

Chapter 1

Global Spread of Hemorrhagic Fever Viruses: Predicting Pandemics

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Abstract

As successive epidemics have swept the world, the scientific community has quickly learned from them about the emergence and transmission of communicable diseases. Epidemics usually occur when health systems are unprepared. During an unexpected epidemic, health authorities engage in damage control, fear drives action, and the desire to understand the threat is greatest. As humanity recovers, policy-makers seek scientific expertise to improve their “preparedness” to face future events.

Global spread of disease is exemplified by the spread of yellow fever from Africa to the Americas, by the spread of dengue fever through transcontinental migration of mosquitos, by the relentless influenza virus pandemics, and, most recently, by the unexpected emergence of Ebola virus, spread by motorbike and long haul carriers. Other pathogens that are remarkable for their epidemic expansions include the arenavirus hemorrhagic fevers and hantavirus diseases carried by rodents over great geographic distances and the arthropod-borne viruses (West Nile, chikungunya and Zika) enabled by ecology and vector adaptations. Did we learn from the past epidemics? Are we prepared for the worst?

The ultimate goal is to develop a resilient global health infrastructure. Besides acquiring treatments, vaccines, and other preventive medicine, bio-surveillance is critical to preventing disease emergence and to counteracting its spread. So far, only the western hemisphere has a large and established monitoring system; however, diseases continue to emerge sporadically, in particular in Southeast Asia and South America, illuminating the imperfections of our surveillance. Epidemics destabilize fragile governments, ravage the most vulnerable populations, and threaten the global community.

Pandemic risk calculations employ new technologies like computerized maintenance of geographical and historical datasets, Geographic Information Systems (GIS), Next Generation sequencing, and Metagenomics to trace the molecular changes in pathogens during their emergence, and mathematical models to assess risk. Predictions help to pinpoint the hot spots of emergence, the populations at risk, and the pathogens under genetic evolution. Preparedness anticipates the risks, the needs of the population, the capacities of infrastructure, the sources of emergency funding, and finally, the international partnerships needed to manage a disaster before it occurs. At present, the world is in an intermediate phase of trying to reduce health disparities despite exponential population growth, political conflicts, migration, global trade, urbanization, and major environmental changes due to global warming. For the sake of humanity, we must focus on developing the necessary capacities for health surveillance, epidemic preparedness, and pandemic response.

Key words Viral hemorrhagic fever, Pandemic, Global biosecurity, Predicting epidemic risk (i.e., pathogenic threat and vulnerability)

1 Introduction

1.1 Preamble

Infectious diseases have swept the world, taking the lives of millions of people, causing considerable upheaval, and transforming the future of entire populations. Every year pathogens cause nearly 14 million deaths worldwide, mostly in developing countries. More than 350 infectious diseases have emerged between the 1940s and 2004 [1]. Also among the 500 known arboviruses, only 50 are known to be human pathogens, while the others only infect wild animals and/or arthropods. To anticipate an epidemic one must identify the risk, prepare an appropriate response, and control the disease spread by first identifying the vulnerabilities of the population and circumscribing the potential space into which a disease will extend. When the epidemic expansion risk is identified, adequate information must be communicated to decision makers. Ultimately, an appropriate response will depend on biosurveillance, prevention, sustained data processing, communication, strategic immunization campaigns, resilience, and mitigation strategies.

The viral hemorrhagic fevers (VHFs) are a diverse group of human illnesses caused by RNA viruses including approximately 50 species of the *Arenaviridae*, *Filoviridae*, *Bunyavirales*, *Flaviviridae*, and *Rhabdoviridae* (Table 1). Despite the efforts placed on early detection, viruses like dengue, Ebola, Lassa, Crimean-Congo hemorrhagic fevers continue to threaten the health of millions of people, mostly in areas where demographic changes, and political and socio-economic instability interrupt vaccination campaigns [2]. However, the threat of VHF to global health is increased by intercontinental travel and global trade. Moreover, because of the high case fatality rate of some of these pathogens, such concerns extend to the potential use of these viruses by bio-terrorists [3].

1.2 Historical Perspectives

Global expansion of several diseases is exemplified by the spread of yellow fever from Africa to the Americas, the spread of dengue Fever across continents, and recently, the spread of Ebola virus from the Democratic Republic of the Congo to Western Africa. The concept of an epidemic, as a disease affecting many persons at the same time and spreading from person to person in a locality where the disease was not previously prevalent, was not enunciated until 1854 when John Snow produced his admirable demonstration of the emergence of an infectious disease in an urban area: the emergence of a cholera epidemic in London. At that time, none could clearly comprehend the mechanisms of emergence and spread since the existence of microbes had just been demonstrated by Louis Pasteur in the late 1830s and microbe transmission modes were more speculative than based on medical or scientific facts, until 1876 when Robert Koch demonstrated that bacteria can be transmitted and responsible for diseases. Nowadays, it is extremely difficult to make a retrospective diagnosis of historical pandemics,

Table 1
Most common hemorrhagic fever viruses and their associated disease

Family	Virus	Disease	Origin
<i>Arenaviridae</i>	Junín virus	Argentinian HF ^a	Argentina
<i>Arenaviridae</i>	Whitewater Arroyo virus	Whitewater Arroyo HF	N. America
<i>Arenaviridae</i>	Chapare virus	Chapare HF	Bolivia
<i>Arenaviridae</i>	Guanarito virus	Venezuelan HF	Venezuela
<i>Arenaviridae</i>	Lassa fever virus	Lassa fever	Africa
<i>Arenaviridae</i>	Lujo virus	Lujo HF	Africa
<i>Arenaviridae</i>	Lymphocytic choriomeningitis virus	Lymphocytic choriomeningitis	World
<i>Arenaviridae</i>	Machupo virus	Bolivian HF	Bolivia
<i>Arenaviridae</i>	Sabiá virus	Brazilian HF	Brazil
<i>Filoviridae</i>	Marburgviruses	Marburg virus disease	Africa
<i>Filoviridae</i>	Ebolaviruses ^b	Ebola virus disease	Africa
<i>Flaviviridae</i>	Alkhurma virus	Alkhurma HF	Saudi Arabia
<i>Flaviviridae</i>	Dengue viruses	severe dengue	World
<i>Flaviviridae</i>	Kyasanur Forest disease virus	Kyasanur Forest disease	India
<i>Flaviviridae</i>	virus	Kyasanur Forest disease virus	China
<i>Flaviviridae</i>	Omsk hemorrhagic fever virus	Omsk HF	India
<i>Flaviviridae</i>	Tick-borne encephalitis virus	Tick-borne encephalitis	Eurasia
<i>Flaviviridae</i>	Yellow fever virus	Yellow fever	Africa/S. America
<i>Hantaviridae</i>	Hantaan virus ^c	HF with renal syndrome	World
<i>Hantaviridae</i>	Puumala virus	Nephropathia epidemica	World
<i>Paramyxoviridae</i>	Hendra virus	Hendra virus encephalitis	Australia
<i>Paramyxoviridae</i>	Nipah virus	Nipah virus encephalitis	Asia
<i>Nairoviridae</i>	Crimean-Congo hemorrhagic fever virus	Crimean-Congo HF	Africa/Asia
<i>Peribunyaviridae</i>	Ngari virus	Garissa HF	Africa
<i>Peribunyaviridae</i>	Ilesha virus	Ilesha HF	Africa
<i>Phenuiviridae</i>	Rift Valley fever virus	Rift Valley fever	Africa
<i>Rhabdoviridae</i>	Bas-Congo virus	Bas-Congo HF	Africa

^aHF is hemorrhagic fever

^bEbolaviruses pathogenic for humans include *Bundibugyo*, *Ebola*, *Sudan*, and *Tai Forest viruses*

^cThere are currently 41 species in the *Orthohantavirus* genus. The pathogeny of most of them is unknown

during times when clinical descriptions were rare or lacking accuracy, and the extent of an epidemic was extremely subjective. Thus, it is common to note that the first outbreak described in the Western World was that of the plague of Athens for which Thucydides rather precisely reported the symptoms; today this epidemic has often been attributed to typhus through its clinical picture and epidemic profile [4].

The first historically recorded outbreaks due to viral agents date to antiquity when the Roman armies were returning from distant countries bringing with them “exotic” diseases. Indeed, the rise of a “new” virus is an extremely rare event. Most often, in terms of pathogen emergence, a virus adapts through mutation and selection pressure to a human host causing disease. Presumably, smallpox, measles, and influenza were among the plagues that struck the ancient Latins in gusts of epidemics more or less severe. The Antonin plague that extended from 167 to 172 AD in much of Western Europe, when the troops of Emperor Lucius Verus returned from war against the Parthians, is often attributed to a smallpox pandemic by historians. In the Middle Ages, it seems that smallpox made a return around 541 AD to France, Germany, Belgium, and the British Islands [5]. The acute respiratory infections reported during the winter of 876–877 AD accompanying the return of the Carolingian armies from Italy have been attributed by historians to a flu epidemic. Many soldiers of Charlemagne died then. The disease returned regularly and fiercely in 927 and 1105 AD to the western European peninsula [6, 7] (Table 2).

1.3 Past and Present Viral Pandemics

From the plague (*sensu lato*, including all transmissible diseases) of antiquity, to the severe acute respiratory syndrome that emerged on the eve of the third millennium, pandemics have followed in the history of mankind. As noted by Mirko Grmek, a historian of medicine, it seems that one pandemic will drive in another. If several diseases circulate concomitantly, one of them will take precedence over the other, an epidemic over the previous, and it is more likely that a pandemic will prevail [8]. Plague temporarily replaced the leprosy that appeared in Eurasia for over 50,000 years; during the first millennium, plague was manifested by successive pandemics that crossed continents. During the first half of the past millennium, syphilis started its expansions, crossed oceans, and became global. Tuberculosis originated in Europe more than 15,000 years ago, but it was only at the turn of the seventeenth century that it was considered a pandemic; smallpox was also manifest as epidemics and then was pandemic at its peak in the late nineteenth century, then smallpox persisted until the Jenner area. Although early medical records of smallpox are available (Egypt, China, India), large and devastating epidemics were only identified in the late fifteenth century of the millennium. Smallpox was introduced into the Americas by Spanish settlers in the Caribbean island of Hispaniola in 1492 and arrived in Mexico in 1509. On Hispaniola

Table 2
Viral pandemics

	Disease	Origin	Inception/end	Morbidity/mortality
Measles virus (<i>Paramyxoviridae</i>)	Measles	Asia, Northern Africa	Third century ^a	/200m ^b
Variola virus (<i>Poxviridae</i>)	Smallpox	North Eastern Africa	Tenth century–1979 ^c	50m year/20 m
Yellow fever virus (<i>Flaviviridae</i>)	Yellow fever	Africa	Fourteenth century ^d -	30–70m/year
Influenza A virus (<i>Orthomyxoviridae</i>)	Pandemic flu	Northern China	1580 ^e	/0.023%
Influenza A virus (<i>Orthomyxoviridae</i>)	Russian flu	Uzbekistan	1889–1890	/1m
Poliovirus (<i>Enteroviridae</i>)	Poliomyelitis	Western hemisphere	1900–1960s	/5%
Influenza A virus H1N1 (<i>Orthomyxoviridae</i>)	Spanish flu	US Kansas	1918–1919	/50m
Influenza A virus H2N2 (<i>Orthomyxoviridae</i>)	Asian flu	China	1956–1958	/2m
Marburgviruses (<i>Filoviridae</i>)	Marburg virus disease	Eastern Africa?	1967 ^f	/55%
Influenza A virus H3N2 flu (<i>Orthomyxoviridae</i>)	Hong Kong flu	Hong Kong	1968–1969	/1m
Crimean-Congo hemorrhagic fever virus (<i>Nairoviridae</i>)	Crimean-Congo HF	Central Africa	1969 - ^g	/40%
Lassa virus (<i>Arenaviridae</i>)	Lassa fever	Western Africa	1969 - ^h	
Ebolaviruses (<i>Filoviridae</i>)	Ebola virus disease	Central Africa	1976 - ⁱ	>30,000/50%
HIV-1, -2 (<i>Lentiviridae</i>)	HIV/AIDS	Cameroon	1981–2012	35.3m/25m
Rift Valley fever virus (<i>Phenuiviridae</i>)	Rift Valley fever	North East Africa ^l	1987–2000	/1%
SARS-CoV (<i>Coronavirinae</i>)	SARS ^k	China	2003 -	/36%

(continued)

Table 2 (continued)

	Disease	Origin	Inception/end	Morbidity/mortality
MERS-CoV (<i>Coronavirinae</i>)	MERS-CoV	Saudi Arabia	2012 -	/36%
Ebola virus (<i>Filoviridae</i>)	Ebola virus disease	Guinea (Western Africa)	2014–2016	2000

^a“-” = uncertainty about virus circulation and endemics

^bm = million

^ceradicated

^dc. = century

^eLarge pandemic occurring every 10–30 years

^fWest Germany, Yugoslavia and then discovered in Africa

^gOccurred South of 50 °N latitude then extended to the Western Asia, Balkans, Asia

^hImported cases to Canada, Germany, Israel, Japan, Netherlands, United Kingdom, USA

ⁱContinental sparse repetitive epidemics in different countries, expansion within the African Rain forest

^jExpansion to Western Africa and Western Asia (and also Saudi Arabia, Yemen)

^kSevere acute respiratory syndrome

Island, one third of a million of the inhabitants died of smallpox in the following 20 years. Smallpox devastated the native Amerindian population and was an important factor in the conquest of the Aztecs and the Incas by the Spaniards [9]. In 1545, 8000 children died in Goa, India, from a smallpox epidemic. In Europe, smallpox was a leading cause of death in the eighteenth century, killing an estimated 400,000 Europeans each year [10]. During the twentieth century, it is estimated that smallpox was responsible for 300–500 million deaths. The last known natural case of smallpox occurred in Somalia in 1977 [11].

It is only at the end of the first millennium that all these pathologies were better understood and their infectious origins elucidated. The first pandemic of the twentieth century was attributed to the H1N1 Spanish Flu that emerged in Kansas in 1918. However, this “flu pandemic” is now thought to have had sub-epidemic circulation earlier in France or Germany or even prior emergence in China in 1916 or 1917 [12], and to be exacerbated by concurrent bacterial infections. Although it burned out quickly by 1920, it has been estimated that one third of the world’s population was afflicted; 50 million people died, half of them in the first 25 weeks of the outbreak.

Since the 1960s, the frequency and magnitude of dengue fever epidemics increased dramatically as the viruses and the mosquito vectors have both expanded geographically in pandemic proportions [13] largely extending the pandemic to all the intertropical zone. In the early 1980s, human immunodeficiency viruses (HIV-1 and HIV-2) spread as an acquired immunodeficiency syndrome (AIDS), a pandemic that continues to take its terrible toll at the global level. Since the emergence of AIDS, 78 million people have been infected and 39 million have died. According to World Health

Organization updates, as of June 2015 only 17 million people were accessing antiretroviral treatment and among them, seven of ten pregnant women received treatment.

In 2003, a severe acute respiratory syndrome, SARS, inaugurated the twenty-first century as a first pandemic of the millennium, involving more than 24 countries with secondary epidemic chains in Asia, Europe, North America, South America, and a total of 8098 cases [14].

Ultimately, one of the major characteristics that defines today's pandemics, apart from the introduction of the disease within several continents or the rapid expansion across the administrative borders of countries, is the initiation of locally active transmission of the pathogen. Although, the first Ebola virus disease outbreak of Western Africa was considered a pandemic and witnessed several exported cases with secondary epidemic chains in distant countries of the African continent (i.e., Nigeria, Mali), outside of Africa, exported cases rarely sparked local transmission.

1.4 Understanding the Transition from Outbreak, to Epidemic, to Pandemic.

1.4.1 From Focal to Global

Emergence from a sporadic case to an outbreak, to an epidemic, and ultimately to a pandemic depends upon effective transmission among nonimmune hosts, host availability (density), characteristics of the vector (natural or human made) that would enable it to circumvent distances, and the pathogen infectiousness. All these dynamics are essential for an effective disease transmission and spread. An outbreak is a sudden increase in occurrences of a disease in a particular time and place, more localized than an epidemic. An epidemic occurs as the disease spreads to a large number of people in a given population within a short period of time. To spark an epidemic chain of transmission depends on factors like immune population density, virus infectiousness, promiscuity, vulnerability, etc., while the efficiency of such transmission depends on how many persons will be infected by one person (i.e., the reproductive ratio or R_0). An epidemic event will therefore expand in space (beyond the first cluster of cases) and time (rapid spread). A pandemic is essentially spatial, and represents an epidemic of infectious disease that has spread through human populations across a large region, extensively across two or more continents, to worldwide. However, all these typologies harbor the same fundamentals: emergence from one index case, transmission from one host to another, and spatial expansion. Altogether, an epidemic and a pandemic are respectively a local and a global network of interconnected infectious disease outbreaks (i.e., epidemic chains). Ultimately, understanding how disease (i.e., pathogens) spread in the social system is fundamental in order to prevent and control outbreaks, with broad implications for a functioning health system and its associated costs [15]. Also, after the last case occurs at the end of an epidemic, the goal is to control the risk of transmission for a 21-day time period. This three-week period represents an incubation when the infected subject does not transmit the virus and remains asymptomatic. The "21 days" is based on

experimental methods use in virology to detect virus replication: Influenza virus infected eggs should hatch in 21 days, there is a 21-day limit for an arbovirus to infect a living model (suckling mice, mice, rats, guinea pigs, cell lines). Moreover, most viral infectious diseases have a maximal incubation period of 21 days, with few exceptions (e.g., HIV, and rabies). Ultimately, such 21-day periods multiplied by the potential of a carrier to travel will produce the risk area for the emergence of secondary cases (from a walking distance to the long distances covered by commercial jets). However, it is important to clarify that many VHF including Ebola virus can be carried by an asymptomatic host for several months [16, 17].

1.4.2 Transmission and Spread

The mode of transmission profiles the epidemic pattern of a transmissible disease. It is extremely helpful when a disease emerges to rapidly surmise the mode of transmission and how to respond (e.g., water-borne disease, arthropod-borne disease, human-to-human transmission). Pathogen transmission can be interspecific or hetero-specific, direct or indirect. Direct transmission occurs by close contact with infected biological products (e.g., blood, urine, saliva). Indirect transmission occurs with intermediate hosts such as arthropod vectors (e.g., mosquito, tick) or mammalian vector/reservoir (e.g., rodent, chiropteran) or from infected environmental means (e.g., soil, water, etc.). Mobility and transportation are the main factors for diseases dispersion, as an emblematic example, one can simply show how the 2013–2016 EVD outbreak of Western Africa expanded due to the transportation of patients during their 21-day incubation periods, first by foot-paths, then by motorbike, then taxis and public transportation, finally becoming a global concern with patients traveling by boat or commercial airline [18, 19].

Host population density and promiscuity, crowded places (like schools, markets, mass transportation system) also play an important role in the efficiency of transmission as well as the level of herd immunity (e.g., annual pandemic flu), altogether this gives us the level of population susceptibility (i.e., vulnerability). Environmental factors can also be major drivers of pathogen expansion, for example the emergence of Nipah encephalitis. The Nipah virus, when it emerged for the first time in Malaysia in 1998, was transported by its natural host, a frugivorous chiropteran. A year earlier, an immense forest fire affecting several Indonesian islands had forced the escape of disease-carrying bats that took refuge in Malaysian orchards, planted to nurture newly developed pig farms. Both pigs and farmers became infected and Nipah virus was discovered for the first time. Another classical example, more associated with human environment and behavior, is the old story of the spread of dengue virus via the used tires carrying infected *Aedes aegypti* eggs and transporting dengue across oceans and continents [20].

Understanding the mechanisms of transmission and expansion of disease vectors with respect to the typology (epidemic pattern) of a disease is the ultimate challenge for controlling and preventing

disease. Typologies from human-to-human transmission, zoonotic diseases, arboviruses, water-borne diseases, and others play different roles in the rate of disease spread and need to be clearly understood. Finally, while an epidemic pattern is driven intrinsically by the virus and its vector, the host population, the mode of transmission, and even the human environment (e.g., population density, urbanization, agricultural practices, health system, public health policies) as well as physical environment (season, meteorology, climate changing, latitude, altitude) factor into the rate of disease spread.

1.4.3 *The Virus*

With respect to pandemic risk (the rapidity and area covered by disease), the main characteristics of a virus are found in its environmental persistence while remaining infectious. Environmental persistence depends on: virus structure, enveloped viruses are more sensitive than the naked viruses; its mode of entry into the body of the susceptible subject (transdermal, oral, respiratory); its ability to diffuse out of the body for a sufficient period of time which will, in turn, enable transmission to a greater number of subjects (R_0). Altogether these intrinsic factors link to the infectivity of the virus, indeed, viruses transmitted by aerosol possess certainly the most efficient way to spark an epidemic that increases with population density and vulnerability as well as with the resistance of the virus to environmental factors outside the host cells.

1.4.4 *Hosts*

The cycle of transmission shapes the epidemic in time and spatial dispersion. For example, animal to human zoonoses are dictated by chance encounters between host (population density, animal farming, pets, hunting) and, eventually transmission such as that observed between human and nonhuman primates [21]. Vector-transmitted diseases (i.e., arthropod-borne diseases) depend on the vector ecology (ability to transmit, length of the intrinsic cycle of the virus, trophic preferences, vector density, seasonality, reproduction, breeding sites, food abundance for hematophagous arthropods). Mobility of hosts/vectors that are part of the natural cycle will also play a role in the potential for disease expansion (e.g., mosquito-flying distance, cattle transhumance, human migration). Also, other factors associated with the hosts will render a more efficient transmission: human behaviors like fear/social responses, nosocomial infections, super-spreaders); viruses having multiple natural hosts (vicariates) or vectors; vectors with multiple trophic preferences (e.g., biting cattle, birds, and primates); the incubation period in the vertebrate hosts as well as the intrinsic replication in the arthropod vectors will also intervene; ultimately subclinical infection is also an underestimated factor of virus dispersion and transmission that modifies the epidemiological pattern of disease.

One can distinguish also a typology of communicable diseases that reflects the spatial and temporal mode of transmission including arthropod-borne transmission, human-to-human transmission, human-to-animal (and vice versa) transmitted diseases (i.e., zoo-

noses) including vector and nonvector transmitted diseases, and some other types of environmentally transmitted diseases. All of them represent unique types of transmission and risk of spread with a variable path of time, and also dependent on multiple factors (environment, climate, behavior, etc.).

1.4.5 Territories

We have to consider territories as spaces where disease can potentially expand and that can be characterized by the fundamental factors of emergence and spread: the vulnerability of the population, the level of favorable transmission factors, and the probability for the population to be exposed to the virus. VHF are exemplary for their epidemic patterns of expansion dependent on the above reviewed factors (i.e., fundamentals of emergence) and their epidemiological characteristics (i.e., virus, host, environments). For example, let us consider the control of arenavirus spread by their strong host-species association. On a geological time scale, arenaviruses such as the agent for Argentinian hemorrhagic fever (AHF) coevolved with their natural rodent host and then spread according to the expansion of the rodent host. One host–one virus ultimately produces a localized endemic cycle, the distribution of the disease overlaps the distribution of the rodent host while enzootic patterns appear naturally limited to an ecosystem (e.g., local rodent populations, behaviors, and environmental factors). Hantaviruses also appear as a global complex, resulting from the coevolution of virus and rodent hosts and a global dispersion of generally localized enzootic diseases [22–24]. As for the pandemic risk associated with a natural virus reservoir, chiropterans are unique flying and migratory mammals that have been associated with *flaviviruses* and other viruses of major public health importance [25], their potential as vectors will eventually favor the spread of these viruses into new territories. Also because there is potential for a long coevolution, epidemiological patterns are also dependent on virus-host spillover, host vicariate, and other environmental factors (e.g., climate change and man-made changes in land use). Other arboviruses such as yellow fever virus, dengue virus, as well as West Nile, chikungunya, or Zika viruses show a pandemic risk associated with the existing distribution of their respective arthropod vector, vector density, and ability to transmit virus.

Investigating the fundamental factors of transmission and favorable territories for disease emergence are necessary to evaluate the risk, respond to the epidemic, and control its expansion from an index case to a pandemic. Ultimately, when the fundamentals are understood and epidemic/pandemic risk identified, suitable emergency funding needs to be identified and made available in endemic areas to insure political willingness and community participation. Ultimately, a suitable response will improve biosurveillance, data processing, communication, strategic immunization campaigns, and research for future risk prevention. Several emblematic VHF and their original “epidemiological engineering” are presented in herein.

2 Viral Hemorrhagic Fevers

2.1 Viral Hemorrhagic Fevers and Hemorrhagic Fever Viruses

VHF such as Ebola Virus Disease, Lassa fever, Rift Valley fever, or Marburg virus disease are highly contagious and deadly diseases, with potential to become pandemics. Remarkably, VHF are essentially caused by viruses of eight families; *Arenaviridae*, *Filoviridae*, *Hantaviridae*, *Nairoviridae*, *Peribunyaviridae*, *Phenuiviridae*, *Flaviviridae*, and more recently *Rhabdoviridae* [26] (Table 3).

Hemorrhagic fever viruses (HFV) have been classified as “Select Agents” because they are considered to pose a severe threat to both human and animal health due to high mortality rate, human-to-human transmission, and, in some cases, the potential to be aerosolized and used as bioweapons [27]. Each of these HFV shares some common features that define the nosology of the VHF group, from virus structures to the clinical and epidemiological characteristics of their diseases.

Table 3
Viral hemorrhagic fever emergence and pandemics

Date	Disease ^a	Place	Type ^a
3000 BCE ^b	Yellow fever	Africa	E
1976 to date	Yellow fever	Nigeria	LEE
Seventeenth century to 1998	Yellow fever	Brazil	LEE
1952 (1978 ^c)	HFRS	Korea	E
1976	EVD	DRC	E
2014	EVD	Western Africa	P
1967	MVD	Europe	E
1953	DF/DHF	South East Asia	E, LEE
1970s	DF/DHF	Oceania, Central and South America	E, LEE, P
1980s	DF/DHF	Africa	E, LEE, P
1969	Lassa fever	Nigeria	E
1972	Lassa fever	Liberia, Sierra Leone	LEE
Twelfth century (1944 ^d)	CCHF	Central Asia (Crimea)	E
1956	CCHF	Africa (DRC)	E
Mid 1900s	CCHF	Western Asia	LEE

^aE is Emergence; P is Pandemic; LEE is Large Emerging Events

^bFrom the third millennium to the present, multiple outbreaks of yellow fever were recorded in Africa, largely spreading as long-term pandemics to the Americas during the seventeenth century and thereafter

^cHantavirus identified as a hitherto etiologic agent

^dCCHF virus isolation

^eHFRS is hemorrhagic fever with renal syndrome; EVD is Ebola virus disease, DF/DHF is dengue fever/severe dengue; CCHF is Crimean-Congo hemorrhagic fever virus

- HFV are RNA viruses with envelope proteins embedded in a lipid bilayer, they are dependent on their animal and/or insect hosts for survival, and their geographical spread overlaps the areas where their natural hosts live.
- HFV spread person-to-person through direct contact with symptomatic or asymptomatic patients, body fluids, or cadavers.
- VHF can have a zoonotic origin, as when humans have contact with infected livestock via slaughter or consumption of raw meat, unpasteurized milk, bushmeat, inhalation or contact with materials contaminated with excreta from rodents or bats.
- HFV can be vector-borne, i.e., transmitted via rodents, mosquitos, and ticks.
- VHF are zoonotic diseases. Accidental transmission from the natural host to humans can eventually lead to human-to-human transmission, human infection, and sporadic outbreaks.
- With a few noteworthy exceptions (i.e., ribavirin), there is no cure or established drug treatment for VHF, while limited vaccines could be available, including YF, AHF, and RVF (the latter is for animals only).
- VHF have common features: they affect many organs, they damage blood vessels, and they affect the body's ability to regulate itself. Clinical case definitions describe VHF with at least two of the following clinical signs: hemorrhagic or purpuric rash; epistaxis, hematemesis, hemoptysis, melena, among other hemorrhagic symptoms without known predisposing host factors for hemorrhagic manifestations. In fact, during an epidemic, all infected patients do not show these signs and a specific case definition needs to be defined in accordance with the suspected or proven viral etiology of the disease [28]. Also, VHF pathogenesis encompasses a variety of mechanisms including: (1) alteration of hepatic synthesis of coagulation factors, cytokine storm, increased vascular permeability, complement activation, disseminated intravascular coagulation. Moreover, severe pathogenic syndrome is often supported by an ineffective immunity, high viral loads, and severe plasma leakage and co-infection with other pathogens [29].

2.2 Study Cases: VHF Pandemic Risk Today

The present chapter will mainly focus on the factors that can specifically and eventually contribute to a pandemic risk and how did we learn from historical spread of the VHF.

2.2.1 Yellow Fever Virus, YFV: A Timeless Plague

The yellow fever disease pandemic is thought to have originated in Africa, where the virus emerged in East or Central Africa and spread to Western Africa. In the seventeenth century, it spread to South America through the “triangular” slave trade, after which several major outbreaks occurred in the Americas, Africa, and Europe [30, 31]. The yellow fever vaccine is a fantastic gift from pioneering vac-

cinology; it is efficient, affordable for developing countries, and protects for at least a decade or even life-long. However, YF remains a particular concern at the global level and the number of cases has unexpectedly increased this past decade. Nowadays, YFV causes 200,000 infections and 30,000 deaths every year, with nearly 90% occurring in Africa. Nearly a billion people live in an endemic area [32]. Although YFV is common in tropical areas of South America and Africa, it has never been isolated in Asia [33]. Ultimately, the pandemic risk is there, from the uncontrolled epidemic as for example in the inland remote area of the Brazilian Mato Grosso state, to the recent burst of epidemics in West and Central Africa including Angola, DRC, as well as imported cases in Kenya and China [34, 35]. Indeed, the risk of a pandemic exists if any imported case goes to an area where the fundamentals of emergence are present (i.e., *Aedes aegypti* and a nonimmune human population). For years it has been stressed that YF coverage needs to be exhaustive in the endemic area, and the WHO international health regulations (IHR) need to be strictly respected when peoples are crossing frontiers to or from an endemic area [36].

2.2.2 Dengue Hemorrhagic Fever, DHF: An Expanding Pathogeny

Even though the virus was known to actively circulate in Asia, North America, and Africa 200 years ago, a global pandemic of dengue fever began in Southeast Asia in the 1950s [37, 38]. Dengue virus (DENV) expansion was followed by the emergence of a DHF pandemic that occurred in the late twentieth century (see above, the “tire-mosquito larvae connection”). By the end of the century, DHF emerged in the Pacific and the Americas, and extended to all Asian continents [32]. Lately, in the 1980s, epidemic dengue fever occurs in Africa, with a predominant activity in East Africa, while sylvatic DENV circulation was described in Western Africa [39]. The different dengue virus serotypes spread also independently to all continents. While it is remarkable that infection with one serotype does not provide cross-protective immunity against the others, epidemics caused by multiple serotypes became more frequent, and highly pathogenic DENV were identified [40]. Dengue fever to date has a global distribution with an estimated 2.5 billion people at risk. Yearly, hundreds of thousands of DHF cases occur [32]. Altogether, the requirements for a DHF pandemic are globally present [41]: the highly competent *Aedes aegypti* and *Aedes albopictus* DENV vectors, the globally distributed DENV serotypes and highly pathogenic strains, and finally, climate change that opens new breeding opportunities for these mosquitoes to expand and eventually transmit imported DENV into new populations and territories [42]. Mankind will have to live with this pandemic until the new DENV vaccines can be implemented.

2.2.3 Marburg Virus Disease: A Brief, but Disturbing History

In 1967, an unknown disease was reported by a group of laboratory workers in West Germany and former Yugoslavia [43]. Over the course of 2 months, 31 cases and seven deaths occurred.

Conclusions made by treating physicians at the time (and published shortly thereafter) highlighted the following: high fatality rate, risk of relapse; risk of sexual transmission [38]. A connection was made to infected African primates, *Chlorocebus aethiops*, when laboratory workers were exposed to their imported tissues. It took 43 years to effectively connect Marburg virus, MARV, to a bat, *Rousettus aegyptiacus*, as a natural MARV reservoir in Central Africa [44]. MARV is considered to be extremely dangerous for humans, is classified as a Risk Group 4 Pathogen, and also is listed as a Select Agent; however, the pandemic risk cannot be assessed because only four epidemics have occurred. Although MARV expansion appears to be limited to a few countries in Africa, the recent emergence (estimated at a few decades ago) of a second human pathogenic marburgvirus known as Ravn virus, and the widely distributed Old World rousette fruit bats (*Rousettus* spp.) serving as reservoir for both viruses [45], are two factors that favor pandemic risk.

2.2.4 Ebola Virus Disease: Disconcerting and Cryptic Silent Periods

Although more than 35 years after its emergence from a remote area on the Ebola river in the Central African rain forest, Ebola virus (EBOV) remained hidden in a cryptic natural cycle. Then a series of 23 outbreaks occurred in the large Congolese rain forest of Central Africa [46]. The epidemic risk was always considered to be localized and circumscribed [47]. Then, suddenly without warning, in the late months of 2013, EBOV emerged for the first time in a remote area of Western Africa and sparked an outbreak more massive than ever witnessed before. More than 28,000 people were infected, ten countries recorded cases (transmitted or imported), the pandemic risk raised fear, and WHO declared it as an international health emergency that requires a coordinated global approach [48].

Besides the lack of preparedness of national and international public health systems, the other major factor that played an immense role for the dispersion of EVD in Western Africa was the extreme mobility of village populations. They followed the Kissidougou forest foot-paths to the towns in Guinea using motor-bikes, cars, and other public transportation, then later EVD traveled by plane to the global level. The EVD epidemic went from outbreak to pandemic risk. Like Marburg virus, another member of the *Filoviridae*, Ebola virus, shares bats as a potential virus reservoir, human and nonhuman primates are highly sensitive to the virus, and inter-epidemic periods play an important role since the epidemic silences tend to diminish the attention of health services and increase epidemic risk. In this way, the first Western African EVD epidemic is exemplary for showing the hidden risks contained in the natural cycle of a virus, and the sudden emergence followed by an unprecedented velocity of spreading. In the absence of bio-surveillance, a pandemic risk remains.

2.2.5 Hemorrhagic Fever with Renal Syndrome: No Pandemic Risk but a Recently Growing Ancient Family That Can Still Be Surprising

Hemorrhagic Fever with Renal Syndrome, HFRS, appears first as a global concern of one virus family, several human pathogenic viruses of the genus *Orthohantavirus*, multiple clinical presentations, and different epidemiological patterns [49]. Hantaviruses and HFRS were first described in Asia [50]; nowadays, Hantaviruses are the cause of zoonoses that are expanding worldwide. Indeed, since 1993 when a previously unknown hantavirus was implicated in the first hantavirus pulmonary syndrome (HPS) outbreak in the United States, several other hantavirus infections were reported in western Europe, and then hantaviruses were described in South America. Ultimately, after an early suspicion of the presence of the Hantaviruses in Africa [51], a novel hantavirus, Sangassou virus, was isolated in 2012 in Guinea [52]. Altogether we observed the emergence of the *Hantaviridae* in the Western hemisphere, from the old World to the new World, and recently discovered its first tentative steps on the African continent. With respect to the Orthohantavirus genus, a real pandemic exists even when multiple viruses are involved. Ultimately, as for the *Arenaviridae*, hosts are specific and certainly the major vectors of virus dispersion.

2.2.6 Lassa Fever and Other Arenaviruses: A Global Dispersion with Localized Epidemics

The *Arenaviridae* includes 33 different viral species grouped as Old or New World arenaviruses [53], each is maintained by rodents of individual species as natural reservoir host and as vector for the viruses that are human pathogens. The rodent hosts are chronically infected without obvious illness and they pass virus vertically to their offspring. De facto, the distribution of the virus covers that of its natural hosts but is isolated in an ecosystem generally limited by natural barriers, e.g., mountains, river. A phenomenon in which rodent lineages are naturally infected by a virus and remain in such a limited environment is called “nidality” [54]. This is what it is observed for Argentinian HF, Venezuelan HF, Bolivian HF, and Lassa HF. Regarding the pandemic risk of any of these HF, arenaviruses because of their strict association with their natural hosts, like the hantaviruses, have their expansion potential limited by their natural hosts even though the latter are widely spread and could certainly be infected. Such risk lies in an unexpected encounter between infected and noninfected populations under the pressures of (as yet unknown) factors that favor their migration from enzootic to non-enzootic areas. In that matter, lymphocytic choriomeningitis virus, another member of the *Arenaviridae*, has a worldwide distribution through its domesticated natural host, the ubiquitous house mouse, *Mus musculus*.

2.2.7 Crimean-Congo Hemorrhagic Fever: An Emerging Threat

Although Crimean-Congo hemorrhagic fever, CCHF, is a widespread disease endemic to Africa, the Balkans, Western Asia, and Asian countries south of the 50th parallel North, it is generally transmitted by ticks to livestock or humans and therefore geographically limited to regions where tick vectors feed on humans.

Although the competent ixodid vector is limited, as is the abundance of their natural hosts, climate change modifies the distribution and abundance of tick hosts (i.e., tick abundance) [55]. Additionally the CCHFV pandemic risk is limited by low mobility, geographical repartition, and seasonal activity, although its main natural hosts are widely dispersed from Africa, to Asia and Europe [56]. Ultimately, human-to-human transmission occurs from close contact with the blood, secretions, or other biological fluids of infected persons but these remain rare events with a $R_0 < 1$. Altogether, a CCHF pandemic risk remains hypothetical but underlined by the risk of human-to-human transmission [57].

2.2.8 Rift Valley Fever

As for CCHF, Rift Valley fever, RVF, is first a disease of cattle and illustrates a unique subcontinental zoonotic spread along the path of traditional herders. RVF became a transcontinental risk with trade and transportation when the virus spread from North East Africa to Western Africa, and even to Madagascar [58]. If one considers its pandemic risk, with respect to RVF epidemiology as a mosquito-transmitted disease, two factors have to play concomitantly: the presence of infected cattle (i.e., nonimmune) and competent mosquito abundance, both considered hazards, while concretizing the risks from human vulnerability (nonimmune; mosquito bite; direct exposure to infected blood).

3 Response Preparedness

3.1 Framework

In order to streamline the prevention and the actions to reduce epidemic risk, the various elements involved in an outbreak are here considered from a systemic point of view, considering the risk as the convergence of a hazard and vulnerability:

- The presence of the threat (or “hazard” pathogen, i.e., vector, virus reservoir) is considered to be a necessary—but not sufficient—condition for the development of a disease. It is often known only in terms of probabilities, sometimes very low and therefore often subject to significant random variability in time and space. We often seek to evaluate the spatial and temporal differences of this probability, trying to measure its significance. Sometimes, it only uses one character necessary to the presence of the pathogen or vector (e.g., the presence of water, a minimum temperature, a type of vegetation).
- The susceptibility of the host (which is essentially linked to individual characters, genetic, biological, such as immune status or age) is individual, and often given by a probability.
- Direct exposure of the host to the hazard is an element of active vulnerability, depending on the behavior of the host that increases the likelihood of contact between host and hazard by

exposing it to an environment conducive to his presence (e.g., travel and contacts, professional activities). It also includes all the known “risk” behaviors that increase the likelihood of direct exposure to the hazard.

- Passive vulnerability of the host, which is not directly dependent on the pathology, is not even necessary nor sufficient for pathology, but influences the exposure of the host to the hazard or to protection from the pathology. This protection consists of prophylaxis, access to care, availability of care. It is independent of the real presence of the hazard; the host can be vulnerable without being exposed to the threat. The vulnerability is often defined by several levels (individual, context). It is very often “spatial” as linked to phenomena of segregation or spatial concentration. This is an area primarily studied by geography.

Ultimately, this vision can differentiate what is active, often subject to high variability, random in time and space (the emergence or the presence of hazards is often difficult if not impossible to control) from what is passive, generally situated among more stable population levels (sensitivities, exhibitions, behaviors, and vulnerabilities). This allows for better public health preventive actions, and also to understand rationally crisis situations by preemptively targeting the most important elements of the system in terms of vulnerability, and secondly by optimizing risk reduction (elimination of vectors, vaccinations, quarantine, etc.). In all cases, these actions must be adapted to social contexts to have a real impact on risk behaviors and vulnerabilities that they generate, hence the increasing role of anthropology in the field of health.

To prevent or reduce the epidemic risk, it is necessary to act on each component of this system:

- Reducing the susceptibility of the host (e.g., immunization, vaccination, prophylaxis).
- Reducing host exposure to the pathogen (e.g., vector control, quarantine, exclusion zone).
- Eliminating the pathogen directly (e.g., animal slaughter, disinfection, hygiene), or indirectly (e.g., suppress transmission).
- Reducing host vulnerability (e.g., socio-economic, behavioral, access to health care system).
- Reducing host exposure to emergency condition (e.g., real-time data collection, warning systems for emergency, crisis management, implementation of treatment).

The rapid detection of emergence is the key to controlling the spread of an epidemic. It requires comprehensive monitoring to trigger alerts and all other risk-reducing actions, in particular, reducing the exposure of the host to the pathogen and, if possible,

the elimination of the pathogen. In parallel to the monitoring and warning systems, protocols must always take into account local characteristics of political power and decision-making bodies that could otherwise render ineffective year-long action plans or warning systems (for example, the management of the chikungunya epidemic in Reunion Island was largely impacted by bottlenecks related to local political system) [59].

3.2 Global Surveillance and Data Collection

Biosurveillance and efficiency in data collection and management will be the technical keys for prevention (early detection of epidemic risk) and forecasting epidemic emergence and spread (i.e., analyzing the data in near real time taking into account the vulnerability of a given population). Also, this can be achieved only by exhaustive capacity building (human and technical) mostly in the more vulnerable developing countries but also where the most advanced technology needs to be developed. Networking biosurveillance systems are a major undertaking from regional to global, involving politics and diplomacy. Taking in account the local characteristics of political structures and decision systems is fundamental.

Despite our current recognition of the risks posed by emerging and re-emerging infectious diseases to global public health and stability, reliable structured data remains a major gap in our ability to measure (and therefore manage) globally infectious diseases. WHO has long served as an information hub for infectious disease events worldwide; however, extracting quantitative data from WHO information bulletins (*Weekly Epidemiological Record* and the more recent *Disease Outbreak News alerts*) proves to be a time-consuming effort with limited results in terms of operability, and exists more for the record and future analysis. The current proliferation of geospatial information tools (i.e., Geographical Information System, GIS) and stepwise advances in data extraction capabilities have made it possible to develop robust, systematic databases facilitating anomaly detection (like clusters), infectious disease models (and model evaluation), and apples-to-apples comparisons of historic infectious disease events worldwide. However, biosurveillance capabilities—the key to global prevention and health security—remain inadequate to support true early detection and response. Increased access to technology, rapidly developing communications infrastructures, smartphone usage for suspected-case reporting, and global networks of (formal and informal) disease surveillance practitioners provide an explosive opportunity to patch and improve surveillance networks. The challenge is to leverage all these developments, implement technical and capacity building where needed, before the next epidemic with global impact emerges.

Several organizations have developed systems to collect epidemic information and facilitate rapid response: WHO has the Department of Pandemic and Epidemic Diseases (PED) that

develops mechanisms to address epidemic diseases, thereby reducing their impact on affected populations and limiting their international spread. Among them some have self-explanatory titles: the Battle against Respiratory Viruses (BRaVe); Early Warning and Response systems for Epidemics in emergency (EWARE); Emerging and Dangerous Pathogens Laboratory Network (EDPLN); International Coordinating Group for access to vaccines for epidemics (ICG); Global Infection Prevention and Control Network; (GIPCN); Global Influenza Surveillance and Response System (GISRS); Global Leptospirosis Environmental Action Network (GLEAN); Meningitis Environmental Risk Information Technologies (MERIT); Weekly Epidemiological Record (WER); Emerging Diseases Clinical Assessment and Response Network (EDCARN). Global commitment to these efforts will insure their readiness in times of need.

3.3 Emergency Funding for Outbreaks, Epidemics, and Pandemics

Most certainly and most importantly, any preparedness and response requires emergency funding [60]. It has been estimated that if the Ebola virus disease response started 2 months earlier, it could have reduced the total number of deaths by 80% in Liberia and Sierra Leone [61]. We learned from this last EVD epidemic that in March 2015, the African Union's Minister of Finance requested the African Risk Capacity (ARC) Agency to help Member States to better plan, prepare, and respond to devastating outbreaks by developing new applications for financial tools, like insurance, that can significantly improve the speed of funds to affected countries and shorten the time between event and response. The Agency is now developing an outbreak and epidemic insurance product primarily based on responsibly and timely budget reallocation; however, viruses do not wait. Moreover, the World Bank's Pandemic Emergency Facility is designed to finance surge capacity and support international government partners to actively participate to the response. Ultimately, epidemics are not one-off events, but rather demonstrate financial patterns similar to other natural catastrophes. As natural catastrophes, large epidemics can be insured by creating financial mechanisms to facilitate the movement of critical resources within affected countries and ultimately manage the spread of disease and minimizing macroeconomic impact [62].

3.4 Tools and Strategies for a Global Prevention of Pandemic Risk

Classical tools and strategies for predicting epidemics encompass human disease surveillance (e.g., public health and hospital statistics) and, sometimes, environmental surveys (e.g., climate, el Niño, earthquake, tsunami); also more recently complying with One Health concept, human and veterinary health as well environmental risk factors have been reunited in a comprehensive approach of Public Health risk (i.e., outbreak, epidemic risks). However, this heuristic approach of health remains limited to specific diseases and territories and does not apply as a global predictor of pandemics.

First, historical data is the only available objective view of past epidemics and pandemics, needs to be collected, formatted, corrected, and analyzed. This will be the foundation of the different tools and strategies described below. In that matter, with respect to the depth of the past data available, time series of disease observation, modern tools such as Internet Search Data have actually led to the development of several specific sites (e.g., Google Flu and Dengue) [63], whose search-term reports have correlated strongly with incidence estimates in several public health reports in Europe, Asia, and the U.S. However, even though such tools can complement classical disease surveillance, most of these sites are geographically limited and cannot be used for live monitoring of epidemic risk and for Neglected Tropical Disease Surveillance [64, 65]. However, from such historical and live-collected data, health alert systems can be implemented, and prediction models can be developed. Moreover, thanks to the spatial analyses, combining multiple data sources will provide the ultimate tools for live-mapping an outbreak, which will lead to an efficient response when tools and strategy have been specifically identified (i.e., sufficient and available in-country health system resources and funding; identifying variations in pathogen sequences that contribute to R_0 and pathogenicity; monitoring population movement; etc.).

3.4.1 “Big Data” Analysis

The amount of data being digitally collected and stored is exponentially accumulating. It is estimated that, as of September of 2016, the World Wide Web reached 5.02 billion pages containing eight zettabytes of accessible data, and the accumulation of information is growing around 40% every year [66]. This situation has generated much discussion about how to use the unprecedented availability of information and computational resources and the sophistication of new analytic and visualization algorithms for decision-making to reduce the impact of infectious diseases. In fact, it is argued that the paradigm of “Big Data” will change not only the way business and research is done, but significantly improve the understanding of factors leading to the emergence of infectious diseases. Big Data could lead to the implementation of a decentralized biosurveillance enterprise allowing organizations and individuals to take full advantage of a large collection of disparate, unstructured qualitative, and quantitative datasets. With the proper integration and the right analytics, Big Data could find unusual data trends leading to better pathogen detection systems, as well as therapeutic and prophylactic countermeasures. However, the impact of these analyses and forecasts depends not only on how the data is collected, ingested, disambiguated and processed, but also on how it is relayed in different operational contexts to users with different backgrounds and understandings of technology. While impressive in data mining capabilities, real-time content analysis of social media data misses much of the factual complexity.

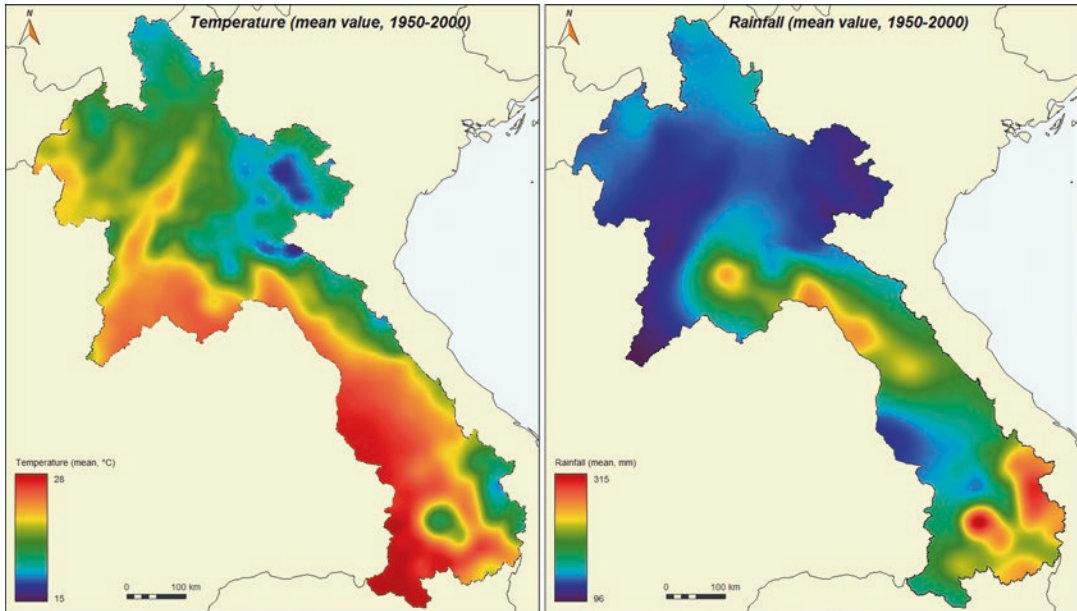


Fig. 1 Mapping environmental factors that have a major impact on insect vector population (i.e., mosquitoes and ticks). This map of Laos constitutes the basis of a risk map showing part of the hazards contributing to virus vector density that could be matched with human density and pathogen prevalence leading to a risk map (spatial risk) and eventually extended through seasonality (temporal risk). Mean temperature and mean rainfalls are interpolated as climatic conditions, as environmental factors influencing the presence of mosquitoes

Quality issues within freeform user-provided hashtags and biased referencing can significantly undermine our confidence in the information obtained to make critical decisions about the natural versus intentional emergence of a pathogen.

3.4.2 Spatial Analysis

Risk factors associated with a health event in a population are often linked to environmental factors (Fig. 1). They are also linked to spatial relationships between individuals, especially for infectious diseases. The geographical distribution of these phenomena reflects spatial relationships. Beyond “classic” epidemiology mainly based on statistical analysis, using the location and spatial distribution is essential in the understanding of health events and analysis of their mechanisms.

Spatial analysis in epidemiology is a method to help determine the location (georeferenced) of risk factors. It allows one to identify the spatial and temporal differentiation in the distribution of events, using their location in time and space. When the location is available, with precision for each studied object (i.e., individuals or geographical units), it is possible to:

- Characterize the overall spatial distribution, using synthetic indices on the absolute position of an object, on the average spatial arrangement of objects or their values (grouping/

dispersion, spatial dependence, variogram measure of Auto-correlation Space).

- Look for characteristics of the overall shape of the phenomenon (tendency, shape), and search for a theoretical spatial distribution, or for a process to model the observed spatial distribution.
- Look for unusual places (geographical centers and source sites; aggregates; exclusions; hot spots, cold spots), and to study the spatial relationships at the individual level.
- Conduct spatiotemporal analysis: search index cases, reconstruction of paths, diffusion models, models of extinction, etc.
- Spatial analysis allows the development of applications for modeling epidemics, preparing warning systems, as well as crisis management systems, risk prevention and analysis systems, and vaccination campaigns. Many tools for biomonitoring and prevention of epidemic risk have been developed (Fig. 2), as well as software tools to:
 - (a) Visualize spatial distributions.
 - (b) Synthesize and analyze position and spatial relationships between events (continuity, consolidation, attraction-repulsion, shape, centrality, displacement, diffusion processes).
 - (c) To analyze the relationship between spatial distribution of attributed values and environmental characteristics of the phenomenon (environmental correlations).
 - (d) To model the phenomena of emergence, dissemination, extinguishment of an epidemic.

Cluster detection, space-time analysis, and spatial integration with environmental and demographic data are widely used in such warning systems.

3.4.3 Genomic-Based Biosurveillance

Multiple and complex factors are associated with the emergence and impact of pathogens in a given geographical area. Therefore, public health analysts are confronted with the task to identify the likely, and unlikely, consequences and alternative critical outcomes of a given VHF outbreak. This requires the ability to monitor in near real time the dynamics of the geographical dissemination of these viruses in villages, cities, countries, continents, or the globe using new analytical techniques within the emerging field of *genomic-based biosurveillance*. This concept integrates microbial genotyping, next generation sequencing, metagenomics, big data and database analytics, and contextualized visualization to identify, characterize, and attribute known and unknown pathogens and generate estimates of how different contingencies will affect their impact [67]. A genomic-based biosurveillance system includes

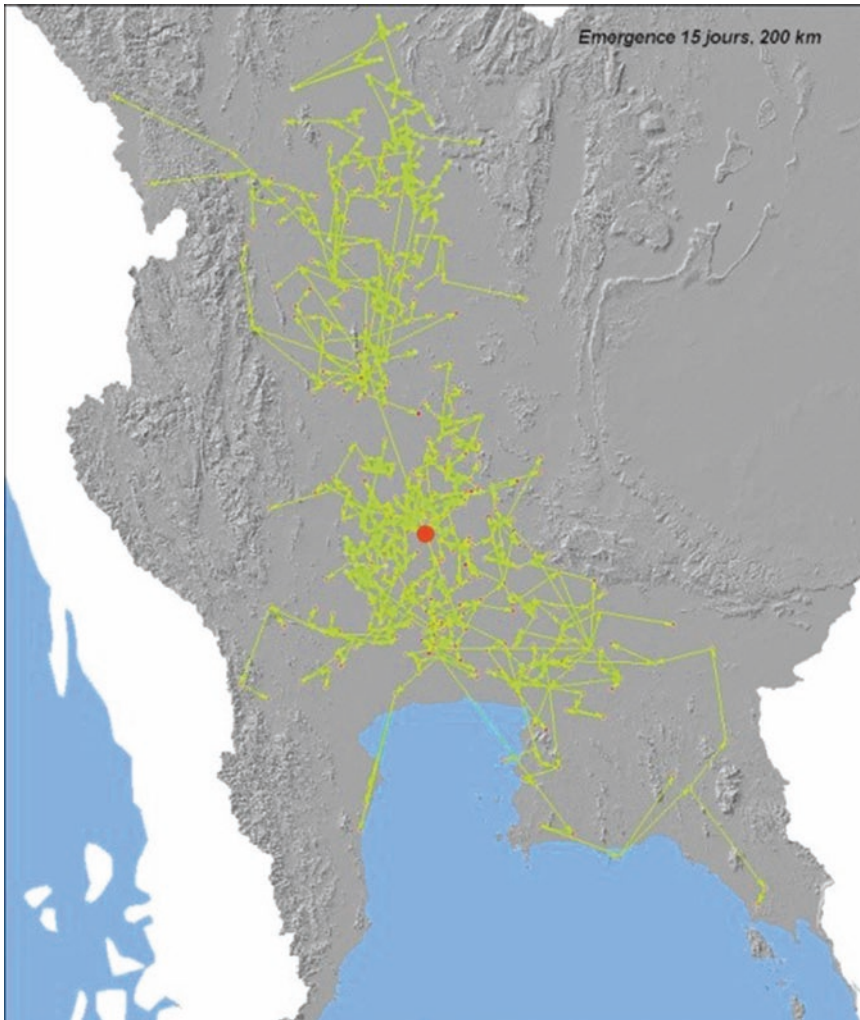


Fig. 2 From the point of emergence of H5N1 to the pathways of spread: The exemplary case of the highly pathogenic avian influenza virus H5N1 in Thailand. From the emergence of one imported case (*red-filled circle*), the pathway direction (*arrowed green lines*) of H5N1 infection in farms (*yellow points*) is reconstituted, using dates of infection and distance between farms. Results show local spread with time-to-time medium distance jumps

powerful microbial genomic characterization to rapidly identify a pathogen [67]. This characteristic makes a genomic-based biosurveillance a useful approach not only for public health but serves as a deterrence tool for intentional biological weapon development and deployment. The initial step consists of integration of signals generated by molecular-based assays and next generation DNA sequencing and unbiased microbial characterization for pathogen source tracing, attribution and forensics. While each of these techniques has been discussed in the literature in detail [68], the integration of this information can yield a more extended view of the scale of a pathogen outbreak. The development of high-throughput

DNA sequencing technologies (i.e., DNA and cDNA forms of RNA viral genomes) is allowing the genomic characterization of previously unknown pathogens without relying on prior reference molecular information [69, 70]. This information is available within days, and even hours, of sample collection, and well before the development of animal infection models. Because of their portability, this technology will become widely used in the next 5 years in routine clinical settings. However, to be clinically and epidemiologically relevant, DNA sequences must be rapidly and effectively translated into actionable information defining pathogen characteristics (i.e., virulence or drug resistance), it must point to a source of origin, and discriminate a natural event from a manmade release [71]. While some government agencies are considering use of genomic information to develop next generation Level-0 and Level-1 detection/surveillance devices [72, 73], there is no reference database where researchers can retrieve standardized genomic signatures and motif fingerprints to develop primer-, probe-, and antibody-based detection technology using reference moieties. The impact of genomic-based biosurveillance in public health and biodefense will not be fully realized until addressing the current impracticality of transferring the terabytes of genomic data generated by DNA sequencing devices to a centralized architecture performing analysis operations, as that might take hours or even days. Therefore, a new paradigm could emerge from encouraging the development of decentralized algorithms that first determine in situ the presence of pathogen-specific genomic signatures or motif fingerprints, summarize and relay the results into an operational biosurveillance metadata format for contextualized decision support.

3.4.4 Database Management and Geographical Information System (GIS)

The localized data management, time, and space required for spatial analysis is performed by geographic information systems (GIS). These are computer systems that manage large volumes of data and easily use the location to perform spatial analysis. Most GIS are not limited to data management functions, but also integrate multiple analysis tools, data transformation, and cartographic representation. These are for the most part complex applications with enormous features. The “GIS” designation covers a wide variety of software projects built according to different technical options, functionality, and diverse performances. A GIS is essentially a management tool (structure, organization, entry, storage), an analytical tool (statistical and geographical treatment, spatial analysis), and a communication tool (data visualization, descriptive mapping, thematic mapping, atlas). It is also a tool that allows the use of a spatial model for the simulation of a process, such as the development of an epidemic. GIS facilitates the interface between modeling and simulation program, and the geographic database, and can ultimately take over the whole of access to spatial information

needed by the modeling program. The GIS should thus be at the heart of organizing the collection and processing of monitoring data. To ensure the management of this system, it is important to set up a body specifying all the collection, validation, processing and dissemination of information and results (alerts, risk modeling, near real-time dissemination of results). This body must be proposed and validated by political authorities, preemptively, to avoid further blockage and to ensure effectiveness in situations of epidemic crisis.

3.4.5 *Mathematical Modeling*

Mathematical modeling is a mathematical formulation of a parameter or risk; it depends on identified or hypothesized risk factors whose coefficients are determined by a statistical or heuristic analysis from historical or observed data with the use of R_0 , as a basic reproduction rate, to timely and spatially predict the spread-speed of an emerging outbreak. Spatial-temporal modeling of health events can be seen as the final stage of the analysis. It is different from statistical modeling. Despite using risk factors, it considers the epidemic phenomenon as a whole, taking into account the spatial relationships between agents (hosts, vectors, reservoirs, and pathogens), between individuals, and relationships between individuals and their environment. This model is thus useful for understanding and anticipating the epidemics, and can be generally used to classify individuals in different states (susceptible, infected, sick healed, immune) and to model the major phenomena that can change the state of an individual. However, when a model takes into account many phenomena, it can quickly become very complex. The vast majority of models are simplifications of assumed reality. Two broad categories of methods are usually developed in modeling:

- A deterministic approach, based on differential equations whose coefficients are adjusted from observed data, or monitoring data from epidemics. In this model, one can introduce stochastic types of components in the coefficients, studying the variability of observed data. Taking no account of spatial relationships is difficult in these models, which deal in general populations, not individuals.
- A nondeterministic approach, which is based on agents whose behavior is described by expertly determined rules (multi-agent models). The status of each agent is calculated at each time step, from its behavior, environment, and relations between the agent and all other agents. These models take into account a more realistic description of the phenomenon, near the complex system finely describing reality. They allow us to consider spatial relationships in each time step. These models require intensive calculation, and their use is made possible by development of the power of computer calculations.

4 Conclusion

Let us first honestly address the fundamental questions about epidemics and preparedness: What did we learn from all the past epidemics, what will we remember in times of need? Are we prepared for the worst of these hypothetical pandemics abundantly illustrated in the cinema and unfortunately sometimes overwhelmed when reality goes beyond fiction? Certainly, we are not “globally” prepared, unfortunately, at that scale, the immense natural and human disparities do not permit it, but we do our best in our own societies. The concept of disease emergence, born only at the end of the twentieth century, is a societal marker, our desire to be on alert, understand and predict epidemics. Ultimately, there are a few, but necessary and difficult goals to reach for the prevention and control of any epidemic, also these goals are part of the development of our societies, as well as for education, they become part of the well-being for all: First, beyond understanding transmission, is needed a clear understanding of the epidemiological pattern and the spread of a given disease, before it is too late; then, which is certainly one of the more complex and costly things to achieve, is having an efficient health system to respond to an epidemic and an operational network to respond at the regional and global levels; and last but certainly not a least, having identified funding for any public health emergency will be crucial to changing our world. Perhaps, in a shrinking global community, after too many Ebola virus disease outbreaks, we will learn and be prepared for future epidemic challenges? The progress made, mostly by computer sciences in the overall analysis of health data, should serve as a tool in the prevention of major epidemics. Let us ultimately use our predictions of pandemic risk to meet and unite beyond the current frontiers of political and social wills.

Acknowledgments

W.A. Valdivia-Granda has been funded by the Department of Homeland Security and the Department of Defense. We are grateful to Sarah Cheeseman Barthel, Director, Data Acquisition & Management Metabiota, Inc., for her review and input of the section on “global surveillance and data collection.”

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