



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

The history of the plague and the research on the causative agent *Yersinia pestis*

Björn P. Zietz, Hartmut Dunkelberg

Medical Institute of General Hygiene and Environmental Health, University of Göttingen, Germany

Received October 23, 2002 · Revision received June 29, 2003 · Accepted July 19, 2003

Abstract

The plague is an infectious bacterial disease having a high fatality rate without treatment. It has occurred in three huge pandemics since the 6th century with millions of deaths and numerous smaller epidemics and sporadic cases. Referring to specific clinical symptoms of pulmonary plague the disease became known as the Black Death. This pandemic probably originated in central Asia and began spreading westward along major trade routes. Upon the arrival in the eastern Mediterranean the disease quickly spread especially by sea traffic to Italy, Greece and France and later throughout Europe by land. Until the 18th century many European cities were frequently affected by other great plague epidemics. The worldwide spread of the third pandemic began when the plague reached Hong Kong and Canton in the year 1894. The gram-negative coccobacillus now designated as *Yersinia pestis* has been discovered as the causative agent of plague in this Hong Kong outbreak. In the following years the role of rats and fleas and their detailed role in the transmission of plague has been discovered and experimentally verified. Today the plague is still endemic in many countries of the world.

Key words: Plague – *Yersinia pestis* – Black Death – pandemic – rat – flea – history

Introduction

In recent times fears about terrorist's attacks with bioweapons has grown. One of the possible agents for bioweapons is the bacterium *Yersinia pestis*. Additionally, SARS as a new epidemic disease caused by a before unknown corona virus has arisen on a global scale (Fouchier, 2003; Knight, 2003; WHO, 2003). These new events bring up the question how the course of other important epidemic agents had been in the past. The plague has

been without doubt one of the most important and devastating epidemic diseases of mankind.

This article wants to give a concise overview of the history of the plague and the research on the causative agent *Yersinia pestis*. It does not want to refer all details of research efforts, concepts or epidemic outbreaks. This would be even difficult in a multi-volume monograph. This accomplishes especially to events from the 20th century which are only highlighted with a few selected details due to the numerous new scientific results.

Corresponding author: Dr. Björn P. Zietz, Medical Institute of General Hygiene and Environmental Health, University of Göttingen, Windausweg 2, D-37073 Göttingen, Germany. Phone: +49 551 39 4971, Fax: +49 551 39 4957, E-mail: bzietz@gwdg.de

At the time of discovery many of the new concepts were subject to lengthy disputes. Naturally the view of the historical events is made in a retrospective way funded on concepts now considered as proven. To support any further searches of the user, original references are cited although they were not used to compile this article in many cases.

The plague is a bacterial infectious disease that has a high fatality rate without treatment. The disease occurred in three huge pandemics since the 6th century and numerous smaller epidemics and sporadic cases. It is still extant in several countries in Eurasia, Africa and the Americas. Causative agent of plague is *Yersinia pestis*, which is a gram-negative, nonmotile, non-spore-forming coccobacillus (0.5 to 0.8 µm in diameter and 1 to 3 µm long) that exhibits bipolar staining with Giemsa, Wright's, or Wayson staining (Perry and Fetherston, 1997). The plague has an incubation period of 1 to 6 days. There are three primary clinical forms of *Y. pestis* infections in human beings: bubonic plague, primary septicaemic plague and primary pneumonic plague (WHO, 2002).

Bubonic plague is characterized by regional inflammation and swelling in one or several lymph nodes (buboes). This type is predominantly resulting from flea bite or direct contamination of a skin lesion with contaminated material and spreading of the infection via the lymphatic system. Buboes can occur in any regional lymph node sites in the body. The early symptoms of bubonic plague are characterized by headache, shaking chills, fever, malaise and pain in the affected regional lymph nodes with a sudden onset of the disease (WHO, 2002; Perry and Fetherston, 1997).

Primary septicaemic plague is a progressive, overwhelming bloodstream infection in the apparent absence of a primary lymphadenopathy. A bacterial endotoxin may initiate a cascade of immunologic responses that can result in a spectrum of pathological events including disseminated intravascular coagulopathy (DIC), multiple organ failure (MOF), and acute respiratory distress syndrome (ARDS) (WHO, 2002; Perry and Fetherston, 1997).

Primary pneumonic plague caused by the respiratory droplet route is the most fulminating and fatal form of plague. Following a rapid onset of the disease symptoms like chills, fever, headache, body pains, weakness, and chest discomfort occur. Cough, sputum production, difficulty in breathing, hypoxia, and haemoptysis become apparent in the fast progress of the disease. Primary pneumonic plague without treatment is fatal in most cases. Since *Y. pestis* is not a truly airborne agent, person-to-person transmission requires face-to-face exposure

within 2 metres of a coughing patient (WHO, 2002; Perry and Fetherston, 1997).

Other clinical forms, such as secondary septicaemic plague, secondary pneumonic plague, or meningial plague, result from bacteriaemic dissemination of the agent (WHO, 2002).

The plague is still endemic in many countries and a substantial number of cases are reported every year. There are seven countries, namely Brazil, Democratic Republic of the Congo, Madagascar, Myanmar, Peru, the USA, and Viet Nam which have been affected by plague nearly every year during the period of 1954 to 1997. The total number of reported plague cases per year ranged between 200 and 6004 in that period. (WHO, 2000). Figure 1 is depicting the plague cases reported to the WHO for four decades up to the year 1998.

The first pandemic

The oldest account of the plague is possibly given in the Bible. In the book of Samuel an outbreak of a disease with buboes is described (I. Samuel V 9–12). Another important report of possible plague is given by Rufus of Ephesus in the first century of our time. He describes the outbreak of an epidemic causing buboes and states its occurrence in Libya, Syria and Egypt. He also cites other reports of the plague dating back to about 300 years before our time that are now lost (Haeser, 1882, p. 15f; Sticker, 1908, p. 20f). In the recent literature there are doubts whether this epidemic is caused by plague or plague alone. Generally it is very difficult or in many cases impossible to give a clear diagnosis from descriptions of antique authors. At that time probably other infectious diseases such as smallpox or typhus caused epidemics and the symptoms of the final state of these untreatable diseases were similar (Bergdolt, 2000, p. 12ff).

The first indubitable report of the plague is the "plague of Justinian" named after the roman emperor of that time. It possibly originated around the year 532 in northern Africa (Ethiopia or Egypt) and spread through the Middle East and Mediterranean basin in the following years. Probably the commercial city of Pelusium in the mouth of the Nile in Egypt served as an important centre from which the infection was distributed (Haeser, 1882, p. 37f; Hirst, 1953, p. 10ff; Sticker, 1908, p. 24f). This first part of the epidemic may also be caused by a disease other than "real" plague (Bergdolt, 2000, p. 12ff). The indubitable great plague pandemic started when Constantinople (modern Istanbul, Turkey) and

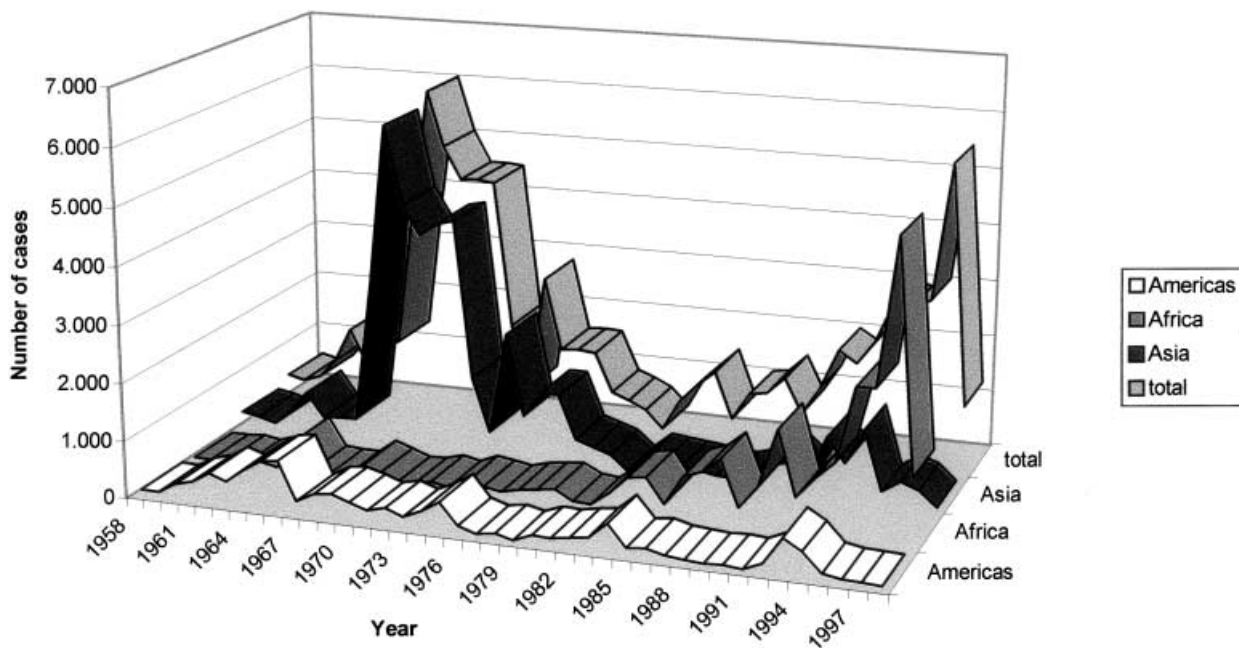


Fig. 1. Plague cases reported to the WHO for the years 1958 to 1998 from Africa, Asia and North and South America. Data source: WHO, 2000.

Greece were reached in the year 541/542. The territory of Italy was affected in the year 543 and the territory of France and Germany in the years 545/546. This great epidemic was followed by several additional epidemics in the following two centuries. In this first plague pandemic northern Africa, Europe, central and southern Asia, and Arabia were especially affected (Haeser, 1882, p. 37f; Hirst, 1953, p. 10ff; Sticker, 1908, p. 24f; Bergdolt, 2000, p. 14ff). A detailed account of the outbreak of bubonic plague in Constantinople is given by Procopius of Caesarea in his book “*De bello persico*”. According to this source half of the inhabitants of the Byzantine Empire were dead by the year A. D. 565 which is probably exaggerated for rhetorical reasons (Hirst, 1953, p. 10f; Sticker, 1908, p. 33; Bergdolt, 2000, p. 14ff).

The gap of several centuries between the end of the first pandemic and the beginning of the second pandemic is partially bridged by short and sometimes dubious records of outbreaks in Europe (mostly Russia) and Asia. (Haeser, 1882, p. 92f; Hirst, 1953, p. 10f).

The dominating medical theory on epidemics of that time has been contributed by Hippocrates (ca 430 – ca 370) and later Galen (129–199 (?)) who believed in the idea of a miasmatic corruption of the air as reason for disease. In his theory inhalation of air fouled by putrid exhalations coming from different sources such as swamps lead to epidemic

diseases. He has developed these ideas in his work “*De febrium differentis*” in the second century and they played an important role throughout the whole Middle Ages (Hirst, 1953, p. 37f). Galen also said that contact with exhalations of plague cases is also dangerous. Therefore the correct observation that plague and other epidemic diseases can be transmitted between persons has imperfectly been integrated in a theory of disease which assumes that diseases are manifestations of false mixtures of the four body fluids (blood, phlegm, cholera or yellow bile). But this transmission via exhalation of plague agents was not regarded as the most important way. Well beyond the Middle Ages there had been a lengthy discussion what exactly can be regarded as putrid exhalation (Bergdolt, 2000, p. 21ff; Leven, 1997, p. 33ff; Hirst, 1953, p. 46).

The second pandemic

In contrast to earlier epidemics the great medieval plague is well documented by many authors and documents (Haeser, 1882, p. 97ff). For example, the plague epidemic of Florence in the year 1348 is described by Giovanni Boccaccio (1313–1375) in his famous book “*Decamerone*”. The plague began spreading again probably from the Himalayas westward along three major trade routes from the

Table 1. Spreading of the European Black Death in the 14th century.

Year		Locations of important epidemics
1347	Spring	Constantinople
	Summer	Greece, Cyprus, Malta, Corsica, Sardinia
	Fall	Messina
	November	Marseille
	Winter	Genoa, Venice
1348	Beginning	Spain, southern France
	Spring	Jerusalem, Florence
	March	Modena
	May	Valencia (Spain)
	June	Piacenza, Padua, Barcellona; Syria, Gaza
	July	Damascus (with a daily mortality of 2,000–2,400 people)
	Summer	Paris, Rome
	August	Calais; southern England
	November	London, Norway (Bergen)
	December	Dalmatia, Denmark
1349	January	Austria (Villach), Poland
	Spring	Vienna, Frankfurt/Main
	Summer	Ireland
	August	Danzig, Lübeck, Schleswig
1350	Fall	Scotland
	Beginning	Paderborn, Osnabrück, Minden, Erfurt
	May	Bremen, Magdeburg

Source: modified after Haeser, 1882, p. 127 and Sticker, 1908, p. 42f.

years 1332 (?) to 1346. The introduction into Europe in the year 1347 resulted in the start of the first epidemic of the second pandemic that was active until the year 1352. This epidemic again encompassed all of the “known world” at that time and later became known as the Black Death. Even the island of Greenland in the North Atlantic was effected (Haeser, 1882, p. 97f; Sticker, 1908, p. 42f). Upon the arrival in the eastern Mediterranean the disease quickly spread especially by sea traffic to Italy, Greece and France, and later throughout Europe by land (Table 1). In the outbreaks in medieval towns often several tens of thousands of people died. It is reported that in Venice alone 100,000 inhabitants died of plague, in Paris 50,000 to 80,000 and in London about 100,000. In Genoa at least 40,000 people died which equals about half the population of that time (Haeser, 1882, p. 97f). These figures may be exaggerated symbolic numbers but they testify the immense impression of the catastrophe upon the minds of the people (Aberth, 2001, 109f).

The outbreak killed an estimated 15 to 23.5 million Europeans, representing about one-fourth to one-third of the population in those days (Zinn, 1989, p. 150f; Bergdolt, 2000, p. 10, 192f; Polzer, 1982), although there are local records that suggest an even higher mortality rate (Aberth, 2001, 109f). Despite the high mortality of this Black Death

epidemic, the most devastating effects resulted from the numerous following outbreaks and greater epidemics that continued into the early 18th century, although not as frequent as in the 14th and 15th century. Between the years 1349 and 1665 only a few decades remain without a plague epidemic. In most cases they originate from residual foci and in some cases the plague was reintroduced easterly (Sticker, 1908, p. 74). It is documented that there were great regional variations in the severity of the death rate (Bean, 1982). To fight the Black Death measures such as burning fires in the streets and in the houses, using aromatic substances (both to fight putrid exhalations) and also making barriers or just flight was recommended for prophylaxis (Haeser, 1882, p. 183f). At the time of the Black Death and the following centuries the real cause of the disease remained unknown and beside the concepts developed by Galen and other physicians of the antique it was attributed among others to unfavourable constellations of stars, to comets and to the wrath of supernatural powers (Aberth, 2001, 109f; Leven, 1997, p. 20f). Following the epidemic of the Black Death many cities introduced quarantine measurements to avoid plague epidemics. The name quarantine is based on the forty day restrictions on travel imposed in Marseille in the year 1384 (Leven, 1997, p. 31). In the 17th century a “protective” clothing was invented consisting of a long cape and a mask

Table 2. Selected historic events related to plague and plague research (locations are cited with their current name).

Year	Event
1 st century	Possible report of a plague epidemic
251–266	Plague of Cyprian in Egypt and Ethiopia; probably plague epidemics combined with outbreaks of other diseases
542–546	Justinian plague; first epidemic of the first pandemic
558– ca. 595	Additional epidemics of the first pandemic
599–775	Several outbreaks in Italy, Germany, Syria, Iraq, Egypt, Turkey
1332–1346	The plague spread westward from Asia, probably from the steppes of central Asia
1347–1352	First epidemic of the second pandemic in Europe, later known as the Black Death
1359–1361	Outbreaks in France, England, Scotland, Poland, Russia, Italy
1546	First complete theory of infection by G. Fracastoro
1575–1577	Plague epidemics in Italy resulting in active medical discussions; plague in Germany, Belgium, Sweden, England, France
1603–1611	Epidemics in Germany, England, France, Switzerland, Russia, Egypt
1629–1631	Plague in many Italian towns with tens of thousands of deaths each
1658	First claim of an observation of a microorganism causing plague by Athanasius Kircher
1663–1684	Epidemics in northern Africa, Turkey, Poland, Austria, Germany, England, Italy, the Netherlands
1663–1664	Amsterdam major epidemic
1665	London major urban epidemic
1674	Discovery of bacteria by Antoni van Leeuwenhoek
1701–1714	Plague in eastern Europe
1720–1721	Marseille and Provence major epidemic
1770–1772	Plague in eastern Europe, Moscow major urban epidemic in 1771
1776	Demonstration by Lazzaro Spallanzani that infusoria do not generate spontaneously
1798	Epidemic in Alexandria (Egypt) affecting Napoleon's invasion of the country
1834–1840	Plague in Egypt
Ca. 1855	Start of the third pandemic, probably in the Chinese province of Yunnan
1866	While investigating fermentation Louis Pasteur discovered that bacteria in wine can be eliminated by treating them with heat. This procedure is now known as pasteurisation
1876	Pasteur demonstrated that contamination of beer was caused by microorganisms found in the air and not spontaneously generated as previously believed
1876	Discovery of <i>Bacillus anthracis</i> as the causative agent of anthrax by Robert Koch
1882	<i>Mycobacterium tuberculosis</i> was discovered as the causative agent of tuberculosis, again by Robert Koch
1894	The plague reached Canton (Guangzhou) and Hong Kong
1894	Within days Yersin and Kitasato independently announced the isolation of the plague organism
1896	Plague in Bombay
1896	Yersin used an antiserum against organisms isolated by him to cure a plague patient
1897	Haffkine demonstrated the efficacy of his inactivated vaccine during an outbreak in Bombay, India
1897	Yersin proposed a connection between rats and plague
1897	Masanori Ogata proposed that fleas may play a role in the transmission of plague (among other ways of transmission)
1898	Paul-Louis Simond proposed the central role of the flea in plague transmission
1899 / 1900	Steamships had disseminated the disease in Africa, Australia, Europe, Hawaii, the Middle East, North America, South America and to many countries in Asia
1902	Gauthier and Raybaud were able to show that plague can be transmitted between rats without direct contact by fleas
1911 / 1912	Manchurian outbreak, Wu Lien-Teh recognized that the epidemic was the pneumonic form of plague and instituted the use of protective measures against aerosol spread of the disease
1914	The specific transmission mode of fleas with obstructed proventriculi was discovered by Martin and Bacot while studying suckling fleas
1927	Wild living rodents were found to be the infection reservoir of the endemic plague by Jorge
1938	Antibiotics introduced in plague therapy (Prontosil)
1940	A Japanese plane is supposed to have dropped plague contaminated rice and fleas over the city of Chuhsien
1945	First use of insecticides in an outbreak control in Peru
1946	Streptomycin proved highly efficient for plague therapy in mice
1946	First therapy of human plague with streptomycin
1950	First therapy of human plague with tetracyclines
1966–1972	Large plague epidemic in Viet Nam
2000	Molecular identification of <i>Y. pestis</i> as the agent of medieval Black Death by Raoult et al.
2001	Genome sequence of <i>Y. pestis</i> published by Parkhill et al.

The table was compiled from references cited in the text, especially Haeser, 1882; Hirst, 1953; Eckart, 1994; Kupferschmidt, 1993 and Sticker, 1908; Pollitzer, 1954; Porter, 2000.

with a bill like part in front of the nose and mouth containing aromatic substances (Leven, 1997, p. 34).

The second pandemic is believed to have induced great changes in society, economics, politics, and science (Haeser, 1882, p. 183f; Roedig, 1996). Existing economic and social problems were severely intensified due to the great demographic losses even many years after the first epidemic. On the one hand plague fatalities in the town led to shortcuts in many handicrafts and resulted in an inflow of rural inhabitants to replace these losses. This inflow and changes in the social structure (and social power of craftsmen) led to many conflicts. On the other hand a relative overproduction of agricultural products in the years following the epidemic and structural changes in agriculture caused severe social and economic problems in the rural population. Details of these and many other complex changes and conflicts due to the plague are subject to continuous scientific research and discussion (Bergdolt, 2000, p. 191–207; Zinn, 1989, p. 150f; Aberth, 2001, 109f). The great losses of population due to the plague (and for other reasons such as war, famine, and other contagious diseases) probably were also the reason that themes such as the apocalypse, “ars morieni” (the art of dying) and “the dance of death” became an important part in art and literature of that time (Schneider et al., 1991; Roedig, 1996). This is especially true for the “the dance of death”-theme which probably evolved a few year after the great first epidemic (Bergdolt, 2000, p. 207–218). The importance of these aforementioned themes is documented for example in many medieval paintings, woodcuts or in block book prints. Medieval block books (*incunabula xylographica*) were printed from woodblocks without using single types. They were predominantly made in the middle of the 15th century (Schneider et al., 1991). Figure 2 is depicting a page of a block book edition of the apocalypse printed around 1465. Figure 3 shows a woodcut of the book “Ars morieni” printed ca. 1497 and Figure 4 depicts the woodcut “the dance of death” from the Latin edition of the Nuremberg Chronicle of 1493.

Since the 14th century the British Isles were affected by numerous smaller and greater plague epidemics similar to the countries of the European continent. At a national scale at least eighteen outbreaks can be identified between the years 1348 and 1485. From the late 15th century when national and urban population began to rise again plague continued to take a heavy toll (Porter, 2000, p. 13f). In the last years the plague on the British Isles has been topic of many investigations, especially on the time interval

between the 16th and 17th century. For example, attempts to install effective quarantine measures and the planning and building of pest-houses in different parts of the island are well documented. Based upon an Italian model bills of mortality were introduced, to provide warning of a threatening outbreak and allow measures to be put in place. In 1519 the earliest London Bill was compiled and from the early 1610s onwards the weekly bills were printed, making them widely available (Porter, 2000, p. 15f). In the year 1665 London was struck by a great plague epidemic after several years of a low number of plague cases with a first focus at the parish of St Giles-in-the-Fields close to the western edge of the town. In June the number of deaths documented in the London Bills had been doubled compared to



Fig. 2. Single page of a mediaeval block book on the apocalypse printed around 1465 (edition Schreiber IV). All pages of this copy were coloured by hand. The book contains pictures and short texts describing mainly the revelation of St. John (Johannes Apostolus) given in the last chapter of the new testament. The scene depicted here is the pouring out of the seventh bowl by an angel bringing earthquakes and hail over mankind. Towns are destroyed, mountains were lost and islands sink (Apc. XVI, 17–21; cf. Schneider et al., 1991). Reproduced with permission from a copy of the state and university library of Göttingen (signature 4° Th bib 1060/31 Rara).



Fig. 3. Woodcut from the book "Ars moriendi ex variis Scripturarum sententiis collecta cum fig." printed in Leipzig by Konrad Kachelofen around 1497/1498. The book is compiled from several sources and contains 14 full-page woodcuts coloured by hand. The text and the woodcuts are based on an earlier block book edition. It intends to teach a method of overcoming the temptations of life and of putting to flight the devils that recommended them. In this woodcut several devils surround the bed, and three get ready to lend a crown to the dying man as a symbol for false fame. In the background are God father, Christ and the community of the holy ones to save the soul of the man portrayed as a naked child (cf. Schneider et al., 1991). Reproduced with permission from a copy of the state and university library of Göttingen (signature 8° Th Mor 204/65 Inc Rara).

the figures of the previous years. Since the outbreak was obvious to the people they began to avoid public places and to leave the town if possible (Porter, 2000, p. 33f). In October 1665, plague fatalities began to decline and reached a low level in January of the following year. The annual bill for 1665 lists a number of 97,306 deaths in total and 68,596 deaths caused by the plague. Due to imperfections and movements of population it can be estimated that in London and adjacent parishes 70,000 to 100,000 persons died of plague which equals 15 % to 20 % of the population before the outbreak (Porter, 2000,



Fig. 4. Woodcut depicting "the dance of death" from the Latin edition of the Nuremberg Chronicle of 1493 by Hartmann Schedel illustrated by Michael Wolgemut and Wilhelm Pleydenwurff (Liber chronicarum. Nuremberg, Anton Koberger, 12.VII.1493). The dead rose from their graves and organize a wild, exuberant dance accompanied by the flute play of the skeleton shown in the left part of the woodcut. Reproduced with permission from a copy of the state and university library of Göttingen (signature 2° H Un II, 53/Inc).

p. 33f). The epidemic also spread to the provinces including smaller towns such as Colchester with roughly half of the 11,000 inhabitants dying of plague until September of the following year. Other badly affected towns were, for example, Cambridge, Norwich, Harwich, and Southampton. Some other towns only suffered from a few cases such as Bristol which had acted promptly to prevent anyone from London entering the city (Porter, 2000, p. 79f). The severe impact of the plague epidemic was also reflected in sharp falls in production and trade worsened by a great fire in London and the war with the Dutch (Porter, 2000, p. 114f). The outbreak and its impact on the people are well documented, for example, in the famous diary of Samuel Pepys (1633–1703), the secretary to the admiralty in the reigns of Charles II. and James II, first published in 1825 in selections (Pepys, 1971–1983 and 1980; Porter, 2000, p. 146f). In 1722 Daniel Defoe

(1660(?)–1731) published an imaginative reconstruction of the London outbreak named “A journal of the plague year” (Porter, 2000, p. 163f; Defoe, 1990). In continental Europe three major plague corridors along which plague epidemics moved in the 16th to early 18th century can be identified. The first route linked the Low Countries with the Rhineland, the second ran parallel to the rivers Weser and Elbe linking north-western Germany to Bohemia. The third important corridor was along the coastal region of the Baltic Sea and the North Sea. Since the middle of the 17th century generally there can be seen a reduction in plague activity in this area (Eckert, 2000).

Following the invention of printing with western types by Gutenberg in the middle of the 15th century many books were printed concerned with the plague. For example there is a monograph on the plague written in German by the famous physician Hieronymus Brunschwig (ca 1450–ca 1512) issued in the year 1500 (Figure 5). The book contains on 80 pages a description of plague symptoms, on how to distinguish between affected and unaffected persons, how to treat “bubones carbunculus” and the disease itself and what preventive measures such as medication and correct food can be used. Of course, at that time there was no effective treatment and plague was not recognized as an infective disease in the modern view, although some hygienic measures like quarantine were frequently used. The books offer several recipes for prophylactic medication which are called “medication to strengthen heart and nature”. These medicines contained herbal plants and sometimes mineral substances such as “Tormentillen wurtzeln”, “Tormentillen wasser” (roots and extract probably of *Potentilla erecta*), and “Bibinelle wurzel” (roots of *Pimpinella spec.*) among many others. The section of how to treat and care for people with plague is much shorter but some recommendations are given, too (Brunschwig, 1500; Sudhoff, 1908).

In the 16th and the 17th century and even well into the 18th century numerous books and tracts on the plague and other “fevers” were published but only a few have contributed significantly to medical progress. The first complete theory of infection had been developed by Girolamo Fracastoro (1478–1553) and it was published in the year 1546. He proposed a theory of infective agents of minute size, called “seminaria contagionis”. In his theory the semina caused a spoiling of the substance and were transferred by minute particles. He did not regard the semina as organisms but as particles with material and spiritual properties. In contrast to poisons the semina should be able to generate in affected

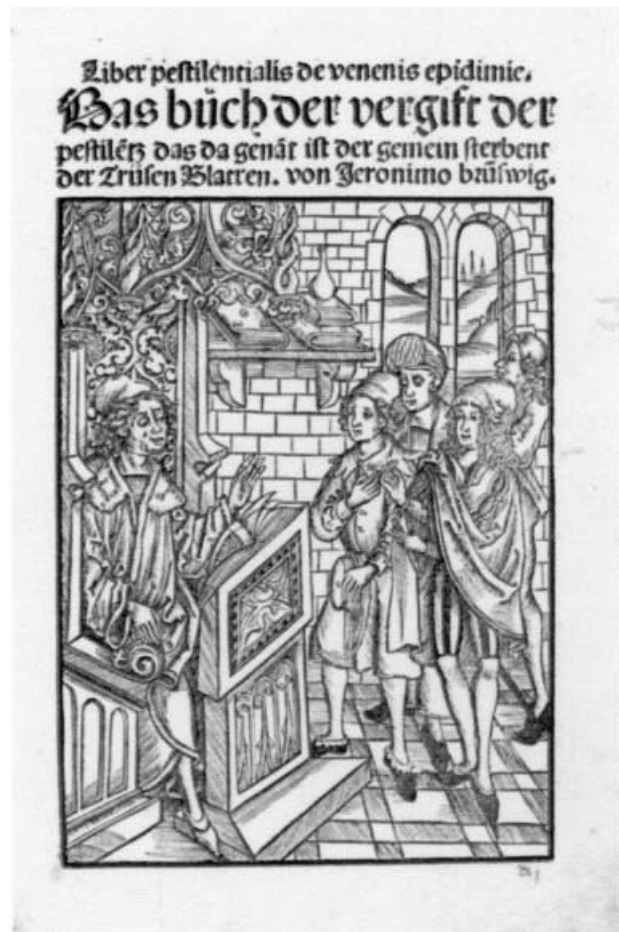


Fig. 5. First page of the German book on the plague “Liber pestilentialis de venenis epidimie: das buch der vergift der pestilenz, das da genant ist der gemein sterbens der Trüsen Blatren.” written by Hieronymus Brunschwig and printed in Strasbourg in the year 1500. Reproduced with permission from a copy of the state and university library of Göttingen (signature 4° Med Pract 2310/53 Inc).

persons (Fracastoro, 1546 and 1910; Leven, 1997, 36f). Although his semina look similar to our concept of microorganisms they can not be regarded as the same (Hirst, 1953, p. 47f; Leven, 1997, p. 36f). In the year 1658, Athanasius Kircher (1602–1680) made the first explicit claim to an observation of a microorganism causing plague in blood of febrile patients given in his book “Scrutinium physico-medicum contagiosae luis, quae pestis dicitur.” (Figure 6). He added that these corpuscles were lifeless at first and they were then changed into little invisible worms by heat from the contaminated air. It has to be taken into account that Kircher still believed in spontaneous generation (Kircher, 1658; Hirst, 1953, p. 79f; Leven, 1997, p. 65f). Due to the resolution of the used microscope he was not able to



Fig. 6. Title page of the first edition of the book "Scrutinium physico-medicum contagiosae luis, quae pestis dicitur." by Athanasius Kircher printed in Rome in the year 1658. Reproduced with permission from a copy of the state and university library of Göttingen (signature 8° Med Pract 2348/30).

detect bacteria and he possibly had observed clotted blood cells (Hirst, 1953, p. 79f). With the development of efficient microscopes the Dutch Antoni van Leeuwenhoek (1632–1723) was the first to undoubtedly discover living bacteria in the year 1674 beside of his many other discoveries in the microcosm. He published his various descriptions in a long series of letters to the Royal Society of London (van Leeuwenhoek, 1686–1702; cf. Hirst, 1953, p. 79; Leven, 1997, p. 68f). About one hundred years later Lazzaro Spallanzani (1729–1799) was able to demonstrate that infusoria do not generate spontaneously (Spallanzani, 1776; Leven, 1997, p. 69). Again one hundred years later Louis Pasteur (1822–1895) proved that bacteria do not generate spontaneously by demonstrating that contamination of beer is caused by microorganisms found in the air (Pasteur, 1876; Leven, 1997, p. 96f) and he was also able to treat a bacterial wine disease by heating (Pasteur, 1866). After the discovery of *Bacillus anthracis* as the causative agent of anthrax by

Robert Koch (1843–1910) in the year 1876 and many other pathogens in the following years the widespread theory of a miasmatic cause of disease was replaced by the foundation of a scientific bacteriology (Eckart, 1994, p. 228ff).

The third pandemic and discovery of the causative agent

The third pandemic probably originated in the Chinese province of Yunnan around 1855 with local outbreaks and it was spread to the southern coast of China especially by heavy troop traffic in the following years. By reaching Hong Kong and Canton in 1894 and causing great epidemics this marked the beginning of the third plague pandemic. The disease was quickly disseminated all over the world affecting all inhabited continents (Hirst, 1953, p. 101f; Kupferschmidt, 1993, p. 14f). The next countries hit were Japan, Formosa (today Taiwan) and the border region of today's Iran and Pakistan. Bombay was affected in the year 1896 and the disease quickly spread to many parts of India from that focus. Other imported epidemics were seen in South America, South Africa and western North America (Kupferschmidt, 1993, p. 14f). In India alone, which had been severely affected, a total of 12.5 million Indians are estimated to have died of plague between 1898 and 1918 (Perry and Fetherston, 1997).

Discovery of the plague bacteria and the role of fleas and rats

When the plague epidemic reached Hong Kong in 1894 the Japanese government dispatched a commission including the bacteriologist Shibasaburo Kitasato (1856–1931). About the same time Alexandre Yersin (1863–1943) was dispatched by the French colonial minister on a similar mission. Both arrived in Hong Kong in June 1894, with the Japanese commission several days earlier. Both discovered almost immediately a new kind of bacterium in specimens of plague patients and were able to culture it. Both also found the same bacteria in organs of dead rats from the plague area (Hirst, 1953, p. 106f; Kupferschmidt, 1993, p. 21f). Possibly Kitasato was the first to describe the new microorganism (a few days ahead) and a preliminary note appeared in *The Lancet* of 25th August 1894 (Kitasato, 1894). On the other hand, the description of Yersin is more accurate with all striking characteristics well emphasized (Yersin, 1894; Butler,

1983, p. 9f; Gross, 1995; Solomon, 1995 and 1997) and there can be no doubt that his organism was *Yersinia pestis* (Hirst, 1953, p. 106f; Kupferschmidt, 1993, p. 21f). In contrast to Kitasato Yersin correctly described the bacterium as gram-negative. Kitasato incorrectly described the nonmotile bacterium as slightly motile whereas Yersin did not mention this point at all. Therefore there can be doubts whether Kitasato has correctly identified *Y. pestis*. But he may also have suffered from technical insufficiencies for example in his staining methods (Hirst, 1953, p. 106f; Kupferschmidt, 1993, p. 21f). Following the first reports there was a series of confusing statements and self-contradictions by Kitasato and his colleagues that tended to discredit his claim to have been the co-discoverer of the plague bacillus (Butler, 1983, p. 9f). There are hints that some of his samples were contaminated with *Streptococcus pneumoniae* producing these inconsistent results (Butler, 1983, p. 9f; Solomon, 1997). In the following 80 years there had been a lengthy dispute on whom the first description should be ascribed (Butler, 1983, p. 9f; Kupferschmidt, 1993, p. 21f; Solomon, 1995 and 1997). Figure 7 depicts the original plate of Yersin's article with different microscopic views published in the *Annales de l'Institut Pasteur*. The microorganism causing plague has undergone several nomenclature changes: *Bacterium pestis* until 1900, *Bacillus pestis* until 1923, *Pasteurella pestis* (after Yersin's mentor), and, finally, *Yersinia pestis* since 1970 (Perry and Fetherston, 1997; Butler, 1983, p. 9f). These nomenclature changes were due to changing taxonomical classifications (Bercovier and Mollaret, 1984; Williams, 1983; Butler, 1983, p. 9f).

In the last decade of the 19th century several researchers were convinced of an association between the plague of rats and human beings although the detailed way of transmission was not known. Epidemiological details of plague outbreaks gave clear hints to that assumption (Kupferschmidt, 1993, p. 55f). A proposal that fleas may play a role in the transmission of plague among other ways of transmission was published in the year 1897 by Masanori Ogata based on his researches into the spread of plague in Taiwan in 1896. In an experiment he was able to show that an emulsion of internal organs of dead fleas from plague-infected rats injected subcutaneously was able to infect mice (Ogata, 1897; Hirst, 1953, p. 161; Kupferschmidt, 1993, p. 65). After research on the Indian epidemic Paul-Louis Simond (1858–1947) proposed the central role of the flea in plague transmission in the year 1898, although he was not able to give an indubitable experimental evidence of this theory. He

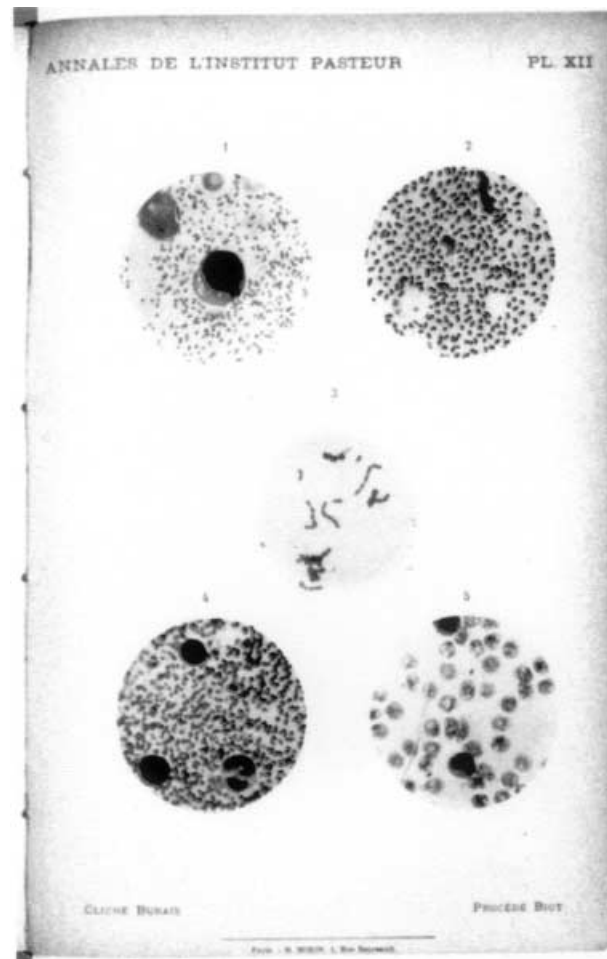


Fig. 7. Original plate from the article in which Yersin described his discovery of the plague bacterium issued in the *Annales de l'Institut Pasteur* 1894. The photos depict microscopic images of different plague-related material: Photo 1 – material from a bubo of a plague-infected Chinese; photo 2 – material of a lymph node from a rat that died of plague; photo 3 – pure culture of plague bacteria in bouillon; photo 4 – lymph node of a mouse inoculated with a culture; photo 5 – blood collected from a man who died of plague, collected 15 minutes after his death. Two bacteria are in the visual field. Reproduced with permission from a copy of the state and university library of Göttingen (signature 8° Med Path 120/75).

had deduced this theory mostly by explaining epidemiological details of plague outbreaks (Simmond, 1898; Gross, 1995; Hirst, 1953, p. 152f; Kupferschmidt, 1993, p. 66f). The most important evidence of Simmond's theory was given by J. C. Gauthier and A. Raybaud who could show that plague can be transmitted between two rats without direct body contact by fleas. The rats were placed separated in mesh cages that were permissible by fleas. They used two different flea species in this experiment in the year 1902 in Marseille (Gauthier and Raybaud 1903; Hirst, 1953, p. 162; Kupfer-

schmidt, 1993, p. 72f). A previous but less elaborated experiment with two rats and two mice and cat fleas by Simmond had only given two positive and two negative results (Hirst, 1953, p. 152f). The specific transmission mode of fleas was discovered by Charles James Martin (1866–1955) and Arthur William Bacot (1866–1922) while studying suckling fleas. They found that some of the fleas had proventriculi that were obstructed with a solid culture of plague bacteria (Bacot and Martin, 1914). These fleas turned out to be the most efficient vector of the infection especially when the obstruction was partially autolysed. The importance of the blocking for transmission and the anatomical preconditions for it also explained the varying importance of different species of ectoparasites in transmitting plague (Kupferschmidt, 1993, p. 80f; Hirst, 1953, p. 184f).

An explanation for the endemic occurrence of sporadic cases and outbreaks of the plague in some areas was discovered by Ricardo Jorge. In the year 1927 he found wild living rodents to be the infection reservoir of the endemic plague (Jorge, 1927; Kupferschmidt, 1993, p. 87ff). This type is also called sylvatic plague and is extant especially in Russia, South Africa and North and South America.

Prophylaxis

The first immunisation against the plague bacillus with an inactivated vaccine was developed by Alexandre Yersin together with Albert Calmette (1863–1933) and Amédée Borrel (1867–1936) by treating virulent bacteria with heat in the year 1895. They showed its efficacy in tests with rabbits (Yersin et al., 1895; Kupferschmidt, 1993, p. 121f). The most widely used plague immunisation of humans of that time had been developed by Waldemar Modceai Wolff Haffkine (1860–1930) in the year 1896. It was produced by culturing the bacteria in nutrient fluid together with clarified butter producing an opaque milky emulsion after shaking which is then inactivated by employing a temperature of 70 °C. Haffkine demonstrated the efficacy of his vaccine during an outbreak in Bombay, India (Haffkine, 1897; Kupferschmidt, 1993, p. 121f). The first immunisation with an attenuated plague strain was developed by Calmette and Borrel in rabbits and guinea-pigs (Yersin, 1897; Kupferschmidt, 1993, p. 121f).

Insecticides were first introduced in 1945 to kill fleas in an outbreak of plague in Tumbes (Peru). The outbreak was stopped successfully by using DDT as insecticides (Macchiavello, 1946; Kupferschmidt, 1993, p. 130f).

Therapy

Therapeutic approaches to cure plague infected patients were again made by Yersin, Calmette and Borrel by using serum of vaccinated rabbits to cure infected animals (Yersin et al., 1895; Kupferschmidt, 1993, p. 151f). In the year 1896 Yersin was able to cure several patients in Asia with a horse serum. Experiences of other researchers with plague serum were less successful (Kupferschmidt, 1993, p. 151f).

Antibiotics in the treatment of plague patients were first introduced in the year 1938. The sulphonamide Prontosil (active metabolite sulfanilamide) had successfully been used by John A. Carman. Lethality was lowered by the antibiotic from 100 % to 50 % (Carman, 1938; Kupferschmidt, 1993, p. 154f). Following the isolation of streptomycin in the year 1943 it was successfully applied to cure plague in mice by J. W. Hornibrook (Hornibrook, 1946). It turned out to be a highly efficient antibiotic and it seems to have been used first for treatment of human plague cases in December 1946 (Pollitzer, 1954). A few years later tetracyclines were introduced as therapeutics in human bubonic plague and pneumonic plague (Ramachandran, 1952; McCrumb, 1953; Kupferschmidt, 1993, p. 154f; Pollitzer, 1954). A detailed description of therapeutic approaches until the 1950s is given by Pollitzer (1954) and Kupferschmidt (1993, p. 151f).

Yersinia pestis as a biological weapon

There are reports of several attempts to develop and in some cases also to use a biological weapon containing *Y. pestis* in the last millennium. The first known use of plague as a weapon is reported from a Tatar attack on the Genoese controlled seaport town of Caffa (today Feodosiya, Ukraine) in the year 1346. In this battle victims of plague were catapulted into the town by the plague-weakened aggressors followed by an epidemic in the Genoese forces (Eitzen and Takafuji, 1997). In 1710 Russian troops battling Swedish forces in Reval resorted to throwing plague victims over the city walls, too.

From the beginning of the 20th century several countries probably conducted defensive or in some cases also offensive research on plague as biological weapon. For example, it is known that Japan had been conducting experiments on biological warfare in occupied Manchuria from approximately 1932 until the end of World War II in their Imperial Units 731 and 100. At least 3,000 prisoners of war were used for experiments with plague and several other agents and toxins. In October 1940 a Japanese plane

is supposed to have dropped plague contaminated rice and fleas over the city of Chuhsien in China which was soon followed by an outbreak of bubonic plague. Several other mysterious flights of Japanese aircraft over at least 11 Chinese cities included the dropping of other materials suspected of being contaminated took place through August 1942 (Eitzen and Takafuji, 1997; Inglesby et al., 2000; McGovern and Friedlander, 1997).

Recent research on plague

Since the middle of the 20th century many biochemical, physiological and genetic details of *Y. pestis* and the factors that determine its virulence have been revealed. In the year 2001 the complete genome sequence of *Y. pestis* comprising 4.65 million base pairs and three plasmids has been published by a working group from the United Kingdom (Parkhill et al. 2001).

When comparing the chromosomal DNAs from wild-type *Y. pestis* and *Y. pseudotuberculosis* a very high degree of relatedness can be found. The chromosomal DNA of *Y. enterocolitica* is not that closely related. Phylogenetically three biovars of *Y. pestis* can be distinguished: Antiqua, Medievalis and Orientalis, each associated with one pandemic wave (Achtman et al., 1999; Hinnebusch 1997).

Acknowledgements. The authors want to thank the staff of the department of manuscripts and rare prints of the university library of Göttingen for their valuable support, the university library for the permission to reproduce the photos and Dr. Udo Zietz and Patricia Zietz for reviewing the manuscript.

References

- Aberth, J.: From the brink of the apocalypse: confronting famine, war, plague, and death in the later Middle Ages. New York, Routledge, 2001.
- Achtman, M., Zurth, K., Morelli, G., Torrea, G., Guiyoule, A., Carniel, E. *Yersinia pestis*, the cause of plague, is a recently emerged clone of *Yersinia pseudotuberculosis*. Proc. Nat. Acc. Sci. 96, 14043–14048 (1999).
- Anonymous: *Ars moriendi ex variis Scripturarum sententiis collecta cum fig.* Leipzig, Konrad Kachelofen, around 1497/1498.
- Bacot, A. W., Martin, C. J.: Reports on plague investigations in India. LXVII. Observations on the mechanism of the transmission of plague by fleas. J. Hyg. 13 (Plague Suppl. 3), 423–439 (1914).
- Bean, J. M. W.: The Black Death: the crisis and its social and economic consequences. In: The black death: the impact of the fourteenth-century plague; papers of the Eleventh Annual Conference of the Center for Medieval & Early Renaissance Studies (ed. by D. Williman). Binghamton, NY: Center for Medieval & Early Renaissance Studies, 1982, pp. 23–38.
- Bercovier, H.; Mollaret, H. H.: Genus XVI. *Yersinia* Van Longhem 1944. In: Bergey's manual of systematic bacteriology. (Krieg, N. R.; Holt, J. G. edd.). Baltimore, Williams & Wilkins, 1984, pp. 498–506.
- Bergdolt, K.: *Der Schwarze Tod. Die Große Pest und das Ende des Mittelalters.* 4. Aufl. München, C. H. Beck, 2000.
- Brunschwig H.: *Liber pestilentialis de venenis epidimie: das buch der vergift der pestilentz, das da genannt ist der gemein sterbens der Trüsen Blatern.* Strasbourg, Grüninger, 18 VIII 1500.
- Butler, T.: *Plague and other Yersinia infections.* Plenum Press, New York, 1983.
- Carman, J. A.: *Prontosil in the treatment of oriental plague.* East Afr. Med. J. 14, 362–366 (1938).
- Defoe, D.: *A journal of the plague year: being observations or memorials of the most remarkable occurrences, as well publick as private, which happened in London during the last great visitation in 1665.* Edited by Louis Landa. With a new introduction by David Roberts. Oxford, Oxford Univ. Press, 1990.
- Eckart W. *Geschichte der Medizin.* 2nd edition. Berlin, Springer, 1994.
- Eckert, E. A.: *The Retreat of Plague from Central Europe, 1640–1720: A Geomedical Approach.* Bulletin of the History of Medicine 74, 1–28 (2000).
- Eitzen, E. M., Takafuji, E. T.: *Historical Overview of Biological Warfare.* Chapter 18. In: *Medical Aspects of Chemical and Biological Warfare.* Textbook of Military Medicine series. Part I, Warfare, weaponry, and the casualty. (Sidell FR, Takafuji ET, Franz DR edd.). Washington, 1997. pp. 415–423. Accessed June 2002 at <http://www.nbc-med.org/SiteContent/HomePage/WhatsNew/MedAspects/contents.html>
- Fouchier, R. A. M., Kuiken, T., Schutten, M., van Amerongen, G., van Doornum, G. J. J., van den Hoogen, B. G., Peiris, M., Lim, W., Stöhr, K., Osterhaus, A. D. M. E.: *Aetiology: Koch's postulates fulfilled for SARS virus.* Nature 423, 240 (2003).
- Fracastoro, G.: *De sympathia et antipathia rerum, liber primus de contagione et contagiosis morbis et eorum curatione libri III.* Venice, heirs of Lucantonio Giunta, 1546.
- Fracastoro, G.: (German edition of “De contagione et contagiosis morbis”). *Drei Bücher von den Kontagien, den Kontagiösen Krankheiten und deren Behandlung* 1546. Übers. und eingel. von Victor Fossel. Leipzig, Barth, 1910.
- Gauthier, J. C., Raybaud, A.: *Sur le rôle des parasites du rat dans la transmission de la peste.* Rev. d'hyg. 25, 426–438 (1903).
- Gross, L.: *How the plague bacillus and its transmission through fleas were discovered: reminiscences from my years at the Pasteur Institute in Paris.* Proc. Natl. Acad. Sci. USA 92, 7609–7611 (1995).

- Haeser, H.: Lehrbuch der Geschichte der Medicin und der epidemischen Krankheiten. Band 3. Geschichte der epidemischen Krankheiten. Jena, G. Fischer, 1882.
- Haffkine, W. M.: Remarks on the plague prophylactic fluid. *Brit. Med. J.* (I), 1461 (1897).
- Hinnebusch, B. J.: Bubonic plague: a molecular genetic case history of the emergence of an infectious disease. *J. Mol. Med.* 75, 645–652 (1997).
- Hirst, L. F.: The conquest of plague. A study of the evolution of epidemiology. Oxford, Clarendon Press, 1953.
- Hornibrook, J. W.: Streptomycin in experimental plague. *Publ. Health Rep.* 61, 535–538 (1946).
- Inglesby, T. V., Dennis, D. T., Henderson, D. A., Bartlett, J. G., Ascher, M. S., Eitzen, E., Fine, A. D., Friedlander, A. M., Hauer, J., Koerner, J. F., Layton, M., McDade, J., Osterholm, M. T., O'Toole, T., Parker, G., Perl, T. M., Russell, P. K., Schoch-Spana, M., Tonat, K.: Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* 283, 2281–2290 (2000).
- Johannes Apostolus (St. John): *Historia St. Johannis Evangelistae ejusque visiones Apocalypticae*. Block book, edition Schreiber IV, probably printed in Germany before 1467.
- Knight, J.: Researchers get to grips with cause of pneumonia epidemic. *Nature* 422, 547–548 (2003).
- Kircher, A.: *Scrutinium physico-medicum contagiosae luis, quae pestis dicitur. Quo origo, causae, signa, prognostica pestis, ... unà cum appropriatis remedium antidotis nova doctrina in lucem eruuntur*. Rome, Mascardi, 1658.
- Kitasato, S.: The bacillus of bubonic plague. *Lancet* 2, 428–430 (1894).
- Kupferschmidt, H.: Die Epidemiologie der Pest. *Gesnerus* 43 (Suppl.), 1–222 (1993).
- Leeuwenhoek, A. van: *Ontleding en Ontdekkingen van levende Dierkens in de Teel – deelen, van verscheide Dieren, Vogelen en Visschen: van het Hout med der selver menigvuldige vaaten ; van Hair, Vlees en Vis ; Als mede van de grootemenigte der Dierkens in de Excrementen ... vervat in verscheide Brieven geschreven aan de Koniglijke Societeit in London*. Leyden, Boutesteyn, 1686–1702.
- Leven, K.-H.: Die Geschichte der Infektionskrankheiten von der Antike bis ins 20. Jahrhundert. Landsberg/Lech, ecomed, 1997.
- Macchiavello, A.: Plague control with DDT and “1080”. Results achieved in a plague epidemic at Tumbes, Peru, 1945. *Am. J. Publ. Health* 36, 842–854 (1946).
- McCrum, F. R., Mercier, S., Robic, J., Bouillat, M., Smadel, J. E., Woodward, T. E., Goodner, K.: Chloramphenicol and Terramycin in the treatment of pneumonic plague. *Am. J. Med.* 14, 284–293 (1953).
- McGovern, T. W., Friedlander, A. M.: Plague. Chapter 23. In: *Medical Aspects of Chemical and Biological Warfare*. Textbook of Military Medicine series. Part I, Warfare, weaponry, and the casualty. (Sidell, F. R., Takafuji, E. T., Franz, D. R. edd.). Washington, 1997. pp. 479–502. Accessed June 2002 at <http://www.nbc-med.org/SiteContent/HomePage/WhatsNew/MedAspects/contents.html>
- Ogata, M.: Ueber die Pestepidemie in Formosa. *Cbl. Bakt. (Abt. 1, Orig.)* 21, 769–777 (1897).
- Parkhill, J., Wren, B. W., Thomson, N. R., Titball, R. W., Holden, M. T., Prentice, M. B., Sebahia, M., James, K. D., Churcher, C., Mungall, K. L., Baker, S., Basham, D., Bentley, S. D., Brooks, K., Cerdeno-Tarraga, A. M., Chillingworth, T., Cronin, A., Davies, R. M., Davis, P., Dougan, G., Feltwell, T., Hamlin, N., Holroyd, S., Jagels, K., Karlyshev, A. V., Leather, S., Moule, S., Oyston, P. C., Quail, M., Rutherford, K., Simmonds, M., Skelton, J., Stevens, K., Whitehead, S., Barrell, B. G.: Genome sequence of *Yersinia pestis*, the causative agent of plague. *Nature* 413, 523–527 (2001).
- Pasteur, L.: *Études sur la bière, ses maladies, causes qui les provoquent, procédé pour la rendre inaltérable: avec une théorie nouvelle de la fermentation*. Paris, Gauthier-Villars, 1876.
- Pasteur, L.: *Etudes sur le vin, ses maladies, causes qui les provoquent, procédés nouveaux pour le conserver et pour le vieillir*. Paris, Imprimerie Imperiale, 1866.
- Pepys, S.: *The diary*. Comprising the years 1660 to 1669. Ed. Latham, R. C. etc. 11 volumes. Berkley, 1971–1983.
- Pepys, S.: *Das geheime Tagebuch*. Mit Wiedergaben von zeitgenöss. Kupfern. Hrsg. von Anselm Schlösser u. übertr. von Jutta Schlösser. Leipzig: Insel-Verl., 1980.
- Perry, R. D., Fetherston, J. D.: *Yersinia pestis* – etiologic agent of plague. *Clin. Microbiol. Rev.* 10, 35–66 (1997).
- Pollitzer, R.: *Plague*. Geneva, WHO, 1954, p. 453f.
- Polzer, J.: Aspects of the fourteenth-century iconography of death and the plague. In: *The black death: the impact of the fourteenth-century plague; papers of the Eleventh Annual Conference of the Center for Medieval & Early Renaissance Studies* (ed. by D. Williman). Binghamton, NY: Center for Medieval & Early Renaissance Studies, 1982, pp. 107–130.
- Porter, S.: *The Great Plague*. Stroud, Sutton, 2000.
- Ramachandran, K.: Treatment of plague with Aureomycin. *J. Indian Med. Assoc.* 21, 217–218 (1952).
- Raoult, D., Aboudharam, G., Crubezy, E., Larrouy, G., Ludes, B., Drancourt, M.: Molecular identification by “suicide PCR” of *Yersinia pestis* as the agent of medieval black death. *Proc. Natl. Acad. Sci. USA* 97, 12800–12803 (2000).
- Roedig, C.: *Alltagsleben in der Gotik*. In: *Nationen, Städte, Steppenvölker. Die Welt im späten Mittelalter*. Weltgeschichte Band 6 (Hrsg.: Pleticha, H.), pp. 224–249. Gütersloh, Bertelsmann, 1996.
- Schedel, H.: *Liber chronicarum: Registrum huius operis libri chronicarum cu(m) figuris et ymagi(ni)bus ab inicio mu(n)di*. Nuremberg, Anton Koberger, 12.VII.1493.
- Schneider, C., Mertens, S., Purpus, E.: *Blockbücher des Mittelalters. Bilderfolgen als Lektüre*. (Ed. by Gutenberg-Gesellschaft und Gutenberg-Museum Mainz). Mainz, Philipp v. Zabern, 1991.

- Simmond, P. L.: La propagation de la peste. *Ann. Inst. Pasteur* 12, 625–687 (1898).
- Solomon T.: Alexandre Yersin and the plague bacillus. *J Trop Med Hyg* 98:209–12 (1995).
- Solomon T.: Hong Kong, 1894: the role of James A Lowson in the controversial discovery of the plague bacillus. *Lancet* 350 (No. 9070): 59–62 (1997).
- Spallanzani, L.: *Opuscoli di Fisica animale e vegetabile / dell'Abate Lazzaro Spallanzani. Aggiuntevi aleune lettere relative ad essi opuscoli dal celebre Signor Bonnet di Ginevie, e da altri scritte all'Autore.* 2 volumes. Modena, Societa tipografica, 1776.
- Sticker, G.: *Abhandlungen aus der Seuchengeschichte und Seuchenlehre. Band I: Die Pest. Teil I. Die Geschichte der Pest.* Gießen, A. Töpelmann, 1908.
- Sudhoff, K.: *Deutsche medizinische Inkunabeln: bibliographisch-literarische Untersuchungen.* Leipzig, Barth, 1908.
- Williams, J. E.: Warning on a new potential for laboratory-acquired infections as a result of the new nomenclature for the plague bacillus. *Bull. World Health Organ.* 61; 545–548 (1983).
- World Health Organization (WHO): Global Surveillance for Severe Acute Respiratory Syndrome (SARS). *Weekly epidemiol. record* 78; 100–110 (2003).
- World Health Organization (WHO): *Plague Manual: Epidemiology, Distribution, Surveillance and Control.* WHO/CDS/CSR/EDC/99.2. 2002. Accessed in June 2002 at <http://www.who.int/emc-documents/plague/whocdscsre992c.html>
- World Health Organization (WHO): Department of Communicable Disease Surveillance and Response. Chapter 3. Plague In: *WHO Report on Global Surveillance of Epidemic-prone Infectious Diseases.* WHO/CDS/CSR/ISR/2000.1. Geneva, WHO, 2000. pp. 25–37. Accessed in September 2002 at <http://www.who.int/emc-documents/surveillance/docs/whocdscsr2001.html/plague/plague.htm>
- Yersin, A.: La peste bubonique à Hong Kong. *Ann. Inst. Pasteur* 8, 662–667 (1894).
- Yersin, A.: Sur la peste bubonique (sérothérapie). *Ann. Inst. Pasteur* 11, 81–93 (1897).
- Yersin, A., Calmette, A., Borrel, A.: La peste bubonique (deuxième note). *Ann. Inst. Pasteur* 9, 589–592 (1895).
- Zinn, K. G.: *Kanonen und Pest: über die Ursprünge der Neuzeit im 14. und 15. Jahrhundert.* Opladen, Westdt. Verl., 1989.