WE CANNOT AFFORD TO IGNORE THE ANCIENT PANDEMIC ZOONOTIC SCOURGE OF MANKIND: PLAGUE

Rajeshwar Reddy Kasarla
Department of Microbiology
Universal College of Medical Sciences, Bhairahawa, Nepal

Plague, caused by *Yersinia pestis* is one of the greatest killer diseases known to mankind. Innumerable villages, towns, and cities used to be swept away by the fury of this scourge. Epidemics of plague were recorded in the Bhagavata Purana which urged house holders to flee when rat falls were noticed. Central Asia or Himalayas was thought to be the original home of plague, where epidemics and pandemics began.[1]

It is easy to forget plague in the 21st century, seeing it as a historical curiosity, as the disease has been slowed in the past century by improvement in rodent-proof housing, urban hygiene, and clothing that protects against flea bites. But plague remains a poorly understood threat that we cannot afford to ignore, because plague bacillus still causes several thousand human cases per year. Over the last 20 years, there have been 1,000 to 5,000 human cases of plague and 100 to 200 deaths reported to the WHO each year[1]. Over the years, there has been a major shift in cases from Asia to Africa. Climate change may increase the risk of plague outbreaks where plague is currently endemic and new plague areas might arise, and little is known about the dynamics of plague in its natural reservoirs and hence about changing risks for humans. Therefore, plague should be taken much more seriously by the International community than appears to be the case.[2]

Recently, three cases of plague have been diagnosed in China, sparking widespread fears about the spread of the disease. In early November, 2019 a Mongolian couple died from pneumonic plague after eating the raw kidney of a marmot, a local folk health remedy, from the Chinese Province of inner Mongolia. On November 16, 2019 a third case of bubonic plague was reported in a 55-year-old man from inner Mongolia, who killed and ate wild rabbit meat on 5 November, 2019. Rodent populations have risen in inner Mongolia after persistent droughts, worsened by climatic change. The area was hit by a rat plague in summer, a few months before this outbreak.[3]

The major pandemics of plague occurred at intervals of 600 years, each pandemic occurred at the end of a major historical epoch: Justinian Plague (541-544 AD) at the end of antiquity, Black Death (1347 AD) at the close of Middle Ages, and modern pandemic (1855 AD) at the beginning of current era.[2,4]

Black death claimed an estimated 60% of the entire population. Entire towns were wiped out, and there were not enough survivors remaining to bury the dead. Despite the vast devastation caused by this pandemic, however, massive labor shortages due to high mortality rates sped up the development of many economic, social, and technical modernizations. It has even been considered a factor in the emergence of the renaissance in the late 14th century. Thus, plague has a remarkable place in history and has had enormous effects on the development of modern civilization.[2,4]

During the last third pandemic (Modern plague), scientists identified the causative agent as a bacterium and determined that plague is spread by infectious flea bites. Rat-associated plague was soon brought under control in most urban areas, but the infection easily spread to local populations of ground squirrels and other small mammals in the Americas, Africa and Asia. These new species of carriers have allowed plague to become endemic in many rural areas, including the Western U.S.[4]

Plague is now commonly found in sub-Saharan Africa and Madagascar areas, which now account for over 95% of reported cases. The three most endemic countries are the Democratic Republic of the Congo, Madagascar and Peru.[5,6]

Table 1. Plague outbreaks in India[4,7,8]

1896 - 1918	Hong Kong pandemic entered India; about ten millions of people were killed
1918 – 1967	Plague gradually declined, occasional cases continued to be reported from endemic foci
1967 – 1994	No plague cases were reported
1994 (Surat epidemic)	It started as bubonic plague from Beed-Latur belt in Maharashtra. But, it soon became pneumonic plague and spread to Surat and adjoining regions of Gujarat. More than 6000 suspected plague cases with 60 deaths were reported over a period of two months (August – September 1994)
2002 (Shimla outbreak)	A short outbreak occurred at Rohru, near Shimla, Himachal Pradesh. Four deaths were reported
2004 (Uttarakashi outbreak)	Localized outbreak of bubonic plague (8 cases and 3 deaths) was reported from Dangud village of Uttarakashi district, Uttaranchal

Four potential endemic foci of plague are known to exist in India. 1) The area near Kolar at the junction of Tamil Nadu, Andhra Pradesh and Karnataka states, 2) Beed-Latur belt in Maharashtra, 3) Rhoru in Himachal Pradesh, and 4) Dangud village in Uttaranchal.

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During the year 1960-1962 AD, about 150 cases were recorded in Rupandehi and Mahotari districts of Nepal. It was recognized that 26 cases occurred in the village of Nawra between 6 September and 5 November 1967, out of which 18 died. Since no evidence of a rodent epizootic was uncovered in the village itself, human-to-human spread of plague by infected ectoparasite vectors, presumably *Pulex irritans* (human flea), was thought to have occurred.[9]

Plague is a zoonotic disease, endemic in various rodents like rats, mice, ground squirrels, rabbits, prairie dogs, chipmunks, and voles etc. with humans as accidental hosts. The main reservoir hosts are wild rodents such as gerbils (*Tatera indica*), field mice and the bandicoot found in forests. The chief enzootic areas include India, South-East Asia (Especially Vietnam), Africa, and North and South America.[5,6] The vector is rat flea, commonest being *Xenopsylla cheopis* but other fleas like *Xenopsylla astia*, *Xenopsylla brasiliensis* (in South Africa and Brazil) and *Ceratophyllus fasciatus* may also transmit the infection.[10]

Table 2. Mode of transmission of human plague

• Bite of an infected rat flea (Most common)
• Direct contact with tissues of infected animal (rodents)
• By ingestion of rodent meat (raw/undercooked)
• Air-borne droplet inhalation (Man to man) from pneumonic plague cases
• Bite of an infected human flea (*Pulex irritans*)

In man, plague is a systemic, fulminant disease and occurs in three forms bubonic, pneumonic, and septicemic plague (Black death). The name Black Death (Pestilence in the air) is derived from the black hemorrhagic splotches that develop in the extremities in plague. Bubonic plague is the most common form. Pneumonic plague may occur during epidemics. Less common forms of plague include plague meningitis (typically a secondary focus resulting from hematogenous dissemination of the organisms), cutaneous plague results from handling, and pharyngitis from ingestion of contaminated animal tissue.[11]

Unless promptly treated, plague is fatal in 50% of bubonic cases, and nearly in 100% in pneumonic and septicemic cases. Streptomycin has been the choice of treatment for plague, in the past, given for 10 days. Gentamycin is superior to streptomycin and currently recommended for treatment. Alternative drugs, such as doxycycline and chloramphenicol are also effective. Beta lactams and macrolides are generally not recommended as the response is poor.[4] People with plague are very ill and may require additional treatment, including oxygen, respiratory support, and medications to maintain adequate blood pressure. Patients with pneumonic plague must be isolated while in treatment to avoid spreading the infection.

Plague cannot be eradicated, since it is widespread in wildlife rodent reservoirs. Plague is one of the internationally quarantinable diseases, and reporting of cases is mandatory.[12] General measures of prevention of plague include control of rodent/ rat population by rodenticides and eradication of rat fleas from the rats by the use of insecticides.[1,4] Chemoprophylaxis should be given to all contacts of pneumonic plague. Doxycycline (100 mg twice a day) or tetracycline (500 mg six hourly) is the drug of choice, given for seven days.[12]

Vaccination is recommended by WHO only for prevention of an anticipated outbreak and not for general use.[12] Formalin killed vaccine (Sokhey's modification of Haffkin's vaccine)[13] prepared at Haffkine Institute, Mumbai, is widely used for active immunization. It is given subcutaneously, two doses four weeks apart and a booster given after six months. The protection is short-lived, lasting for not more than six months. It is not protective against pneumonic and septicemic plague and has considerable side effects. Live attenuated vaccine is prepared from two avirulent strains of *Yersinia pestis*, Otten's Tjiwidej strain from Java, Indonesia, and Girard's EV76 strain from Madagascar.[14] These vaccines confer much greater protection in animals than killed vaccine, but because of significant side effects, they are not in use. Subunit recombinant F1 (rF1) vaccine is under trial in USA.[4,12]

Because of the highly contagious nature and high mortality rate if left untreated, *Yersinia pestis* has been used as a weapon of biological warfare for centuries. Historical examples include the catapulting of infected corpses over city walls and dropping infected fleas from airplanes, and aerosolizing the bacteria during the cold war.[4] The danger of using this organism by terrorists is great and raised concern as an important security threat. In the case of either a bioterrorism attack or just a natural outbreak, it may be necessary to avoid contact with infected people or just remain inside for a period of time until the infected people are no longer contagious.[4]

Plague remains a poorly understood reemerging threat that we cannot afford to ignore. It would be a mistake to overlook its threat to humanity, because of the disease's inherent communicability, rapid spread, rapid clinical course, and high mortality if left untreated. Hence, clinicians worldwide need to be aware and alert.

REFERENCES

1. Ananthanarayan & Paniker's Textbook of Microbiology. Universities Press, Hyderabad, India; 9th edition, page no 319-324.
2. Bertherat E. Plague around the world, 2010-2015. Weekly Epidemiological Record. 2016; 91: 89104.
3. Science alert Reuters. 18 Nov, 2019.
4. Bjorn P. Zietz, Hartmut Dunkelberg. The history of the plague and the research on the causative agent *Yersinia pestis*. Int J Hyg Environ Health. 2004; 207(2): 165-178.
5. James H. Jorgensen, Michael A. Pfaller, Carroll K, Funke G. Manual of Clinical Microbiology. ASM Press, Washington DC.11th Edition, Volume 2, page no 2213-2315.
6. WHO Report on Global Surveillance of Epidemic-prone Infectious Diseases. World Health Organization Department of Communicable Disease Surveillance and Response. WHO/ CDS /CSR/ISR/2000.1
7. Grant L. Campbell, James M. Hughes. Plague in India: A New Warning from an Old Nemesis. Annals of Internal Medicine. January 1995; 122(2): 151-153.
8. Apurba Shankar Sastry, Sandhya Bhat K. Essentials of Medical Microbiology, Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, 2016; 1st edition, page no 311-314.
9. LaForce FM, Acharya IL, Stott G, Brachman PS, Kaufman AF, Clapp RF, Shah NK. Clinical and epidemiological observations on an outbreak of plague in Nepal. Bull World Health organ. 1971; 45(6): 693-706.
10. Robert D. Perry, Jacqueline D. Fetherson. *Yersinia pestis*-etiologic agent of plague. Clinical Microbiology Reviews. Jan 1997; 10(1): 3566.
11. John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas and Bennett's principles and practice of Infectious diseases. Elsevier. 8th edition, page no 2607-2615.
12. Jae-Llane Ditchburn and Ryan Hodgkins. *Yersinia pestis*, a problem of the past and a re-emerging threat. Biosafety and Health. Science Direct, Elsevier. 2019.
13. Christian E. Demeure, Olivier Dussurget, Guillem Mas Fiol, Anne-Sophie Le Guern, Cyril Savin, Javier Pizarro-Cerdá. Yersinia pestis and plague: an updated view on evolution, virulence determinants, immune subversion, vaccination, and diagnostics. Genes & Immunity. 2019; 20: 357-370.
14. Rajeshwar Reddy K. Medical Microbiology. New Age International Publishers, New Delhi. 2009. 1st edition, page no.502-506,