

Lessons Learned from Infectious Diseases' History

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ABSTRACT

Global reports of infectious diseases - such as the measles, tuberculosis, HIV, syphilis, cholera, a persistently high incidence of malaria as well as other transmissible diseases - denote a periodical occurrence, often associated with an increase in the numbers of affected people. In addition, new infectious diseases, caused by unknown pathogens or by organisms known yet not considered pathogenic to humans, are emerging.

With the propagation of Covid-19, caused by the 'new' coronavirus SARS-CoV-2, the biomedical research efforts have been redirected toward an early diagnosis and rational therapy of respiratory viruses. These latter have been associated with conventional means (limitation of direct contacts, face masks protection, hand hygiene, testing and tracking of cases, quarantine of infected people and their contacts) to prevent further spreading. As a result, ensuring the rapid development of safe and effective vaccines, using the latest biomedical technology (e.g., the sequencing of the SARS-CoV-2 genome), is essential to stop further contaminations.

Keywords: Infectious diseases, Epidemic, Pandemic, Eradication, Anthro-p-zoonoses, Focus of infection, Spread infections, Population growth, Migration, Intercontinental transport

INTRODUCTION

Vaccination programs, increasing the level of hygiene in housing estates and the working environment, ensuring the health safety of drinking water and food in industrialized countries, have dramatically reduced perinatal, infant and child mortality from infectious diseases and has significantly extended life expectancy for both women and men. In the early 1960s, 181 years after the discovery of vaccination by Edward Jenner, Professor Karel Raška, Head of the Division of Communicable Diseases at the World Health Organization (WHO) in Geneva, greatly contributed to the eradication of the smallpox (*Variola vera*) - caused by the poxvirus (*Poxviridae*) - and of one of the most serious infectious diseases.

The worldwide successful eradication of the smallpox triggered a wave of optimism in regards to the possibility to deal with other dangerous infections to a similar extent in the foreseeable future. This hope was reflected in 1967 by US Chief Hygienist WH Stewart's statement: "We can close the book on infectious diseases". Unfortunately, two years later, limits to this statement had already been reached [1].

A decade later, on December 14, 1977, the WHO announced, through the voice of its then director H. Mahler "We have signed the death certificate of smallpox in Asia

and the last case of smallpox in the world. There has been a real way to abolish smallpox via vaccination since 1980, which means saving \$2 billion a year" [2]. Following the global scale smallpox vaccination program, last reservoirs of smallpox in Latin America disappeared in 1971, in Afghanistan and Pakistan in 1974, in India and Nepal in 1975. In October of the same year, the last case of smallpox in Bangladesh was three-year-old Rahima Banu. The last sick person in Africa was Ali MaowMaalin in 1977 [3,4]. The global eradication of the disease was solemnly declared in 1980 during the 33rd World Health Assembly solemnly.

In the biomedical research field, the epidemiological problem of infections and their immunological aspects importance has receded into the background [5], especially in industrialized countries, with a number of clinics and

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specialized departments focusing on the treatment of infectious diseases being shut down. Warning reports of new infections, especially in developing countries, have not been taken seriously enough [6,7].

Czechoslovakia became, in 1961, the first country in the world being poliomyelitis-free. In effect, following the eradication of the smallpox, poliomyelitis (polio) was the next focus of eradication. Even though it had been eliminated on some continent, there was still a need for global vaccination against it. The contribution of Czech experts and researchers, especially the one of virologist Dimitrij Slonim (1925-2017), in the search for a vaccine against polio, led to making Czechoslovakia one of the five countries in the world in 1957 to produce an effective vaccine against this disease, and two years later,

Czechoslovakia became the first in the world to vaccinate children.

Vaccination against other infectious diseases has also been effective in reducing the number of patients to a minimum in a number of countries. An example would be the one of the measles, that was declared by the World Health Organization (WHO) to be under control i.e., per 1 million inhabitants, one or even fewer diseases would occur in the span of a year.

Infectious diseases are usually classified according to either taxonomic aspect, the pathogen causing them, or the organs they attack, however for practice, the classification according to their method of transmission is more illustrative (**Table 1**). Still, each classification has its specific informational value in terms of epidemiology.

Table 1. Basic methods of transmission of the most serious infectious diseases.

Method of Transmission	Examples of Serious Pathogens and Diseases
Air (droplets, aerosol)	Viruses (influenza, measles, mumps, rubella, SARS); Bacteria (tuberculosis, legionnaires' disease, pulmonary chlamydia)
Contact Sexual Transmission	Viruses (mononucleosis, herpes diseases); Bacteria (impetigo, scabies, leprosy); Parasites (scabies); Viruses (HIV / AIDS, genital herpes, hepatitis B, papillomaviruses, molluscum contagiosum); Bacteria (gonorrhea, syphilis, chlamydia)
Blood and Blood Preparations	Viruses (HIV / AIDS, hepatitis B and C)
Fecal Contamination	Viruses (hepatitis A, rotaviruses, enteroviruses, adenoviruses, polioviruses); Bacteria (cholera, bacillary dysentery such as shigellosis, and salmonellosis, typhus, <i>Escherichia coli</i>); Protozoa (giardiasis, toxocariasis, toxoplasmosis, amebiasis)
Contaminated Food and Water	Viruses (adenovirus, rotavirus and norovirus gastroenterides, HIV); Bacteria (salmonellosis, cryptosporidiosis, listeriosis, <i>Escherichia coli</i> , <i>Helicobacter pylori</i> , campylobacter enteritis); parasites (ascariasis, tapeworms, echinococci, bellows)
Through the skin anthropods scratching, biting, injections	Viruses (hemorrhagic fevers); Bacteria (plague); Protozoa (malaria); Bacteria, cat scratch disease (bartonellosis); Parasites (schistosomiasis); Viruses (rabies); Viruses (HIV, hepatitis)
Mother fetus	Viruses (rubella, HIV, herpes diseases); Bacteria (syphilis, gonorrhea, rubella, hepatitis B and C, chlamydiosis)
Nosocomially	Viruses (HIV, hepatitis B and C, rhinoviruses, coronaviruses, influenza); Bacteria (chlamydia, klebsiella, clostridia, legionella, pseudomonads, staphylococci / methicillin resistant-MRSA, VRSA, streptococci, fungi (cryptococcosis)

PRE-EPIDEMIC PHASE OF ANTHROPOGENESIS

The number of people living in a certain area was really low, reducing contact between members of a population. It was therefore estimated that gathering and hunting would happen

over an area of 1 to 10 km². With such a low population density, pathogens causing acute diseases had little chances of spreading, or the infections were contained within the same groups, making the probability of infectious diseases spreading very low. This period, right before the onset of the

Neolithic area i.e., the beginning of the agrarian revolution, was thus referred to as the pre-epidemic phase of anthropogenesis [6]. Everything changed with the development of agriculture, which, however, could only develop under very specific conditions (fertile soil, enough water for irrigation...), and in relatively limited regions with a mild climate and no significant weather fluctuations.

More people were also needed to carry out agricultural work. Only horticulture (i.e., primitive tillage, often without irrigation) could feed 1-3 people per 1 km² more advanced agriculture [10-20] people and in combination with animal husbandry up to 165 people in the same area [7]. Increasing population, the emergence of settlements with a low hygienic standard within a large population, and the domestication of wild animals were the cause of an unprecedented onset and increase in the number of new infectious diseases, which then began to accompany humans more and more often. All this happened in a relatively short period of human development. This is aptly summed up by the American historian and writer S. Budiansky in his book "The Treaty of the Wilderness: Why Animals Chose Domestication": "For two million years we have been hunters; then in tens of thousands of years we have become farmers". The epidemic phase in human history began [8-12].

PATHOGENS IN COEVOLUTION WITH HUMAN

As is the case with other species of living organisms, many viral, bacterial, fungal and parasitic pathogens are inherent to humans and live in close coevolution with them. It is typical for these to cause only clinically milder diseases with relatively low mortality. They usually also live in their hosts throughout their lives and are passed vertically from parents to future generations. Examples are herpes viruses (Eppstein-Barr virus, γ -herpesvirus), polyomaviruses (JC virus, John Cunningham virus), papovaviruses, papillomaviruses (HPV), retroviruses and oncogenic viruses but there are many others.

PATHOGENIC AGENTS TRANSMITTED BETWEEN ANIMALS, FROM ANIMALS TO HUMANS AND FROM HUMANS TO ANIMALS

The origin of other pathogenic agents causing human infections, known as anthroozoonoses, can be traced back to animal sources. We know more than 500 agents (viruses, prions, bacteria, yeasts, fungi, protozoa and multicellular parasites) transmitting diseases from animals to humans and vice versa (Table 2) [13]. They have accompanied mankind since the beginning of time, and their detailed presentation would be beyond the scope of this Communication.

Leptospirosis is considered to be the world's most common zoonosis [14]. The zoonoses also lies epizoonoses, skin parasitic diseases which are caused by the imbalance of integument mostly insect parasites living on the surface and so may lead to penetration of infectious agents into the body

(viruses, rickettsia, bacteria). In a broader sense, epizoonoses also cover the spectrum of skin disorders, e.g., after insect bites.

Infections of wild animals did not initially attract attention until they began to cause large-scale epidemics among livestock and spread to humans. In 1889, a large plague starting from Asia broke out among African even-toed ungulates. It was caused by a paramyxovirus, thought to have developed the measles virus 5,000 years ago. This panzoonosis spread to a distance of 5,000 km in less than 10 years and in 1897 reached the Cape of Good Hope. It reduced herd numbers by 90% in Kenya alone. It also caused the local extinction of the tsetse fly and indirectly affected the conditions of other species, especially predators. After more than a hundred years, it still threatens herds of even-toed ungulates in East Africa. This was also the case with brucellosis introduced to the American continent, which permanent reservoir was even-toed ungulates in Yellowstone National Park [15]. Another example of the emergence and spread of a new infectious disease was the reforestation and introduction of ungulates and bison in the northeastern United States in the 1920s and 1930s as part of so-called rescue programs. There had been an increase in tick-borne infections, febrile protozoa (babesiosis) and, in addition, a widespread epidemic of the hitherto unknown infectious disease first described for almost half a century (1975), Lyme borreliosis, caused by *Borrelia burgdorferi*. in 1981 [16]. To illustrate this point, one can also mention the introduction of flavivirus-induced zoonosis (identified as early as 1937), which in 1999 in New York, caused an outbreak of West Nile fever affecting 62 people. At the same time, the virus was isolated from dead birds. Previously, the disease occurred only in Africa, the Middle East and Western Asia, and sporadically in Central and Southern Europe. Further monitoring had shown that the virus was spreading via mosquitoes' bites and had already become endemic in the bird populations of East America and South Canada.

To this day, it is not known how the virus penetrated the American continent i.e., who was the vector, whether an infected person, migrating birds, or an airborne mosquito. Some of the blame for its spread was attributed to long-distance truck transport (infected eggs and mosquito larvae), or mosquitoes hatching in water in discarded tires or transported to the USA for recycling from Asia and Africa.

CAUSES OF EPIDEMIA AND PANDEMIA OF INFECTIOUS DISEASES

From ancient times to almost the 18th century, epidemics were viewed as punishments from demons or gods for the guilt and transgression of men. The unfavorable position of the stars or the 'miasmas' were also accused.

The theory of miasma was emitted by Galen (129-199 AD), one of the most famous physicians of the Roman period

[17]. According to this idea, diseases were caused and transmitted by the presence of toxic vapor (miasma) in the air, which contained particles of decaying matter and had a characteristic odor [18].

Table 2. Overview of the main zoo noses in human history.

Disease	Originator	Source	Known from
Rabies	Lyssavirus	Birds, Bats, Wild / Domestic Animals	~ 10,000 BC
Malaria	Parasite (Plasmodium)	Chimpanzees	~ 8000 BC
Measles	Virus	Sheep, Goats	~ 6000 BC
Smallpox	Virus	Rodents	~ 2000 BC
Tuberculosis, Leprosy	Mycobacteria	Rodents	~ 1000 BC
Typhus	Rickettsie	Rodents	430 BC
Malleus	Bacteria	Solipeds	~ 400 BC (description 1783)
Leishmaniasis (Kala-Azar, Dum-Dum Fever)	Protozoa (Leishmania)	Rodents, Dogs	~ 100 AD (identification of the originator 1903)
Plague	Bacteria	Rodents	541 AD
Dengue Fever	Virus	Monkey	~ 1000 AD
Yellow Fever	Arbovirus	Monkey	1141 AD
Leptospirosis	Bacteria	Rodents	1886 (identification of originator 1907)
Trypanosomiasis (Sleeping Sickness)	Protozoa (Trypanosomes)	Wild Animals, Cattle	Since ancient times (identification of the originator 1901)
'Spanish' Flu	Virus	Birds, Pigs	1918
AIDS / HIV-1, -2	Virus	Monkeys, Chimpanzees	20 th century
Borreliosis	Bacteria	Small Mammals, Wildlife, Reptiles, Domestic Animals	1975 (identification of the originator 1982)
Bleeding (Hemorrhagic) Fever Ebola	Filovirus Ebola (5 Strains)	Waterfowl, Monkey, Antelope, Pigs?	1976
Balamutium Amoebic Encephalitis	Protozoa (Amoebas)	Monkey	1986
MERS-CoV	Coronavirus	Camel, Bat	2012

This idea was later challenged by the 'disease theory' proposed by Girolamo Fracastoro in 1546, which considered germs to be chemical rather than living organisms, and revealed three different modes of disease transmission: direct contact with a sick person, indirect contact through

objects and clothing belonging to the sick and remote transmission by air [19,20]).

At the beginning of the 19th century, both the theory of 'miasma' and the principle of 'contagion' began to be replaced by the 'germ theory' postulated by Louis Pasteur

and supported by the evidence presented by Robert Koch [9,10]. However, under pressure from shipowners in 1818, the British Parliament voted that the plague was not contagious, and when a local epidemic of yellow fever broke out in Barcelona in 1821, French doctors explained its cause by miasma theory. In 1828 the French House ruled that yellow fever was not a contagious disease, and in that context, Nicolas Chervin was awarded the Grand Prize for Medicine by the Academy.

When a cholera epidemic broke out in Europe a year later (1829), believers of the germ theory of contagious disease were considered to be completely ignorant. This was another half a century before Robert Koch definitively confirmed, in 1876, Louis Pasteur's germline theory of infectivity [21]. Epidemics have always triggered feelings of guilt and repentance (flagellation). Even the English historian E. Gibbon (1737-1794) interpreted the causes of the disintegration and demise of the Western Roman Empire as a punishment for softened and immoral life [16-18]. Almost at the same time, the English economist TR Malthus (1766-1834) published his population theory [19], which had a significant impact on demography, sociology and economics. He was the first to explain the causes of epidemics sociologically: uncontrollable population growth, associated with scarce food and other resources, resulted in poverty, hunger, social storms, and ultimately the outbreak of an epidemic as a natural brake on overpopulation.

Misinterpretations of the causes of epidemic outbreaks have arisen, on one hand, from the limited knowledge we had at the time, but also from clinging to earlier, seemingly proven evidences and facts. As an example, in the recent past, gastroduodenal ulcers were thought to be the result of so-called civilization stress, but their presumed etiological agent is *Helicobacter pylori* (discovered in 1982) [21].

NEW FOCUSES ON DISEASES AND THE WAYS OF THEIR SPREAD

As in the past, outbreaks of disease are still emerging in overcrowded urban agglomerations. Mass migration from rural regions brings specific infections to cities where newcomers live in primitive unhygienic conditions, without sanitation, electricity or affordable healthcare. The nutritional habits, social and sexual behaviors of the population are changing.

As far as the transmission of diseases directly between people is concerned, tourism and intercontinental air transport of people constitute a serious threat. The populations travel more and more often, especially between climatically diverse localities with a different history of infections. Migration represents the greatest cause of infections spreading. Populations from different ethnicities and religions, political and war conflicts all contributed to an increased traffic between different parts of the world. There is no shortage of examples from the past. Already at the time

of the migration of nations, infections such as the plague, the typhoid fever, the smallpox and measles, were spreading, decimating America's original population within decades of their discovery. However, it is not just about human migration. The transport of livestock's, through which pathogens enter new areas, plays an important role in the emergence and spread of infections.

The relocation of critically endangered plants and animals also plays a role here as part of rescue programs organized by, for example, the International Fund for Animal Welfare (IFAW) and a number of other organizations. In the last few decades alone, there have been several hundred relocations of livestock and wildlife worldwide without recording their health status or systematically monitoring their morbidity. To this can be added harvested timber as well as agricultural and food products international mass transport. Another vector spreading infectious diseases are the dozens of species of microorganisms (viruses, bacteria, protozoa) and multicellular parasites that contaminate wastewater. Therefore, some of the most serious infections are spread, especially in third world countries. Their incidence and number of victims are quantified in millions and are constantly changing. Up-to-date information can be obtained from the relevant WHO references [22]. Another potential risk is bioterrorism, the misuse of highly virulent pathogenic microorganisms capable of causing difficult-to-manage epidemics. Potentially, these are mainly viral (hemorrhagic fevers) and bacterial (plague and anthrax) infections [8,9].

COMMUNICATIONS DISEASES AFFECTING THE CURRENT GENERATION

'Old' infectious diseases

These include, in particular, tuberculosis, which still affects a large part of the world's population, regional leprosy and cholera. This latter is an indicator of the social and hygienic conditions that millions of refugees and migrants find themselves in (see above) remaining therefore a global threat. According to the WHO, it still affects 1.3 to 4 million people a year and causes 21,000 to 143,000 deaths a year. While some diseases were the causes of epidemics and pandemics that destroyed humanity more than wars, others, such as diarrheal diseases, malaria, measles and twentieth-century diseases, AIDS are also dangerous. Pertussis, cryptosporidiosis and hepatitis C and *Mycobacterium leprae*, which are still surviving in leprosarium's, are also considered to be potentially threatening [23].

New Infections

Over the past fifty years, a number of previously unknown and undiagnosed infections have emerged. These mainly include AIDS, and a number of hemorrhagic fevers of viral origin, namely Ebola caused by filoviruses derived from monkeys (recorded in 1976). Between 2014 and 2016, local epidemic arose in West Africa (Guinea, Sierra Leone and Liberia), and in Congo between 2018 and 2020. Due to

strict, uncompromising anti-epidemic measures, enforced by high mortality, which ranged from 40 to 60%, the foci were eliminated before an active vaccine was developed. New viral hepatitis, new influenza diseases (caused by H5N1, H7N7, H1N1 viruses) and coronaviruses (SARS, MERS,

SARS-CoV-2) also developed (**Table 3**). Typical features of these diseases include their rapid spread and acute course. The vast majority of their agents is pathogenic, especially for humans, and begins as anthroponozoonoses.

Table 3. The most important causes of new diseases since 1950.

Year identification	Originator	Disease
1951	Hantavirus Soul (<i>Bunyaviridae</i>)	Korean hemorrhagic fever
1953	Arenavirus Junin (<i>Arenaviridae</i>)	Argentine hemorrhagic fever
1953	Fengivirus Dengu (<i>Flaviviridae</i>)	Hemorrhagic fever
1957	<i>Babesia microti</i> , <i>B. divergens</i> (protozoa)	Febrile illness with symptoms of muscle pain, tremor and fatigue
1959	Alfavirus O'nyong-nyong (<i>Togaviridae</i>)	Hemorrhagic fever
1967	Filovirus Marburg (<i>Filoviridae</i>)	Hemorrhagic fever
1969	Arenavirus Lassa (<i>Arenaviridae</i>)	Hemorrhagic fever
1973	Various rotaviruses (<i>Reoviridae</i>)	Diarrhea
1973	Hepatitis A virus (HBA) (<i>Picornaviridae</i>)	Acute hepatitis
1973	Hepatitis B virus (HBV) (<i>Hepadnaviridae</i>)	Chronic hepatitis
1976	Filovirus Ebola (<i>Filoviridae</i>)	Hemorrhagic fever
1976	<i>Cryptosporidium parvum</i> (element)	Enterocolitis
1977	<i>Legionella pneumophila</i> (bacteria)	Legionnaires' disease
1977	Hepatitis D deltavirus (HBD) (HBV satellite virus)	Hepatitis
1977	Hantaan hantavirus (<i>Bunyaviridae</i>)	Hemorrhagic fever, renal syndrome (HFRS)
1982	<i>Borrelia burgdorferi</i> (bacteria)	Lyme disease
1982	<i>Escherichia coli</i> O157: H7 (bacteria)	Bleeding enteritis
1983	HIV1, HIV2 (<i>Lentiviridae</i>)	AIDS
1983	<i>Helicobacter pylori</i> (bacteria)	Gastrointestinal ulcer disease
1988	Hepatitis C virus (HBC) (<i>Flaviviridae</i>)	Post-transfusion inflammation of the liver
1990	hepatitis E virus (HBE) (related to <i>Caliciviridae</i>)	Hepatitis
1993	hantavirus Sin nombre (<i>Bunyaviridae</i>)	Hantavirus pulmonary syndrome (HPS)
1992	<i>Bartonella henselae</i> (bacteria)	Cat scratch disease
1994	herpesvirus 8 (<i>Herpesviridae</i>)	Kaposi's sarcoma*
1994	Hendravirus (<i>Paramyxoviridae</i>)	Meningoencephalitis
1996	prion BSE	Variant of Creutzfeld-Jacob syndrome
1995-96	hepatitis G virus (HBG) (related to <i>Flaviviridae</i>)	Coincidence with AIDS
1999	Nipah virus (<i>Paramyxoviridae</i>)	Meningoencephalitis
2001	Metapneumovirus (<i>Paramyxoviridae</i>)	Bronchiolitis
2002-03	coronavirus SARS (<i>Coronaviridae</i>)	Acute respiratory distress syndrome with severe pneumonia
2008	Merkel polyomavirus (MCV)	Merkel cell carcinoma of the skin
2012	MERS-CoV (<i>Coronaviridae</i>)	Middle Eastern respiratory syndrome (MERS: Middle East Respiratory Syndrome)
2019/2020	Coronavirus SARS-CoV-2I (<i>Coronaviridae</i>)	Severe acute respiratory syndrome (SARS: Severe Acute Respiratory Syndrome)

The disease was described as early as 1872 by the Hungarian physician M. Kaposim, rare at that time, today it mainly affects patients with impaired immunity (AIDS).

At the beginning of this century, completely new epidemic diseases appeared, caused by corona viruses (Coronaviridae). The first human coronavirus was discovered by the Scottish virologist JD Almeida (1930-2007) as early as 1964 [24]. The first epidemic of the disease occurred in 2002-2003, and because it was characterized by severe breathing difficulties, it was called Serious Acute Respiratory Syndrome (SARS). In 2012, a new coronavirus disease appeared in Saudi Arabia, which spread to 27 countries in the Mediterranean, Africa and Asia. It was referred to as MERS (Middle East Respiratory Syndrome) and manifested by an inflammation of the lungs and digestive system. As an anthroozoonosis, its original source of infection was bats and it was transmitted to humans from camels [25-27]. We are currently witnessing a completely new pandemic, which is again caused by coronaviruses. The disease broke out in 2019 and has since spread globally. In the short time taken by the disease to spread, dozens of studies, often contradictory, have been published. However, it is still too early to evaluate accurately its course or the number of infected people or deaths. Current data can again be found on the WHO portals [28].

CONCLUSION

Despite the unmissable achievements of biomedicine, humanity will still be threatened by both recurring and emerging infectious diseases. Some diseases (namely poliomyelitis) are already approaching eradication, but others, mainly caused by viral pathogens (influenza, hepatitis and similar viruses), are not yet close to disappear. We still have to reckon the high genetic variability of viruses, antibiotic resistance of pathogenic bacteria and adaptability of multicellular parasites or their vectors. Potential problems could also arise from permafrost thawing. In the future, practicing traditional preventive measures, such as basic hygienic anti-epidemic measures or restricting the movement of people in an effort to prevent the spread of infections in the community would not be enough. The development of reliable diagnostic tests, effective and at the same time safe vaccines as well as new effective medicines is primordial. Regarding the testing and tracing of contacts, it is important especially in the initial phase of the epidemic before mass, community spread, i.e., in the phase enabling effective tracing and subsequent isolation of contacts.

Monitoring of SARS-CoV-2 in municipal wastewater using RNA polymerase reverse transcription (RT-qPCR) is now considered as a promising tool for virus surveillance and impeding epidemic prediction [29]. Within endangered, high-risk areas, adopting social programs to improve living conditions, including tolerable hygiene standards for local populations, ensuring early detection and reliable

identification of the pathogens, early initiation of the above-mentioned anti-epidemic measures and clear identification of the population at risk of infection, are desirable steps. The occurrence of the current SARS CoV-2 pandemic is considered positive in the sense that it is a 'wake-up call' for a situation in which an epidemic such as a virus with mortality at the Ebola level develops. In this context, criminally enforceable rules could be voted to palliate the often indiscipline of part of the population.

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