Thailand, Malaysia, and Siberia. In nature, *Ixodes spp.* are the vectors from one vertebrate to another: *Ixodes granulatus* in Malaysia, *Ixodes persulcatus* in Siberia, and *Haemaphysalis papuana* in Thailand are the main vectors of the Langat virus. (I) Underlined are tick species present in Thailand; (II) probably surviving after accidental infection, potential to transmit; (III) *spp* (number of unidentified species).

Finally, if several territories like Europe or North America have been well documented regarding acarina fauna and their associated diseases, tick inventory and spread are very scarce for Asia at large, where studies have been limited and/or data not published. The present inventory and distribution are unique and pioneer the domain for Thailand. [64]. It is the first comprehensive biogeography of ticks from Thailand including potential vectors of human and animal diseases in Thailand.

The number of arboviruses isolated in Asia can be estimated at 126 (53 are transmitted by ticks and 30 of them are not known as pathogenic for vertebrates) among a total of 526 known to date for the world. Most of them belong to the *Flaviviridae* and *Bunyaviridae* families. Finally, 15 tick species can transmit a virus to humans in ASIA and 14 of them are present in Thailand. The present maps show a georeferenced distribution of ticks by species and can be compared to the table for preliminary risk assessment.

### 32.3.5.1 The filovirus: a virus family without host or reservoir—first evidence on ebola virus natural reservoir

Since the appearance of the first epidemic in 1976 and the first description of Ebola virus, many studies were undertaken in order to solve the mystery of the natural history of Ebola virus in Africa and to understand in priority, the emergence of epidemics so devastating to man and then also in nonhuman primates [14,46]. The natural history can be defined by viewing the whole system of transmission methods and virus circulation in its natural environment from its natural host (or reservoir) to humans. It thus includes determination of the natural Ebola virus reservoir, circulation of the virus within the population of its natural host, the passage of the virus to intermediate animal species, sensitive to the virus (i.e., developing a lethal infection), and finally the contamination of humans from the natural host or from the intermediate species. This text gives a progress report on all of these stages.

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10 In Europe and Asia, others vectors transmit Lyme disease respectively, *Ix. ricinus*, and *Ix. persulcatus*, which spread will map a risk geography.
32.3.5.1.1 A homogeneous ecological framework

Since the discovery of Ebola virus in 1976, thirteen epidemic outbreaks (nine due to the subtype Ebola Zaire and four to Ebola Sudan) and two isolated cases (one due to Ebola Zaire and the other in Ebola Ivory Coast) have affected the African continent in three distinct periods: three outbreaks between 1976 and 1979, four between 1994 and 1997, and six between 2000 and 2004. On the whole, Ebola virus was

**Fig. 32.12.** Tick survey in Thailand. Top (left): Location of tick collection sites during the period 1999–2005 survey in Thailand; (right) Absolute number of specimen collected by province (abundance). Bottom (left): Dark grey are the provinces where new tick species have been identified for the first time in Thailand; (right) the absolute number of species identified by province (biodiversity).
responsible for approximately 1850 clinical infections including nearly 1300 deaths. In addition, the descriptions show a tendency to a regional specificity of the subtypes of Ebola virus: Ebola Ivory Coast in West Africa [15,39]; Ebola Sudan in East Africa [3,17,31,42,61,72,74] and Ebola Zaire in Central Africa [30]. However, in spite of this relative geographical specificity, the ecological context of the human epidemics due to the African subtypes of the Ebola virus is relatively homogeneous and includes various forest areas located around the equator. These areas have similar ecological and climatic characteristics. The vegetation is dense, and the climate is tropical, hot and wet with two peaks of precipitation separated by two dry seasons.

32.3.5.1.2 The passage of the virus to the man In the majority of epidemics, the source of contamination of the

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Fig. 32.13. Distribution of Haemaphysalis genus in Thailand. See color plates.
first person identified as infected (first case) is unknown. It is the case for all epidemics of the period 1976–1979, of epidemics of Mékouka (Gabon) in 1995, of Booué (Gabon) in 1996, of Kikwit (RDC) in 1995, and of all the epidemics due to Ebola Sudan in 1976, 1979, and 2004 in Sudan and in 2000 in Uganda. Recent work however, allowed us to reveal that human contamination appeared these last years following the handling of infected carcasses of gorillas, chimpanzees, and duikers. Thus, it is probable that the carcasses of gorillas were at the origin of the transmission chains of Olloba 2001, Grand Etoumbi 2002, Entsiami 2002 and Yembelengoye 2002. Carcasses of chimpanzees were at the origin of the chains of Etakangaye 2001 and Olloba 2002. Lastly, carcasses of duikers were at the origin of the chains of Mendemba 2001, Ekata 2001, and Mvoula 2003.

### 32.3.5.1.3 The intermediate animal species sensitive to the virus

At the time of epidemic episodes, which have occurred in Gabon and in R.C between 2001 and 2004, many dead animals were found in the forest areas touched by the epidemics. On the whole, 44 carcasses were discovered, samples taken then analyzed at the laboratory of the CIREF.11 Centre International de Recherche Médicale de Franceville; engl.: International Medical Research Center of Franceville (Gabon).
CHAPTER 32 FUNDAMENTALS, DOMAINS, AND DIFFUSION OF DISEASE EMERGENCE

32.3.5.1.4 Infection of large monkeys  The Ebola virus is a virus with very genetically stable ARN. For example, the mutation rate between the strains Bououé 96 (Gabon) and Zaire 76 are only 1.7% for the glycoprotein membrane (GP), 1.3% for the nucleoprotein (NP), 1.2% for viral protein structure of 40 kDa (VP40) and 0.9% for viral protein structure of 24 kDa (VP24), whereas these strains were separated by more than 1000 km and spaced by 20 years [41]. Similar differences were found between genes in the epidemic strains of 2001–2003, the strain Mékouka 94 (Gabon) and Zaire 76. In the same way, sequencing of the most variable part of GP, bearing 249 nucleotides, did not show any change between nine patients (five convalescents and four deceased) taken at the time of the epidemic of Kikwit in Zaire (RDC) in 1995 [55].

In order to understand modes of contamination in large monkeys, studies based on this stability then amplified and sequenced the coding part of GP starting from samples taken from all gorilla and chimpanzee carcasses. These studies identified a different viral sequence for each analyzed carcass. Different sequences were obtained starting from the carcasses belonging to the same species (gorillas or chimpanzees) discovered at the same time at a few hundred meters from each other. The presence of many mutations between sequences obtained from the animal carcasses suggests that large monkeys were contaminated independently from each other. The presence of positive serologies detected in chimpanzees taken before the appearance of the first epidemic in this area confirms these conclusions.

It appears that Ebola epidemics in large monkeys result from massive and simultaneous contaminations of these primates starting with the animal reservoir and during particular environmental conditions (epidemics always occur at the same time of year, during transitional periods between the dry and rainy season). The contamination of humans is perhaps carried out in the second period, generally by contact with the animal corpses.

However, other authors explain the appearance of these epidemics differently. After mathematical modeling of various epidemic episodes carried out in Gabon and the Republic of Congo between 1995 and 2005 and also of coding sequences of GP for various viral strains, it is proposed that a displacement of an “epidemic wave” already existing for ten years according to a north–west, south–east movement and originating from Yambuku, town of RDC touched by the first epidemic of Ebola in 1976 [68]. This epidemic wave would then have affected the sensitive animal populations in a dramatic way at the time of its passage.

32.3.5.1.5 The reservoir of ebola virus  In 2002 and 2003, studies include three animal trapping expeditions in two forest belts affected by the various epidemics, which have occurred between 2001 and 2005. The captures were carried out in a radius of 10 km around a gorilla carcass infected by Ebola virus, during a period of three weeks, and began only a few days after the discovery of the carcass. Conditions were met so that the captures were made at the height of virus circulation in its natural environment. A total of 1030 animals were captured, autopsied, and analyzed over a period of 4 years. These analyses showed that three species of frugivorous bats were asymptotically infected by the Ebola virus: Hypsignathus monstrosus, Epomops franqueti, and Myonycteris torquata. Thus, anti-Ebola IgG were detected in serum of 16 bats including four Hypsignathus, eight Epomops, and four Myonycteris whereas they were found in no other bat or animal species. In addition, viral nucleotide sequences were detected in the bodies of 13 bats including three Hypsignathus, five Epomops, and five Myonycteris. The sequencing of amplified fragments confirmed the specificity of sequences. The phylogenetic analysis of these sequences shows that they belong to the subtype of the Ebola virus found in Zaire. Even if this research did not achieve virus isolation, it constitutes the first biological evidence for identifying certain frugivorous bat species as Ebola virus reservoirs. In addition, these results agree with species distribution covering the epidemic areas [4].

Fig. 32.14. Tracking the deadly path of Ebola virus. The state of the carcasses allows for dating up to a few days from the death of the animal and to isolate the virus from tissue in sufficient state of preservation. Top (left): On the field sampling of cadavers and remains of animals potentially infected by Ebola virus during an epizooty of large monkeys (Gabon). Carcasses of large monkeys who died of Ebola virus infection: skull and hips (top right), hand and arm (bottom left), head in decomposition (bottom right).
This discovery consolidates certain epidemiologic indices collected at the time of the epidemics due to the virus of Marburg, another member of Filoviridae. Many bats were located on several occasions in warehouses of the cotton factory where the first patients of the epidemics worked in Nzara, Sudan, during 1976 and 1979. No source of contamination having been identified for these two epidemics, a contamination by bats in the cotton factory has been considered.

The Australian case of Marburg who contaminated two other people at Johannesburg in 1975, revealed that he had just returned from a voyage to Zimbabwe during which he had slept outdoors and once in an abandoned house whose attic was inhabited by many bats [16]. The French engineer, infected by the virus of Marburg in Kenya in 1980 and responsible for the contamination of the doctor who had treated him, had, a few days before becoming sick, visited several caves inhabited by significant populations of bats [62]. In order to explore the assumption of the contamination by the bats within these caves, caged baboons and vervets were placed inside these caves. But none of them became sick (Johnson, personal communication, 1996).

The characterization of nucleotidic sequences in Ebola genes, which codes the ARN polymerase (protein L) and the nucleoprotein (NP) highlighted significant areas homologous with equivalent genes of Paramyxoviridae and Rhabdoviridae [48,60] reinforcing the genetic relationship of these two viral families with Filoviridae. Several studies evoke the possibility of direct contamination of humans by some of these viruses originating in bats. As an example, the viruses Hendra [24] and Nipah [29] could be directly transmitted to the humans by the saliva of frugivorous bats deposited on fruits [44]. In the same way, certain variable of the rabies virus would be transmitted directly to the man by insectivorous bites of bats [13, 19].

Lastly, certain species of chiropteran (of the genus Eptomophorus and Tadarida) developed a transitory viremia lasting four weeks after intravenous inoculation, suggesting that the Ebola virus can infect bats without developing disease [63]. Certain observations suppose that the contamination of the large monkeys would intervene in favor of direct contacts with blood and/or placental tissue of the females at the time of parturition. The epidemiologic field surveys carried out showed that large monkeys died from Ebola virus at the end of the dry season. Food resources would be scarcer during the dry season in the tropical forests of Africa, which would cause various frugivorous animal species to move at the same place. This promiscuity would support the contacts between large monkeys and bats and thus the viral transmissions of the virus between the two animal species.

32.3.5.2 Avifauna and infectious diseases Migratory and non migratory birds take part in maintaining pathogenic agents responsible for infectious disease transmission to humans; they act as vector or intermediate host for germs which, for the bird itself, may be pathogenic (e.g., Psittacosis) or not (e.g., West Nile). What interests the particular field of disease emergence, is less in the role of vector-host that birds...
play in germ transmission to humans but rather more their role as “carrier” transporting the germ (or an ectoparasite vector of a germ) beyond the normal fields of disease circulation and being able to play a significant role in pathogenic virus dispersion. If this role seems obvious to explain geographical emergence of certain diseases it still remains badly known, and little studied (e.g., Bird Flu; virus West Nile). This is due to the immense variety of avifauna, the difficulty in making representative biological samplings, the mobility of these hosts, the exchanges of germs, which can be done in rest areas (stop over, roosting sites) of migrating species. Recent events in bird associated pathogen emergence, have lent topicality to the question of the bird’s role in virus transport and research in this field has beneficed from technological progress and accumulated knowledge on avian fauna in all continents.

Bird behavior is largely influenced by environment particularly climate in relation to vegetation and abundance of food and also human behavior which often displaces wild bird’s habitats to exploit the land or by regrouping domestic birds for breeding and exploitation.

In this chapter we will focus on the role of birds as virus vector within the framework of dispersion. Two exemplary virus diseases come to mind: the West Nile virus encephalitis and avian and swine flu. For these two types of virus, the birds can infect themselves and develop a more or less severe clinical picture or be a healthy virus carrier.

![Fig. 32.16. Tracking birds for a follow up on their potential role of pathogen dispersion. Top to bottom: Biological sampling (blood, swabbing) an Ombrette in Burkina Faso; storks ringed with four solar transmitters Argos—GPS with their antenna visible ready to be equipped; the transmitter in place on the back of bird ready to be set free. Background map: Migration route of Black Stork (2004–2005); red line: Aurélia: Migration outward journey (April–June 2004); orange line: Aurélia: Migration Return (July–September 2004); green line: Camille: Migration outward journey (August–October 2005). Left to right, from top to bottom: (A) biological sampling (blood, swabbing) on a Hamerkop in Burkina Faso; (B) Young Storks captured to be ringed and equipped with GPS Argos solar transmitters; (C) Young Storks to be ringed, transmitters with their antenna are visible next to birds ready to be equipped. (C) Argos GPS solar transmitter placed on bird’s back, ready to release bird. See color plates.](image_url)
32.3.5.2.1 Where do birds and their viruses migrate?

Tracking birds to determine their potential role in pathogen dispersion\(^{12}\) The current use of satellite radio transmitter for following wild fauna opens many new ways of exploring and understanding animal behavior, its strategies of reproduction of alimentation, the degree of adaptation to its environment or the seasonal migration of these species. Coupled with geographical, field data, these techniques of localization by satellite reception provide incomparable information, in real time, on the occupation of space or the exploitation of natural resources.

For the migrating avifauna, nesting in the palearctic region and wintering in West Africa, the first experiments on migratory birds by satellite localization go back ten years but involved only battery powered transmitter, without built-in geopositioning by satellite (GPS), not very precise but nevertheless useful because they made it possible to specify the axes of migrations of certain species. Today, it is possible to determine the migrations with a precision of a few dozen meters, and to post the results almost on line on the screens of the microcomputers of users of this service.

In this context, IRD ornithologist researchers, developed since 2004, scientific work on the winter ecoethology of *Ciconia nigra* starting from Burkina Faso by using a 70g solar transmitter, equipped with a GPS system (Argos\(^{®}\) type). This research is completely innovative as regards follow-up of avifauna in sub-Saharan Africa and constitutes a pilot study for follow-up of migrating birds of medical interest (as potential vector of pathogenic viruses) that could provide invaluable information on the spatial and temporal dynamics of this avifauna and, in consequence, on that of the cycle of viral agents which they can carry. The role of soft ticks, common ectoparasites in birds and vector of pathogenic viruses could also be studied by targeting species of birds of medical interest.

32.3.5.2.2 Highly pathogenic avian influenza (Hpai) emergence in Thailand: the spatial aspect of emergence and the dynamics of an epizooty

In 1997, the appearance in Hong Kong of human cases of influenza related to an avian influenza caught the world’s attention and made influenza a central public health care issue in many countries. Virus A of influenza always presents a significant potential danger to human populations, by its effective mode of transmission in the event of promiscuity, by its mutation capacities and genetic reassortment, which prevent installation of an effective natural immunization in human populations, and by the existence of an enormous and badly defined natural reservoir (in particular the many wild migrating birds), which contributes to maintain its genetic diversity. Strain H5N1 had been isolated on several occasions since 1959 on birds, in the United Kingdom (1959, 1991), in the United States (1975, 1983), and in China (1996), but without causing epidemics in the birds and especially without causing human cases (all the viral strains of H5 type are avian and all the H5Nx combinations were already isolated on birds, except H5N4 none had ever caused human cases). The avian viruses develop primarily in the digestive tract, contrary to the human viruses, which touch initially the respiratory tract, the receptor of the hemagglutinin being different according to species.

The H5N1 virus emerged in Hong Kong with a very significant pathogenic capacity for chickens, and the capacity to infect humans directly with a death rate of 30 %, well beyond 2.8 % of the strain type H1N1 responsible for the 1918 Spanish influenza pandemic. But the virus infected humans only in a very marginal way, and was unable to be transmitted directly from person to person, a quality, which is still not acquired in 2005. These marginal infections (18 cases in Hong Kong in 1997, six of it died) nevertheless created fear of a generalized human diffusion in the event of genetic viral modification (the hemagglutinin induces a highly protective humoral response in humans, but antibodies corresponding to the H5 antigen do not exist in humans). Fearing the worst, the Hong Kong authorities had then taken drastic measures to try to eliminate the virus from the peninsula, by ordering the destruction of all birds, whether they were wild, or domestic (1.5 million birds). Actually eradicated in 1997 by these measures, the virus nevertheless reappeared on a small scale in 1998 (China, Hong Kong), then more widely since 2003 (China, Japan, Korea, Indonesia, Vietnam, Laos, Kampuchea, Thailand), to extend unrelentingly in a large part of South Asia from 2003 to 2005, then progressing slowly toward the west to Eurasia and Europe in 2005 and Africa in 2006.

\(^{12}\)François Baillon and Damien Chevallier, IRD—C.N.R.S, unpublished data.
Among great pandemics of twentieth century, the influenza has been greatly studied, the pathogen is well known, surveillance networks exist in many countries, the recommendations of FAO, OIE, and OMS largely diffused, but the emergence of a new viral strain potentially very pathogenic for humans reveals the many questions that remain related to emergence, and which make influenza an exemplary and always topical disease by the danger which it represents. The control of the influenza is never a local question, but too many countries do not yet adopt the recommendations of international organizations, and sometimes several months are necessary before the emergence of an epizooty alerts political attention, whereas speed of action is essential to contain the geographical expansion of the disease, whether it is human or avian. In Hong Kong, the response of the authorities was fast and effective as soon as human cases were detected, and made it possible to remove epizooty and the epidemic. But the many studies which had been led in Hong Kong really did not make it possible to understand the emergence mechanisms and the progression of the disease toward other areas of the continent could not be contained, more especially as it reached countries where the monitoring and control do not have the desired effectiveness.

In the case of avian influenza, the questions are numerous: Is the reservoir badly defined or too broad to be understood (wild birds or/and mammals)? The initial vector is badly known (migratory birds)? What is the mode of diffusion, displacement of wild birds, poultry transport, or other mammals? Human practices? Cause of seasonality and disappearance period is unknown (Migrations of birds? Climatic conditions?). We will highlight these questions by studying the epizooty of avian influenza in Thailand since 2003. Thailand, large poultry producer and exporter, had made an exemplary step in the management of this crisis (delay in political awareness, delay in initial detection of the disease, usual propaganda—chicken meat tasting—but at same time active veterinary monitoring, data collection faltering at the beginning but quickly effective, monitoring of wild birds and fauna, research of reservoirs and infected nonsick animals, strict application of the recommendations of OIE, etc.).

### 32.3.5.2.3 Avian influenza in Thailand since 2003

Thailand was reached by avian influenza of the strain H5N1 at the end of 2003. Then, after the disappearance of epizooty by May 2004, the disease was recorded again, as from July 2004 and in 2005, according to a regular and seasonal cycle. Probably thanks to the medical measurements applied strictly since November 2004, but perhaps also by a reduction in the virulence of the stock, the third wave of epizooty (2005) was much weaker.

#### 32.3.5.2.4 The first wave, January–April 2004

After China and Hong Kong, the avian influenza due to virus H5N1 was detected at the beginning of 2004 simultaneously in Thailand, in Laos, and in Kampuchea, after having been reported from Korea and Vietnam (December 2003), Japan and Taiwan (at the beginning of January 2004). It then reached Indonesia in February. Surprisingly, certain countries did not report any cases (Burma, Malaysia).

Avian influenza most probably appeared in Thailand around the middle of 2003 without being immediately reported. The first veterinary report dates from January 23, 2004 (Suphanburi province, eggs producing farm) and then cases in poultry farms

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**TABLE 32.4. History of Avian Influenza in Hong-Kong Since 1997**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>March/Apr</td>
<td>Avian flu outbreak among chicken farms in northwestern part of Hong</td>
</tr>
<tr>
<td>9.5.1997</td>
<td>Kong</td>
</tr>
<tr>
<td>18.8.1997</td>
<td>Onset of illness for the first case of influenza A (H5N1)</td>
</tr>
<tr>
<td>26.11.1997</td>
<td>Laboratory confirmation of H5N1 infection for the first case</td>
</tr>
<tr>
<td>December</td>
<td>Isolation of H5N1 virus for chicken markets. More human cases</td>
</tr>
<tr>
<td>23.12.1997</td>
<td>Poultry export from Mainland suspended at midnight</td>
</tr>
<tr>
<td>28.12.1997</td>
<td>Evidence of widespread H5N1 infection in a chicken farm and wholesale</td>
</tr>
<tr>
<td>29.12.1997</td>
<td>Slaughter of chickens and poultry commenced. No new human infections</td>
</tr>
<tr>
<td></td>
<td>occurred since then in Hong Kong</td>
</tr>
</tbody>
</table>

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![Fig. 32.17. Avian flu Histogram of reported positive foci by district previously not infected from July 2004 to November 2005. The X-axes numbers indicate the number of elapsed weeks starting from July 2004. The Y-axes values are given by the number of foci reported positive by week. All data presented come from reports of cases focus carried out by the DLD (Department of Livestock Development, Ministry of Agriculture, Thailand). The data are mapped by district. Thailand comprises 921 districts, which are the intermediate administrative divisions between provinces and the local level.](image-url)
followed one after another very quickly (in the last week of January 2004, the disease was reported 157 times in 36 provinces in Thailand). Meanwhile in Thailand, the human cases preceded the declaration of avian cases (first human case on January 3, 2004 in the province of Suphanburi, a total nine cases in January, including seven deaths). In February, the last human cases of this first wave were detected (three cases including two deaths), whereas the avian influenza was reported 22 times in 12 provinces, in March 6 times in five provinces, in April 4 times in three provinces, in May only once. No case was recorded between May 24 and July 3, 2004, beginning of the second wave. In poultry farms, this first wave reached primarily the chickens (60%), the distribution by species being virtually identical to that of the epidemic of Hong Kong in 1997. The human cases were always related to the presence of an avian case.

At the time of the first wave of expansion in 2004 (January 2004–May 2004), information was not clearly disseminated, certain countries denying quickly any infection, others maintaining an opacity related to the economic importance of the sector’s poultry industry. It is only during the second wave of epidemic (July 2004–February 2005 in Thailand) that the authorities adopted a certain transparency, in particular in Thailand. Once installed, medical measures were quickly effective in stopping the diffusion of epizooty, but it is probable that the seasonal character of epizooty supported the fast eradication in Thailand. The country was declared free from avian influenza in May 2004.

32.3.5.2.5 The second wave: July 2004–April 2005

In Thailand, the second wave begins in July 2004 and persists until April 2005, with a significant peak in October–November. The reports of cases are now much better organized, laboratory tests are carried out systematically by the DLD (Department of Livestock Development, Ministry of Agriculture, Thailand), and main information is available very quickly on the DLD Website. The reported cases are much more numerous than during the first wave (1669 cases tested positive). Many monitoring tests are carried out on the domestic animals and on wild fauna (migratory birds, rodents). In November, the government “declares the war with epizooty,” carries out active and passive monitoring, takes control measures aiming to eradicate the disease in the short term and releases significant funds (National Strategic Plan and Avian Influenza and Plan for Pandemic Preparedness, 2005–2007, USD 105 million).

The emergence of the first cases is located in the zone, which had already seen the appearance of the first detected cases at the beginning of 2004. The geographical expansion seems to show initial cases in the north of the central plain, then a local extension starting from these cases. The initial cases do not correspond to the most active zones of industrial avian production, but rather to ecological zones favorable to the natural reservoir. However, the role of wild birds in local or national diffusion was not highlighted. The human practices and behaviors (transport of poultries, markets, cockfights) are also probable causes of the diffusion by proximity. The domestic chickens were the most hit by epizooty (57%), then the ducks (29%), the industrial chicken farms (5%), and the farms producing eggs (5%). The cases relate primarily to farms where the number of birds is modest (the median is 75). Culling is systematic in farms as soon as several birds are found dead (10% of farms), and measures of containment are applied during 21 days (no displacement of poultry for all exploitations in a radius of 5 km around the infected farm).

Reemergence after a silent period leads to three assumptions: either the virus circulates asymptomatically in certain reservoir animals, or it is maintained in the environment in water), or seasonal migratory birds reintroduce it.

![Fig. 32.18. Highly pathogenic avian influenza in Thailand. Top left: Geographic expansion of first wave of H5N1 epizootic in Thailand (January–February 2004) reported by day and by district. Top right: Geographic expansion of second wave of H5N1 epizootic in Thailand (July–April 2005) reported by week and by district. Bottom left: Number of foci reported by week and by district during the third wave of H5N1 epizootic in Thailand (July 2005–November 2005). Bottom right: A poultry farm from the Samut Sakhorn province, Thailand. See color plates.](image-url)
No cases were notified between April 12 and July 1, 2005. The third epidemic wave begins in the province of Suphanburi, where the epizooty was detected for the first time in Thailand. From July 1 to November 15, 75 cases were reported: Epizooty was thus much less active, either because of surveillance and control measures or by a reduction in virulence. This reduction, which was reported in certain articles, is not confirmed by the observations by the DLD (average mortality of 95 %), but these results are difficult to interpret (many reports of cases do not indicate the number of dead or sick birds).

### Table 32.5. Origin of Avian Flu Human Infections in Thailand, 2004

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Address</th>
<th>Onset</th>
<th>Hospital</th>
<th>Diagnosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>18</td>
<td>Tambon Khao Maikaew, Kabinburi district, Prachinburi</td>
<td>August 31, 2004</td>
<td>Kabinburi</td>
<td>Pneumonia</td>
<td>Died, September 8, 2004</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>26</td>
<td>Tambon Pang Maka, Khanuworakumbi district, Kamphaeng Phet*</td>
<td>September 11, 2004</td>
<td>Pakkretvejakan</td>
<td>Pneumonia</td>
<td>Died, September 20, 2004</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>32</td>
<td>Tambon Pang Maka, Khanuworakumbi district, Kamphaeng Phet</td>
<td>September 16, 2004</td>
<td>Kamphaeng Phet</td>
<td>Pneumonia</td>
<td>Discharged, October 8, 2004</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>9</td>
<td>Tambon Budhabat, Chondaen district, Phetchabun</td>
<td>September 23, 2004</td>
<td>Chondaen and referred to Phetchabun Hospital</td>
<td>Pneumonia</td>
<td>Died, October 3, 2004</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>14</td>
<td>Tambon Pa-ngew, Srisachanalai district, Sukhothai</td>
<td>October 8, 2004</td>
<td>Srisangworn</td>
<td>Pneumonia</td>
<td>Died, October 19, 2004</td>
</tr>
</tbody>
</table>

The migratory birds were immediately blamed as the factor of emergence for avian influenza in Thailand, with no evidence for this thesis. Indeed, some colonies of storks (Open bill stork) present in Thailand migrate from Bangladesh, and the mortality of these birds increased considerably in 2004, but as no case of avian influenza was listed in Bangladesh: It is more than probable that these birds were more victims than responsible for epizooty.

Many wild birds perform local migrations (in particular wild ducks, which mix with domestic farm birds), and can be responsible for local diffusion. Natural and artificial ponds are very numerous in Thailand, and open-air chicken or ducks farm are frequent particular farmyard chickens.

The diffusion of epizooty according to a north–south axis, which follows the large road network in Thailand, can also let us think of a diffusion related to transport related to poultry industry. Very restrictive measures of limitation of displacements of poultry, with more than 150 points of control between areas, were taken since 2004 on this assumption. The practice of cockfights was also blamed like a factor of significant risk in the diffusion of the disease in animals.

A silent period, from April to July, has been noted for 2 years. The viral flu can be probably maintained several weeks in cold water, but this period corresponds to a very hot weather in Thailand.

#### 32.3.6.1 Rodents and virus: how a viral family can have a global distribution

The rodent vectors of virus to humans can be represented by two exemplary systems, the “Rodents and Hantavirus” model and the “Rodents and Arenavirus” model. In both cases, there is a narrow association between a type of virus and a species of rodents. With the development of compared phylogenetic analysis of the hosts-vectors, it appeared clearly that the rodent–virus couples had followed an evolutionary process in the form of coevolution and of cospeciation. What was in the years 80s still a hypot-

**Fig. 32.19.** H5N1 infected Open bill stork dying in the natural resting area. The agonizing stork showed in the pictures has probably been infected by nearby poultry during the second epizootic of H5N1 in Thailand.
esis became a dogma with the emergence of new virus taxa in two models [5, 9, 20, 21]. The process of coevolution was modulated by phenomena of disappearance of one of the partners, or the discovery of hosts without virus or a virus taxon without known host. Finally, after a second review of host phylogeny and of their known virus it is possible to predict the presence of an undeclared virus in a domain where potential hosts are present: Thus, like the “Hantavirus in Africa” suspected by the demonstration of serologic markers, without viral insolation, “the Arenavirus of Asia” also remains to discover. Let us see through the history of Murids how could Arenaviridae be spread to understand the vast domains these two families colonize world-wide in the present day.

32.3.6.1.1 The rodent: a brief history Because it is often mentioned in literature, the term of “Murid” corresponds to the Murinae subfamily [Musser and Carleton, 1993 in 21]. What it is called Cricetids, needs to be specified as “New World Cricetids” including the New World rat and mice or the Sigmodontinae subfamily.

We use the most common theory on rodent radiation to support part of our hypothesis. From the Eurasian continent, the Cricetids, ancestors of the Murids, spread into the Americas, and then, from Asia, the Murids spread to Europe and Africa.

As early as the Eocene, 65 millions years before present (My.B.P.), within North America, a rodent ancestor, Siminys, is found bearing Cricetid characteristics. During the Oligocene (37 My.B.P.), the Cricetid repartition became holoarctic. The New World Cricetids colonized by waves of migration northward and southward to the Americas. As a result, the Cricetid fauna from South America is coming from North America and today; it appears that the group from South America can be separated to the less diversified group of Neotoma-Peromyscus from North America.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Virus</th>
<th>Country and Date of Emergence</th>
<th>Virus Reservoir</th>
</tr>
</thead>
<tbody>
<tr>
<td>LASV</td>
<td>Lassa</td>
<td>Nigeria, 1970</td>
<td>Mastomys huberti</td>
</tr>
<tr>
<td>MOBV</td>
<td>Mobala+</td>
<td>Central African Republic, 1982</td>
<td>Praomys sp.</td>
</tr>
<tr>
<td>MOPV</td>
<td>Mopeia</td>
<td>Mozambique, 1977</td>
<td>Mastomys natalensis</td>
</tr>
<tr>
<td>IPPYV</td>
<td>Ippy</td>
<td>Central African Republic, 1978</td>
<td>Arvicantus niloticus</td>
</tr>
<tr>
<td>LCMV</td>
<td>Lymphocytic Choriomeningitis</td>
<td>USA, 1934</td>
<td>Mus musculus</td>
</tr>
</tbody>
</table>

New World Arenaviruses (North Central America)

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Virus</th>
<th>Country and Date of Emergence</th>
<th>Virus Reservoir</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCNV</td>
<td>Bear Canyon</td>
<td>USA, California, 1966</td>
<td>Peromyscus californicus.</td>
</tr>
<tr>
<td>TAMV</td>
<td>Tamiami</td>
<td>USA, Florida Everglades, 1970</td>
<td>Sigmodon hispidus</td>
</tr>
<tr>
<td>WWAV</td>
<td>White Water Arroyo</td>
<td>Southwestern USA, 1996</td>
<td>Neotoma albigula</td>
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New World Arenaviruses (South America)

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Virus</th>
<th>Country and Date of Emergence</th>
<th>Virus Reservoir</th>
</tr>
</thead>
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<tr>
<td>ALLV</td>
<td>Allpahuayto</td>
<td>Peru, 2001</td>
<td>Oecomys bicolor</td>
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<tr>
<td>FLEV</td>
<td>Flexal</td>
<td>Brazil, Amazonia, 1977</td>
<td>Oryzomys capito</td>
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<td>PARV</td>
<td>Para</td>
<td>Paraguay, 1970</td>
<td>Oryzomys buxcinatus</td>
</tr>
<tr>
<td>PICV</td>
<td>Pichinde</td>
<td>Colombia, 1971</td>
<td>Oryzomys albignarla</td>
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<tr>
<td>PIRV</td>
<td>Pirital</td>
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Lineage B

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<td>Amapri</td>
<td>Brazil, 1966</td>
<td>Oryzomys capito</td>
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<tr>
<td>CPXV</td>
<td>Cupixi</td>
<td>Brazil, North Easter, 2002n</td>
<td>Oryzomys capito</td>
</tr>
<tr>
<td>JUNV</td>
<td>Junin</td>
<td>Argentina, 1958</td>
<td>Calomys musculus</td>
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<td>GTOV</td>
<td>Guanarito</td>
<td>Venezuela, 1991</td>
<td>Zygopantomys brevicauda</td>
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<td>MACV</td>
<td>Machup</td>
<td>Bolivia, 1965</td>
<td>Calomys callosus</td>
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<td>SABV</td>
<td>Sabia</td>
<td>Brazil, 1994</td>
<td>Unknown</td>
</tr>
<tr>
<td>TCRV</td>
<td>Tacaribe</td>
<td>Trinidad, 1963</td>
<td>Artibes spp. (bat)</td>
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Lineage C

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<th>Virus Reservoir</th>
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<td>Latino</td>
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<td>Calomys callosus</td>
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<tr>
<td>OLVV</td>
<td>Olivero</td>
<td>Argentina, 1996</td>
<td>Bolomys obscurus</td>
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* Date of emergence and/or publication.
In Asia, the Cricetids came more likely from North America and were present during the Oligocene (35 My.B.P.). Although, from an original pool, and by successive waves, Cricetids spread to Europe during the late Miocene (15 My.B.P.), they became underrepresented in Africa with a limited extension.

From Asia, 14 My.B.P. Murid spread around the Mediterranean basin to Europe. During that period, Murinae extend from Europe to North Africa and rapidly became the most widely spread rodents in Africa.

Beginning the Pleistocene (2 My.B.P.), Murids are present in sub-Saharan Africa. Then they largely spread from the north and south, while severely influenced in their radiation by arid climate and geomorphology. During that time, speciation became at its highest point influenced by climate changes and physical isolations: the Rift Valley and the Sahara divide the African continent. More recently, humans must have played an important role for the spread of rodents and mostly with the comensal species. Some genera from the Pleistocene are still present in East Africa, whereas others from North Africa disappeared. However, it likely that Murid ancestors were very closely related to the present genus.

In conclusion one can consider that the arenaviruses in general had as a principal mechanism of evolution a narrow process of coevolution and cospeciation with their reservoir the rodents. The dispersion of the arenaviruses and their diversification followed those of the rodent hosts. The emergence of strains pathogen for humans remains entirely misunderstood, undoubtedly due to the rarity and specificity of emergence conditions. As the encounters of these vectors with humans increased in a context of exploration with growing human populations, the probability of meeting an infected rodent also increased. On the Asian continent, even if there is evidence in South East Asia of their circulation, the discovery of the Arenaviruses still remains elusive. It is the same in Australia where only the Lymphocytic Choriomeningitis virus of mice (LCMV) has been announced in a laboratory mice-breeding center. These viruses, which remain to be identified, would certainly give additional elements to the

Fig. 32.20. The rodent dispersion from an Asian origin.

Fig. 32.21. A putative coevolution of Asian Murids and their arenavirus parasite.
coevolution of the rodents and their virus having migrated very early from Asia then toward Australia.

Above and below each horizontal line appear the main murid group and its corresponding arenavirus in a coevolution pattern. A specific arenavirus of Asian rodents has not yet been discovered and a putative new clade of “Asian arenavirus” is speculated in the present figure. This diagram represents large groups of viruses and their rodent hosts with which they have coevolved. In Asian rodents, among the oldest no arenavirus has yet been identified, a new taxon is proposed but remains to be identified.

32.3.6.2 From wildlife to humans: the SARS or the risk of early domestication process

32.3.6.2.1 The SARS outbreak or the first emerging disease of the twenty-first century First epidemic emergent disease, which marks the twenty-first century, the SARS (Severe Acute Respiratory Syndrome) diffused around the world in a few months. The principal mechanism of this fast planetary dispersion resides primarily in the displacement of infected people on airways. In spite of the great number of cases (8096 cases counted for 28 countries during the preepidemic and epidemic periods, and the strong mortality (9.6 %; that is to say 774 reported deaths) associated with this Severe Acute Respiratory Syndrome, the disease is eradicated relatively quickly. Less than four months after its isolation and its molecular characterization (mid-March 2003), the virus diffusion is restricted, thanks to simple protection measures of the individuals at risk and by isolation of the patients, new infections became sporadic with the last case reported in early September 2003. The ecology, origin, and evolutionary history of this virus remain to be established.

32.3.6.2.2 From a chinese market to the toronto airport: the lessons of SARS On November 16, 2002, a respiratory syndrome, associated to myalgias and a strong fever is reported in populations of the province of Guangdong, in South China. The data is missing to determine with certainty the number of cases before and after this period undoubtedly preepidemic. The Chinese ministry for health communicates its concerns with respect to this epidemic starting from the mid-February 2003 and announces, at the end of February, that the probable responsible agent would be the bacterium *Chlamydia pneumoniae*. No other official source confirms this assumption.

The epidemic extends then out of China with two particularly remarkable initial cases: A 65-year-old doctor, residing in a Hong Kong hotel, and a Vietnamese in his 50s, admitted to Hanoi hospital at the beginning of March. These two patients present in turn the symptoms of disease and demonstrate the facility with which the infectious agent carries out inter-human transmission. The Hong Kong hotel counts 12 additional infections, among residents and visitors, in the hours, which follow the diagnosis of the 65-year-old doctor. Still in Hong Kong, in the Prince of Wales Hospital, only a few hours later 18 members of the personnel declared themselves sick, more than 50 employees of this hospital develop a fever accompanied by respiratory symptoms. Similarly, in Hanoi, hospital counts 20 contaminations among its medical personnel; mainly nurses, doctors, and surgeons constitute the victims of this epidemic. The hospital environment seems to have become a privileged medium in which the epidemic of Severe Acute Respiratory Syndrome (SARS, this name was given on March 10, 2003) makes most of its victims.

At the end of March, researchers of Hong Kong, the United States, and Germany identify the etiologic agent responsible for SARS [34, 52, 54, 57]. This new *Coronavirus* (order: *Nidovirales*), is unknown and named *Severe acute respiratory syndrome Coronavirus* or [SARS-CoV]. Whereas knowledge relating to this new *Coronavirus* increases exceptionally quickly thanks to an international scientific collaboration without precedent, the epidemic progresses and touches more and more cities in Asia (Hanoi, Hong Kong, Singapore) and in North America (Toronto). At the end of April, governmental measures are taken in particular in China where the regrouping of populations is prohibited [75].

May 23, 2003, two teams of Hong Kong and Shenzhen detect a *Coronavirus* in wild animals collected in markets in the south of China. Species tested positive: the masked palm civet (*Paguma larvata* Smith, 1827), the burmese ferret-badger (*Moloch personata* Geoffroy Saint-Hilaire, 1831) and the racoon-dog (*Nyctereutes procyonoides* Gray, 1834; only serological evidence), belong to the Carnivora order and carry several coronaviruses, some being very close to [SARS-CoV].

Civet appears in the menu of many hotel establishments and is a revered delicacy of southern China. Culturally, the consumption of civet is well established in the area of Guangdong and Li Shizhen describes wild civet as invaluable in his “Great treaty on medical matters,” during the Ming dynasty.

Professional civet breeding for gastronomy has been practiced by certain Asian populations for several years, and is well developed in southern China and the province of Guangdong. The change of techniques for provisioning restaurants and markets, from hunting to organized breeding, already reveals in a few years of selection, that certain specimens are favored for their interest to the stockbreeder. The breeding at productive ends, involves physiological modifications characteristic of processes of domestication (increase in the annual number of parturition, increase in the weight, lowers aggressiveness) due to efforts of selection by the stockbreeder. These physiologic modifications which are made, are typical of the domestication process; faster production with reduced manpower, and is accompanied by a decrease of genetic diversity, which, associated with an increase in animal density, can support the incubation and diffusion of a virus and its variant virus in a breeding batch, thus increasing the probability of transmission to humans. It is in contact with these animals that stockbreeders and consumers contracted SARS [23,69]. In addition to clinical cases, several stockbreeders sero-converted without ever having developed SARS [70].
32.3.6.2.3 CORONAVIRUS in livestock and [Sars-Cov] evolution potentiality

The Coronavirus genus, included in the order of Nidovirales (linear, nonsegmented, positive sense, ssRNA viruses, comprising the families Coronaviridae and Arteriviridae) is well known to veterinary surgeons who observe it in many domestic mammals, in which it generally starts a serious enteric pathology, respiratory and/or neurological. Almost all domestic species and some semidomestic species are prone to infection with Coronavirus: pig (described in 1946), cow, turkey, chicken (1937), rabbit, dog, cat, and mice (1949) have all one or more Coronavirus which cause a high mortality during epidemics. Since the Sixties, a regular increase in the number of Coronavirus infections is observed. Coronavirus infecting humans with mostly enteric and respiratory tropism ([HCoVs], 229E and OC43) was discovered in the years 1960 [12].

The significant rate of evolution of the Coronavirus genus can be explained by three intrinsic factors. Coronaviruses are capable not only of recombinations in vitro but also in vivo (type) (case of Avian infectious bronchitis virus), they generally adapt without significant problems of deletions (1986 porcine epidemic of gastroenteritis due to a mutant) and finally, they do not have the mechanism of error correction of RNA, which is characteristic of the RNA-dependent RNA polymerases [28]. In the case of [SARS-CoV], a high rate of evolution was observed in a comparative study of evolution in [SARS-CoV] and in Nipah viruses of Chiroptera [43]. A large deletion involving 29 nucleotides (out of 30,000 in the genome of Coronavirus) occurred shortly after the passage of the virus to humans. This deletion, located between Orf11 and Orf12, which are not membrane proteins and which have unknown functions, does not seem to induce any notable effect.

32.3.6.2.4 An elusive virus reservoir: distribution and ethology of the host species and elements of the natural viral cycle

In reference to the first isolation of [SARS-CoV] in wild animals and domesticated civets, these species were initially believed to have the role of the wild reservoir of the virus. But after the discovery of SARS-Like coronaviruses [SL-CoVs] in chiropteran, it seems more judicious to regard civet as semidomestic amplifier of [SL-CoVs] or intermediate host responsible of the transfer of the virus of wild origin to mankind. Multiple species of Chiroptera are carrying [SARS-CoV], among which, many bats, mainly insectivorous of the genus Rhinolophus (horseshoe bat): R. pusillus Temminck, 1834; R. macrois Blyth 1844; R. pearsoni, Horsfield, 1851; R. sinicus [37]. Another species, Rousettus leschenaulti Desmarest, 1820, have sometimes anti- [SARS-CoV] antibodies. Two other species, Miniopterus magnater Samborn, 1931 and Miniopterus pusillus Dobson, 1878 can transport another coronaviruses [53]. The genetic variability of [SL-CoVs] is much more marked in chiropteran than in civet (and racoon dog) or humans, which tends to show on the one hand that the [SL-CoVs] from these species find most probably their wild
origin in bats, and also that Chiroptera have been hosts and carriers of [SL-CoVs] for a long time. In addition, as chiropteran show persistent infections by several groups of virus (Nipah, Hendra, Lyssavirus, Ebola, . . .) by developing very seldom a pathology, one can think of this group as a reservoir for certain coronaviruses and possibly for [SL-CoVs].

In the case of interspecific viral transmission, the question crucial is how it happens; either there is a great ubiquity of the viral agent conferred by a particular genetic material or a diversifying mechanism of extremely fast evolution and, able to produce viral communities with very variable potentialities. Coronaviruses have these characteristics.

The theory of quasi-species makes it possible to design mechanisms (as above) which ensure the perennially “of a virus”: The virus remains and evolves thanks to the coexistence in the same host of several viral communities or populations, of the same origin, conferring on this viral agent a reticulated and diversified population structure, with probably the numerical and functional predominance of one of these quasi-species over the others. Consequently, a virus is not characterized by a monomolecular genome, but by a reticulated genome, composed of several variants, dispersed in a great number of viral particles, which have each one the possibility of repeating itself to give other lines, themselves more or less alternatives compared to the virus of origin. These various lines can also exchange genetic material in a horizontal way by recombination. In Coronavirus genus, this mechanism of recombination is frequent and give great evolutionary capacities.

In addition to these characteristics of coronaviruses, from the molecular level to the structure of viral populations, the characteristics of the host species are also determining in the evolutionary history of these viruses. The structure of these populations, the ethology and ecology of many species of Chiroptera carrying [SARS-CoV] are very favorable to the installation of viral mechanisms of evolution. The daily regrouping in large and dense colonies, the variable and sometimes weak periodicity of mobility (of the day or season range), the relatively heavy, mobile and diversified parasitic load, the mixture of species in sleeping areas and the long life expectancy (sometimes more than 20 years), are many factors supporting circulation, evolution, and diffusion of Coronavirus in general and [SL-CoVs] in particular.

Moreover, the various host species are generally distributed over large areas, partially covering each other, which allows for the meetings essential to interspecific passages of viruses (cf., Figs. 23B and 23C). For example, the Rhinolophus genus counts 69 species and is present in Australia and Europe. It is very probable that Chiroptera in general, and this genus in particular, still conceal several other coronaviruses, being given the potentialities of evolution and the ancient common history which the genetic diversity observed in these viruses suggests.

**Fig. 32.23.** (A) Chiroptera of genus Rhinolophus. (B) Range of Paguma larvata, the civet suspected to be the intermediate host of [SARS-CoV]. (C) Ranges of the family Rhinolophidae and of the species Rhinolophus pusillus. The photograph shows the species pusillus Temminck, 1834 or refugens Andersen, 1905 (caught in north–east of Lamphang, center–north of Thailand). From Refs. [11,40].
The settlements of Chiroptera are often of variable structure (changing specific diversity, effective unwanted) and the populations widely fluctuate (variable sex-ratio, fluctuating structure of age) [36]. These observations suggest a strong mobility (daily or seasonal) of individuals and groups, within the range of distribution. Frequently, at the time of the operations of capture, one observes some individuals in bad physical condition (dull pelage, depilatory patches and open wounds on the abdomen or head, points of patagium necroses, charges heavy ectoparasitic burden). These individuals, weakened, but active since captured during their nycthemeral displacement, are more receptive to the viruses and may excrete them more and for a longer period than healthy individuals and thus can play the role of micro-reservoirs for local populations, dispersing the virus by their frequent movement.

32.3.6.2.5 Perpetual viral interactions with their hosts, a possible scenario for an emergence During emergence of new coronaviruses in the wild, by genetic drift, recombination or deletion, the genetic, ethologic and ecological characteristics of species of host determine the success of the process. Dispersion outside the species implies the existence of distribution surfaces overlapping those of other Chiroptera or other animal groups. In the case of [SL-CoVs], the passage in an intermediate animal host (civet) can be carried out by contact, licking, ingestion of fresh faeces from chiropteran or inhalation of dust contaminated in the caves (the ground of the caves is generally covered with a thick carpet of faeces dried and disaggregated into fine particles).

Civet, are preferentially nocturne like many small carnivorous, can be infected during night hunting in the caves and the trees where the bats excrete in great quantity from the middle of night to early morning. If the virus is well adapted to its new host, the infection is fast but this does not mean that it can be retransmitted as the individual may die or if the probability of meeting a congeneric is weak. In the case of a very virulent and very contagious agent, the individual will die and the virus will generally not be transmitted, except if the probabilities of meeting of a new host increase, for example as with the human activity of hunting (it is the case of Ebola, where humans are contaminated by another primate). In the case of civet, the original Coronavirus is undoubtedly not virulent enough to dangerously infect humans starting from only one meeting with a wild animal, but if the concentration of civets is increased artificially by breeding and the contacts human–animal are favored in the same way, the virus finds an excellent support for its evolutionary capacity and the emergence of alternative strains possibly pathogenic for humans is favored. Processes of domestication and breeding, by modifying ecological and biological characteristics of a species, and its relationship with humans, can then support the passage of emergent wild viruses from animals to humans. Afterward it is again humans who, by their behavior (sociality, manners) and the particular characteristics of modern life (fast global displacement, by airplane for example), disseminate the virus and contaminate other species and humans.

32.4 CONCLUDING REMARKS

The Emerging Infectious Diseases framework and the concept of a disease emergence both, as a system (together) have paved the way for developing preventive measures, controlling disease extension and forecasting epidemics at regional but also global levels.

The emergence of new diseases no longer has the exotic stamp, which stigmatized countries of the intertropical zone for being unhealthy territories producing plagues threatening to affect the occident. The concept of Ebola virus born form the darkest heart of Central Africa has matured, to the VIH suspected of a common geographical origin but this time quickly becoming pandemic, with the Avian flu virus, not yet pandemic but definitively pan-epizootic, or the Lyme Disease which, established slowly where its vectors (ticks) and their hosts (deers) broadened their field; and finally, with the chronic and degenerative diseases which, with another timing than the infectious diseases, emerge as much in the Northern countries (obesity) as in the urbanized areas of Southern countries (obesity, cardiovascular diseases).

Northern and Southern Countries, developing countries and industrialized countries all, know new diseases and have face the arrival of, up to that point, unknown diseases on previously virus free territories. However, if the emergence of new diseases is not the prerogative of countries known as “Southern,” the populations of the developing countries are much more vulnerable than those of industrialized countries. This disparity is source of medical insecurity and increases inequality. To make cheaper curative treatments for developing countries is an evident task in modern medical thinking, which aims to protect vulnerable populations—to increase healthcare in the South for a globally better medical safety—and not to impose the same cost of curative treatments developed for a market of rich countries, in the context of tough commercial competition.

32.4.1 To Favor Prevention not Treatment

The emerging viral diseases are at the center of the debate on health in the developing countries of the often under medicalized intertropical zone where the epidemic manifestations have considerable impact on society and sanitary conditions. The priority of health for the developing countries is to prevent (fast diagnosis, systems of detection, control, protection) to avoid further treatment. It is this approach, which is necessary for the poorer populations. The double objective is to characterize emergence and, to identify and develop advanced warning systems for prevention of viral diseases.

32.4.2 The Emerging Viral Diseases Are Also a Growing Concern for the Northern Countries

A new Hantavirus in America; the encephalitic virus West Nile from Bucharest to New York, viruses of AIDS, a dramatic model of emergence, from germs in evolution to a pandemic of exceptional amplitude and gravity. Lastly, beyond the nature there are emergent dangers of bio-terrorism and invented emergences.
32.4.3 Development and the Economy of Prevention

Emerging diseases and the emergence of the diseases have been and are of particular significance—and concern—when it comes to developing countries. Because the specificity of the phenomenon of emergence, including inedited germ or syndrome, a rapid extension of the disease, the unprepared population at risk, when such diseases strike it is over vulnerable population, with often a limited access to health care and limited medical support by all means. Consequently, the emergence of a disease in a developing country is multiplied by as much as the cited factors are deficient, the human and economical costs are of the same magnitude.

Moreover, many of the known emerging diseases in recent years, have their roots in the subtropical and tropical zones where most of the developing countries are situated.

Also, biodiversity exists as much for the microorganisms and pathogens as for the macro-organisms, the tropical zone gives the richest biodiversity.

Altogether, developing countries are badly hit and also a cradle for numerous pathogens and other pathologies, which were known to be related to industrialized countries but became also a main health problem for developing countries facing rapid evolution of their societies in a changing world.

32.4.4 Diseases Will Emerge

New pathogens have threatened living beings since the origin of life on Earth. Unknown germs, new hosts and vectors will emerge as evolutionary process or in human knowledge. Growing human populations and global exchanges will intensively participate in the extension of new infectious diseases, as well as human and animal behavior, environmental changes of natural and anthropic origin will not only expose human populations to new germs and favor inedited epidermics to develop pandemics, but will also see the rise of chronic and degenerative diseases. Understanding the process of disease emergence will give the necessary tools and strategies in order that human beings continue to adapt in finding the right balance between control and prevention.

ACKNOWLEDGMENTS

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