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Plague history: Yersin's discovery of the causative bacterium in 1894 enabled, in the subsequent century, scientific progress in understanding the disease and the development of treatments and vaccines

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Abstract

The causative bacterium of plague was described and cultured by Alexandre Yersin in Hong Kong in 1894, after which transmission of bacteria from rodents by flea bites was discovered by Jean-Paul Simond in 1898. Effective treatment with antiserum was initiated in 1896, but this therapy was supplanted by sulphonamides in the 1930s and by streptomycin starting in 1947. India suffered an estimated 6 million deaths in 1900–1909, and Vietnam, during its war in 1965–1975, accounted for approximately 80% of the world's cases; since then, African countries have dominated, with >90% of the world's cases in the 1990s and early 21st century. Serological diagnosis with fraction 1 antigen to detect anti-plague antibodies was developed in the 1950s. Vaccine development started in 1897 with killed whole bacterial cells, and this was followed by a live attenuated bacterial vaccine, leading to millions of persons receiving injections, but the benefits of these vaccines remain clouded by controversy. Plasmid-mediated virulence was established in 1981, and this was followed by specific DNA methods that have allowed detection of plague genes in skeletal specimens from European graves of the sixth to 17th centuries.

Keywords: Alexandre Yersin, epidemics, plague, plague history, Yersin
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Introduction

The modern history of plague began in 1894, when Alexandre Yersin isolated the causative bacterium in culture and identified it under the microscope. This event allowed laboratory confirmation for accurate diagnoses. There followed many advances in treatment and diagnosis, as well as scientific understanding of the disease, which will be reviewed here. Table 1 gives a guide to some of these historic milestones [1–31].

Discovery of *Yersinia pestis* as the cause of Plague: Yersin as the Underdog

Credit for discovering the bacterial cause of plague is accorded to the French physician Alexandre Yersin (1863–1943), for his bacteriological investigations in June 1894 in Hong Kong during a deadly epidemic [32]. However, credit was not given to Yersin initially, and nor in the ensuing years by everyone, because he had a rival in Shibasaburo Kitasato (1851–1935), a Japanese bacteriologist sent by his government to investigate the cause of plague. Rarely in the history of medicine were conditions more ripe for fruitful investigation of a disease that is now known to have abundant bacteria in both blood and swollen lymph nodes (buboes) that are cultivatable and stainable on microscope slides, as well as readily obtainable in autopsy specimens. Both scientists were qualified and had portable laboratory equipment and supplies with which to solve the mystery of plague's cause. Yersin had worked with Emile Roux in Louis Pasteur's laboratories in Paris to characterize diphtheria toxin, and Kitasato had worked in Robert Koch's laboratories in Berlin, where he discovered the bacterial cause of tetanus.

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TABLE 1. Modern milestones in the history of plague investigations

Year	Discovery	References
1894	Isolation in culture and microscopic description of causative bacteria	1,2
1898	Flea-borne transmission	3,4
1896	Usefulness of antiserum for therapy	5
1897	First vaccine consisting of heat-killed bacteria developed and tested	6
1900–1909	Six million deaths in India	7
1931	Live attenuated bacterial vaccine EV developed and tested	8,9
1937	Usefulness of sulphonamides for therapy	10,11
1939	Formalin-killed bacterial vaccine developed and tested	12
1940–1947	Large concentrations of blood bacteria correlated with mortality	13
1947	Usefulness of streptomycin for therapy	13,14
1954	Development of serological tests for diagnosis	15
1965–1975	Vietnam's ascendancy in incidence	16
1973	Usefulness of trimethoprim–sulphamethoxazole for therapy	17
1975	Measurement of blood endotoxin correlated with severity and large concentrations of blood bacteria	18
1980	Genetic relatedness of *Yersinia pestis* and *Yersinia pseudotuberculosis*	19
1981	Three virulence-associated plasmids in *Y. pestis*	20–22
1982-present	Africa's ascendancy in incidence	23
1985–1999	Usefulness of gentamicin for therapy	24
1995	Isolation of plasmid-mediated streptomycin-resistant *Y. pestis* from patients	25,26
2003	Usefulness of fluoroquinolones for therapy	27
2005–2011	DNA of *Y. pestis* found in human graves from the Justinian and medieval eras	28–31

Yersin was clearly the underdog. Kitasato arrived 3 days earlier than Yersin, and was accompanied by a team of six assistants, whereas Yersin had travelled alone from French Indochina, carrying in his baggage a microscope, sterilizer, and culture supplies [1]. Kitasato was more senior and famous, and obtained immediate access to autopsies of plague victims, whereas Yersin was denied such access for several days. Yersin was regarded as a small and shy man, spoke no English, and had an inherent disadvantage, perhaps, of being French in a British colony. Kitasato got a head start, observing bacteria in the blood and injecting animals with specimens before Yersin even arrived. The two rivals were introduced, but they exchanged little information in their common language of German. The story was related that, at a meeting of the two during an autopsy that Kitasato was conducting, Yersin was surprised to observe that Kitasato was examining blood rather than buboes [1]. Yersin relayed the suggestion via an intermediary that buboes should be examined too, with the result that Kitasato subsequently examined buboes. Both men found bacteria that they designated as the cause of the disease. Yersin correctly described his as Gram-negative, whereas Kitasato insisted that his organism was Gram-positive. Kitasato described his blood organism as diplococcal and his bubo organism as bacillary, causing confusion and suggesting to some that his cultures were contaminated by the pneumococcus. In the ensuing months and years, Kitasato asserted that his bacillus was different from that of Yersin [33].

Eventually, against the odds, Yersin took the prize of finding the cause of plague. His descriptions were accurate and consistent. Also, Yersin's reputation benefited from his links with colleagues in Paris. During his first autopsy in Hong Kong, he related his method of obtaining fluid from the bubo, seeing Gram-negative bacilli, injecting animals that he observed to die with bacteria in their tissues, and sealing a bubo specimen in a glass tube that was immediately mailed to Paris [2]. These specimens were received by Albert Calmette and Amedee Borrel, both destined to be famous for, respectively, a tuberculosis vaccine and the name of the cause of Lyme disease, who confirmed Yersin's findings and carried out research with the bacteria to produce a therapeutic antiserum. In 1895, the last year of Louis Pasteur's life, Yersin returned to Paris to collaborate with his associates in Pasteur's laboratories. Before the end of that year, he was back in Indochina, and in 1896 he went to Hong Kong again to treat plague victims with his new antiserum [1].

The name of the organism underwent several changes. It was *Bacterium pestis* until 1900, when it changed to *Bacillus pestis*. In 1923, it acquired a new designation as *Pasteurella pestis*, which it kept up to about 1970, when Yersin obtained posthumous honour through its final name, *Yersinia pestis* [32].

Role of James Lowson in the Discovery

A hundred years after the discovery of the plague bacillus, the daughter of James Lowson showed his diary to Yule [34], and Solomon [35] subsequently carried out historical research by obtaining further information from Lowson's granddaughter. Lowson was a Scottish physician sent by the British Colonial Medical Service to Hong Kong, where he served as acting Superintendent of the Civil Hospital, dealing with patient care, and as Port Medical Officer, dealing with quarantine needs. When plague broke out in Canton in May 1894, Lowson travelled there to witness fatal cases. When cases appeared in Hong Kong later in May, he advocated quarantine measures, established a hospital ship in the harbour for cases, and persuaded the Governor to initiate disinfection of houses in affected areas of the city. He was responsible for showing both Kitasato and Yersin the colony's facilities for patient care and diagnosis. He was preferentially hospitable to Kitasato's team, dining with them several times, and announcing to the *Lancet* by wire on 15 June, the same day on which Yersin arrived, that Kitasato had succeeded in finding the cause of plague. Although Lowson did not befriend Yersin, he spoke to him occasionally, recording in his diary on 22 June that the 'Frenchman' had found his bacillus. Lowson was aware of the rivalry between the two scientists, and also of the inaccurate descriptions by

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