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### Epidemics: Lessons from the past and current patterns of response

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#### Abstract

Hippocrates gave the term 'epidemic' its medical meaning. From antiquity to modern times, the meaning of the word epidemic has continued to evolve. Over the centuries, researchers have reached an understanding of the varying aspects of epidemics and have tried to combat them. The role played by travel, trade, and human exchanges in the propagation of epidemic infectious diseases has been understood. In 1948, the World Health Organization was created and given the task of advancing ways of combating epidemics. An early warning system to combat epidemics has been implemented by the WHO. The Global Outbreak Alert and Response Network (GOARN) is collaboration between existing institutions and networks that pool their human and technical resources to fight outbreaks. Avian influenza constitutes currently the most deadly epidemic threat, with fears that it could rapidly reach pandemic proportions and put several thousands of lives in jeopardy. Thanks to the WHO's support, most of the world's countries have mobilised and implemented an 'Action Plan for Pandemic Influenza'. As a result, most outbreaks of the H5N1 avian flu virus have so far been speedily contained. Cases of dengue virus introduction in countries possessing every circumstance required for its epidemic spread provide another example pertinent to the prevention of epidemics caused by vector-borne pathogens. *To cite this article: P. Martin, C. R. Geoscience 340 (2008).* 

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#### Résumé

Les épidémies : des leçons du passé au dispositif actuel de réponse. Hippocrate a donné au terme « épidémie » son sens médical. Depuis l'Antiquité jusqu'à l'Époque moderne, la signification du mot a évolué. Avec les siècles, les chercheurs ont compris les différents aspects des épidémies et ont essayé de les combattre. Le rôle des voyages, du commerce et des échanges humains dans la propagation des maladies infectieuses épidémiques a été compris. En 1948, l'Organisation mondiale de la santé (OMS) a été créée, avec pour tâche de mettre en place des moyens pour combattre les épidémies. Un système d'alerte précoce a été mis en place par l'OMS. Le GOARN (Global Outbreak Alert and Response Network) est un réseau de collaborations entre les institutions existantes et leurs propres réseaux, qui mettent en commun leurs potentiels humains et leurs ressources techniques pour lutter contre les épidémies. La grippe aviaire constitue aujourd'hui la menace épidémique la plus grave, avec la crainte de la voir prendre des proportions pandémiques et menacer des milliers et des milliers de vies. Grâce au support de l'OMS, la plupart des épidémies de virus aviaire H5N1 ont pour l'instant pu être contenues. Les cas d'introduction de virus de la dengue dans des pays possédant toutes les caractéristiques requises pour le développement épidémique de cette maladie infectieuse fournissent un autre exemple

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pertinent des méthodes de prévention épidémiques, appliquées à une maladie transmise par un vecteur. Pour citer cet article : P. Martin, C. R. Geoscience 340 (2008).

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## **1.** Epidemic: from the emergence of the word to the current concept

The term 'epidemic' (from the Greek: epi (upon) and dêmos (people)) was used by Homer in the Odyssev (Book I, verses 194 and 230), two centuries before Hippocrates. Other authors (Plato, Xenophon, Thucydides, and Sophocles, in particular) also used this word. Hippocrates even used it as the title for one of his works, in 430 BC. Books 1 and 3 of The Epidemics comprise lists of clinical cases. Hippocrates compared and classified these cases, looking for clinical similarities, and developed the fundamental notion of 'syndrome'. The father of Medicine grouped together these collections of signs and syndromes and focused on those occurring at a particular place, at a particular time: winter coughs on the island of Cos, summer diarrhoea at certain places, and so on. In chapter 3 of Book I, he wrote  $\kappa \alpha i \gamma \alpha \rho \alpha \lambda \lambda \omega \zeta$  to  $\nu o \dot{\mu} \sigma \eta \pi \alpha \epsilon \pi i \delta \eta \mu o \nu \eta$  ("it is clear that the disease was epidemic") and used the adjective epidemos to mean "which circulates and propagates in a country", giving this term a medical meaning. However, medicine has radically changed since this period, and with it, the word 'epidemic' has undergone a long semantic evolution of its current meaning [7].

The succession of plague epidemics in the Middle Ages helped to define 'epidemic' as the propagation of the same, single, well-identified disease, by teaching doctors to recognise this disease. In the 19th century, advances in microbiology led to further changes in the meaning of this word. From the 1880s onwards, the search for a causal microorganism replaced academic disputes and revolutionised analytical approaches to epidemic diseases. In 1883, Koch described the cholera vibrion for the first time, whilst working in Calcutta during a terrible epidemic that raged throughout India. In 1894, Alexandre Yersin identified the bacillus that now bears his name, Yersinia pestis, as the cause of a plague epidemic in China. At the end of the 20th century, genomics led to a new semantic change. The use of phenotypic, then molecular markers, and the recent mapping of bacterial genomes, using series of epidemic strains, has made it possible to demonstrate that an epidemic is almost always caused by a welldefined bacterial or viral clone. The concept of epidemic strain 'clonality' became widely accepted at the end of the 1970s [9]. Table 1 summarises this semantic evolution of the word 'epidemic' since ancient Greece.

#### 2. What is an epidemic?

Bizarre as it may seem, there is no complete definition of an 'epidemic'. Even that given by the *Dictionary of Epidemiology* [5], although interesting, does not mention the environment, which is known to play a major role in epidemics.

We can now says that an epidemic is an increase, limited in space and time, in the number of cases of a given infectious disease, caused by a pathogenic agent – almost always a single agent, and mostly clonal – the expansion of which in a population of susceptible hosts depends on environmental factors specific to that population. This process is dynamic and involves three elements: the host population, the population of pathogenic agents and their environment. These three elements are the three apices of the classical "epidemic triangle."

The host, the microorganism, and the environment each play a determinant role in the initiation and development of the epidemic. It is important to keep this notion in mind when investigating an epidemic, particularly if we wish to improve epidemic management.

#### 3. Are epidemics extreme events?

The extent to which an epidemic can be considered an extreme event depends on its impact on human, animal or plant populations. "They did not all die, but everyone was affected", wrote La Fontaine about the plague. During an epidemic, an often very large proportion of the susceptible population is infected with the pathogenic agent, resulting in a proportion of P. Martin/C. R. Geoscience 340 (2008) 670-678

Table 1 Semantic evolution of the word 'epidemic' Tableau 1 Évolution sémantique du mot « épidémie »



The left column summarises the major stages in the evolution of the word used for epidemics of infectious diseases, and the right column provides an illustration, for cholera.

La colonne de gauche décrit les étapes majeures dans l'évolution du mot, la colonne de droite illustre cette évolution par l'exemple du choléra.

dead or immunised individuals, the size of which depends on the pathogenicity of the agent concerned.

During the history of mankind, the populations of several geographic zones have been decimated by epidemics. In the Middle Ages, Europe is estimated to have lost more than 30 million people – at least a quarter of its population – from successive outbreaks of plague [1]. Epidemics of smallpox and other pathogenic agents killed about 50 million out of the 60 to 65 million Amerindians between 1492 and 1650 [4]. Epidemics in the South Pacific in the 18th and 19th centuries were associated with extremely high mortality rates [8]. The example of the Marquise Islands, where a succession of five epidemics reduced the population by more than 90% over a century and a half [6] is illustrated in Table 2.

The three components of the epidemic phenomenon determine whether an epidemic develops into an

extreme event: microbes, target host populations, environment.

#### 3.1. Microbes

Some microbes are associated with extremely high death rates. This is the case for *Yersinia pestis*, smallpox virus and the bird flu virus (and possible variants). The resistance of certain bacteria to widely used antibiotics is currently leading to mortality rates much higher than generally expected for infections with these bacteria.

#### 3.2. Target host populations

Some populations, such as those living on isolated islands, for example, may have limited cohort immunity to certain 'families' of microorganisms, facilitating the dissemination of immunologically similar pathogenic

Tal	ole	2

Mortality and epidemics in the Marquise Islands, 1769–1911

Mortalités et épidémies aux îles Marquises, 1769-1911

Tableau 2

Number of habitants on the following dates (±2 years)								
1769	1843	1857	1881	1897	1902	1911		
#50,000	20,200	11,900	5,776	4,279	3,563	3,116		
Tuberculosis	Typhoid	Flu and smallpox	Dengue fever					

The epidemics listed occurred between the date at the top of the column and that at the top of the next column.

Les épidémies mentionnées sont survenues entre la date mentionnée en haut de la colonne et celle en haut de la colonne suivante.

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agents after their introduction into these populations [3]. Other populations have a genetic predisposition rendering them particularly susceptible to certain pathogenic agents. This is the case for the Aringa populations of Sudan, who have at least one gene rendering them highly susceptible to infections with parasites of the species *Leismania donovani* [2].

#### 3.3. Environment

The environment may also play an important role, as illustrated by the recent Chikungunya virus epidemic on Reunion Island. Following its arrival on the island, the virus rapidly became adapted to a new mosquito vector, *Aedes albopictus*, which transmits the infection much more efficiently than its original African vector, *Aedes africanus*.

## 4. A brief history of the response to epidemics: from the plague to the creation of the WHO

Let us return to plague: the successive waves of this disease in Europe helped the doctors of the Middle Ages to comprehend that an epidemic was due to a single, distinct disease. These doctors rapidly realised that this disease arrived via ports, on boats. Both doctors and political authorities came to understand the role played by travel, and exchanges of goods and people in the propagation of epidemic infectious diseases. They therefore took measures to combat the introduction of these diseases. The first lazarets (quarantine stations) and quarantines were created in the ports of the Mediterranean.

The first quarantine was established in 1348 in Ragusa. The first lazaret (from the Italian word *lazzaretto*, itself a corruption of Nazareth) was created in 1423 on a small island in the Venetian lagoon, Santa Maria di Nazareth. It harboured individuals with the plague. Genoa, which always followed the trends set by Venice, created its own lazaret in 1467. These structures subsequently became common throughout the ports of the Mediterranean (e.g., at Marseilles in 1526), and in large European towns, such as Milan (1488) and Berlin (1710). They rapidly became major sanitary control sites and holding stations for patients in quarantine, but subsequently fell into disuse after the last major plague epidemics.

In the 19th century, the arrival of new contagious diseases, via ships, led to the revival of lazarets throughout Europe. The major epidemic of yellow fever in Catalonia in 1821 triggered the start of a new process of international coordination in the fight against epidemics, in Europe and the Mediterranean Basin. This approach was punctuated by epidemics of cholera, yellow fever, and typhus.

The first international conference on epidemics was held in Paris in 1851. All the major European countries were represented, but only three of these countries signed a common convention. A new epidemic of yellow fever broke out in Lisbon in 1857, and a second international health conference was held in 1859. Cholera struck in Istanbul in 1863, and the third such conference was held in this town in 1866. Eight such conferences were held until 1894, when it was decided to set up international control at the source of the infection. This agreement led to the setting up of lazarets in Egypt (Suez, Port Said, and Alexandria) and in the Sinai (El Tor).

In 1903, largely thanks to the efforts of the tenacious Dr Proust, the tenth international health conference decided to set up the 'Office international d'hygiène publique' (OIHP), which was established in Paris in 1908. Just after World War I, in 1923, the League of Nations set up the Health Organisation of the League of Nations. This organisation was subsequently fused with the OIHP in 1948 to form the World Health Organisation (WHO). In 1951, the WHO published the first International Sanitary Regulations, designed to combat six major epidemic diseases: cholera, plague, yellow fever, smallpox, recurrent fever, and typhus.

## 5. Current international efforts to combat epidemics

One of the major victories of the WHO was the eradication of smallpox in the 1970s. This led to the widespread belief that infectious diseases would all eventually be eliminated. A few years later, the AIDS epidemic had spread worldwide. Several haemorrhagic fevers (Ebola, Marburg, and Lhassa) rapidly emerged and have since caused repeated outbreaks in Central Africa. In Asia, epidemics of bird flu and SARS have threatened the whole of humanity. After the euphoria of the 1970s, it had become increasingly evident, towards the turn of the century, that an international epidemic alert and response system was required. The WHO and most developed countries now have such a system in place. Its ultimate objective is the prevention of emerging diseases and diseases of an epidemic nature that might spread across different countries. This earlywarning and management system is based partly on the WHO's International Sanitary Regulations and partly on operational systems. The WHO also set up a training course on the epidemiological and microbiological management of epidemics at its training centre in Lyon (France) in 2001.

The new International Sanitary Regulations, in force since June 2007, require:

- the notification and verification of all potentially epidemic diseases;
- the evaluation, by the country concerned (with the help of the WHO if necessary) of its ability to deal with the phenomenon;
- risk evaluation, particularly as concerns the risk of the disease crossing international borders;
- rapid assistance from the WHO if necessary.

The Global Outbreak, Alert and Response Network, GOARN, was set up by the WHO in April 2000 and provides the operational support required for countries in need of assistance. The specific objectives of the GOARN are to carry out continuous epidemiological monitoring, with a view to:

- studying all epidemic alerts in real time;
- checking all events notified;
- managing and diffusing information concerning epidemics;
- organising a rapid and coordinated response to all serious international threats.

The GOARN alert network, known as Epidemic Intelligence, has set up technical collaborations with major institutions (e.g., the CDC in Atlanta and the Pasteur Institute in Paris), existing networks (e.g., the International Network of Pasteur Institutes, the network of non-governmental organisations (NGOs) such as 'Médecins sans frontières' and 'Médecins du monde'), the regional offices of the WHO and the health ministries of most countries. All these actors have placed their human and technical resources at the disposal of the network, for rapid identification and confirmation of epidemics of international importance and response to such epidemics. Every day, the GOARN receives information, from simple rumour to more precise data, from its various sources. A large amount of information is received and co-ordinated daily by the Strategic Health Operation Centre (SHOC).

For each event notified, the following six criteria are checked:

- Is the disease known or unknown?
- What potential does it have for dissemination across national borders?

- What impact is it likely to have on health, in terms of morbidity and mortality?
- How likely is it to interfere with the transport system and economy of the country concerned?
- Is the concerned country likely to be able to contain the epidemic?
- Does this outbreak appear to have begun spontaneously or to have been initiated deliberately?

Following this verification, the GOARN decides what kind of international action (if any) should be taken. This international action may take the form of simple advice for the country concerned or may extend to the supervision of epidemic management by national authorities, the provision of reagents, vaccines, or drugs, or direct support from the WHO in the form of a specialist team sent to the country concerned. In this last case, there is generally an international call for volunteers with the required skills (logistics experts, epidemiologists, clinicians, specialist microbiologists, etc.), based on pre-existing lists and electronic networks. The WHO handpicks the experts required for each mission. For its own interventions, the WHO relies on the help of national authorities wherever possible, but also on NGOs such as 'Médecins sans frontières' and its epidemiological intervention group, Epicentre. The Pasteur Institute in Paris, like the CDC in Atlanta, has provided expert assistance to the GOARN since its creation in 2000. The Pasteur Institute in Paris set up a specific body, CARE ('Cellule d'alerte et de réponse aux épidémies' - Epidemic Alert and Response Cell) in 2002. This has given rise to a more operational structure, CIBU ('Cellule d'intervention biologique d'urgence' - Emergency Biological Intervention Cell), which participates in WHO interventions.

It would not be appropriate here to describe the French national system of epidemic alerts and prevention. In essence, it is based on an extremely effective association of two skills bases: the National Reference Centres (CNRs), which are responsible for microbiological surveillance and alerts, each CNR specialising in a particular pathogenic agent, and the 'Institut de veille sanitaire' (InVS; the Health Surveillance Institute), which is responsible for monitoring epidemiological alerts and also coordinates, at the national level, the entire system and all those involved in it, including the CNRs. On the ground, France is endowed with a number of interregional epidemiological cells (CIREs), coordinated by the InVS and responsible for providing a rapid response to all public health alerts. They are responsible for issuing alerts, analysing and providing expert advice concerning signals, investigation, and alert management. The CIREs specialise in the epidemiology of intervention and in the evaluation of health risks, particularly in the domain of infectious diseases and risks associated with the environment.

## 6. The future: epidemic prevention. Example of dengue fever in New Caledonia

The prevention of epidemics is the present and future of epidemic response systems. The most extreme current epidemic threat is that posed by bird flu, which experts fear may rapidly become pandemic, threatening the lives of millions of people. With the support of the WHO, most countries worldwide have set up action plans for dealing with the risk of a flu pandemic, based on a strategy combining early-warning systems, rapid identification of the virus involved, close collaboration between the services, institutions and organisations responsible for monitoring wild and domestic bird populations and human health, together with public and private hospital departments. In other words, extreme measures should be taken to tackle extreme events like epidemics. Thanks to this strategy, the many introductions of the highly virulent bird flu strain H5N1, in countries as diverse as Egypt, Great Britain, Nigeria, China and Romania, have been kept under control. This exercise is likely to stand us in good stead for the unfortunate time ahead when the virus introduced is no longer avian, but is instead a recombinant, highly contagious human virus.

A clear understanding of the natural course of epidemics is essential for the development of *epidemic* prevention strategies. This process involves the establishment, for potentially epidemic pathogenic agents, of principles of prevention, based on an understanding of the mechanisms underlying epidemic function, i.e. host-pathogen interactions, vectors densities, host behaviour, interaction of populations, etc. For each of these principles, a certain number of tools are developed and implemented to predict the occurrence of epidemics or, at least, to identify them very early, so as to prevent their subsequent spread. This system already functions satisfactorily for a certain number of epidemic diseases. We can only hope that this sophisticated approach will eventually be extended to most, if not all, known epidemic diseases. We will illustrate this approach with the example of dengue fever epidemic prevention on a small island in the South Pacific, New Caledonia.

Dengue fever is caused by a virus transmitted to humans by a vector – generally *Aedes aegypti*, a mosquito found in and around human dwellings. This virus, which has four known serotypes, causes epidemics with very high attack rates. The incubation period is short (about five days), with major consequences for the prevention of epidemics. Dengue fever is mostly introduced into new countries by the arrival of infected people from a zone in which the disease is rife. It is only rarely introduced by the transfer of infected mosquitoes between countries.

#### 6.1. Epidemic prevention strategy

The principles underlying the prevention of dengue fever epidemics are as follows:

- avoidance of the introduction of the disease into zones currently free of the disease, but susceptible to it (i.e. zones in which the vector is present and/or the climate is favourable for its multiplication);
- vector monitoring and control;
- early case detection (the disease has a short incubation period);
- limitation of the spread of the virus following its introduction (i.e. transfer between humans and vectors).

# 6.2. Tools for epidemic prevention associated with each of these principles for preventing dengue fever epidemics

Three tools can be used to prevent the introduction of the virus into areas free of the disease, such as New Caledonia:

- elimination of mosquitoes from aeroplanes arriving from zones with dengue fever epidemics or endemics;
- detection on arrival at the airport, using a heatsensitive camera, of individuals with fever. All febrile passengers detected in this manner are considered possible cases of dengue fever (advice to remain in isolation and use a mosquito net and mosquitoes repellent, biological diagnosis for confirmation, elimination of mosquitoes from the place at which the passenger will be staying);
- provision of advice to travellers from infected zones (in case of a flu-like syndrome, with fever and myalgia in particular, during the week following their arrival, such travellers should immediately consult a doctor and inform him or her of their recent arrival from an infected zone).

Any country located in a zone in which *Aedes aegypti* or another dengue fever vector develops should set up a continuous vector monitoring system. Four tools are available for vector monitoring and control:

- continuous monitoring of zones with dense populations, carried out monthly, to monitor entomological larval and adult (nymph) indices, making it possible to evaluate the risk of the virus being spread by the populations of vectors actually present;
- the education of populations in terms of vector control (destruction of potential and/or active breeding sites) should be based on information delivered via media routinely used by those populations (radio, television, newspapers) as often as possible, and on dedicated 'dengue days'. Municipal or regional agents responsible for vector control could also provide such information directly to members of the population during the monthly entomological monitoring of houses, gardens, garages etc.;
- entomological monitoring should also include monitoring of the susceptibility of vector populations to the available insecticides that might be used against them;
- finally, the training and appropriate equipment of vector control teams (municipal or regional) are essential.

Early detection of the first cases is crucial for epidemic prevention. Dengue fever has a very short incubation period – only five days (time between the infectious bite and the appearance of the first symptoms). Patients are viraemic between the fourth and the tenth days after the bite. During this period, they are likely to contaminate any mosquito that bites them. Things therefore move very fast and it is necessary to act rapidly as a result. Four elements are essential for this rapid response:

- the establishment and coordination of a network of sentinel doctors systematically requesting biological confirmation in all cases suspected on clinical grounds. The examinations prescribed by doctors of the sentinel network are free of charge;
- programmes to inform general practitioners regularly and to raise their awareness, making it possible, in particular, to conserve a high level of awareness between epidemics;
- declaration to the health authorities of all confirmed and suspected cases (those in which the suspicion is strong enough for biological confirmation to have been requested);
- availability at the laboratory of sufficiently rapid and specific confirmation tests, such as those based on the detection of viral antigens or of the viral genome by real-time PCR, for example.

Once the virus has been introduced into a previously unaffected but susceptible area, a cascade of coordinated and sophisticated measures is required to prevent its spread:

- all doctors should notify all suspected or confirmed cases to the health authorities of the country concerned ('Direction de l'Action sanitaire et sociale' for France and New Caledonia). This step is essential, as these authorities are responsible for collecting additional epidemiological information and evaluating each case, and for notifying vector control teams if necessary;
- important information must therefore be recorded for clinical cases- the date on which the symptoms first occurred and any recent travel (within the last ten days) to known epidemic or endemic areas (South-East Asia in particular);
- it is then essential to classify cases, based on the clinical and epidemiological information collected, into primary cases (contaminated outside the country, in a country in which dengue fever is endemic or epidemic and from which the subject is returning) and secondary cases (who have not recently left the country and were therefore infected within the country, indicating vector transmission);
- the vector control team ('Service municipal d'hygiène' in New Caledonia) carries out perifocal (in and around the case's home) insecticide (killing adult mosquitoes) treatment as soon as they receive notification of a suspected or confirmed case. This first treatment is usually carried out on day 0 (day on which the infection is first suspected). If the case is confirmed by laboratory testing, further treatments are carried out on days 2 or 3 and 10;
- if one or several secondary cases occur, the network of sentinel doctors is extended to all general practitioners in the zone concerned (all biological confirmation free of charge);
- biological confirmation must be extremely rapid, making it possible to adapt vector control as closely as possible to the reality of the cases. Confirmation tests, which are often carried out weekly, must be carried out several times per week, or even daily, during epidemic alert periods;
- if one or several secondary cases are identified (i.e. the virus has already begun to spread in the vector population), then the vector control services may decide, based on entomological indices, to clear an entire zone, by carrying out massive insecticide treatment over an entire residential district rather than just around the cases' homes;
- the awareness of the local populations must be raised, so that they understand better the reasons for these

Table 3

Sequence of actions and actors involved in the prevention of dengue fever epidemics in New Caledonia Tableau 3

Séquence d'actions et leurs acteurs, impliqués dans la prévention des épidémies de dengue en Nouvelle-Calédonie



highly focused insecticide treatments and increase their vigilance and the destruction of larval reservoirs in and around their homes;

• finally, those responsible for entomological monitoring should check the efficacy of insecticidal treatments targeting adult insects in the treated zones.

We therefore have an entire range of measures for preventing dengue fever epidemics in New Caledonia, as summarised in Table 3. In 2006 and 2007, a relatively large number of dengue cases were diagnosed in New Caledonia, and all these measures were implemented. This made it possible to avoid an epidemic of dengue fever. This system is sophisticated, but effective, mobilising the entire curative and preventive healthcare network, a specialist laboratory, municipal vector control services, and the media. However, dengue epidemics are extreme events considering the number of cases generated in a relatively short period of time.

In other cases, and for other pathogens, the prevention of epidemics is much simpler, as there is

an effective vaccine against the pathogen. This is the case for flu in Europe, meningococcal meningitis in Subsaharan Africa and typhoid in a number of developing countries in tropical areas. However, even when a tool as effective as a vaccine is available, as in all cases of epidemic prevention, the rapidity of the reaction after the first cases and the coordinated and combined action of microbiologists and epidemiologists are determinant. Epidemics appear to be emblematic of extreme events that humans may keep under control by preventive measures. We tried showing this for epidemics developing in human populations. However, epidemics are threats for all living beings: humans, animals, and plants. One of the largest epidemics ever was that of the Phylloxera vastatrix pandemic in the 19th century, a parasite that destroyed most of the European vineyard. Thanks to science and research, preventive measures (graft of genetically resistant vines varieties) were successfully applied.

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