Two-millennia fighting against port-imported epidemics, Marseille. 1 2 Barbieri, R, Colson, P., Raoult, D., Drancourt, M\* 3 4 1. Aix-Marseille Univ, IRD, APHM, MEPHI, IHU-Méditerranée Infection, 5 Marseille, France. 6 2. IHU Méditerranée Infection, Marseille, France. 7 8 \*Corresponding author: Prof. Michel Drancourt, IHU Méditerranée Infection, 19-21 9 Bd Jean Moulin 13005 Marseille, France. Tel: +33 (0)4 13 73 24 01 fax: +33 (0) 13 10 73 24 02. Email: michel.drancourt@univ-amu.fr 11 12 Abstract word count = 91. 13 Text word count = 3,426. 14

# **ABSTRACT**

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Marseille port, one of the major Mediterranean Basin trading ports for more than two 16 millennia, has been the portal of entry of numerous outbreaks of deadly epidemics 17 including among others, plague, cholera and yellow fever. This long history of 18 exposure to deadly epidemics gave Marseille some particular expertise in preventing 19 and fighting port-imported epidemics, with successive lazarettos alternated with 20 quarantines, paving the way to the Institut Hospitalier Universitaire Méditerranée 21 Infection where SARS-CoV-2-infected patients were diagnosed, isolated and treated, 22 following a strategy undertaken by countries where COVID-19 outbreak has been 23 successfully controlled. 24

### INTRODUCTION

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After its foundation by Greek sailors coming from Phocée (in modern-day Turkey) along the Aegean sea around 600 BC [1], Marseille progressively opened to foreign countries and became one of the major trading ports of the Mediterranean Basin, with ships connecting the city for centuries with Spain, Greece, Italy, North Africa, North Europe, the Americas, Middle East, Reunion Island and the East Indies [2,3]; and then, particularly with sub-Saharan Africa, Atlantic and Pacific Oceans with the development of steamboats in the 19th century [3,4]; while the opening of the international Marseille-Provence [5] airport in 1922 extended the geographical connections with the Americas and Oceania; as illustrated by the 2019 traffic of around 10 million travelers to more than 120 different destinations in 34 different countries. World openness exposed Marseille and neighbor Provence area to portimported epidemics, as traced by historical texts as old as the description of the Roman proconsul Julius Caesar [6]; historical sculptural and pictorial representations of epidemics [7,8]; archaeological and anthropological data issued from the uncovering of numerous multiple burials in Provence [9–11]; completed by paleomicrobiological studies which illuminated ancient plague, as an example [12].

Facing deadly port-imported outbreaks of what are now understood as epidemics of infectious diseases, Marseille developed two alternate and complementary strategies of quarantines and lazarettos, to prevent and fight these epidemics; culminating with the 2017 opening of the Institut Hospitalier Universitaire (IHU) Méditerranée Infection, where SARS-CoV-2-infected patients were diagnosed, isolated and treated. We are here shortly reviewing the fact that the IHU did not

- fortuitously open in Marseille but was indeed built in one particular historical
- 50 background of port-imported epidemics in Marseille.

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## Marseille, a 2,000-year-old Mediterranean Sea port.

Since its foundation, Marseille resolutely turned its economy towards the Mediterranean Sea rather than the surrounding lands [13], following its initial role as a Phocaean portal of entry to Northwestern Europe [14]. The Greek geographer Strabon stated that "They possess a country which, although planted with olive-trees and vines, is, on account of its ruggedness, too poor for grain; so that, trusting the sea rather than the land, they preferred their natural fitness for a seafaring life" [15]. The geographic area of influence of the Massaliotes extended over the entire Mediterranean Basin and probably in the Atlantic Ocean [13]. From the 6th century BC, Marseille became a port of prime importance as well as a transit port through which products from all over Europe were exchanged such as copper, tin, gold, ambergris, yellow and other Hellenistic luxury goods [14]. The hold of Marseille on the Mediterranean maritime trade saw some halting, especially during the Gallic Wars (capitulation to the Roman proconsul Julius Caesar in 49 BC): the first "plague" outbreak was mentioned during the siege of Marseille by the Roman legions [6]. During this Antiquity, Greek medical tradition, deeply rooted in Marseille, impressed Julius Caesar and served as a model for the Roman Empire. Accordingly, along the first century of our era, Romans came to Marseille rather than to Athens, to learn medicine [14]. The 11th-12th century crusades reopened the maritime routes to the Middle East and Marseille was a major port to embark pilgrims as well as for commercial tights with modern-day Syria; which may have contributed to smallpox spreading in Europe [16]. In the 13th century, Marseille had installed caravanserails

in Oran, Béjaïa, Tlemcen and Tunis for the traffic of pepper, perfumes, dye plants, alum or wax, all goods imported through Marseille port [14]. One step forward in 1669 (under the reign of King Louis XIV), Marseille was granted with trade monopoly and custom duty exemption with the so-called Barbary coast (for cereals, coral, leather, textiles and oil) and trade monopoly with the so-called "Levant" (for Black gall, cereals, spices, leather, skins, cottons and silks) [17].

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# Port-imported epidemics, Marseille.

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The advantageous location of Marseille made the city a crossroad in the Mediterranean Basin, yet permanently exposed to port-imported outbreaks: at least 6 of 60 outbreaks affecting Marseille throughout two millennia (Table1) [18] have been port-imported outbreaks, (including plague, cholera, yellow fever, smallpox and modern-day COVID-19) and spread throughout Marseille and eventually the surrounding Provence; while at least 29 outbreaks were contained in the lazarettos [19,20], and some epidemics including cholera, smallpox and typhus were imported via terrestrial routes, most often following armies [21]. Indeed, as for plague most epidemics followed men and the goods they transported [22] to the Mediterranean region; as illustrated by the plague epidemics of Marseille in 1347 and 1720 [23–25]. The contamination of the Mediterranean basin resulted from the fact that it was situated at the end of the Silk Road and Fur roads [26], embarking many goods, men and dromedaries [27]; and was further favored by pilgrimage routes, as it was the case for the cholera epidemic in Marseille in 1865 brought by pilgrims returning from Mecca [18], and by wars and military campaigns, as with epidemics of typhus, an illness which had been named "camp fever" [28].

Plague, the deadly zoonosis caused by Yersinia pestis [12,29], affected Marseille 22 times [6,30] during the first pandemic (541-767) and the second one (1346-19<sup>th</sup> century [24,26]), both occurring in France through maritime introduction of the zoonosis in Marseille. The Frank chronicler Gregory of Tours described in 588 the arrival of plague in Marseille by the goods sold by a ship sailing from Spain [31]. Then, the so-called Black Death (1346-1352) [26] was acknowledged to have been brought by Genoese ships on November 1st, 1347 into the rifle-rafle street before ravaging the entire city [20]: plague will remain endemic for three centuries throughout Europe, as quoted by Jean-Noël Biraben: "From that point onward, and until 1670, the plague raged every year in Europe, sometimes in vast territories, sometimes only in certain localities, but without skipping a single annual link in this long and painful chain" [32]. On May 25th, 1720, a ship sailing back from Lebanon entered the port of Marseille and spread the deadliest plague outbreak that the city has ever experienced, lasting until 1722 and claiming life for nearly half of the population [33]. The very last cases of plague in Marseille were diagnosed in 1919-1920 [30], in echo to the "plague of rag-pickers" in Paris in 1920 [34]. Cholera, a deadly toxinic infection by Vibrio cholerae [35], reached the city of Arles in 1832 and Marseille in 1834, during the second cholera pandemic where the first case was diagnosed on 7th December. Two outbreaks in 1835 totalized 3,441 deaths out of 7,073 attacks (Lethality, 48.6%) [18] mainly in areas served by water from the main outlet of the Huveaune aqueduct [20]. In 1865, a large cholera epidemic broke out during annual pilgrimage to Mecca and spread in Africa following the pilgrims' return path [18]. According to Laugier and Olive [18] eight boats from Alexandria, Egypt (in the midst of a cholera outbreak) (i.e. about 1,025 passengers) arrived in Marseille port on June 15th-20th, 1865, without any sanitary control. Sporadic cases

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declared on June 15th-26th, before the epidemic broke out on July 22th, 1865 first in the unhealthy and marine quarters located near the port. Accordingly, 19 of 30 patients received at the Hôtel-Dieu hospital were sailors. This epidemic lasted for 166 days and claimed 2,037 victims. Finally, two additional outbreaks were recorded in June-October 1884 and July-December 1885 for a total of 3,052 deaths, following the displacement of people from Toulon where cholera had been diagnosed in June 1884 [20]. During these last episodes, a new hospital was specifically set up at the Pharo Hospital. In total, Marseille suffered 10 cholera epidemics as part of the second, third, fourth and fifth pandemics between 1834 and 1885 [36]. Smallpox has become an endemic disease in Europe and in Marseille in particular, with regular epidemic flushes; after its introduction in Europe in the sixth century [37]. This viral disease caused by Variola major and minor was responsible for a lethality rate of 70 to 100% for cholera gravis [38,39]. From 1827 to 1829, a major epidemic struck Marseille, with a balance of 1,507 victims out of 120,000 inhabitants (1.2%). In 1874, a new epidemic caused 1,017 victims, particularly among ragmen [18]. Rags imported from North Africa and the Middle East were seen as a vector for transmission of the disease [40,41]. In 1885-86, Marseille experienced a large smallpox epidemic with 2,381 victims. The last 38 cases of smallpox were diagnosed in Marseille in 1952 after the maritime repatriation of one soldier from Indochina [42] which claimed 38 cases [43]. In Marseille, yellow fever, a non-contagious deadly flavivirus infection vectorized by the mosquito Aedes aegypti [44], was confined to lazaretto. In August 1802, a ship named "La Colombia" came from La Havana (Cuba) and Providence (USA) with a clean patent. After a 10-day quarantine, three cases of yellow fever occurred among the crew, 2 sailors died while the third one was treated in the lazaretto [45]. In

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October and November, 1,804 cases were reported among crews of five Danish ships and one Swedish ship [18]. In 1821, a Danish schooner left the port of Barcelona which suffered an epidemic of yellow fever, to sail to Malaga where it brought contagion. The schooner then left the port of Malaga on August 26th to arrive at the Pomègues island, Marseille on September 7, 1821 [46]. In total, three yellow fever epidemics including 34 cases have been identified in Marseille in between 1802 and 1821 [20].

As for COVID-19, the emergence in Marseille area of a new SARS-CoV-2 variant named Marseille-1 coincided during summer 2020 with a rise of SARS-CoV-2 diagnoses among patients who had traveled by ferry between North Africa (Tunisia and Algeria) and Marseille, after the resumption of passenger ship traffic with France [47]. Three dozens of patients who had traveled or worked on ships of a passenger ferry company that sailed between Maghreb and Marseille were found to be infected. Further investigations by sequencing and analyzing SARS-CoV-2 genomes led us to assume that the ancestors of this viral variant originated in sub-Saharan Africa [47]. We recently detected in Marseille the SARS-CoV-2 20I/501Y.V1 "English" variant that currently predominates in UK and has started to spread in Europe [48]. We first identified this variant in family members returning from England using whole-genome sequencing. We then identified it in two students returning from Lebanon and a young woman who stayed in Dubai, United Arab Emirates, using a specific in-house real-time RT-PCR assay.

In order to protect itself from these epidemics, the city of Marseille will set up several defense systems against diseases.

### Quarantine in Marseille port.

To halt the epidemics raging across the Mediterranean basin (mainly plague), and 174 especially those ones that came from the East, an area for a long time suspected of being the source of many epidemics, Marseille had developed over the centuries, a system of prevention and control of infectious diseases, which had been taken as an 177 example by other European cities [49]. The quarantine system in Europe was born [50] in 1377 in Dubrovnik, Croatia in the frame of the second plague pandemic [51]. 179 The Republic of Venice was the first to set up a permanent hospital for plague victims in 1423 on the island of Santa Maria Di Nazareth. This system will be reproduced in several port cities of Europe including Genoa in 1467 and Marseille in 1476 [49]. The 182 183 lazaretto became the place where the quarantine was carried out to isolate people, animals or goods suspected of being infected [52]. The duration of the quarantine 184 was usually 40 days (from the Italian "quaranta" meaning forty) [53]. This duration could refer to Hippocrates who explained that an acute illness manifests itself in 40 days; or to Pythagorean mathematics in which the number 4 is of particular importance. Finally, in the Christian Middle Ages, the number 40 refers to the number 188 of days of fasting of Jesus in the desert and is strongly associated with the idea of 190 purification [49,54]. The quarantine system in Marseille lasted from 1620 to 1830 [54]. Other decisions had been taken such as fumigation, vinegar disinfection of letter and 191 movables, lighting big fires to purify the air (believed to be infected by pestilential 192 miasma), slaughter of dogs suspected of dispersing the contagious tatters of plague victims, reinforced police service and capital execution for looters and smugglers 194 [55]. In parallel, Marseille took political decisions to fight against epidemics: in 1546-1547, the city contracted a debt of 2.600 ecus to fight the epidemic. During the 196 epidemic of 1586 the parliament of Aix took drastic measures to prevent the spread 197

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of the disease such as prohibiting the flight of inhabitants [20]. This measure will henceforth be systematically applied and even pushed further in 1720 with the construction of the 27-km-long plague wall to protect the nearby Comtat Venaissin from contagion [17,56]. In order to fortify safety related to maritime routes, bills of health were reinforced during the reign of King Louis XIV [57]. Every ship arriving at the port of Marseille had to anchor on Pomègues Island and the captain of the vessel had to present the bill of health issued by the health authorities of the last port visited attesting to the good health of the crew members. Once the ship had arrived, the duration of the quarantine (performed at the lazaretto) for people was set by health officers [17]. It was of 14-18 days for a "clean" bill, 25 days for a suspicion of contagion and 32-35 days for confirmed contagion on board. Quarantine periods were even longer for goods, up to 60 days [54]. In the situation of proven plague on board, the ship was directed to the Jarre island, south of Marseille [17]. This system proved to be extremely effective as it is estimated that between 1700 and 1829, plague was declared 29 times inside the lazaretto without ever getting beyond these walls [20,58]. Bypassing included corruption of local elected officials (as in 1720) [54], smuggling, illegal landing of people [55], counterfeiting of the bill of health or false declaration [59]. During the 19th century, arrival of cholera and yellow fever makes quarantine practically ineffective and anti-contagionists make pressure for a reduction of health measures [49]. Quarantine measures were charged with creating a false sense of security, being ineffective, no longer being in phase with the new, faster means of communication (a 12-day quarantine for a 6-day trip [54]) and harming maritime trade [60]. In the 19th century in Marseille, the sanitary measures were sometimes boiled down to simple fumigation of passengers and their personal effects before disembarking. These measures were completely abandoned at the end of the

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19th century with the arrival of prophylaxis medicine against contagious diseases such as plague, cholera or yellow fever [61].

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## From Lazarettos to Hospitals for the contagious in Marseille.

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In parallel to quarantine measures, lazarettos or infirmaries were built to carry out the quarantine by grouping together people who were ill or suspected of being ill (sometimes without any medical care) in a place, closed, supervised and relatively isolated from the rest of the city [54]. The assumed social goal was to sacrifice a small group of people for the benefit of the greater common good [62]. In 1476, Marseille converted the leprosy into a hospital dedicated to plague victims, which was to be considered as the first lazaretto [49]. The second lazaretto, erected in 1526 near the cove "des ours" at the northern edge of the city, then moved to the south of the Marseille harbor (current Catalan district), today called "vieilles infirmeries" [17]. Furthermore, Marseille (with Toulon) became one of the Exclusive entry points in France from 1622 for all ships coming from Muslim countries and from 1669 for all ships coming from Levant because they were the only cities to oppose an effective sanitary defense system for people and goods coming from these countries said to be "susceptible to contagion" [63,64]. Finally, facing the construction of Fort Saint-Nicolas at the entrance of the port of Marseille, the lazaretto was transferred in 1663 to the west of the city to become the lazaretto of Saint-Martin d'Arenc which will operate for nearly two centuries [17] (figure1). Between 1823 and 1828, Caroline hospital was built on the Ratonneau island to replace Arenc lazaretto, located on the mainland and considered too close to the city [65]. The Caroline hospital was a compromise between the contagionist and aerial theories that were in vogue in the

19th century. Indeed, it was built on an island in order to better isolate patients but its architecture was made for it to act as an air purifier: to let air circulate between the different rooms [54]. From the 19th century the lazaretto gradually turned into a place to isolate and provide health care to patients. The so-called Lazarettos-Hospitals like Caroline hospital will no longer be coercive places where patients were locked up but a place of study of infectious diseases and medical progress. The sanitary administration of Marseille was abolished in 1849 under the pressure of anticontagionists during the second pandemic of cholera [54,65]. Beyond the lazarettos, the patients were also grouped together in hospitals in order to also deal with other epidemics. The first healthcare facilities were built under the impetus of religious communities or rich lords at the beginning of the 13th century, with Sainte Marthe, Saint Canna or Saint-Michel Hospital. In the 14th century the general hospitals of Saint-Esprit and Saint Jacques de Galice were funded [66]. In 1593 the reunion of these two hospitals will give birth to the Hotel-Dieu, the first hospital administered by lay people [67]. This hospital occupied a special place in the history of infectious diseases in Marseille as being linked to the great epidemics of plague and cholera that the city will experience. Until the 20th century, the Hotel-Dieu accommodated the poorest patients in the city because the rich preferred to be treated at home, so the mortality observed in this hospital was not representative of the general mortality in Marseille. For example in 1835, only 12% of patients were registered in the hospitals [18]. In the frame of the third (current) plague pandemic which probably started in 1772 in the Chinese province of Yunnan [68,69], plague returned to Marseille in 1903 [70]. This epidemic gave rise to the organization of a special service hosting plague victims in the Entremond property intended to become the Salvator hospital five

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years later. A pavilion hosting a plague service for contagious patients was built inside Salvator hospital to isolate patients and contacts. During the 1919-1920 plague epidemics, 79 patients suffering bubonic plague with a few secondary pulmonary forms, were isolated and treated by serotherapy [71,72]. Noteworthy, one patient suffered from *Streptococcus pneumoniae* and *Y. pestis* co-infection found in the pus of the bubo and the sputum [73], similarly to what was described by S. Kitasato (from the blood) when the plague bacillus was discovered in 1894 [74]. The last case was diagnosed in 1936 in Marseille [75].

Finally, the new IHU Méditerranée Infection building erected in 2013-2016 on the Marseille University Medical Campus opened in December, 2016 to welcome infectious and tropical disease patients into a brand-new, access-controlled building featuring a daycare facility, and 75 hospital one-bed rooms entirely and specifically dedicated to contagious patients; all in a baseline biosafety level 2, upgradeable to a biosafety level 3 by sectors of 7 rooms [76]; where COVID-19 patients and contacts

#### CONCLUSIONS

were taken onto consideration in 2020-2021.

Marseille was exposed for two millennia to epidemics that crossed the Mediterranean basin. Since its foundation it had been staying the first port of France for centuries, this importance in the maritime trade has also subjected the city to the danger of epidemics from the East and Africa like plague or cholera or the Americas like yellow fever. This long coexistence with infectious diseases has made Marseille a veritable social laboratory for the fight against the epidemic scourge. The quarantine system has been taken as an example throughout Europe for its efficiency, then its gradual

conversion into a Lazaretto-Hospital enabled doctors of Marseille to perpetuate the long tradition of medical excellence by specializing in study of infectious diseases. Nowadays, IHU Méditerranée Infection is part of this rich history, renewing it with the conceptual and technical tools of our time, a modern approach to contagion including medical research, dissemination of knowledge and their valorization through tools and innovative protocols.

**Acknowledgements.** This manuscript has been edited by a native English speaker.

Table 1. Two-millennia epidemics recorded in Marseille.

Disease	Day and Month	Year(s)	Cases	Victims	Microbiological/paleomicrobiological confirmation	Reference(s)
Cholera	December 9-10	1834-1835	1874	865	No	20
Cholera	July 3	1835	5199	2470	No	20
Cholera	July 9	1837	?	1526	No	20
Cholera	August 8	1849	?	2252	No	20
Cholera	June 15-20	1854	?	3069	No	20
Cholera	August 25	1855	?	1328	No	20
Cholera	June 27	1865	?	2037	No	20
Cholera	July 5	1866	?	1097	No	20
Cholera	June 26	1884	?	1784	?	20
Cholera	July 14	1885	?	1259	?	20
Cholera	?	1892	?	?	?	20
Cholera	?	1893	?	?	?	20
Cholera	?	1911	?	?	?	20
COVID-19	February 24	2020 -Present	21.268*	552*	Yes	APHM Data
Diphtheria	?	1861	?	?	No	18
Diphtheria	?	1886	?	559	?	20
Influenza	?	1837	?	?	No	20
Influenza	?	1848	?	?	No	20
Influenza	?	1889-1890	?	2662	?	18
Measle	?	1808	?	?	No .	18
Measle	?	1823	120	3	No No	18
Measle	?	1852	?	?	No No	20
Plague	?	49 BC	?	?	No No	6
Plague	?	503	?	?	No	6
Plague	?	588	?	?	No	6
Plague	?	591	?	?	No	6
Plague	November 11	1347-1350	?	?	Yes	6
Plague	?	1476	?	?	No	6
	?		?	?		
Plague	?	1484	?	?	No N-	6
Plague	?	1505-1507	?	?	No N-	
Plague	?	1527	?	?	No No	6
Plague	?	1530	?		No	6
Plague	?	1547	?	≈ 8.000 ?	No No	6
Plague	?	1556		?		
Plague	?	1557-1558	?		No	6
Plague	•	1580-1581	?	≈ 30.000	No N-	6
Plague	November 13-15	1586-1587		- 10.000	No	6
Plague	February 12	1630	?	≈ 10.000	No	6
Plague	June	1649-1650	?	- 50 000	No V	6
Plague	May 25	1720	?	≈ 50.000	Yes	17, 23, 25, 77
Plague	?	1903	19	4	Yes	78
Plague	?	1913	1	1	?	78
Plague	August 11	1919	22	4	Yes	78
Plague	June 4	1920	62	22	Yes	78
Smallpox	?	1807-1808	?	?	No N-	18
Smallpox	November	1827-1829	?	1504	No	18
Smallpox	?	1852	?	?	No	18
Smallpox	?	1874-1875	?	1017	No	18
Smallpox	?	1878	?	534	No	18
Smallpox	?	1885-1886	?	2381	?	18
Smallpox	January 14	1952	38	?	Yes	18
Typhoid Fever	?	1852	?	?	No	20
Typhoid Fever	?	1853	?	?	No	20
Typhoid Fever	?	1857	?	?	No	18
Typhoid Fever	?	1858	?	?	No	18
Typhoid Fever	?	1859	?	?	No	18
Typhoid Fever	?	1860	?	?	No	18
Typhoid Fever	?	1862	?	?	No	18
Typhoid Fever	?	1863	?	?	No	18
Typhus	March	1810	25	8	No	18
Typhus	?	1856	?	?	No	18
Yellow Fever	August	1802	3	2	No	18
Yellow Fever	October and November	1804	?	?	No	18
	September	1821	29	20	No	18

<sup>\*</sup> data provided by Assistance Publique – Hôpitaux de Marseille (the public University Hospital System in Marseille), taking into account the number of cases and deaths in the South-East region (including Marseille).

**Figure 1.** Localization of the main lazarettos and hospitals intended to fight infectious diseases in Marseille (Map from 1922) from 1476 to 2016. Source gallica.bnf.fr / Bibliothèque nationale de France.



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- A) Lazaretto « Notre-Dame-de-la-Pitié » 1476-?
- B) Lazaretto « des Ourses » 1526-?
- C) Lazaretto « des Catalans » 16th
- D) Lazaretto « D'Arenc » 1663-1850
- E) Hospital and Lazaretto Caroline 1850-1926
- F) Hospital Hôtel-Dieu 1593-2006
- G) Hospital of Pharo (Temporary Hospital for Cholera) 1884-?
- H) Hospital Salvator 1908-Present
- I) IHU Méditérannée Infection 2016-Present

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