ORIGINAL ARTICLE

Two thousand years of epidemics in Marseille and the Mediterranean Basin

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Abstract

Marseille has been exposed to epidemics for two millennia, including plague, cholera and yellow fever. This long-standing exposure to epidemics has given the people of Marseilles a particular expertise in fighting epidemics. Lazarets and other quarantine measures were implemented as a response to preventing the further spread of the disease in the community. The Institut Hospitalier Universitaire Méditerranée Infection is paving the way today, with its responses built on the region's long history and knowledge of epidemics, infectious diseases and medical microbiology.

Keywords: Cholera, epidemics, infectious diseases, Marseille, medical microbiology, plague, The Institut Hospitalier Universitaire Méditerranée Infection, yellow fever
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Introduction

Since its founding by the Greeks in ca. 600 BC, Marseille's harbour has been open to the entire Mediterranean Basin, and as a consequence the city has been exposed to epidemics from the east and south (Fig. 1). During its long history, Marseille has built a rare expertise in the diagnosis, prevention and fight against epidemics. This was marked by the early creation of quarantine and hospital facilities specializing in contagious diseases, and it is within this historical perspective that the Marseille University Hospital Institute, an institution entirely devoted to infectious and tropical diseases, was officially opened in 2017.

Principal sources of knowledge

The knowledge of two thousand years' worth of epidemics in the Mediterranean Basin is based on anthropologic, historical and paleomicrobiologic studies with a multidisciplinary perspective [1–3]. Archaeologists and anthropologists have uncovered numerous multiple burials in this region in which the absence of signs of violence suggested an epidemic episode. In Marseilles, the anthropologie bio-culturelle, droit, éthique et santé (ADES) laboratory has uncovered numerous mass graves linked to the plague epidemic that ravaged Marseille and Provence in 1720–1722. Archaeologic and anthropologic studies, together with analysis of historical sources, have made it possible to precisely date these mass graves, thus enabling anthropologists to provide quality samples for paleomicrobiologic studies.

The oldest known epidemics in Europe were reported by Greek historian Thucydides in Athens in 430–426 BC [4] and by Sophocles in 429 BC, who described in his tragedy *Oedipus the King* a contemporary epidemic in Thebes [5]. As for the epidemics in Athens, paleomicrobiologic study has detected *Salmonella enterica* Typhi, the agent of typhoid fever [6], but this aetiology remains controversial [7]. During the plague of Justinian, Byzantine historian Procopius described 10<thinsp>000 deaths daily in AD 542 in Constantinople [8], and Evagrius gave an African origin for the malady [9]. The pandemic reached Gaule via Marseilles, and the event was reported by Gregory of Tours [10]. During the Black Death, which began in 1347, Guy de Chauliac gave us a chronicle full of teaching on the symptoms of plague, the localization of buboes and the prophylactic treatments used by medieval doctors [11]. In addition to the

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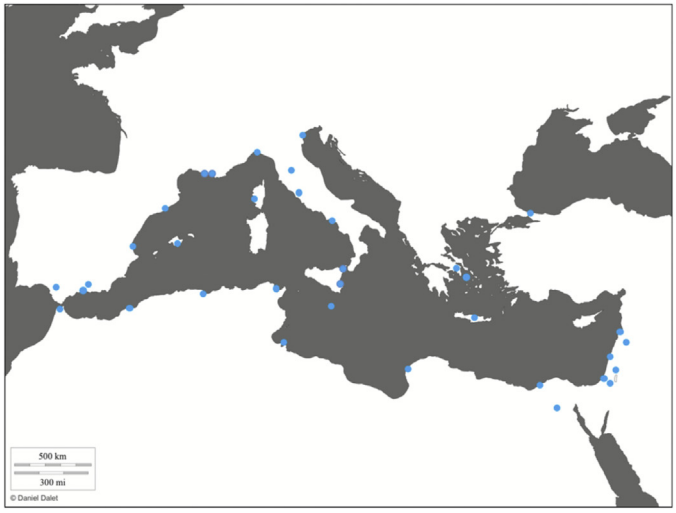

Alexandria ; 1381, 1417,1899, 1907, 1910, 1916, 1923, 1946
Ajaccio ; 1945
Alger ; 1785,1885,1898, 1944
Arles ; 549, 1397, 1579, 1720
Athens ; 430 BC
Barcelona ; 1348, 1396, 1408 1429, 1448, 1457, 1476, 1489, 1493, 1497, 1501, 1507, 1556, 1558, 1564, 1589
Benghazi ; 1917
Djerba : 1837
Cairo ; 1360, 1388, 1398, 1407, 1444, 1492, 1513
Constantinople ; 541, 1334, 1717
Crete ; 1678
Damas ; 1363, 1382, 1514
Firenze ; 1347, 1430, 1437, 1449, 1478, 1527, 1630
Gaza ; 1393, 1497
Genoa ; 1347, 1652
Grenada ; 1348, 1490
Hebron ; 1459
Jaffa ; 1799
Jerusalem ; 1416, 1477
Kea ; 1822
Malaga ; 1637
Malta ; 1592, 1675, 1813, 1945
Majorca ; 1230, 1384,1475, 1523
Marseille ; 49BC, 503, 588, 591, 1347, 1476, 1484, 1505, 1506, 1507, 1527, 1530, 1547, 1556, 1580, 1586, 1587, 1630, 1649, 1720, 1919, 1920
Messina ; 1743
Naples ; 1656
Oran ; 1732, 1919,1944, 2003
Rome ; 165, 575, 589, 1656
Sevilla ; 1383, 1400, 1485, 1508, 1594, 1649
Syracuse ; 396 BC
Tanger ; 1818
Tunis ; 1705, 1784, 1818, 1930
Tripoli ; 1394, 1409
Valencia ; 1394, 1551, 1555, 1647
Venice ; 1575, 1630

FIG. 1. Two millennia of plague outbreaks in Mediterranean Basin.

reports of historians and physicians, there are other sources of knowledge for the study of old epidemic diseases, such as administrative documents and maritime archives as well as vulgar literature. In 1349 Giovanni Boccaccio began writing the *Decameron,* a year after Florence was touched by the Black Death. He wrote, 'Although the cemeteries were full they were forced to dig huge trenches, where they buried the bodies by hundreds. Here they stowed them away like bales in the hold of a ship and covered them with a little earth, until the whole trench was full' [12]. This description is realistic and may be considered as a real source of knowledge for historians. More recently, the 1947 novel *The Plague,* written by French writer and Nobel laureate Albert Camus, factually described the 1944 plague outbreak in Oran (five cases) and Algiers (62 cases) [13].

Written sources were completed by iconography. This included, at the end of the Middle Ages, the so-called macabre dances, which were sarabandes in which the dead danced with the living without distinction of social class. These macabre dances may be seen as an allegory of the inevitability of fate in face of plague, which equally strikes the rich and poor, men and women, adults and children. Likewise, pictorial and sculptural works are a source of knowledge of past epidemics. In Marseille the most remarkable canvases were painted during the great plague of Marseilles by a direct witness of the events, Michel Serre. Other artworks, more propagandist in their purpose but still informative about the epidemics, particularly as they affected armies, include a painting by Antoine-Jean Gros entitled 'Bonaparte Visiting the Plague Victims of Jaffa.' In 1833 Horace Vernet produced a painting entitled 'Cholera Morbus Aboard the *Melpomène*' at the request of the sanitary administration of Marseille. In July of the same year a frigate arrived at the port of Toulon with cholera on board. However, the city was saved from the epidemic thanks to the quarantine system. Vernet's painting was hung in the boardroom of the Health Protection Stewardship in Marseille as a sign of confidence in the health authorities in their fight against the cholera epidemic [14]. Yet it did not prevent the disease from striking Marseille a year later. There are many statues in cities affected by the plague, including Montpellier, Arles and Pezenas, representing Saint Roch, the patron saint evoked against the plague, who is depicted showing his left thigh to reveal a bubo.

Paleomicrobiologic sources

We invented and developed the field of paleomicrobiology, which concerns the retrospective diagnosis of infectious diseases from ancient human samples. In particular, we proposed to use dental pulp for the diagnosis of bacteraemic infections such as plague [15,16]. In addition to this method, which has been used routinely all over the world, we have developed other diagnostic methods from ancient dental pulp, such as immuno-PCR based on the detection of specific antigens [17] and paleoproteomic analysis based on detection of old proteins [18].

Epidemics and Commercial Roads in the Mediterranean Basin

Demonstrated by Gomez and Verdu [19] in 2017, most plague epidemics followed humans and their goods as they traversed the Mediterranean region. We know several examples of epidemic transmission, firstly by maritime trade routes, such as the plague epidemics in Marseille in 1348 and 1720, and secondly by land trade routes, such as that of Smyrna in 1733. The contamination

of the Mediterranean world resulted from the fact that it was situated at the end of the Silk Road, the landing place for many goods, people and dromedaries [20]. It was also favoured by wars and military campaigns (for example, epidemics of typhus were termed 'camp fever' [21]) or by pilgrimage routes (for example, the cholera epidemic in Marseille in 1865 was brought by pilgrims returning from Mecca [22]).

Fighting epidemics

To cope with the epidemics raging across the Mediterranean Basin, and especially those that came from the east (a region long suspected of being the source of many epidemics), the city of Marseille equipped itself over the centuries with a system of prevention and infectious disease control, which was taken as an example by other European cities. The quarantine system in Marseille lasted from 1620 to 1830. Historically, plague, cholera and yellow fever (Fig. 2) were subject to quarantine. Smallpox and typhus were added in 1926. In order to reinforce the safety of the port of Marseille with respect to maritime routes, health patents were made compulsory in 1702 by Louis XIV. Starting in that year, every ship arriving at the port of Marseille had to anchor on the island of Pomègues, and the captain of the vessel had to present the patents to the health steward of the city to attest to good health at the port of departure. The sanitary administration of Marseille was abolished in 1849 under pressure by anticontagionists during the second cholera pandemic [23]. This safety device was based on the establishment of lazarets, or infirmaries, to accommodate patients and ensure quarantines. In Marseille the first lazaret was created in 1526 on the island of Pomègues; Marseilles (and Toulon) became exclusive entry points into France from 1622 for all ships coming in from Muslim countries, and from 1669 for all ships coming from the Levant [24]. The lazaret was transferred in 1663 to the west of the city to become the lazaret of Saint-Martin d'Arenc, which operated for nearly two centuries [25]. The effectiveness of the lazarets is evidenced by the fact that only 16 cases of plague out of 240 vessels receiving a gross health license were diagnosed in the 18th century without causing any epidemics [26]. Between 1823 and 1828 the Caroline hospital was built on Ratonneau island to replace that of Arenc, which was located on the mainland and was considered to be too close to the city. The Caroline hospital was a compromise between the contagionist and aerial theories that were in vogue in the 19th century. Indeed, the hospital was built on an island in order to better isolate patients, but its architecture was created to ensure the circulation of the best, most pure air among different rooms [24].

The most important epidemics

The prevention of epidemics was gradually put into place in response to the many epidemic episodes experienced by Marseille and the Mediterranean.

FIG. 2. Yellow fever outbreaks in Mediterranean Basin, 19th century.

Plague

Plague is a zoonosis caused by the Gram-negative bacteria *Yersinia pestis,* which has affected Marseille 22 times since its founding. The first mention of the plague in the historical record was made by Julius Caesar during the Gallic wars. Marseille was the gateway to France for the three historic pandemics of plague. After the establishment of effective sanitary cordons, Marseille no longer had an episode after June 1649, but on 25 May 1720, an infected ship returning from Lebanon entered the port of Marseille and spread the epidemic of the deadliest plague that the city would ever know. It lasted until 1722 and cost nearly half the population their lives. The last cases of plague in Marseille occurred during the epidemic of 1919 and 1920 [27], which echoes the plague that struck ragpickers in Paris in 1920 [28].

Cholera

Cholera is a contagious infectious disease caused by *Vibrio cholerae* [29] (Fig. 3). Cholera reached Provence in 1832 and Marseille in 1834 during the second pandemic, during which the first case was diagnosed on 7 December. In two outbreaks in 1835, a total of 3441 people died out of 7073 attacks, for a mortality rate of 48.6%. A second episode occurred in 1849, during which 2252 people perished; then 3397 deaths ocurred between 1854 and 1855. A total of 2037 people died during the 1865 epidemic, which probably spread from the port of Alexandria. Finally, two outbreaks were recorded in June–October 1884 and July–December 1885, which resulted in a total of 3052 deaths after the displacement of people from Toulon, where cholera was diagnosed in June 1884. During these last episodes, a specific treatment area was set up at Pharo Hospital.

Typhus

Typhus was diagnosed in Marseilles in the La Valentine district in March 1810. The disease was brought by a deserting soldier who escaped from Aix prison and found refuge in an abandoned village house. In the end 25 people were affected, eight of whom died [24]. In 1856 the disease was diagnosed in several soldiers returning from the east [30].

Smallpox

Since its introduction in Europe in the sixth century, smallpox had become an endemic disease in Europe and Marseilles, with regular epidemic outbreaks. This viral disease was responsible for a mortality rate of 60 to 100 per thousand [24]. From 1827 to 1829 a major epidemic struck Marseille, with 1507 victims (1.2%) out of 120<thinsp>000 inhabitants. In 1874 a new epidemic declared itself with 1017 victims; many ragmen were among the affected. (Rags imported from North Africa and the Middle East were seen as a vector for transmission of the disease [24].) In 1885–1886 Marseille experienced its largest smallpox epidemic; the number of deaths was 2381. The last cases of smallpox were diagnosed in Marseilles in 1952 [31].

FIG. 3. Cholera outbreaks in Mediterranean Basin, 19th century.

Pursuing research on contagious diseases at the Méditerranée Infection

Our laboratory in 1998 was the first to develop paleomicrobiology using ancient human remains from the great plague of Marseilles (1720–1722) [15]. This new field of investigation permitted the development of two new methods to facilitate the detection of ancient microorganisms: the use of dental pulp for the detection of blood-borne pathogens [15], and the development of the so-called suicide PCR method to prevent false-positive findings due to cross-contamination among samples [16]. For the last 20 years our laboratory has focused on the detection of pathogens that have been responsible for huge epidemics and massive mortality, including *Yersinia pestis* [15], *Bartonella quintana* [32] and *Rickettsia prowazekii,* from ancient samples [33]. We also developed original detection methods such as immuno-PCR [17] and amplification of intergenic sequences followed by sequencing. This new approach allowed the first genotyping of *Yersinia pestis* strains [34], opening the way for sequencing the genomes of ancient pathogens. More recently we developed paleoproteomics, which consists of analysing proteins preserved in dental pulp to identify ancient plagues [18]. Interestingly, this method also enabled the detection of host proteins, including immunoglobulin G and A, which could open the door for paleoserology.

Conclusions

The inhabitants of Marseille, a city exposed for two thousand years to the epidemics that crossed the Mediterranean Basin, acquired expertise in the diagnosis, treatment and prevention of these epidemics. The IHU Méditerranée Infection has become part of this rich history by introducing modern conceptual and technical tools, thereby taking a new approach to contagion that includes medical research, the dissemination of knowledge and its valorization through tools and innovative protocols.

Conflict of interest

None declared.

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