

1.5. The Control of Infectious Diseases in a Regional Context

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The post-Second World War years are marked by the launch of ambitious programmes to control – and even eradicate – infectious diseases. The emergence and recent re-emergence of infectious diseases, as well as their increased resistance to medicines and insecticides, makes the issue of controlling infectious diseases more difficult than ever. To this may be added high population growth and increasingly intense movements of people over longer distances. This epidemiological globalisation makes it all the more necessary to coordinate the different policies to control infectious diseases in a regional context. To the inherent complexity of the spatial dynamics of infectious diseases may be added a socio-economic complexity that is characterised by different cultures, political regimes, epidemiological risks and extremely varied economic means in a relatively small geographical area. In such a context, only increasingly more detailed, integrated and realistic models will allow us to manage more efficiently tomorrow's epidemiological problems. Such models can only be constructed if abundant, varied and high quality data are available. Epidemiological surveillance networks and socio-economic monitoring thus play an ever more crucial role not only to increase academic knowledge but also in their practical applications in public health.

1.5.1. Introduction

Epidemiology is the study of the variations in the number of diseases in time and space (Saracci, 2010). The birth of modern epidemiology dates back to the work of Dr. John Snow on the cholera epidemic that struck the area around Broad Street in London in 1854 (Hempel, 2013). On 31st August 1854, this London neighbourhood was struck by a large epidemic that killed more than 500 people in the space of only 10 days. At this period, a decade before the pioneering research work of Pasteur on **germ theory**,^[37] it was the **miasma theory** that prevailed, according to which diseases were propagated by a sort of “bad air”. Through meticulous research and the mapping of cases, Dr. Snow demonstrated that cholera was transmitted through the public water supply that mainly came from the same pump. Snow's work established for the first time the transmittable character of certain diseases and thus marked the birth of the epidemiology of **infectious diseases** (Hempel, 2013). A few years later, the work of the German Robert Koch demonstrated that these diseases that were

[37] Terms defined in the glossary are written in bold letters when first used in the text.

said to be transmittable or infectious (as opposed to chronic diseases such as cancer, cardio-vascular diseases or genetic illnesses) are caused by living organisms such as viruses, bacteria, protozoa and parasites (Wainwright and Lederberg, 1992). We deal with infectious diseases here. Hereafter, the term “epidemiology” will refer, by default, to the epidemiology of infectious diseases.

Nowadays, epidemiology consists of several types of complementary activities (Saracci, *op. cit.*). The first of these activities is surveillance that consists of gathering the number of (new) cases present in a given place over a given period of time. The main goal of such tracking of the number of cases in populations is to detect epidemics as early as possible in order to control them as efficiently as possible. During the first three decades of the 20th century, the doctor Ronald Ross, winner of the Nobel Prize in Medicine in 1902, greatly contributed to the application of mathematical models in the study of the **transmission** processes of infectious diseases (Diekmann and Heesterbeek, 2000). These models allow us to understand transmission mechanisms better, and thus give us the possibility of making high quality quantitative predictions. Today, as well as being used to predict, these models are used for prospection in order to establish the most efficient control policies as possible (Anderson and May, 1992). This is a particularly important aspect of human epidemiology models where experimentation is impossible for obvious ethical reasons. Such models thus contributed to the efficient control of the 2014 cholera epidemics in West Africa (Fisman *et al.*, 2014) and of MERS-CoV in 2015 in Korea (Cowling *et al.*, 2015).

Here we are going to deal with the aspects concerning the surveillance and control of infectious diseases in a regional context, the difficulties and the solutions that are being applied. These two parts will be separated by a section on the spatial dynamics of infectious diseases. Finally, we shall finish with a short conclusion about future challenges, particularly in Southeast Asia.

1.5.2. Monitoring Infectious Diseases in a Regional Context

Surveillance of infectious diseases serves many different objectives (M'ikanatha *et al.*, 2007). As well as the tracking of **incidences** and **prevalence**, surveillance also serves to identify the etiological agents when they are not known, to identify and quantify the risk factors and the modes of transmission. The tracking of incidences and prevalence naturally helps us anticipate epidemics and therefore to control them better. Thus the flu surveillance campaigns carried out in Asia greatly contribute to the development of vaccines against the flu (Bedford *et al.*, 2015). Every season, the flu spreads across the world from Asia. As the flu virus mutates every year, it is necessary to adjust the vaccine against it each epidemical season (Treanor, 2004). The surveillance of the strains circulating in Asia allows us to thus gather crucial information for the development of the optimal vaccine for the whole planet. This example perfectly illustrates that surveillance implemented in a given place can benefit not only the public health of the local population but also that of other populations who may depend on this local population. Finally, the surveillance of infectious diseases also plays a crucial role in the assessment of the efficiency of control policies. The implementation of a surveillance system closely depends on the target objectives.

Once the monitoring goals have been identified, it is necessary to identify the spatial units for surveillance as well as to define the cases.

Box 2

Epidemiological Surveillance. The Different Stages of Implementation and Use of an Epidemiological Surveillance System

Preparation

1. Identifying the goals and the disease
2. Identifying the regions and the reporters
3. Defining the cases

Operation

4. Collecting the data
5. Quality control
6. Data transfer

Usage

7. Making data available
8. Data analysis

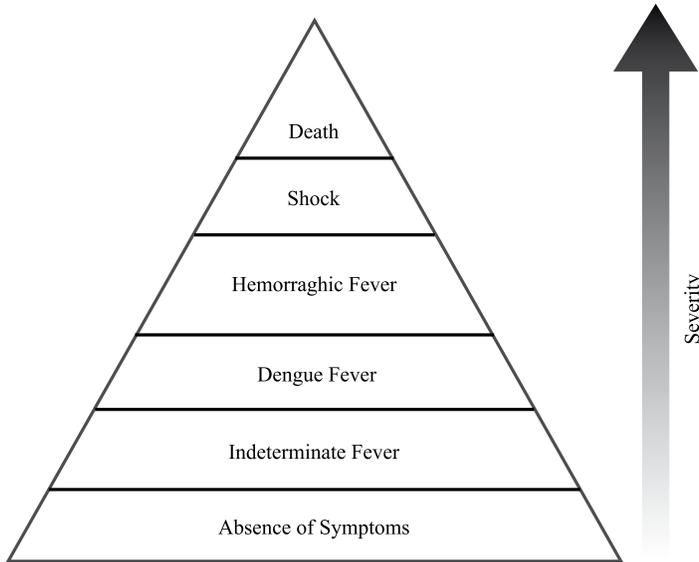
Feedback

9. Dissemination of results
10. Implementation of policies

Source: Author's construction.

For the first aspect, it is particularly important that the surveillance effort is proportional to the size of the population being tracked, if not monitoring bias is introduced. This is a major difficulty when we want to establish a surveillance in several countries with different financial means. The other potential difficulty is linked to the defining of cases, particularly for viruses like dengue whose symptoms may vary greatly (Simmons *et al.*, 2012).

Diagram 3. Definition of Cases: The Example of Dengue



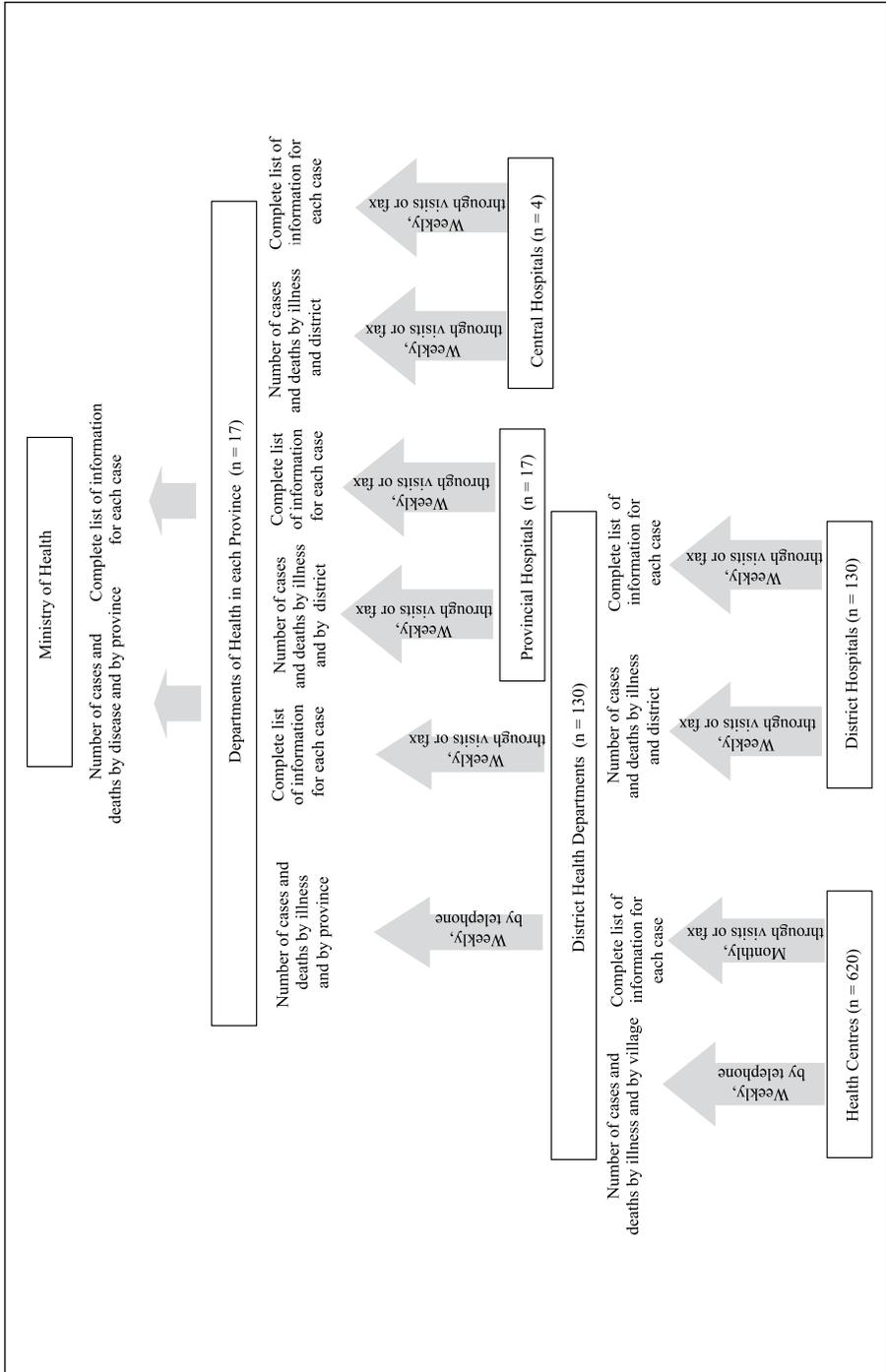
Note. The pyramid represents the breadth of the symptomatic spectrum of dengue from the most numerous and least severe cases to the least numerous and most severe cases.

Source: Author's construction.

Indeed, for the dengue virus, the definition of cases changes not only in space (according to country), but also in time (according to the means at hand to detect cases). This inconsistency makes it difficult to compile surveillance systems on large spatial and temporal scales.

Once the objectives, the spatial units and case definition have been defined, we may begin the actual implementation of the said surveillance network. This implies the gathering of data in the field, controlling their quality, and the transmission and aggregation of information (M'ikanatha *et al.*, 2007). Surveillance systems do indeed have a very hierarchical structure within which the data are sent from the lowest levels (health centres at the community level) towards the higher levels to eventually find itself centralised at the highest level (in general the Ministry of Health).

Diagram 4. A Complex and Hierarchical Structure of a Surveillance System: Example of Laos

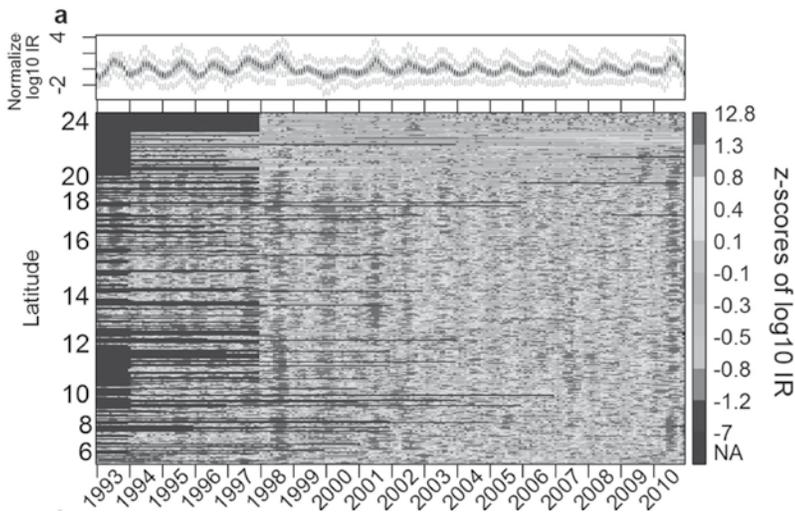


Source: Author's construction.

At each level, the data are aggregated from all the lower levels and sometimes the information is simplified (calculation of averages for example), thus necessarily inducing a loss of information between each level. These transfers and summaries of information may be frequent sources of error. Quality control is thus necessary at each operation. The coherence of communication between the different hierarchical levels must be as clear as possible, to limit ambiguities as much as possible: who receives the information, who transmits the information, etc. (Beatty *et al.*, 2010). The information flow within the network may be done using different media (paper, electronic files, web interface, mobile devices, etc.) and with different frequency.

Once the data have been gathered, aggregated and centralised, the data can be made secure and accessible for analysis. Whatever the means of gathering the data (on paper, electronically, etc.), the database’s final medium must be as homogeneous as possible. Nowadays, the most appropriate medium is an electronic database using a web interface both for entering and usage of the database (van Panhuis *et al.*, 2013). The electronic database must be as secure as possible. Duplication of the database on several independent servers will ensure against any possible loss of data, against any computer breakdown or any other risks such as fire, floods or theft. If access to the database is restricted to just a small number of administrators, this will allow us to limit the risk of human error. Table 12 shows an example of incidence data that contain temporal and spatial data.

Table 12. A Surveillance Database: Example of Dengue in Southeast Asia



Note. Each line of the table represents a spatial unit and each column represents a month from January 1993 to December 2010. The colour of the cells reflects the increasing levels of incidence – grey level. Missing data are represented in black. The curve above the table illustrates the combined dynamics of all the provinces.

Source: Van Panhuis *et al.*, 2015.

We can add to the above-mentioned techniques difficulties that are of a purely human nature and which assume full significance in a regional context. The first of these difficulties is simply linked to differences in language and also, writing. In a regional context, it is important that all the participants in a surveillance system have access to the information regardless of language. The second of these difficulties concerns the heterogeneities that may be observed on behalf of the different contributors. The contributors do not always have the same levels of resources and thus the same financial means. It is clearly essential to reduce to a maximum these differences by improving the surveillance means of the least well-off partners. However, it is also necessary to avoid any sort of discrimination based on the quality of data. Indeed, poor quality data is always more informative than missing data. In such a context, we must make a special effort to convince the partners concerned to contribute to the database in spite of the problems in quality that they may encounter (Choisy *et al.*, 2015).

Finally, let us note that a surveillance system is extremely costly to implement and that the quality of data largely depends on the allocated means and the motivation of the actors. Communicating the analysis results carried out on the database to the surveillance system's financiers and actors is the best way to stimulate their motivation and efforts and thus improve quality.

Most of the above-mentioned difficulties are real in any context but become many fold the moment we work in a regional context in countries that are characterised by public health and resource problems that may be extremely heterogeneous. Supra-national institutions then appear to be a great necessity for the harmonious coordination of a surveillance system. Unfortunately, in Southeast Asia there is no solid initiative, for example at the ASEAN level (as ASEAN's rationale is essentially for the free movement of people and goods) (Beatty *et al.*, 2010). At the global level, there is the World Health Organisation (WHO) (Racloz *et al.*, 2012). However, although the idea is a good one, its implementation for a policy at a regional level is particularly difficult in Southeast Asia. The WHO has actually six large areas of influence in the world, whose definition does not necessarily follow social realities. (see map 13)

This is particularly the case for Southeast Asia that finds itself divided between (i) the "Western Pacific" area that includes Việt Nam, Cambodia, Laos, Malaysia, the Philippines, Papua New Guinea and Sri Lanka, and whose decision-making centre is situated in Manila in the Philippines, and (ii) the "South-East Asia" area that includes India, Nepal, Bhutan, Bangladesh, Myanmar, Thailand and Indonesia whose decision-making centre is in Delhi, India. Southeast Asia is not only divided in two, but these two areas are quite widely intertwined. This situation makes the coordination of a public health policy at the regional scale particularly difficult.

Map 13. The Six Geographical Zones of the WHO



Source: WHO.

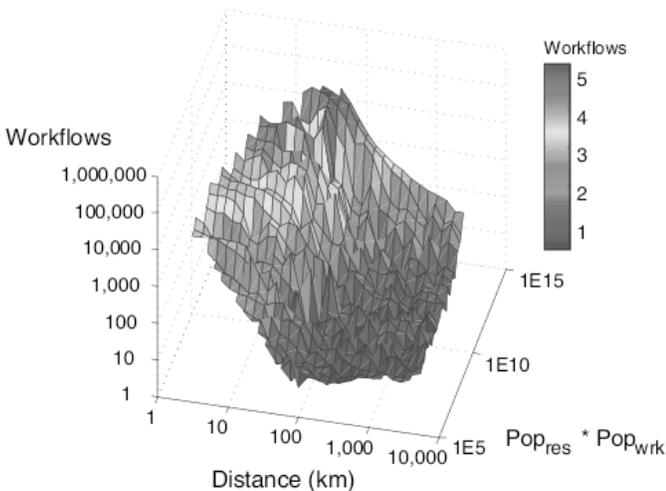
1.5.3. The Spatial Dynamics of Infectious Diseases

Diseases move around in space. They move around either through a process of transmission from person to person, or by being conveyed by their hosts or their vectors or by the environment (wind or water). This is a phenomenon that has only very recently been characterised and quantified, specifically from data from surveillance networks. Depending on the mode of propagation, the spatial diffusion of diseases may take a variety of forms (Choisy and Rohani, 2012). In order to understand the spatial propagation mode of a disease in detail, we use statistical analysis and mathematical modelling approaches, and go constantly back and forth between the two approaches. Statistical analyses basically allow us to separate the **signal** from the **noise** in a data set. The **time series** on which we work in epidemiology are often extremely noisy for reasons stated in the preceding section. The application of **signal processing** techniques (Cazelles *et al.*, 2014) allows us to extract efficiently the signal from these time series in the same way that an archaeologist removes soil from some remains. These statistical analyses allow us to characterise and quantify the spatial propagation of diseases. From this pattern, we can then make a number of hypotheses about propagation mechanisms that we can then test using mathematical models (Bolker, 2008). The idea is the following: each hypothesis is transformed into mathematical equations (model). For each of these mathematical models, the parameters are then estimated by using the data. The principle is to find

the combination of parameters that makes prediction of models as close as possible to the data. The models **calibrated** in this way (*i.e.* whose parameters are estimated from the data) are then compared with each other on the basis of the match between the prediction of models and the data. The model with the maximal adequacy is then retained and its underlying hypothesis is then considered to be the most plausible hypothesis. The other hypotheses are rejected. This is what we call **inference** (or hypotheses testing).

A simple model that was recently proposed to explain the spatial dynamic of infectious diseases is the gravity model in which the intensity of connections between two localities is mainly explained by the product of their population size and the distance that separates them (Xia *et al.*, 2004).

Diagram 5. An Example of a Gravity Model



Note. Example of a gravity model estimated from human movement data between different cities in the USA. The vertical axis represents the intensity of connections between localities that depend on the product of the sizes of population of the localities as well as the distances separating the localities.

Source: Viboud *et al.*, 2006.

This model explains particularly well the spread of directly **transmissible** diseases such as measles in England (Grenfell *et al.*, 2001) or the flu in the USA (Viboud *et al.*, 2006). When transposed to a worldwide scale, this model appears to continue to function well, and especially for directly transmissible diseases such as the flu or SARS, except that the distances between localities do not here necessarily represent the geographical distance. Indeed, Brockmann & Helbing (Brockmann and Helbing, 2013) demonstrated that on a worldwide scale the distances between populations are, for

infectious diseases, better represented by the intensities of aerial connections than by real geographical distances.

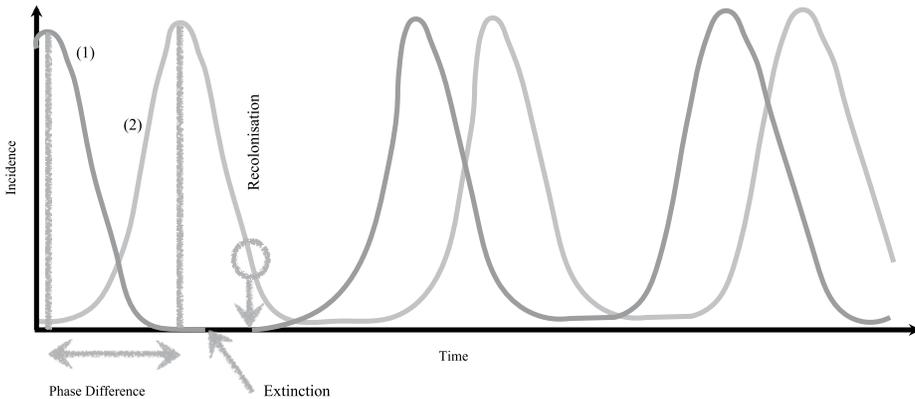
For diseases transmitted by vectors such as dengue, this propagation pattern may be somewhat complicated by the potential influence of environmental factors and local climate. Thus, in such a context of populations placed in a network of interactions it sometimes becomes difficult to distinguish between local and distant influences on the local epidemiology of a given disease. By way of an example, Cummings and his collaborators (Cummings *et al.*, 2004) demonstrated that the spatial dynamic of dengue in Thailand complies quite well with a gravitational model in which the disease spreads from Bangkok to other less densely populated localities in the country. By reanalysing the same data set, Cazelles and his collaborators (Cazelles *et al.*, 2005) demonstrate, to the contrary, that the epidemiology of dengue is strongly driven by climatic factors, particularly the multiannual oscillations of **El Niño**. This phenomenon has been recently confirmed by a study of dengue carried out in eight Southeast Asian countries (van Panhuis *et al.* 2015). The joint influence of demographic and climatic factors to explain the epidemiology of dengue has also been demonstrated on more local spatial scales. Thus, in Cambodia, Teurlai and her collaborators (Teurlai *et al.*, 2012) demonstrated that the spread of dengue is mainly driven by individual movements, with maximal propagation speed along road axes. On even more local spatial scales (the scale of the house or between houses), it seems that the movements of mosquitoes here also play an important role. In Việt Nam, climatic factors have also been highlighted on small spatial scales (Thai *et al.*, 2010; Pham *et al.*, 2011; Cuong *et al.*, 2013). In the following section we are going to take a look at the consequences of the spatial dynamics of infectious diseases for their control, particularly in a spatial context in which the actors have very heterogeneous levels of infection and resources.

1.5.4. The Control of Infectious Diseases in a Regional Context

The control of infectious diseases on large spatial scales began in the middle of the 20th century with the implementation of mass vaccination policies (measles, whooping cough, etc.) (Anderson and May, 1992). The WHO coordinated several campaigns aiming to eradicate some infectious diseases on the global scale. The first of these to be eradicated was smallpox in 1977. The second on the list of candidates is polio, whose eradication seems imminent (Pallansch and Sandhu, 2006). Measles will certainly be next on the list. These eradication programmes are particularly difficult for highly contagious viruses such as measles (Poland and Jacobson, 2012). Diseases are even more difficult to eradicate when there are significant individual movements between populations, and even more so when the populations are heterogeneous in terms of risks and resources.

The ecological theory of **metapopulations** predicts that the global persistence of a disease largely depends on the dynamics of movement of individuals between sub-populations (Hanski, 1999). When these epidemiological dynamics in sub-populations are perfectly synchronous, global persistence is minimal.

Graph 10. Synchrony and Persistence



Notes. The curves (1) and (2) illustrate epidemic dynamics in two localities. When the dynamics are asynchronous as in the figure, an extinction (curve 1) may be compensated by a re-colonisation by infected people from the population in curve (2), thus contributing to global persistence (*i.e.* the two combined populations). When, on the contrary, the epidemic dynamics in the populations are perfectly synchronous, the re-colonisation process can no longer take place because when the virus becomes extinct in a population, it has a very weak prevalence in the other population, thus limiting the chances of re-colonisation and therefore global persistence.

Source: Author's construction.

Contrarily, when the dynamics in sub-populations are asynchronous, global persistence increases as local extinctions may then be compensated by re-colonisations by sub-populations whose local density is still high. What is more, the control policies of infectious diseases may increase or decrease the synchrony between sub-populations. For example, **mass vaccination** tends to decrease the synchrony between sub-populations (Rohani *et al.*, 1999) whereas **pulse vaccination** may on the contrary be used to increase the synchrony between sub-populations (Earn *et al.*, 1998). Knowing this, work is currently being carried out to attempt to optimise control policies in a spatial context by taking into account the spatial dynamic between sub-populations and its effect on global persistence.

The problem becomes even more complicated when the actors in question are not equal in terms of the infectious risk and the means used to contain this risk. This problem was raised particularly in the context of the worldwide risk posed by avian flu where maximal incidences were observed in the poorest countries. It is then that we must raise the question concerning the optimal strategy for the rich and least affected countries faced with contamination from high-incidence (and often poor) countries. Using a mathematical network game theory model, Colizza and her collaborators (Colizza *et al.*, 2007) demonstrated that the optimal strategy of rich countries to minimise their own risk is to allocate a part of their resources directly to countries that are both low in resources and

have high incidences. This result that is to some extent counter-intuitive may be explained by the fact that nowadays populations are very strongly interconnected with each other. Thus the epidemiological situation in France closely depends on the epidemiological situations in other countries of the world, all the more so as the latter experience high incidences and are closely linked to France. Research on the same theme is currently being carried out regarding dengue, in Việt Nam and between Southeast Asian countries.

In Việt Nam dengue currently has very high transmission rates in the south of the country, as well as reduced seasonality. In the north of the country, dengue has been emerging over the last fifteen years (Do *et al.*, 2014). Furthermore, the seasonality of transmission is a lot more pronounced in the south, certainly because of climatic factors. In the north, there is a season with very few cases. **Phylogeographic** analyses have recently demonstrated that the local persistence of the dengue virus in Hà Nội is very weak and that, each year, the outbreak of dengue epidemics is the result of the importation of the virus from the south of the country (Rabaa *et al.*, 2010). In such a context, we can then ask ourselves what is the optimal strategy for the fight against dengue in Hà Nội. Is it preferable to allocate all local resources to fight local vectoral risks or is it preferable to allocate a part of resources to the south of the country in order to contribute to the reduction of incidence in the south of the country and thus reduce the risk of an outbreak of the virus in the north of the country? The answer to such a question can only be provided by a sufficiently detailed epidemiological model that takes into account environmental, demographic, entomological, transport, and economic factors.

Very similar problems may appear in very rich countries such as Singapore, which is very near to much poorer countries with increased risks of dengue such as Cambodia. In order to reduce the risk of dengue in Singapore, is it in the government's interest to allocate a part of its resources directly to Cambodia?

Communication corridors pose a similar problem. These axes that are characterised by very intense individual movements cross through countries at risk with very heterogeneous resources (Fau *et al.*, 2014). An efficient infectious disease control policy on a regional scale can thus only be implemented with supra-regional mutualisation and coordination. Small initiatives are beginning to emerge in this direction that deserve to be further developed.

Conclusion

The transmission process of infectious diseases is by nature **nonlinear**, which generates particularly complex dynamics that can behave in non-intuitive ways (Turchin, 2003). In this context, the mathematical models provide indispensable help in helping us to understand how epidemic dynamics function and thus allow us to predict and control them as efficiently as possible (Anderson and May, 1992; Diekmann and Heesterbeek, 2000; Keeling and Rohani, 2008). The realism of the models directly depends on the quantity of data available for their calibration. For this purpose, the availability of data from surveillance systems is absolutely crucial. These surveillance networks are extremely costly to implement and maintain over time. However, they are absolutely fundamental for a coherent and efficient control policy. They allow us to measure the epidemiological state of the

population as well to assess the efficiency of vaccination policies. Close communication between the authorities in charge of surveillance networks and control policies, as well as with the scientists who analyse the data from surveillance networks, is absolutely necessary. Communication about analysis results and their practical implications particularly allows us to convince the authorities of the necessity of maintaining surveillance networks and guaranteeing their quality (Brownstein *et al.*, 2008; Keller *et al.*, 2009).

In addition to the biological factors and the scientific criteria of the fight against infectious diseases, we should not neglect the importance of the socio-economic factors that greatly add to the complexity of the problem. Here again, modelling approaches are indispensable for resolving problems where the issues may be complex and contradictory. Close integration between biological and socio-economic criteria in the same theoretical framework still has yet to be built.

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Glossary

Calibration: calibrating a model consists of estimating the values of its parameters from the data.

El Niño: multi-annual climatic phenomenon (4-7 years) characterised by abnormally high temperatures.

Incidence: number of new cases by spatial unit over a given period of time.

Inference: inference is testing a hypothesis, which then allows us to answer a question.

Infectious disease: illness caused by a pathogen (virus, bacteria, protozoan, parasite, etc.) as opposed to chronic illnesses such as cancer, heart disease, or genetic illnesses. Infectious diseases are also referred to as transmissible.

Germ theory: theory developed at the end of 19th century stipulating that contagious diseases are caused by pathogenic organisms (viruses, bacteria, etc.). In opposition to the miasma theory that was believed at the time, according to which illnesses were transmitted by “bad air”.

Mass vaccination: vaccination policy aiming to vaccinate the maximum number of children before a certain age. Generally carried out in schools.

Metapopulation: population of populations, the latter being referred to as sub-populations.

Miasma theory: see germ theory.

Noise: the total variation in a data set may be divided into noise and signal. The signal is the interesting part of this variation whereas noise is the nuisance variation. The distinction between noise and signal depends on the question asked. The origin of noise may be multiple: observation error, error of process, co-variable, etc.

Nonlinearity: a function is said to be nonlinear when its outputs are not equal to its inputs. The essence of mathematics assumes hypothesis of linearity whereas the essence of nature is in fact nonlinear. Nonlinearity generates complex and often non-intuitive behaviour.

Parameter: the two ingredients in models are variables and parameters. As its name indicates, a variable is a quantity that varies in function of the values of the parameters and the other variables (of which possibly time and space). Parameters on the contrary are generally fixed quantities whose values are chosen by the modellers. Generally variables chart the number (e.g. number of the sick) whereas parameters chart biological processes (e.g. contact rate).

Phylogeography: a phylogeny is the estimation of a genealogy. Phylogeography is a phylogeny combined with geographical information.

Prevalence: number of cases by spatial unit at a given moment.

Pulse vaccination: vaccination policy proposed in the 90s that consisted of regular vaccination campaigns in which only a certain proportion of the population is vaccinated.

Signal: see noise.

Signal processing: statistical methods for time series analysis.

Time series: a time series is a time-ordered a set of data (typically the number of new cases of an illness per week).

Transmission: contagion process of an infectious disease. Transmission may be direct (*i.e.* through direct contact) or indirect. In the second case, it may be assured by a vector (generally an insect) or by the environment (e.g. water as in the case for cholera).

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