

# HISTORY OF MEDICINE

## What caused the Black Death?

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*Postgrad Med J* 2005;81:315–320. doi: 10.1136/pgmj.2004.024075

For the whole of the 20th century it was believed that the Black Death and all the plagues of Europe (1347–1670) were epidemics of bubonic plague. This review presents evidence that this view is incorrect and that the disease was a viral haemorrhagic fever, characterised by a long incubation period of 32 days, which allowed it to be spread widely even with the limited transport of the Middle Ages. It is suggested that haemorrhagic plague emerged from its animal host in Ethiopia and struck repeatedly at European/Asian civilisations, before appearing as the Black Death. The *CCR5-Δ32* mutation confers protection against HIV-1 in an average of 10% of the people of European origin today. It is suggested that all the *Δccr5* alleles originated from a single mutation event that occurred before 1000 BC and the subsequent epidemics of haemorrhagic plague gently forced up its frequency to  $5 \times 10^{-5}$  at the time of the Black Death. Epidemics of haemorrhagic plague over the next three centuries then steadily raised the frequency in Europe (but not elsewhere) to present day values.

But this unknown disease had not disappeared completely and there were epidemics scattered through Europe during the 1350s.<sup>5</sup> Thereafter, the plague was permanently established in France with epidemics every year that cycled round the main trading routes. From there, infected travellers carried the disease by road and river across the continental landmass and by sea to Britain and Ireland. But all these peripheral epidemics died out completely and were restarted by fresh infectives coming from the focus in France.<sup>4</sup>

The epidemics progressively increased in spread, frequency, and ferocity (fig 1) with a pronounced rise after 1550 because transport improved and the population of the towns steadily grew (that is, there was a greater number of susceptibles). Contemporary accounts, pattern of spread, and mortality all confirm that the same pathogen was responsible for all the plagues, including the first strike of the Black Death.

### PUBLIC HEALTH MEASURES

Even in the 14th century the health authorities in northern Italy had established the importance of a 40 day quarantine period, which became the gold standard for continental Europe for the next 300 years. The 40 day quarantine was not adopted in England until the 16th century and even then it was changed to 30 days only to find that this was completely ineffective, whereupon this regulation was speedily rescinded.

The complete success of the quarantine period confirms that the plague was a directly infectious disease and it also shows that it had a long incubation period. Towns in France gradually realised that the danger lay in the arrival of an infected traveller who may well have come from a considerable distance. Entry was denied if they had come from a town that had suffered an epidemic. Later, in addition to inspecting travellers on arrival, the authorities also required proof that all the towns through which they had journeyed were completely free of plague.

Once an epidemic had erupted, those displaying symptoms were removed to emergency primitive isolation hospitals called pest (an abbreviation of pestilence) houses, which were hurriedly erected outside the town. Once a plague case had been identified, the family was locked up in the house, the well known cross was daubed on the door, and a watchman was appointed to stand guard. These measures were less successful in containing an epidemic because, as shown below, victims were more infectious before the appearance of the symptoms.

Despite only sketchy medical knowledge at the time, the epidemiology of the plague was fully

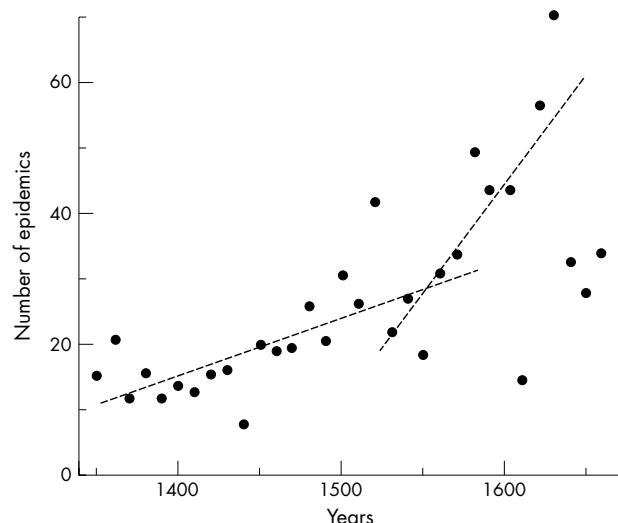
Immediately on its arrival in 1347 in the port of Messina in Sicily the Great Pestilence (or Black Death as it was named in 1823 because of the black blotches caused by subcutaneous haemorrhages that appeared on the skin of victims) was recognised as a directly infectious disease. Michael of Piazza, a Franciscan friar who wrote 10 years after the Black Death had arrived, said "The infection spread to everyone who had any intercourse with the disease".<sup>1</sup> Indeed, they believed (incorrectly) that priests who heard the confessions of the dying "were immediately overcome by death, so that some even remained in the rooms of the dying."<sup>1</sup> Case mortality was 100%. They realised that safety lay in fleeing but this, very effectively, served only to spread the infection.

The Black Death moved as a wave northwards through Europe at an average speed of about 4 km per day and reached the Arctic Circle by 1350, remarkable progress in the days of very limited means of transport.<sup>2–4</sup> Even more impressively: it had earlier appeared in Asia Minor and the Crimea and moved south through Antioch; it was present in the Levant and spread along the north African coastlands and to Mecca in Saudi Arabia, covering, in all, some seven million square km. When it had burnt itself out, 40% of the population of Europe had been killed. This outbreak was a pandemic on a scale never before experienced (or since).

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Submitted 13 May 2004  
Accepted 30 July 2004



**Figure 1** Number of places in Europe reporting a plague epidemic, 1350–1670. Note the increased frequency after 1550. Data from Biraben.<sup>5</sup>

understood at least by the middle of the 17th century. Daniel Defoe<sup>6</sup> had perspicaciously noted that, in the Great Plague of London in 1665, “because of its infectious nature, the disease may be spread by apparently healthy people who harbour the disease but have not yet exhibited the symptoms. Such a person was in fact a poisoner, a walking destroyer perhaps for a week or a fortnight before his death, who might have ruined those that he would have hazarded his life to save... breathing death upon them, even perhaps his tender kissing and embracings of his own children.”

Clearly, they recognised that victims were infectious before the symptoms appeared, the lengthy duration of the incubation period, the necessity of a 40 day quarantine, and the dangers of droplet infection. But there were many features of the epidemics that were mystifying and they also clung to their beliefs in divine intervention, transmission via contaminated clothing and bedding, movements of the planets, and poisonous miasmas.

## YERSINIA PESTIS AND BUBONIC PLAGUE

Even before 1347, bubonic plague had been grumbling along for centuries in Asia with occasional severe epidemics. But from the mid-19th century the disease gathered momentum and erupted in Canton and Hong Kong in 1894, Calcutta in 1895, and Bombay in 1896 and the pandemic of the 20th century had begun. Steamships carried infected rats and fleas from the infested warehouses of the Chinese ports to many of the warmer parts of the world, wherever suitable rodent hosts could be found. But endemic bubonic plague never became established in Europe, despite numerous introductions in the 20th century.

The complex aetiology and biology of bubonic plague was elucidated by Yersin<sup>7</sup> and the Plague Commission of India<sup>8</sup>: it is a disease of wild rodents in which the bacterial pathogen, *Yersinia pestis*, is spread by infected fleas. Occasionally today it is transmitted to humans from peridomestic rats and there are some 1600 cases a year.<sup>9</sup> The characteristic (but not specific) symptom of bubonic plague in humans is the appearance of the bubo.

However, once Yersin had announced his seminal results, it was realised that victims of haemorrhagic plague also sometimes presented with swollen lymph glands. It was, apparently, immediately assumed that the Black Death was caused by bubonic plague. Nobody compared the two

diseases objectively and for the whole of the 20th century this view, based solely on the appearance of one symptom, was universally accepted without question.

## THE BIOLOGY OF BUBONIC PLAGUE

To be able to refute unequivocally the belief that *Yersinia pestis* was the pathogen of the Black Death it is necessary to understand fully the complicated biology of bubonic plague. The key lies in the difference between susceptible and resistant rodent species. Susceptible species, like rats, die from the infection and an outbreak of human bubonic plague was often presaged by the appearance of hundreds of dead rats. Obviously, no outbreak can be maintained for any length of time and bubonic plague cannot become endemic where all the local species are susceptible. In central Colorado an isolated colony of prairie dogs (*Cynomys gunnisoni*) was wiped out when *Yersinia pestis* was introduced.<sup>10</sup>

In Siberia and Mongolia, for example, susliks and tarabagans are susceptible and subject to recurrent, short term outbreaks that might eventually eliminate the plague focus through lack of hosts; but the local gerbils and voles are more resistant to *Y. pestis* and so they can serve to maintain the endemic state in the area because they do not die from an infection.<sup>10</sup>

In warm climates, rodents breed throughout the year and may produce up to nine litters. In this way, the density of a population of rodents living under favourable conditions increases rapidly and outbreaks of bubonic plague can occur at any time of year. The turnover of a rodent population in a subtropical area can be very high: as fast as they breed, infections (including *Yersinia*) and predators act to reduce their numbers. This process generates regular cycles in the population of rodents and prevents the establishment of a stable, plague resistant population. Therefore, any focus of bubonic plague in rodents in subtropical climates is in a continual state of population flux.

The spread of bubonic plague through a rodent population is critically dependent on active fleas. At least 30 species of flea have been proved to be vectors and, as more than 200 species of rodent can carry plague, the host-vector permutations in the Asian subcontinent are formidable and the population dynamics complex.<sup>3 10</sup>

Flea reproduction is strongly dependent on environmental and other factors: temperature and humidity greatly affect both egg laying and the development of the larvae. Temperatures between 18°C and 27°C and a relative humidity of 70% are ideal, whereas temperatures below 7°C are deleterious to all developmental stages except the adult. The fleas, the rats, the resistant rodents, and the susceptible rodents each need specific conditions for the successful completion of their life cycle and the overall maintenance of their populations. All are potentially capable of prodigious reproduction. These life cycles and the environmental requirements for reproduction have to intermesh successfully if an infection of *Yersinia pestis* is to be established in rodents. The dynamics of bubonic plague are complicated but rodents usually keep within their home range and the disease spreads only slowly through the countryside.<sup>3 10</sup>

## SPREAD OF BUBONIC PLAGUE TO HUMANS

If an infected wild rodent strays near human habitations and then shares its fleas with rats living around the settlement, *Yersinia* can spread from rodent to rat, and from rat to man. The rat is just an intermediary and is not a reservoir of bubonic plague: its role is to die and then pass on the infection. A number of dead rats will usually be found during an outbreak of bubonic plague in humans: in a small village perhaps just a few; in a large South African township perhaps many barrow loads.

There are several other ways in which *Yersinia pestis* can spread from a focus among local rodents to humans: when humans go out and invade an area where the rodents are infected—for example when hunting or picnicking—they may catch bubonic plague directly from the fleas living on the wild rodents.<sup>10</sup>

### MANIFESTATIONS OF BUBONIC PLAGUE IN HUMANS

Patients with bubonic plague, who have been bitten by an infected flea, are not normally infectious to other people and can be nursed in open wards. Notably, the incubation period is typically two to six days after exposure and the characteristic symptom is the bubo. Typically the onset is sudden with chills and rigors and a rise of temperature to 38.8°C–39.4°C. The patient has a severe, splitting headache and often pains in the limbs, the back, and abdomen. They become confused, restless, irritable or apathetic, their speech slurred, and they may vomit. Within a day or two the person is prostrate with all the symptoms of shock. Most patients die between the third and sixth day: if they are alive on the seventh day they may struggle through to recovery.<sup>10</sup>

However, in about 5% of the cases of bubonic plague the *Yersinia* reaches the lungs and the patient coughs out the bacteria in the sputum, which may be inhaled by anyone in close contact who then gets pneumonic plague. The victim dies between the third and sixth day and, without medical treatment, pneumonic plague is invariably fatal.<sup>10</sup>

Pneumonic plague cannot occur in the absence of the bubonic form, not can it persist independently. While pneumonic plague increased the mortality locally in an epidemic focus, it was rarely responsible for spreading *Yersinia pestis* over any distance—mortally sick people were unable to move very far in the few days before death. Furthermore, transmissibility of pneumonic plague is low: the average number of secondary cases per primary case ( $R_0$ ) based on past outbreaks was only 1.3.<sup>11</sup>

### MANIFESTATIONS OF HAEMORRHAGIC PLAGUE

We believe that the Black Death was caused by a disease that was completely different from bubonic plague and, to avoid confusion, have named it haemorrhagic plague. Case mortality was 100% and the disease was directly infectious. In the Plague of Athens, victims were stricken suddenly with severe headaches, inflamed eyes, and bleeding in their mouths and throats. The next symptoms were coughing, sneezing, and chest pains followed by stomach cramps, intensive vomiting and diarrhoea, and unquenchable thirst. The skin was flushed, livid, and broken with small blisters and open sores. The patients burned with fever so extreme that they could not tolerate being covered, choosing rather to go naked. Their desire was to cast themselves into cold water, and many of those who were unsupervised did throw themselves into public cisterns, consumed as they were by unceasing thirst. Many became delirious.<sup>3</sup> In the Black Death, prolonged bleeding from the nose and vomiting blood was regarded as a fatal prognostic.<sup>1</sup> Some of the earliest signs were blisters (the “blains”) or carbuncles on the skin and these were followed by the buboes. Gui de Chauillac, physician to the Papal Court at Avignon during the Black Death, saw clearly that the buboes were by no means an invariable symptom and that the mortality was of two types. One died from the first in three days. The second presented with apostumes and carbuncles on the external parts, principally on the armpits and groin and, from this, the victim died in five days.<sup>2</sup> But the most feared signs were the haemorrhagic spots (God’s tokens), which varied in size and colour and could occur anywhere, although the neck, breast,

back, and thighs were the most common site. Necropsies showed general necrosis of the internal organs.

### WHY *YERSINIA PESTIS* WAS NOT RESPONSIBLE FOR THE PLAGUES OF EUROPE

The following is a brief summary of the evidence:

- (1) There were two authentic plague epidemics in Iceland in the 15th century that persisted through the freezing conditions of winter.<sup>12</sup> No rats were present on the island and the conditions were inimical for flea activity.<sup>3</sup>
- (2) The brown rat (*Rattus norvegicus*) did not arrive in Europe until 60 years after the plagues had disappeared.<sup>3</sup> The black rat (*Rattus rattus*) was absent in rural England<sup>13</sup>; no rat species were available to spread the disease throughout the country.
- (3) There are no resistant rodents present in Europe (and never were), which are essential for the establishment of focus of bubonic plague.<sup>3 10</sup>
- (4) The plagues were confined to Europe where the *CCR5-Δ32* mutation is now found, whereas bubonic plague, which was not a serious disease until the late 19th century, was confined to Asia where *CCR5-Δ32* is absent<sup>4 14</sup> (see below).
- (5) The case mortality in haemorrhagic plague was 100% and the total mortality recorded in an epidemic was very much greater (usually at least 10-fold) than that in an outbreak of bubonic plague: humans can be infected with *Yersinia pestis* without suffering from the disease and there are clinical forms (pestitis minor) where there is no danger of dying. In victims who present with fever and the bubo, between 30% and 50% die if not treated.<sup>10</sup> This level of mortality is insufficient to force up the *CCR5-Δ32* mutation to present day levels.<sup>15</sup>
- (6) Flea reproduction was impossible in the climatic conditions of northern Europe.<sup>3</sup>
- (7) The Black Death spread remarkably rapidly—from Sicily to the Arctic Circle in less than three years and covered vast areas of Europe. Many of the subsequent epidemics jumped over 300 km. This is in complete contrast with an epidemic of bubonic plague that moves very slowly<sup>4 14</sup>; the black rat has a home range of 100 metres and rarely strays outside it.<sup>16</sup>
- (8) The bacterium *Yersinia* does not use the *CCR5* receptor.<sup>17</sup>
- (9) The 40 day quarantine for the plague was rigorously established and completely successful for 300 years. It corresponds with the long incubation period that has been established for the plagues of Europe.<sup>4</sup> Quarantine measures are not applicable to bubonic plague.<sup>4 14</sup>
- (10) The plagues were recognised as a directly infectious disease and it was established that it was not safe to come within four metres of an infected person.<sup>4</sup>
- (11) Both normal and *CCR5* deficient mice have been infected with *Yersinia pestis* but there were no differences between the two groups in either bacterial growth or survival time.<sup>17</sup>
- (12) The report that DNA specific for *Y pestis* was amplified from 16th and 18th century human teeth believed to be from French plague victims<sup>18</sup> and 14th century French Black Death victims<sup>19</sup> has not been confirmed and the results have been ascribed to contamination.<sup>20</sup>

### PROFILE OF AN EPIDEMIC OF HAEMORRHAGIC PLAGUE

A full scale plague epidemic developed only in a town above a certain minimum size. Mortality was low in villages. Figure 2 illustrates the profile of a typical epidemic that began in the

spring. It follows the pattern of a person to person infection, but is characterised by its slow generation and its long duration of eight or nine months. The epidemic falls into three stages:

- (1) Rising. Mortality rises exponentially, dependent on the transmission rate. Once the epidemic has killed a proportion of the population, the transmission rate starts to fall and, concomitantly, the mortality rate decreases because there are fewer susceptibles around to infect.
- (2) Plateau. When the transmission rate = 1, the mortality rate remains static.
- (3) Decaying. Once the pool of remaining susceptibles is depleted below a critical level, the transmission rate falls to <1 and, inevitably, the epidemic fizzles out.

### REED AND FROST MODELLING

The unpublished mathematical model of the epidemics of directly infectious diseases developed by Reed and Frost<sup>21</sup> may be summarised as follows. In a closed population of size  $N$  within which people intermingle fairly uniformly, it is assumed that, in a certain period of time  $t$ , every person will have about the same number of contacts with other individuals,  $K$ . If  $t$  is made equal to the serial generation time, the individuals infected during one period will then be infectious during the next.

The probability of an adequate contact between any two given individuals during time  $t$  will be

$$P = \frac{K}{N-1} \quad (1)$$

and

$$q = 1 - p \quad (2)$$

will be the probability of any given person avoiding adequate contact with any other given person during time  $t$ .

Thus, the population is at any time,  $t$ , composed of cases,  $C_t$ , and susceptibles,  $S_t$ , and the probability of any given

person avoiding contact with any of the cases will be  $q$  and, with all the  $C_t$  cases, will be

$$Q_t = q^{C_t} \quad (3)$$

And the probability of any given person having at least one adequate contact with any of the cases will be

$$P_t = 1 - Q_t = 1 - q^{C_t} \quad (4)$$

In the next time period ( $t+1$ ), the number of contacts between cases and susceptibles is given by

$$C_{t+1} = S_t(1 - q^{C_t}) \quad (5)$$

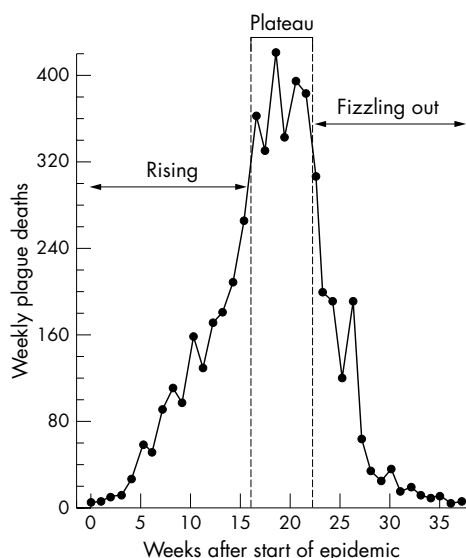
Computer modelling of Reed and Frost dynamics shows that the duration of an epidemic is strongly dependent on the serial generation time of the disease.<sup>4</sup> The epidemic at Newcastle (fig 2) suggests a long serial generation time of 22 days and a low  $R_0$  of 3.

These conclusions are illustrated in figure 3, which shows the results of modelling epidemics of influenza (incubation period = 2–3 days) and a hypothetical plague (incubation period = 32 days), with  $R_0$  standardised at 3.  $N = 1200$ .

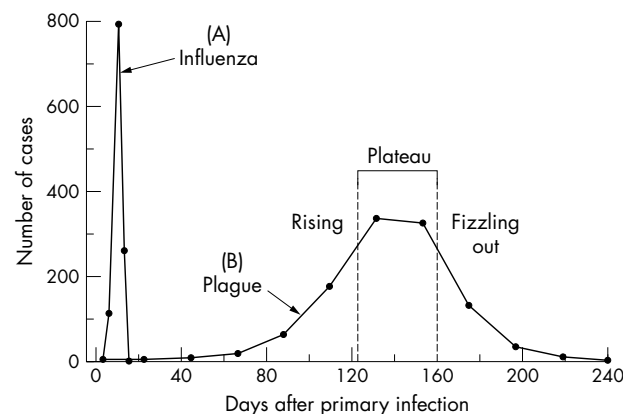
### DETERMINATION OF THE CHARACTERISTICS OF THE DISEASE

From the Elizabethan period vicars and parish clerks were required to mark the registers of plague burials with a "P" or "Pest". Detailed analysis of some 100 plague epidemics recorded in parish registers, coupled with family reconstitution enabled the tracing of the lines of infection both within and between households and the determination of the vital characteristics of the pathogen<sup>4</sup>:

- (1) An epidemic was often specifically recorded as being started by a visiting stranger or by a resident returning from a visit to a place where the plague was raging.
- (2) There was a considerable delay, often more than 15 days, between the death of the primary case and the first secondary case.
- (3) Transmission was much easier within, rather than between, households.



**Figure 2** Weekly plague burials at Newcastle upon Tyne after the start of the epidemic on 14 May 1636.



**Figure 3** Computer modelling of epidemics of influenza (incubation period = 2–3 days) and a plague (incubation period = 32 days) in the same community, with  $R_0$  standardised at 3.  $N = 1200$ .



- (4) Transmission was much more difficult in the colder months and probably impossible out of doors in the depth of winter.
- (5) Four metres was established as a safe distance of separation out of doors.
- (6) From April to October,  $R_0 = 3$  to 4, but with a range of 1 to more than 20, depending on circumstances.
- (7) The characteristic symptom was the appearance of haemorrhagic spots.

By the following of the lines of infection, particularly in the early and late stages of an epidemic, it is possible to determine the following:

- Latent period = 12 days (occasionally 10 days)
- Infectious period before symptoms = 20–22 days
- Incubation period = 32 days
- Period of symptoms = 5 to 6 days (range = 2–15 days). Victim probably less infectious during this time.
- Total infectious period = 25–27 days
- Total time from point of infection to death = 37–38 days, in agreement with the 40 day quarantine instituted in the 14th century.

It was the very long incubation period that, even in the days of very limited transport, allowed travellers and traders to spread the plague widely throughout Europe and across the sea to England, Ireland, and Iceland.

## RESISTANCE

During the Black Death in 1348 there was evidence of a few people who were resistant to the disease. For example, a monk who was the sole survivor in a monastic community, having nursed and buried his fellow inmates. By the 17th century, inspection of the burials registers of London suggests that the percentage of the resident population showing resistance had risen considerably, with the greatest mortality among naive immigrant apprentices and maidservants from the provinces.<sup>4</sup>

Current studies in molecular biology throw light on this phenomenon. The transmembrane *CCR5* chemokine receptor is used by HIV strains to enter cells of the immune system.<sup>22–24</sup> The *CCR5-Δ32* deletion prevents the expression of the receptor and provides almost complete resistance to HIV-1 infection in homozygous people and partial resistance in the heterozygous state.<sup>25–29</sup> The average frequency of the *CCR5-Δ32* deletion allele is estimated at 10% in European populations, but is virtually absent among native sub-Saharan African, Asian, and American Indian populations.<sup>25–29–31</sup>—that is, the *CCR5-Δ32* mutation is found today only in the area that was once ravaged by plague. The age of the *CCR5-Δ32* bearing haplotype has been computed to be about 700 years old (but with a wide range of 275–1875 years) and it has been suggested that it was driven upwards to the present day frequencies of 5% to 15% by a historic, strongly selective event, probably an enormous mortality mediated by a widespread epidemic of a pathogen that, like HIV-1, utilised *CCR5* for entry into lymphoid cells.<sup>30</sup> The Black Death is an excellent candidate for such a catastrophic event<sup>30</sup> but this single pandemic would have raised the frequency of the mutation from the estimated value of  $5 \times 10^{-5}$  to only, at most,  $10^{-4}$ . Rather, we suggest that the virus of haemorrhagic plague used the *CCR5* receptor as a means of entry and that the continuous epidemics for the following 300 years acted as a strong selection pressure that drove up the frequency of the mutation to present day values in Europe of  $10^{-1}$ . Recent research has shown that *Yersinia pestis*, the bacterium of bubonic plague, cannot enter via the *CCR5* receptor.<sup>17</sup>

## Box 1 Epidemics of haemorrhagic plague in history

- (1) Haemorrhagic fevers in the Nile valley in Pharaonic Egypt, 1500–1350 BC.
- (2) Viral haemorrhagic fevers were reported in ancient Mesopotamia ‘If ... his epigastrium [has] a piercing pain, blood flows incessantly [from his mouth], his arms are continually weak, depression continually falls upon him [and] his eyes are suffused with blood [it is] ‘Hand of Marduk’; he will be worried and die.’ (Mesopotamian diagnostic handbook circa 721–453 BC).<sup>36</sup>
- (3) Plague of Athens 430–427 BC. Originated in Ethiopia. The description of the symptoms given by Thucydides correspond closely with those of haemorrhagic plague.<sup>37–38</sup>
- (4) Plague of Justinian AD541–2; continued sporadically until AD700. Originated in Ethiopia. The description of the symptoms given by Procopius correspond closely with those of haemorrhagic plague.<sup>39</sup>
- (5) Plagues of Islam AD627 to 744.<sup>33</sup>
- (6) Haemorrhagic plague in Asia minor and the Levant (the plague focus), 1345–48.<sup>2–40</sup>
- (7) Haemorrhagic plagues of Europe, 1347–1670.
- (8) Epidemics of haemorrhagic plague in Denmark and Sweden, 1710–11.<sup>41</sup>
- (9) Sporadic epidemics in Poland through the 18th century.<sup>41</sup>

## NATURE OF THE PATHOGEN

There is no known disease today that presents with the symptoms of haemorrhagic plague. The studies with the *CCR5* receptor suggest that the pathogen was viral and the symptoms and necropsy reports of haemorrhagic plague are closest to those of Ebola and Marburg, particularly the necrosis of the internal organs and the haemorrhagic manifestations,<sup>32</sup> suggesting that the pathogen may have been a filovirus. ‘Filoviruses are the prototypical emerging pathogens: they cause a haemorrhagic disease of high case-fatality associated with explosive outbreaks due to person-to-person transmission, have no known treatment, occur

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unpredictably, and have an unknown reservoir".<sup>32</sup> We suggest, therefore, that the plagues were an emergent haemorrhagic fever, probably caused by a filovirus.

## ORIGINS OF HAEMORRHAGIC PLAGUE

We suggest that haemorrhagic plague first emerged in Ethiopia, the cradle of human evolution; it is in this area that humans have been in longest association with animals. A number of Arabic sources have traced plague back to there and the disease was carried down the Nile Valley by caravan traffic<sup>33</sup> to Sudan and Egypt and North Africa. We can trace sporadic epidemics of haemorrhagic plague that occurred widely over the eastern Mediterranean area during a very long time span, from the earliest writings. Presumably, the plague was active in the Nile valley, albeit unrecorded, well before these times. Box 1 summarises the written evidence for the historical sequence of epidemics.

## ORIGIN OF THE CCR5-Δ32 MUTATION

It is generally agreed that most, if not all, *Δccr5* alleles originate from a single mutation event that is estimated to have taken place either 3500 (400–13 000) or 1400 (375–3675) years ago.<sup>31</sup> We see from box 1 that this critical mutation could readily have occurred within this predicted time scale, and grumbling and sporadic epidemics during a period of over 2000 years could have gently forced up the mutation to the estimated frequency of  $5 \times 10^{-5}$  by the time of the Black Death. Traces of the *CCR5-Δ32* mutation have been found in Bronze Age skeletons taken from a cave at Liechtenstein dating from 900 BC.<sup>34</sup>

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