

# 12 Be a Virus, See the World

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## 12.1 Abstract

As the recent SARS epidemic has shown, viruses are able to migrate with remarkably high speed, endangering countries around the globe within hours. Since viruses are obligate parasites, their migration speed is dependent on the mobility of the respective host. Several examples of pathogenic viruses with different patterns of migration will be discussed.

*Lassa virus* is endemic in West Africa and causes a highly pathogenic hemorrhagic fever among humans. Lassa virus is transmitted by urine and feces of rodents that are persistently infected. Lassa virus, dependent on its rodent host, seems not to spread significantly outside its endemic regions. The human infection rather represents a dead end for the virus.

*West Nile virus* entered the American public awareness in 1999 with the first human cases in the United States appearing in New York City. The virus is transmitted by mosquitoes that parasitize migrating birds, and also, e.g., crows. Transmitted to humans, West Nile virus can cause encephalitis that is especially dangerous for the elderly. West Nile virus spread remarkably fast over the North American continent. Nowadays, even several Canadian provinces are facing a severe problem with infected birds and human cases.

The *SARS coronavirus* caused not only epidemics with local transmissions in mainland China, Hong Kong, Taiwan, and Toronto, but was also spread to almost every country worldwide by infected patients. So far, this was the most impressive example for the speed a virus can achieve by the mobility of its host. The natural host of the SARS coronavirus is still unknown and, thus future outbreaks cannot be excluded.

The risk imposed by an emerging virus to the human population is a product of migration velocity, transmission route, and speed of detection. Most dangerous for the human population are highly pathogenic viruses that are transmitted from human to human via the air (SARS coronavirus). However, equally dangerous are viruses that are highly pathogenic, transmitted by blood to blood contact but have a long incubation period and, thus, detection and surveillance are complicated (human immunodeficiency virus).

## 12.2 Introduction

The title of the talk goes back to a cartoon by Garry Larson. It shows two people sitting in the lobby of a hotel. The man looks deep into the eyes of a young lady saying: "You are from France? Wow! Say... You have lovely eyes!..." In parallel, the biosphere of viruses is shown, where one can see a couple of these bugs and one of them shouts: "Hey everyone, we are going to Paris!". This little cartoon shows nicely how viruses migrate: they depend on their respective hosts and the migration of the host determines the migration of the virus.

The focus of my talk might already have been adduced without being really named. That is the presence of viruses in most living organisms. If we talk about the migration of plants, microbes or people, it is interesting to have in mind that all of these carry their respective viruses with them.

Viruses are obligate parasites that are highly specialized, each adapted to its particular host. The ideal virus might be the one that you do not notice. In this sense endogenous retroviruses are possibly close to ideal.

Mostly, we can investigate the migration of viruses only by the diseases they cause. The appearance of a specific disease indicates the presence of the causative virus. This paper focuses on emerging viruses that cause dramatic and partly fatal diseases. The concept of emerging viruses evolved in consequence of a phenomenon we have been faced with within the past few decades: Hitherto unidentified viruses appear seemingly out of nowhere and cause very severe and life-threatening diseases.

By definition, emerging viruses are those that have emerged or reemerged in the last two decades and cause serious illness. A prime example of an emerging virus is Ebola virus or Marburg virus; the latter had been identified during an outbreak of hemorrhagic fever here in Marburg in 1967. At that time, Marburg virus was transmitted by infected African green monkeys that had been imported from Uganda in order to grow polio virus on their kidney cells for vaccine production.

The investigation of emerging viruses has revealed that in most cases the natural host of these viruses is not a human but another animal. Additionally, the diseases caused by these viruses often display elements of immunopathology indicating that the human immune response is not adequate. Often there is sort of immune overreaction and consequently the immune response becomes the cause, if unchecked, of fatality. Further on, emerging viruses have very often seemed to be displaced from their original habitat by ecological or social changes, thence to come into contact with a new host. Human infection with an emerging virus is therefore in most cases a kind of accident.

The topic of this conference is migration. Since viruses are parasites that usually cannot survive outside the host cell for any considerable time, the migration of viruses is the history of the migration of the respective hosts. I would like to address three examples of emerging viruses with different migration behaviors. First, Lassa virus, which seems not to migrate very far, if it migrates at all. Second, West Nile virus which migrates quite slowly; and third, SARS coronavirus which migrates exorbitantly fast.

## 12.3 Lassa Virus

*Lassa virus* (Peters et al. 1996) belongs to the family *Arenaviridae*. The family of *Arenaviridae* comprises several members that are divided into *Old World* and *New World* *Arenaviruses*, *Lassa virus* belonging in the *Old world* category. This virus is endemic in West Africa where millions of people are at risk to acquire a *Lassa virus* infection. And indeed, there are more than 150,000 known infections per year with approximately 10,000 fatal cases.

*Lassa virus* is transmitted by rodents, most likely *Mastomys natalensis*, the African soft-furred rat. The transmission route is contact with urine or feces of the rats that are persistently infected by the virus and shed the virus in high amounts.

People in remote areas of Sierra Leone, Guinea, and Ivory Coast often live under quite primitive conditions that lead to close contact between humans and rats that feed on food stored inside the huts. Moreover, *Mastomys* is also part of the diet, and people who hunt rats have the highest risk of infection with *Lassa virus* (terMeulen et al. 1996). Moreover, *Lassa virus* can be transmitted from human to human by contact with infected body fluids. This route is the cause of hospital transmissions and the rare *Lassa virus* outbreaks.

As mentioned before, *Lassa virus* is endemic in western Africa, in countries like Sierra Leone, Ivory Coast, and Guinea. However, *Mastomys natalensis* is distributed widely over the African continent. Currently, it is not understood why *Lassa fever* does not spread more widely in Africa. One possibility is that the biology of *Mastomys* is not very well understood and the species that transmits *Lassa virus* is a special subclass with a more narrow distribution.

Most of the people in the endemic regions seem to survive the infection. However, the convalescence is prolonged and some of the patients display a sustained and pronounced hearing loss whose pathogenicity is not understood. Travelers, however, who have become infected have a very high risk of dying from the infection. Almost the entire imported *Lassa virus* infections reported during recent years resulted in the death of the patients.

Although *Lassa virus* is a serious disease, especially for people that are not indigenous, this virus is not of high risk for the global human population because the primary infections are strictly from contact with *Mastomys* species that are indigenous in western Africa, and because human to human transmission requires close contact with infected body fluids.

Taken together, *Lassa virus* represents a risk for people in endemic regions and in hospitals in western Africa (as a nosocomial infection). *Lassa virus* is not a suitable bioweapon because of the close contact that is needed to transmit the virus from human to human -- apart from the fact that bioweapons might be most dangerous as psychological weapons.

## 12.4 West Nile Virus

The next example of an emerging virus with the obvious potential to spread more widely than Lassa virus is *West Nile virus* (Campbell et al. 2002). This pathogen belongs to a group of viruses that have a special way to be transmitted. They are called arboviruses which is the abbreviation for arthropod-borne viruses. Arboviruses are transmitted by ticks, mosquitoes, or sand flies. The virus is taken up by the mosquito during its blood meal and starts to replicate in the mosquito. During the next blood meal, the virus is transmitted to the next animal.

Two different arbovirus life cycles can be distinguished: (1) the virus cycles from infected mammals to arthropods, back to mammals. This is called the sylvan or savanna cycle. (2) The other possibility is that an infected mosquito feeds on a human being, thereby infection of the human takes place. The infected human is then the source for infection of another mosquito that in turn transmits the virus to other humans. This is called the urban cycle and is established if both the arthropod vector that can grow the virus and the human host are present in the near vicinity. The urban cycle presents a considerable risk for the population in less developed countries especially in highly populated cities in western Africa. Thus, an urban cycle of one highly pathogenic arbovirus, namely, the Yellow Fever virus is a nightmare. Although a vaccine against yellow fever is available, it is not routinely used in African countries for economic reasons.

However, not only are less developed countries at risk to be taken over by arboviruses. I would like to talk about another virus that is a nice example of an emerging virus that can migrate and conquer new biospheres even in highly developed countries. This is the West Nile virus. West Nile virus was known to be endemic in the whole African continent, Middle, and South Europe, western parts of Asia, and Australia.

In the summer 1999, however, New York City was shaken by several mysterious encephalitis cases that were obviously of viral origin. The investigations revealed that the causative agent was a virus of the family Flaviviridae, the family of the yellow fever virus. However, West Nile virus turned out to be the causative agent of the disease, and it is much less virulent than the yellow fever virus. In the elderly, West Nile virus causes the mentioned encephalitis with a case fatality ratio of 10% in the severe cases. The life cycle of West Nile virus includes birds as amplifying hosts and several *Culex* species as vectors. Usually, the birds do not develop a severe disease but grow the virus to high titers. There are, however, incidental avian hosts, e.g., crows that are highly susceptible to the virus. In regions where West Nile virus is reported, hundreds of dead crows have been observed. Humans are incidental hosts, as are horses. Humans and horses represent dead end hosts, however. That is, the virus is not further transmitted.

I showed the situation of the West Nile virus distribution in the USA in the summer of 1999 some slides ago. The bet of this summer among virologists was whether West Nile virus would survive the winter in New York or not. It survived. Since 1999, West Nile virus has spread from New York to other parts of the US,

and today the West Nile virus is endemic in the entire North American continent, including Canada.

## 12.5 SARS Coronavirus

The third example is the *SARS coronavirus*. This virus caused several changes in the behavior of people in some of the Asian megacities, including Hong Kong. For one thing, it led to the wearing of protective face masks in public places. SARS stands for severe acute respiratory syndrome.

In November 2002 a significant outbreak of atypical pneumonia was noted in southern China, however, nobody, including the health authorities, expressed any particular alarm. In February 2003 the detection of the highly pathogenic influenza virus H5N1 in Hong Kong concerned the World Health Organization (WHO), and when in mid-March almost simultaneously several cases of an acute respiratory symptom complex appeared in Vietnam and in Canada a very rare worldwide alert was issued. The hot spot of this outbreak was definitively China. A high number of local transmissions were reported in Beijing, the southern province Guangdong, and in Hong Kong. Canada also faced local transmissions, and many other countries were burdened by individual imported SARS cases.

The first chain of transmission of SARS was determined and is very interesting. It started with a doctor from the province Guangdong who traveled to Hong Kong where he stayed in the now notorious Hotel Metropole. Here, he became seriously ill and was admitted to a local hospital. During his stay in the hotel, he transmitted the disease to about ten other people who lived there. These people either became ill rapidly and were admitted to Hong Kong hospitals or traveled abroad. The next wave of infections then had a high impact on the public health sector. Virtually hundreds of health care workers became infected; infections that all could be traced back to the single case in Hong Kong. This example shows clearly how fast a virus can migrate. Within hours the epidemic was spread over the whole globe.

Altogether, about 8,000 cases of SARS had been detected by June 2003 with about 800 fatalities. The case fatality rate was not uniform but increased dramatically with age. People older than 65 years had a 50% risk of death from the disease.

The global outbreak needed the global response that was organized by the World Health Organization. WHO asked about 11 labs worldwide to participate in the outbreak investigation, and it was agreed to have daily teleconferences and to freely share material and information (WHO 2003). And, indeed, the collaboration worked nicely, and in consequence it was possible to check findings in one group immediately with those from patients at other places in the world. I am convinced that this collaboration was the reason for the extremely short time needed to identify the causative agent of SARS. Not more than 2 weeks after the outbreak investigations started, the virus associated with SARS was identified to be a novel coronavirus that was thereafter named SARS coronavirus (SARS-CoV; Drosten et al. 2003; Ksiazek et al. 2003; Rota et al. 2003).

It is still not completely clear where SARS-CoV came from. However, investigations of a Chinese group showed that the novel coronavirus could be detected in a cat species in Guangdong province where the outbreak originated. The sequence of the cat SARS-CoV is not 100% identical to most of the human isolates. In the latter, a 29-nucleotide deletion is found when compared to the cat isolate. Thus, the current hypothesis is that SARS is the product of an interspecies viral transmission with dramatic consequences for the new involuntary human host. Today, it is not understood whether the nucleotide deletion in the genome of the human isolates is related to the high pathogenicity of SARS-CoV (Guan et al. 2003).

It is sometimes questioned whether the measures taken by the WHO and the countries with local transmission chains were justified, considering the relatively low number of global cases and deaths. However, at the time of the outbreak, the public health services were confronted with a highly pathogenic virus that was transmitted via the air and had high impact on the public health sector by infecting mainly health care workers. Thus, the fact that SARS so far resulted in a relatively small number of diseases and deaths is mainly the result of the global efforts to contain the outbreak -- *not* the benign character of the SARS-CoV.

## 12.6 Conclusion

In conclusion, human populations are threatened by emerging viruses whose danger depends on their migration behavior, transmission route, and speed of detection. Most dangerous are airborne viruses that are transmitted easily from human to human (SARS-CoV). Arboviruses are also of high impact because of the fact that these are difficult to contain. Finally, the emerging viruses that are transmitted by local animals and are transmitted from human to human by blood to blood contact, like Ebola and Lassa viruses, have high impact on indigenous populations but are of only moderate risk to the global population.

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