

Plague in Iran: past and current situation

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Abstract

OBJECTIVES: Plague remains a public health concern worldwide, particularly in old foci. Multiple epidemics of this disease have been registered in Iran's history. Despite the long-standing history of human plague in Iran, it is difficult to get a historical and current overview of the general situation.

METHODS: In this review, available data and reports on human plague occurrences in the past and present in Iran and in neighboring countries are collected and information is compiled on when, where and how many cases occurred.

RESULTS: This paper considers the history of plague in Persia (predecessor of today's Iran) and has a brief review on countries in the WHO Eastern Mediterranean Region, consisting of some of the countries in the Middle East and North Africa.

CONCULTIONS: Considering that Iran has experienced outbreaks of plague for several centuries, neighboring countries have reported the disease in recent years, the disease can be silent for decades, and the reports of the circulation of *Y. pestis* among rodents and dogs in western Iran, more attention should be paid to disease monitoring in areas with previously reported human cases and high-risk regions with previous epizootic and enzootic activities.

Keyword: The Middle East, Iran, History, *Yersinia pestis*

Introduction

23

Plague is one of the life-threatening, infectious diseases still endemic in some areas around the world. It is caused by the bacillus *Yersinia pestis*. In 1894, the plague bacillus was discovered by Alexandre Yersin (1). The natural reservoirs of this disease are wild rodents and the causative agent of the disease is transmitted to different animals and humans via infected fleas (2-3). The most prominent infection vector for humans is the family of *Xenopsylla* and in particular *X. cheopis*. Living in rural areas, hunting or trapping animals, and keeping cats and dogs will increase the risk of infection amongst humans (2). The disease in humans exists in three clinical forms including bubonic, pneumonic and septicemic. Without treatment, the mortality is practically 100%, particularly with pneumonic plague (4).

As *Y. pestis* circulates at low levels in the rodent population in endemic foci of the disease (5), there is always a probability of its outbreak and for the effectiveness of well-timed treatment, the importance of quick diagnosis of the disease becomes obvious (4, 6). *Y. pestis* has also been used in bioterrorism in the past and its similar usage in the future is not far from imagination (2, 7-8). Studies show not only a trend towards a decrease in susceptibility to some antibiotics but also an emergence of multi drug-resistant strains (9-10) and emphasize the need for more attention to plague as a significant public health concern than previously.

There have been three great world pandemics of plague. The first one, called the 'Justinian Plague', occurred in the Byzantine Empire (Constantinople) in the 6th century CE and spread to the Middle East, and Mediterranean regions and Europe. The second pandemic began in India, China, some regions of Russia and reached Western Europe in 1347 CE and is called the "Black Death". The Third one was the Hong Kong epidemic that started in 1855 CE in Yunnan Province, China (2, 4). *Y. pestis* has been reported from all parts of the world, and plague is enzootic in rodents in Africa, North and South America, and Asia (Middle East, Far East, and countries of the former Soviet Union) (2, 11-12). According to the International Health Regulations, the pneumonic form of the disease must be reported to the World Health Organization (WHO) immediately (13).

There are still some plague endemic foci in central Asia, western Arabia (Assir), the Middle East with its center in Iranian Kurdistan, central and southern Africa, and northwestern India (14-17). Between 1987 and 2001, 36,876 confirmed cases of plague with 2,847 deaths were reported to WHO (4, 16). In 2013 there were 783 cases reported worldwide, resulting in 126

deaths (18). In recent years, more than 95% of human cases have been reported from Africa, 54
mainly from Madagascar (19). Plague has a seasonal pattern in most endemic areas which is 55
associate with the predominant vectors and rodent reservoirs and their ecology in their 56
geographical niches (4). In the beginning of the 1990s, plague was believed to have been 57
eliminated due to the few reported cases. However, in 1994, India experienced a large 58
outbreak of pneumonic plague after 30 years without a report of the disease (14) and in 2003, 59
an outbreak of plague was reported in Algeria, in an area considered plague-free for 50 years 60
(15). The reemergence of plague was reported in Libya in 2009, after 25 years without a case 61
of plague (20). In August 2013, in a region of Kyrgyzstan bordering Kazakhstan, a case of 62
bubonic plague was reported (21). 63

Plague is one of the oldest infectious diseases in Iran, which has had devastating effects on 64
the human population throughout history. Understanding of plague pandemics has rapidly 65
expanded in the last decade, largely due to molecular approaches, however much remains to 66
be understood regarding past plague epidemics in various parts of the world, particularly in 67
Iran, as it was the greatest empire in the Middle East at that time. 68

The region of Kurdistan, north of the Zagros Mountains in Iran and stretching across southern 69
Turkey and the north of Iraq and Syria, is considered one of the most significant endemic foci 70
of plague worldwide (22-26). 71

This review considers the history of plague in Persia (predecessor of today's Iran) and has a 72
brief review on countries in the WHO Eastern Mediterranean Region, consisting of some of 73
the countries in the Middle East and North Africa, which frequently experienced disastrous 74
plague outbreaks in the last decades, including Afghanistan, Bahrain, Iraq, Jordan, Kuwait, 75
Lebanon, Saudi Arabia, Syria, United Arab Emirates, Yemen, Egypt, Libya, Morocco and 76
Tunisia. 77

Geography of Persia/Iran 78

Historically, the Persian Empire's territory encompassed all of today's Iran, Iraq, Lebanon, 79
Jordan, Armenia, Turkey, and Syria, as well as parts of Saudi Arabia, Afghanistan, Pakistan, 80
the Caucasus, Central Asia, and Egypt. 81

Iran is a Middle Eastern country, located south of the Caspian Sea and north of the Persian 82
Gulf and Gulf of Oman. It shares borders with Iraq, Turkey, Azerbaijan, Turkmenistan, 83
Armenia, Afghanistan, and Pakistan. With an area of 1,648,000 square kilometers 84

(636,000 sq mi), Iran ranks eighteenth in size among the countries of the world. Iran has a variable, arid climate in which most of the relatively scant annual precipitation falls between October and April. Seven percent of the country is forested.

Plague in Iran

Historical records show that plague has been active in Iran for centuries; however, too little information, invalid documentation, misclassification of plague as a different infectious disease such as cholera, and its interaction with society have affected the true analysis of plague waves throughout time.

Plague frequently recurred in Iran but the dating and the determination of the nature of the plague outbreaks are imprecise. The rapid expansion of plague with high mortality rates may have been related to infrequent treatment centers, a poor public health system, no effective quarantine arrangements, washing the dead bodies in rivers before burial, and transferring the corpses to sacred places such as Mashhad, Qom, Najaf, and Karbala (27). Plague epidemics in Iran typically started from villages or places with poor hygiene and a rural epidemic can run for periods of thirty to forty years with no reported cases (28-29). Throughout history almost all regions of the country, especially near the borders (in the north, south, east and west) have reported plague outbreaks (Figure 1, Table 1).

In 543 CE, plague reached what is modern Iran after passing from Italy to Syria, Palestine and Iraq and infected the Persian imperial army and the population at that time (30). In 544 CE, the plague infected both sides of war, the Roman Empire's army as well as the Persian Empire's army (31). In 627 CE, a large epidemic of plague, which led to the death of more than 100,000 people in Ctesiphon, the Sassanian capital, close to Baghdad, Iraq, was reported. Shortly thereafter, Shiroyeh, the king of Persia, died as a result of plague (32). Another plague epidemic occurred from 634 to 642 CE in the region of Yezdigird III, the Great king of Persia (33). The "Yezdigird Plague" may be another name for the plague epidemic in Syria and Palestine, known as the "Amwas Plague" (or Amawas Plague), which killed almost 25,000 people in 638 or 639 CE (34). The Amwas Plague is considered one of the outbreaks of plague in the 6th, 7th, and 8th centuries that followed the major pandemic of the 6th century, the Justinian Plague (35). In 688-689 CE, a devastating plague swept through Basra and killed 70,000-73,000 people (33). The Persian Empire experienced considerable damage from plague outbreaks to both its population and its military. Its weakened military strength is considered a factor in Persia being unable to prevent the Arab conquest of its territory (36).

To the best of our knowledge there is not any concrete documentation about plague outbreaks and plague's impact on Persia between 689 and 1270 CE; it seems, though, that plague continued to spread throughout Persia, remaining endemic after the outbreaks of 689 until the middle of the thirteenth century. Ali ibn al-Abbas al-Majusi (933-1000 CE) described plague in his medical book titled *Kitāb al-Malakiyy*. Abu Sahl 'Isa ibn Yahya al-Masihi al-Jorjani (960-1000 CE) wrote an article about plague; and, interestingly, the *Canon of Medicine*, Avicenna (980-1037 CE) noted the clinical signs of bubonic plague and Esmail Jorjani (1042- 1137 CE) mentioned inguinal lymphadenopathy as a sign of bubonic plague (37). Marco Polo, the famous Italian merchant traveler, reached the city of Tabriz, in northwestern Iran, in 1270 and in "The Travels of Marco Polo", he mentions that the city gates were closed due to the plague (38). Several outbreaks of human plague occurred during the Safavid period (1495-1735 CE), which affected areas in northern Iran such as Gilan, Tabriz, Qazvin, and Ardabil. Another outbreak occurred in Qom, another city in the north, which continued for 5 years with 12,000 deaths. After the collapse of the Safavid Dynasty and Iran's occupation by Afghan invaders, another plague outbreak was recorded in Gilan in 1727. In 1731 CE, around 20,000 people died due to a plague outbreak in Hamadan and the western region of Iran (39). In the epidemics of 1772-1773 CE in Iran, quarantine practices was introduced in the Persian Gulf region for first time (40). This outbreak is recorded as being one of the most severe epidemics of plague, killing an estimated two million people in Persia (Iran) and Persian controlled lands to the west. Plague was introduced to Baghdad, today the capital of Iraq, in the winter of 1772 and reached to Basra in 1773 CE. The plague killed more than 250,000 people in Basra alone. A thousand deaths were recorded daily and the disease spread to Bombay, India (40). Plague also spread southward along the Persian Gulf to Bushehr expanding over most parts of Persia and moving down to Bahrain in 1773 (40). In 1798 CE, a small outbreak of the plague was recorded in Mosul (40). In 1800 CE, a plague outbreak started from city of Mosul, northern Iraq, and spread to Baghdad and Istanbul. The authorities introduced quarantine measures to prevent the spread of the plague to India. During this wave, the workers of British East India Company were moved to a village outside Basra. This led to no reports of plague among European residents (40).

In 1830 CE, plague was epidemic in the entire Persian Gulf region. The disease began in the fall of 1830 with an outbreak in Tabriz (northern Iran) which led to the death of 30,000 people and the relocation of the Iranian capital from Tabriz to Ardabil (27, 40). In 1831, the disease reached northern Iran and led to the death of thousands of people in Mazandaran and Gilan (Rasht) (27). This plague outbreak reduced the population of Rasht from 60,000 to 15,000-20,000 (27, 41).

A plague epidemic in western Iran – in Kurdistan, Kermanshah and Hamadan regions – from 1829 to 1835 and in 1870, led to thousands of deaths (28). In 1876, a plague epidemic in Shushtar, southwestern Iran, led to 1,800 deaths out of a population of 8,000 within only a few months (42). The plague was again reported in Gilan and had a significant negative impact on the economy (43). An outbreak of plague in villages including Serin Bulagh, Saghez and Baneh in Kurdistan province, western Iran, killed hundreds of people (29, 44). At the time, Italian doctors came from Istanbul to help with the plague epidemic in Persia (45). Moreover, in 1877, plague recurred around Khorasan, eastern Iran, and around the Caspian Sea (29).

Mohammad Razi Tabatabai, the senior physician of the army at the time of King Naser al-Din Shah Qajar wrote a book on plague in 1875 in which he described the medical practices of the time and discussed control strategies for plague (46). Between 1870 and 1882 CE, Dr Joseph Désiré Tholozan documented the common places of plague in Kurdistan and noticed certain villages as foci of this disease in this region (47).

A plague epidemic in a village north of Sabzevar, Khorasan Province in northwest Iran, killed 37 individuals in 1877 (27). Another epidemic in 1878, in two neighboring villages in Khorasan, left hundreds dead (28).

Table 1. Plague outbreaks in Iran during 19th and 20th centuries

Conflict area	Province	Location in Iran	Year	Affected/ Mortality No.	Ref.
Caspian sea littoral	ND	North	1829-1833	ND	(46)
ND	Khorasan	Northeast	1829-1833	ND	(46)
ND	Kurdistan	West	1829-1835	Thousands of deaths	(28)
ND	Kermanshah				(28)
ND	Hamadan				(28)
Rasht	Gilan	North	1830-1	40,000 deaths in Rasht	(43)
ND	Mazandaran		1830-1	80,000 deaths in Barforoosh	(43)
ND	Azerbaijan	Northwest	1830-1	30,000 deaths in Tabriz	(27, 40)
Saghez, Baneh	Kurdistan	West	1871	Thousands of deaths	(29, 44)
Serin Bulagh					
Shushtar	Khuzestan	Southwest	1876	1,800 deaths	(43)
Sabzevar			1877	37 deaths	(27)
			1878	Thousands of deaths	(28)
Rasht	Gilan	North	1877	ND	(43) (29)
Bushehr	Bushehr	South	1877	ND	(48)
ND	Kermanshah	West	1877	ND	(48)
ND	Khorasan	Northeast	1877	ND	(29)
Persian Gulf region	ND	South	1899	ND	(46)
Around Sistan Lake	Sistan & Baluchestan	East	1906	1,409 deaths	(45)
Bushehr	Bushehr	South	1910	66 deaths	(45-46)
			1911	98 deaths	(45-46)
			1912-3	965 cases, 725 deaths	(45-46)
ND	Kurdistan	West	1913	ND	(23)
Torbat-e Jam	Khorasan	Northeast	1913	ND	(23, 46)
Bandar Lengeh	Hormozgan	South	1914	One cases	(49)
Bandar Abbas			1915	Three cases	(49)
Khorramshahr	Khuzestan	Southwest	1915	Three cases	(46)
Khorramshahr			1917	79 cases, 43 deaths	(46)
Abadan			1917	481 cases, 409 deaths	(46)
Torbat-e Jam	Khorasan	Northeast	1921	ND	(25, 46)
Kariz					
Khorramshahr	Khuzestan	Southwest	1922	ND	(49)
Chabahar	Sistan and Baluchestan	East	1923	ND	(49)
Khorramshahr	Khuzestan	Southwest	1923	71 cases, 45 deaths	(49)
Abadan	Khuzestan	Southwest	1923	481 cases, 409 death	(49)
Bandar Lengeh	Hormozgan	South	1923	4 cases	(49)
Khorramshahr	Khuzestan	Southwest	1924	152 cases, 115 deaths	(45, 49)
Abadan	Khuzestan	Southwest	1924	233 cases	(45, 49)
Genaveh	Bushehr	South	1924	17 cases, 14 deaths	(49)
Bandar Abbas	Hormozgan	South	1924	12 cases, 7 deaths	(49)
Bushehr	Bushehr	South	1924	1 case	(49)
Bandar Lengeh	Hormozgan	South	1924	1 case	(49)
Aghbolagh Morshed	Kurdistan	West	1947	56 deaths	(46)
Sameleh and Sarbaghleh	Kurdistan	West	1947	17 deaths	(46)
MazidAbad	Kurdistan	West	1951	2 deaths	(46)
Gozar-darreh	Kurdistan	West	1952	45 deaths	(46)
Gavmichan	Kermanshah	West	1952	8 deaths	(46)
ZenalKandi	Western Azerbaijan	Northwest	1958	6 deaths	(46)
Ghaderabad	Kurdistan	West	1961	7 deaths	(46)
Sarumal	Kurdistan	West	1963	14 deaths	(46)
SeyyedAbad	Kurdistan	West	1966	1 deaths	(46)

ND: Not determined

In 1877 an epidemic of the disease was again reported from the cities of Rasht, Bushehr and Kermanshah. Following that, a very devastating epidemic occurred in the regions around the Persian Gulf; as a result, British forces founded the first quarantining center on Hengam Island, Bushehr, to prevent further transmission of the disease to other points of the country (48).	175 176 177 178 179
The plague epidemic in 1906 CE in the province of Sistan and Baluchestan, southeastern Iran, was restricted to the regions around Sistan Lake and it was believed that the infection was transmitted to this area via old clothes imported from India (45).	180 181 182
During the plague epidemics between 1910 and 1911 in Bushehr, in the south, people fled the city leading to negative influences on business (45). In 1912 and 1913, the plague reemerged in Bushehr, 750 people died and 4,000 vaccinations were conducted at that time. Bushehr was then spared from the disease until 1924 when the next outbreak occurred (45). Most cases of the disease in the Persian Gulf region happened in the first quarter of the 20th century and there is a high probability that the disease had originated from India (43, 50).	183 184 185 186 187 188
In 1913, outbreaks were seen in two provinces in Iran, one in Kurdistan in the west, and the other in Khorasan, in the east (23). A plague outbreak was reported in Khorramshahr and Abadan, in southwestern Iran, in 1924 (45). The disease reemerged in Torbat-e Jam, in Khorasan, after eight years without a reported case (25).	189 190 191 192
Some of the plague outbreaks occurred in the area where the Anglo-Persian Oil Company (APOC), an English company, was active extracting petroleum in the southern part of the country. The measures that were taken by this company had a great impact on the control of plague in the area. In 1925, plague vaccination started in the southern areas of Iran and 4,553 individuals were vaccinated. Houses were disinfected and with any new report of the disease, serious actions were taken such as disinfection of all clothing, isolation of the patient, destruction of the house (with recompense) and prohibition of rebuilding on that spot (40).	193 194 195 196 197 198 199
Plague in Iran since the last century	200
There was no report of the disease for 23 years until an outbreak in Kurdistan, western Iran, in 1947 (25). Owing to the presence of appropriate wild rats and fleas in Kurdistan, this region had become an endemic area for plague. In these natural foci, different species of rodents are present, of which the <i>Meriones</i> genus, including <i>M. libycus</i> , <i>M. persicus</i> , <i>M. vinogradovi</i> , <i>M. tristrami</i> , plays an important role in its persistence. The last two mentioned species are extremely sensitive to the causative agent of the disease whereas the first two are	201 202 203 204 205 206

resistant. The presence of plague in Kurdistan thus depends on the ecological interplay 207
between susceptible and resistant rodent species living in close contact. Along with these 208
species, there are other types of rodents, such as *Microtus*, *Mesocricetus*, *Allactaga* and 209
Cristolus, which are less frequently found and play a minor role in the epizootic evolution of 210
the region (25). In 1953 a research center was founded in the village of Akanlu, 100 km 211
northwest of Hamadan and on the border to Kurdistan; this center was opened to conduct 212
research on plague and has since been working as a surveillance center of plague in western 213
Iran. In the same center, Dr. Younes Karimi and his colleagues concluded that the plague 214
bacteria can survive in soil for several months (51). 215

Marcel Baltazard, the former director of the Pasteur Institute of Iran, and his Iranian 216
colleagues studied 14,102 rodents in this region in 1966 and 1967 and found 66 infected 217
amongst them (25). During this time, nine outbreaks of plague were reported, mostly in 218
Kurdistan, with 156 reported deaths. Evidence showed that outbreaks of bubonic plague in 219
this focus, where there are no domestic rodents, were due to inter-human transmission by the 220
human flea, *Pulex irritans*, starting with rare cases of plague contracted in the fields. Such 221
inter-human plague, originating in villages, tends to die out rapidly due to the scant 222
population of the villages, the long distances between them, and the paucity of the means of 223
communication. However, when imported into an urban area with a denser human population, 224
plague immediately becomes the terrifying disease it was during the Middle Ages (25). The 225
last formally reported outbreak of human plague in Kurdistan was to 1966 (52). 226

A major discovery resulting from their studies in Kurdistan was the concept of burrowing 227
plague (53). It was shown that the *Yersinia Pestis* could remain alive for several years in the 228
burrows of dead rodents, and then re-infect the new rodents colonizing these empty burrows. 229
In addition to the well-established “rodent-flea-rodent” cycle, they demonstrated that the 230
“burrow-rodent-burrow” cycle exists, allowing the inter-epizootic maintenance of the plague 231
bacillus in its endemic foci (54). 232

The surveillance of regions surrounding the plague focus in Kurdistan, by studying wild 233
rodents, revealed the existence of an epizootic in Sarab in Eastern Azerbaijan Province, north 234
of Kurdistan, where plague had not yet been reported(26). In this region in 1976, fourteen 235
samples of *Y. pestis* were isolated from wild rodents (*M. Persicus*, *M. vinogradovi*, and 236
Mesocricetus brandti) and from their fleas (*Xenopsylla conformis* and *Nosopsylla iranus* 237
iranus) (26). 238

Surveillance of plague in Kurdistan by the Pasteur Institute of Iran revealed that the disease remained silent for a period of between three to five years in its natural foci and then reappeared in its rodent hosts (22, 55-56). The same finding was reported from different parts of world including India, Brazil, Argentina, South Africa and the USA (57). It is clear that the disappearance and reappearance of plague after several years is multifactor and very complex and depends on the interactions of its components (rodents, vectors, ectoparasites), population density, life cycle, dynamics and geographical distributions of the components, season, rains, saturation, temperature, and local and global climate fluctuations (58-59).

The monitoring of plague continued from 1978 to 2001 with research centre for emerging and reemerging infectious diseases, located in Akanlu village in Hamadan, as the main center of this study. It concentrated on the monitoring of the disease in rodents and positive rodents and/or fleas were identified. According to the studies of the Pasteur Institute of Iran surveillance team during the Iran-Iraq war (1980-1988 CE), in the areas affected by war there were no *Yersinia pestis* infections in 1,800 rodents and 36,000 fleas monitored (60).

A recent study in 2011 and 2012, based at the Research Center for Emerging and Reemerging Infectious Diseases (Akanlu), in the border area between Kurdistan and Hamadan provinces showed that 1.02% of the rodent population and 3.42% of dogs were positive for the antibody against the bacteria, implying that this focus is still active (17).

Because most cases of plague outbreaks occurred before the introduction of microbiology, both the history and the historical population structure of *Y. pestis* are difficult to identify. Using molecular biology technology on a few available strains from Iran and Kurdistan revealed that all isolates belonged to Medievalis biovar (61), indicating that they are of Asian origin and not from the third pandemic. The Orientalis biovar, as the causative agent of the third pandemic, was widespread and reported from Turkey (61-62), the northwestern neighbor of Iran. Further investigation using Ancient DNA technology (63-64) and studying the population structure of *Y. pestis* in Iran and its neighboring countries can hopefully supply strong evidence to fill the gaps on how the bacterium entered and circulated in Persia (Iran), and which biovar and genotypes of *Y. pestis* affected this region.

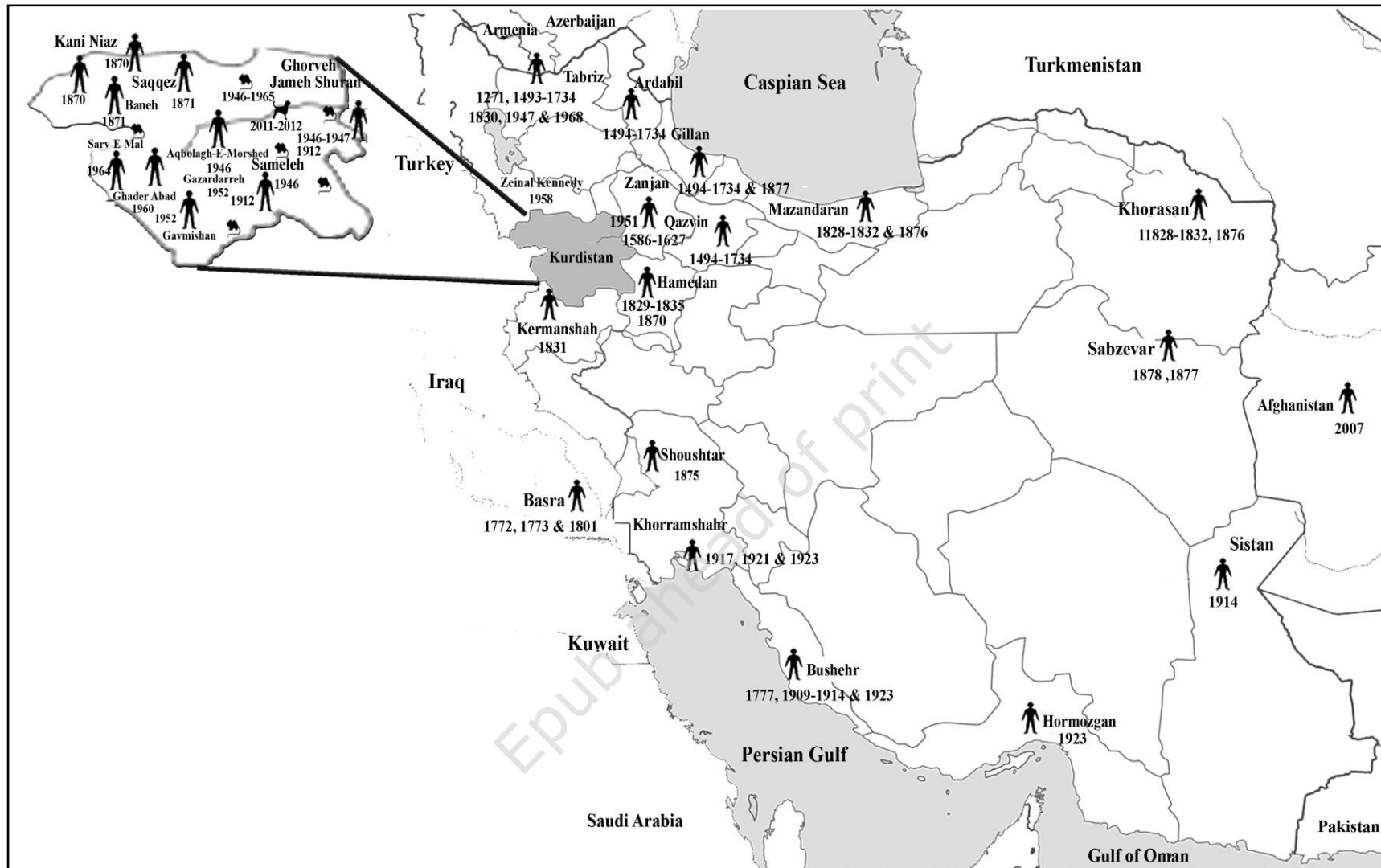


Figure 1: Areas affected by plague throughout Iran's history; Kurdistan, known as the focus of plague in Iran, has been drawn larger.

Plague in the Middle East and North Africa

It is clear that plague frequently recurred in the Middle East and North Africa for over half a millennium, but the dating and the determination of the nature of the plague outbreaks are fairly imprecise. Nevertheless, an attempt has been made to describe the periodicity and nature of plague recurrences. The rapidity as well as the rapacity of these outbreaks raises the question of plague endemicity in this region.

Roughly over the past century, plague outbreaks have been seen in at least fourteen countries in the WHO Eastern Mediterranean Region in the Middle East and North Africa (Figure 2); all of these, as well as many earlier outbreaks, are briefly reviewed here.

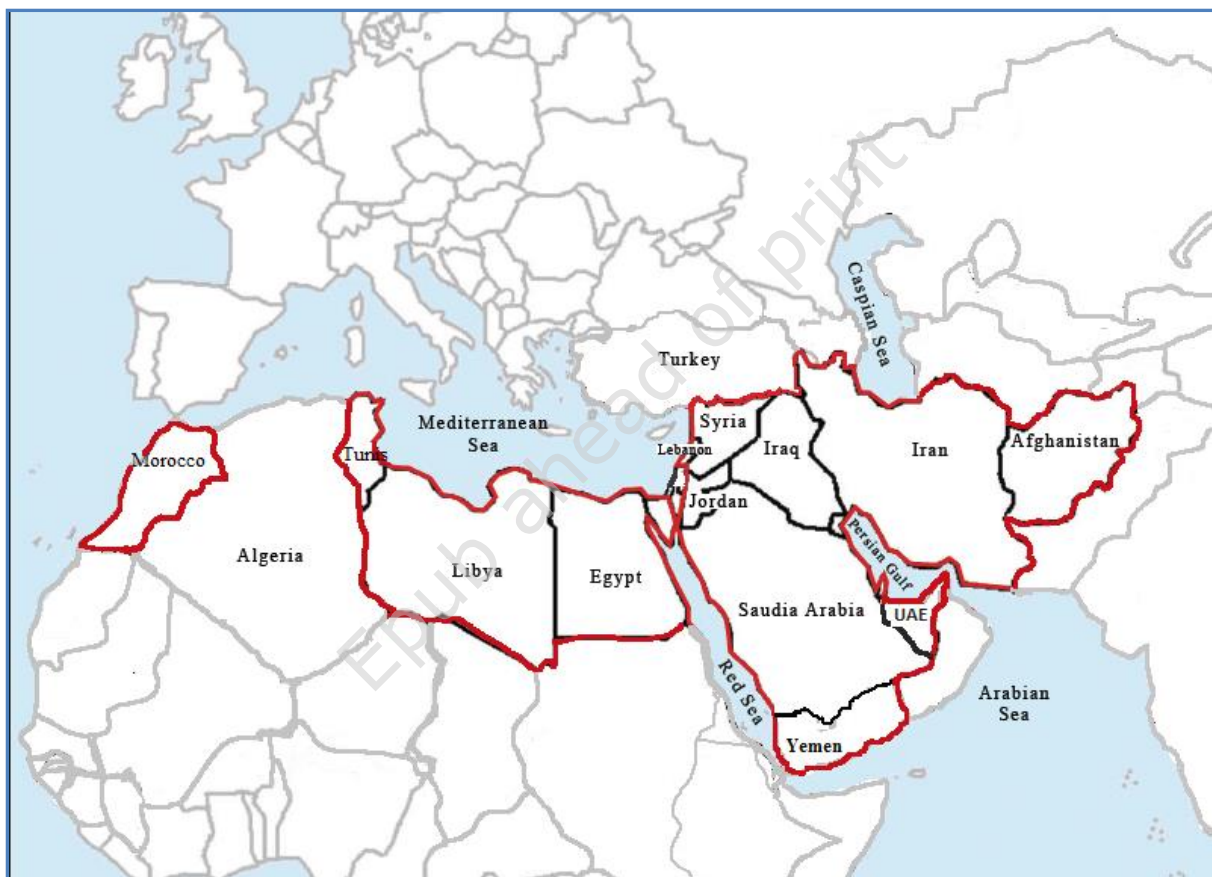


Figure 2: Iran's surrounding countries in the WHO Eastern Mediterranean Region affected by plague

Afghanistan

The WHO Expert Committee on Plague considered Afghanistan a plague endemic focus in its report in 1953 CE (65). The seropositivity rate of plague was recorded in the Afghan population up to 5% in 1996 CE (66). In the late 2007, an outbreak of plague with acute gastroenteritis symptoms occurred in Nimruz Province in southern Afghanistan; in this

outbreak, seventeen out of 83 infected cases died, and consumption of infected camel meat was diagnosed as the source of infection (67).

Bahrain

In 1529 CE, an outbreak of plague occurred in Bahrain; leading to failure of Portuguese attack to this region. The plague in the Arabian littoral also attacked Bahrain in 1773 (40, 68-69). During 1907-1914, two other epidemics of bubonic plague reported in this area (68). In 1914, 1915 and 1924 imported cases of plague were also reported in Bahrain (49).

Iraq

Throughout its history, Iraq has experienced multiple epidemics (70). In 716 and 717 CE, a large outbreak known as "al-Ashraf" (the Notables) was seen in Iraq and Syria (71). In an epidemic of bubonic plague in 1772 and 1773, many affected victims died in cities such as Basrah (with 250,000 deaths) and Musel. In 1801 CE, a large plague epidemic occurred in Musel and Baghdad (40, 72). A plague epidemic occurred again in Baghdad in 1908 (35). From 1923 to 1924, approximately ninety cases of pneumonic plague were reported in Baghdad and there were some reports of plague outbreaks from Basra (49, 73).

Jordan

Plague in Jordan was first seen in the seventh century (24). In 1997 CE, an outbreak of bubonic plague was reported in northeastern Jordan and all affected cases recovered from the disease. At the same time, two dogs tested serologically positive. All cases were infected due to consumption of camel meat (74).

Kuwait

Plague outbreak in 1773 CE in Iraq, spread to Kuwait leading to an outbreak in this region(69).

Lebanon

This country has been affected differently by plague over the ages and has played a significant role in transmitting the disease to other parts of the world. The plague epidemic in Marseille, France, in 1720 led to 50,000 deaths and was via transmission of the infection by a ship from Lebanon (35). In 1900, four cases of plague were reported in Beirut. This outbreak took place after 65 years with no reported cases (71).

Saudi Arabia

This country has experienced several outbreaks of plague in the past (35). There was an outbreak of plague in 1773 CE in Al-Qatif region, an area located in eastern part of Saudi Arabia (69). In 1897 and 1898 several fatal cases of plague were reported in Mecca. In 1899 only two cases, both originating in Jeddah, were observed there (75). In 1994, five cases of bubonic plague were seen in a city located in the desert in southern of Saudi Arabia with one reported death. The source was consumption of an infected camel's liver (76). The presence of plague in wildlife and domestic animals is confirmed in this country and this should be consider a potential risk for the general population as well as for Hajj pilgrims (77).

Syria

The circulation of plague between Syria, Palestine, and Egypt occurred regularly (78-79). Accordingly, the data related to this disease pertaining to these three regions was commonly reported together (71, 80). Outbreaks between 541 and 749 CE in these regions were related to regional trading and via ships entering Syria from Egypt (79). An outbreak in 746 was also due to a military attack on Constantinople (the old capital city of Rome) in which soldiers used swords contaminated with the plague poison (81).

United Arab Emirates

In 1914 and 1924 CE imported cases of plague were reported in Dubai (49).

Yemen

The oldest recorded case of human plague in Yemen occurred near the border with Saudi Arabia, in Asir Province, in 1815 CE and is believed to have spread to Jeddah and Mecca (82). Since the 1815 outbreak in this area there have been few reported outbreaks, owing perhaps to lack of investigation. A plague outbreak was reported in Khawlan in the northern highlands of Yemen in 1969 and left 15 dead in two villages (83). The isolation of *Y. pestis* confirmed the outbreak in 1969.

Egypt

In 1347 CE, plague reached Alexandria in Egypt, probably through the port's trade with Constantinople and ports on the Black Sea (84). Between 1347 and 1517, Egypt experienced more than twenty outbreaks. In an outbreak in 1581, approximately 500,000 people died of this disease (37). In the plague pandemic in the sixth century, more than 900,000 cases in Egypt and 22,000 cases in Gaza (Palestine), which was under the authority of Egypt at that time, were reported (81). In a large outbreak in 1835, about 33,000 people died. In 1899, after

a period of 50 years with no reported cases, plague recurred in this country and between 1899 and 1919, approximately 15,000 cases of human plague were reported (37, 85). Coexistence of the Nile rat, *Arvicanthis niloticus*, and ectoparasites in combination with trade with Asia, Africa and the Mediterranean, together with the Nile floods, suggests that it is possible that *Y. pestis* was primarily a disease of the Nile rat and introduces Egypt as the most probable point of origin of bubonic plague as an epidemic disease (86). A reemergence of plague in Egypt should not be excluded due to the presence of suspected potential natural foci and global climate change.

Libya

Between 1913 and 1920 CE multiple outbreaks occurred in Libya with the largest one taking place in 1917 in Benghazi, where 1,449 people died due to this disease (87). Small outbreaks occurred in 1972, 1976, 1977 and 1984 CE near Tobruk, close to the border with Egypt. In 2009, after 20 years with no reported cases, the reemerging of plague was seen in the country. Three members of a family were infected with the septicemic form and one of them died. This outbreak was of Asian origin (88-89). These data suggest that the plague has active foci in Libya.

Morocco

The first plague cases reported in Morocco refer back to 1909 among 25 military stations in Casablanca. A severe epidemic with 8,000-10,000 deaths took place in 1911. Between 1940-45 almost 5,400 cases were reported in Morocco (90). Another large outbreak of plague occurred in 1977 in which almost 50,000 people died (91).

Tunisia

Plague has not been very prevalent in Tunisia (92). Plague was an epidemic disease in Tunisia between 1870 and 1900. Two major plague epidemics also struck Tunisia in 1784 and 1818 CE; These lasted months (93). Variable susceptibility to plague was reported among the flea and rodent species in Tunisia (94). A plague outbreak was recorded in 1944, which infected 64 persons with 27 deaths (95).

Conclusion

According to the WHO Expert Committee on Plague (1959), (96) and field investigations (22-23, 55-56), Iranian Kurdistan is an active plague foci. A recent surveillance in 2011-2012 also revealed that plague is active in this area (17). Investigations in Turkey, Syria and Iraq

failed to confirm the existence of wild-rodent plague, but an isolated human plague strain in Turkey near the Syrian border (97), with the same biochemical characters as the Iranian strains, supports the view that all these foci form part of a large enzootic area (98).

Almost all of the Middle Eastern and North African countries have reported human plague outbreaks. Less focus has been placed on the epidemic of plague in the wildlife population. In the last 50 years, human plague outbreaks have been reported in Saudi Arabia (76-77), Afghanistan (66-67), , Libya (88-89), Morocco (91), Algeria (99-100), and Jordan (74).

Exemplary studies on the wildlife population in Iran may be due to the existence of a research center founded in 1952 as part of the Pasteur Institute of Iran; extensive studies were done on rodents and other animal hosts of *Y. pestis* in the country in this research center.

Comprehensive studies on places that have historical records of human plague could help clarify the current situation of the disease in this region of the world. Otherwise, without adequate knowledge and preparation, human plague outbreaks are expected to continue in this region.

The lack of reports of the human disease during the past 50 years does not necessarily imply that the disease has not occurred among humans in Iran. Considering that Iran has experienced outbreaks of plague for several centuries, neighboring countries have reported the disease in recent years, the disease can be silent for decades, and the reports of the circulation of *Y. pestis* among rodents and dogs in western Iran, more attention should be paid to disease monitoring in areas with previously reported human cases and high-risk regions with previous epizootic and enzootic activities. Plague should be more strongly emphasized in the medical educational system in Iran. It is highly recommended that general practitioner and healthcare workers gain adequate knowledge of the natural cycle of *Y. pestis* and clinical signs of plague to help them identify the disease. Moreover, further studies are needed to better explain the epidemiology of plague in Iran.

Finally, the following are suggestions to better improve the surveillance system of the disease in Iran:

1. Train health staff and practitioners in areas with prior foci of plague, as well as in the eastern and western border areas of Iran, to be aware of this disease.
2. Design a standard protocol to prepare and dispatch suspected samples from all over the country to the Pasteur Institute of Iran.

3. Prepare educational materials on plague in pamphlets, seminars and conferences concerning zoonotic disease.

4. Equip and empower the infrastructures of the Research Center for Emerging and Reemerging Diseases of the Pasteur Institute of Iran (Akanlu) as the main center of surveillance, research and education about plague and other emerging and reemerging diseases in Iran.

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