World Health Organization

WHO EPI-WIN DIGEST

Plague in the 21st century: New evidence to control a re-emerging zoonotic disease

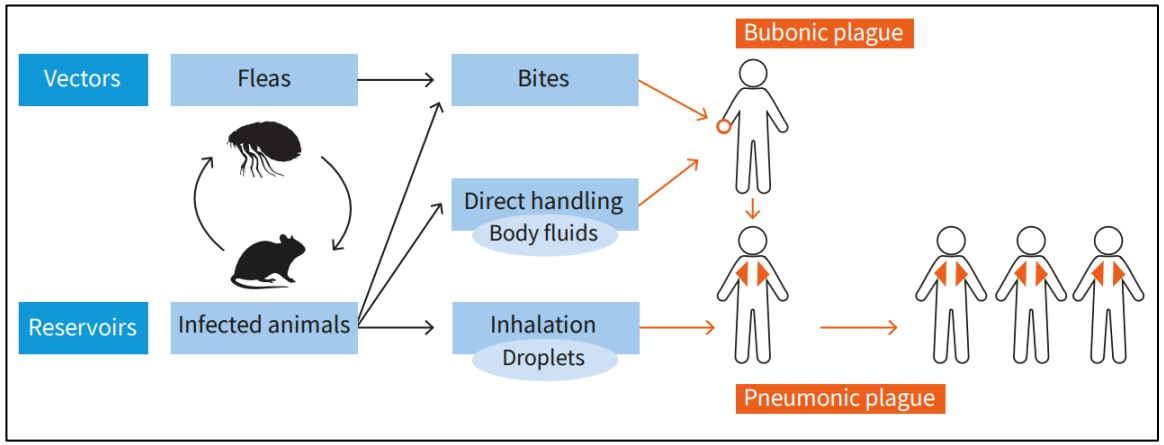
23 July 2025

World Health Organization

Plague: Cause and transmission

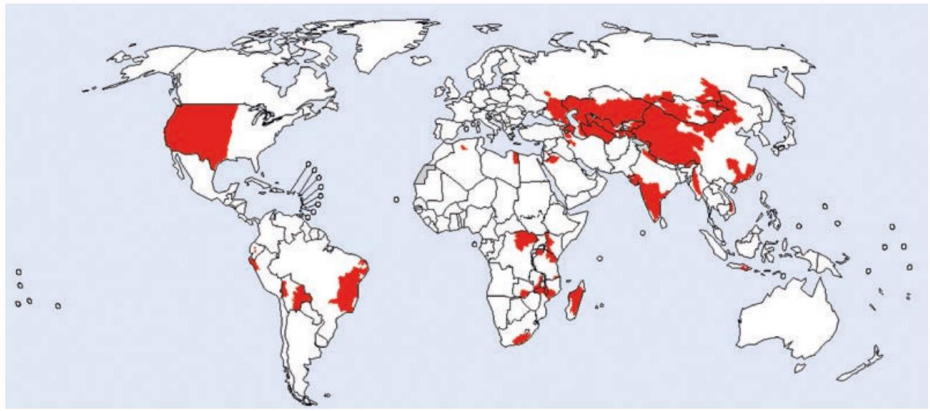
- Plague is caused by *Yersinia pestis*, a non-motile, capsulated, non-spore-forming, Gram-negative coccobacillus.
- It belongs to a group of bacilli with low resistance to environmental factors, meaning that sunlight, high temperatures, and desiccation quickly destroy the bacteria.
- Animal reservoirs: Wild rodents (e.g. squirrels, prairie dogs, wood rats) and commensal rodents or rats, which are more commonly involved in human transmission and usually develop the disease.
- Vectors: Fleas, *Xenopsylla*, particularly *X. cheopis*, are the most prevalent vectors for humans and commonly infest household rodents in many parts of the world.

Plague transmission:
- Flea-borne
- Direct contact
- Droplet



Plague: Epidemiology

- **Natural plague focus**: geographical areas characterized by the presence of *Y. pestis* along with a compatible animal reservoir (rodents) and vector (fleas) with potential transmission to humans.
- Natural plague foci are associated with **sporadic** disease in humans and can lead to **outbreaks** (e.g., large-scale epidemic in Madagascar in 2017)



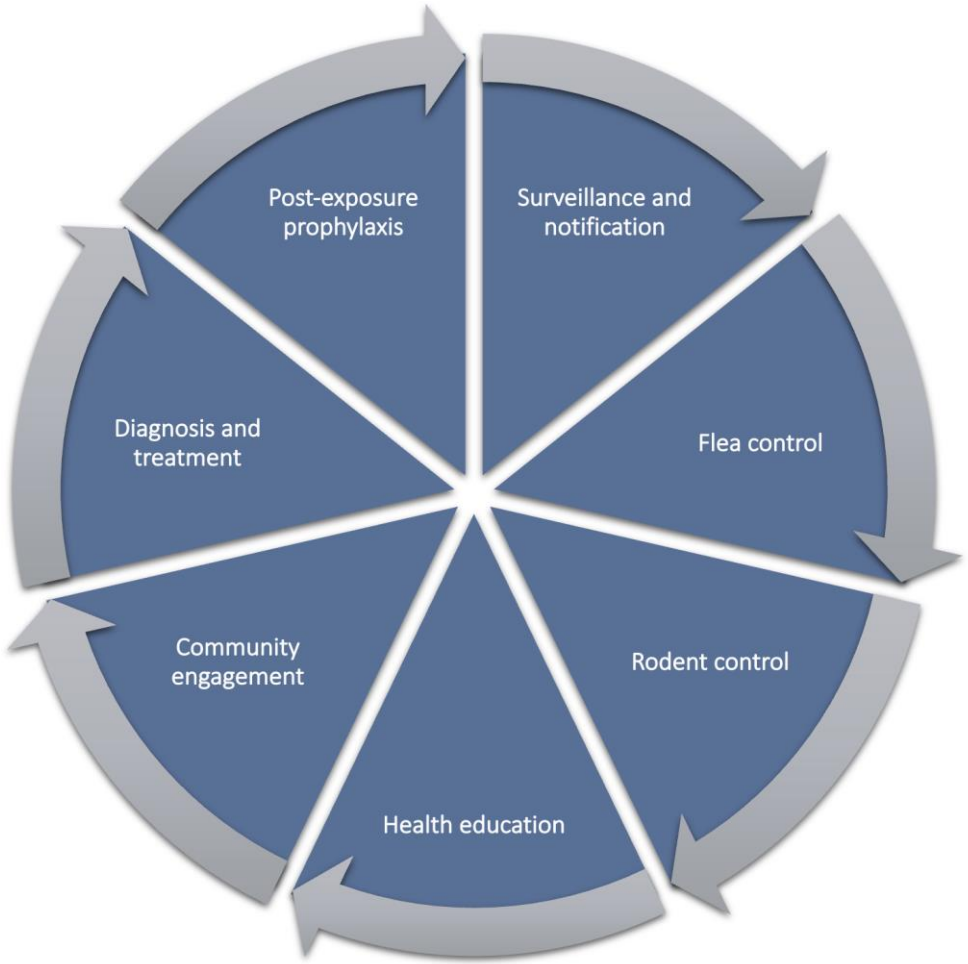
First administrative–level areas with potential natural plague foci, based on historical data and current information

- Incidence humans has remained relatively low since 1945, but the disease resurfaced in several countries during the 1990s and is currently classified as a **re-emerging disease**.
- Since 2000, more than 95% of cases have been reported from Africa – **DRC and Madagascar** are the most endemic countries.

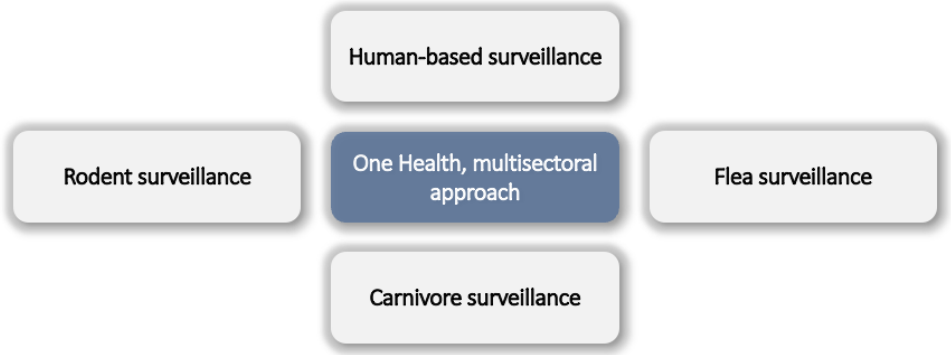
Plague: Prevention and control

Public Health Risk factors

- Unsanitary living conditions
- Lifestyle associated with animal handling
- Traditional death rituals
- Seasonality in tropical-subtropical areas
- Natural disasters Ecological changes



Plague: Surveillance



Plague cases should be notified only if the public health impact can be considered serious (e.g. pneumonic plague) **and** the event has **at least one** of the following characteristics:

1) Unusual or unexpected event;
2) Risk of international spread;
3) A significant need for international restrictions on travel or trade.

- International Health Regulations (2005): A plague event should be notified to WHO in accordance with the International Health Regulations.
- Close collaboration among all surveillance actors is crucial for fully understanding risks and vulnerabilities, enabling timely detection and implementing effective response efforts.
- Fleas, rodents, and other mammals implicated in the transmission cycle should be investigated to identify plague activity and determine whether epizootics are in progress or conditions indicate that an epizootic is likely to occur.

Surveillance in Humans and animals

Human-based surveillance

WHO standard case definitions	
Suspected case	Any individual with a clinical presentation suggestive of plague, associated with epidemiological context suggesting possible exposure to plague.
Probable case	Any suspected case with at least one of the following: • F1 antigen-positive detection test in relevant sample • Single positive anti-F1 serology test without evidence of previous *Y. pestis* infection or vaccination • Direct microscopy in a clinical sample positive for Gram-negative coccobacilli with bipolar staining (Wayson or Giemsa stain)
Confirmed case	Any suspected or probable case and at least one of the following: • Isolation of *Y. pestis* through culture and appropriate microbiological species-detection testing • Seroconversion or a 4-fold difference in anti-F1 antibody titre in paired serum samples drawn at least 2 weeks apart • Detection of *Y. pestis* DNA by species-specific PCR on either clinical sample or culture

Animal-based surveillance

Surveillance mechanism	Early warning signal of increased risk of human plague
Flea surveillance	Total flea index or specific flea index > 1
Rodent surveillance	Sudden decreases in rodent density Higher than normal numbers of dead rats (i.e. rat fall)
Carnivore surveillance	Increase in positive serum samples from canines
Carcass surveillance	Identification of *Y. pestis* in host carcasses

Community protection: Control measures and risk communication

Flea control measures should be undertaken in the presence of **any** of the following:

1) Reported rat fall attributable to plague;
2) Increase in the population of fleas or flea nuisance;
3) Specific flea index >1.

Rodent control measures may include any of the following:

- **Environmental sanitation** (removal of rodent habitat, rodent proofing);
- **Physical barriers** (rodent traps);
- **Chemical methods** (rodenticides, fumigants).

Health education messages

- Never handle a wild animal found dead.
- During a plague outbreak, do not carry out rodent control unless rodents have first been treated with insecticides to kill fleas.
- Protect yourself from flea bites by wearing clothing that covers the body, especially trousers and closed shoes, and by using insect repellents.
- Immediately report any suspicious death of a domestic animal or an unusually high number of dead rats (a “rat fall”) to local authorities.
- Do not kill, prepare, or consume a sick animal as it could be infected with plague.
- Seek medical attention promptly if you develop a fever and a bubo (a painful swelling of a lymph node).

Contact tracing and post-exposure prophylaxis (PEP)

At-risk individuals where PEP should be considered
Individuals who are likely to have been exposed to *Y. pestis*-infected fleas (e.g., members of the household of a patient with bubonic plague) within the previous 10 days.
Individuals who are likely to have been exposed to *Y. pestis*-infected mammals (e.g., directly or through contact with its body fluids or tissues) within the previous 10 days.
Individuals who are likely to have been exposed to *Y. pestis* (e.g., during a laboratory accident) within the previous 10 days.
Individuals who have come into **close contact** (<2 m) within the previous 10 days with a patient who has suspected, probable or confirmed **pneumonic plague**.

First-line antibiotic options are oral **ciprofloxacin**, **doxycycline** or **sulfamethoxazole/trimethoprim**.
Duration is usually 7 days.

Clinical manifestations

Bubonic plague
(80-95% of cases)

Septicemic plague
(10-20% of cases)

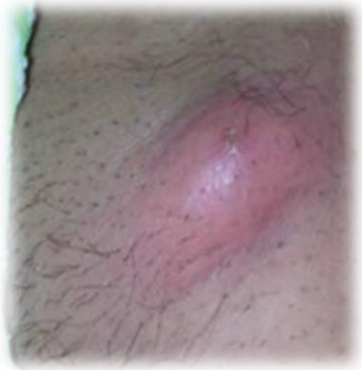
Primary syndrome
(at disease onset)

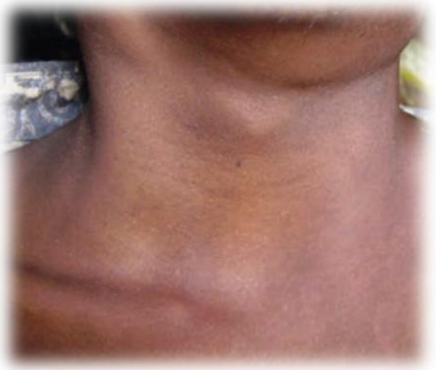
Pneumonic plague

Other (meningeal, pharyngeal plague)

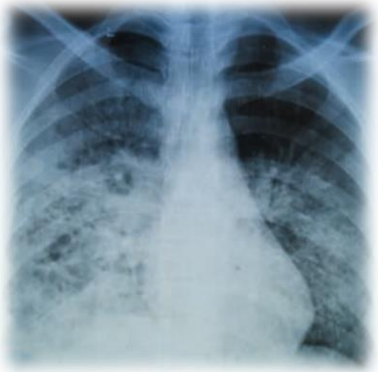
All forms of plague can evolve into **secondary septicemic, pneumonic or meningeal plague**.

Bubonic plague





Pulmonic plague



Management

Diagnostic tests:

- In areas where plague is known to occur, WHO strongly recommends using F1RDTs in people with suspected bubonic plague and suggests their use in individuals with suspected pneumonic plague as a tool to rapidly detect the disease and implement immediate public health control measures.
- During an outbreak, WHO recommends suggests using F1RDT in people with suspected bubonic and pneumonic plague to provide rapid diagnosis at the point of care.
- Due to the limited specificity, however, WHO also indicates that a positive result should be interpreted with caution and always confirmed with culture or PCR.

Antibiotic therapy

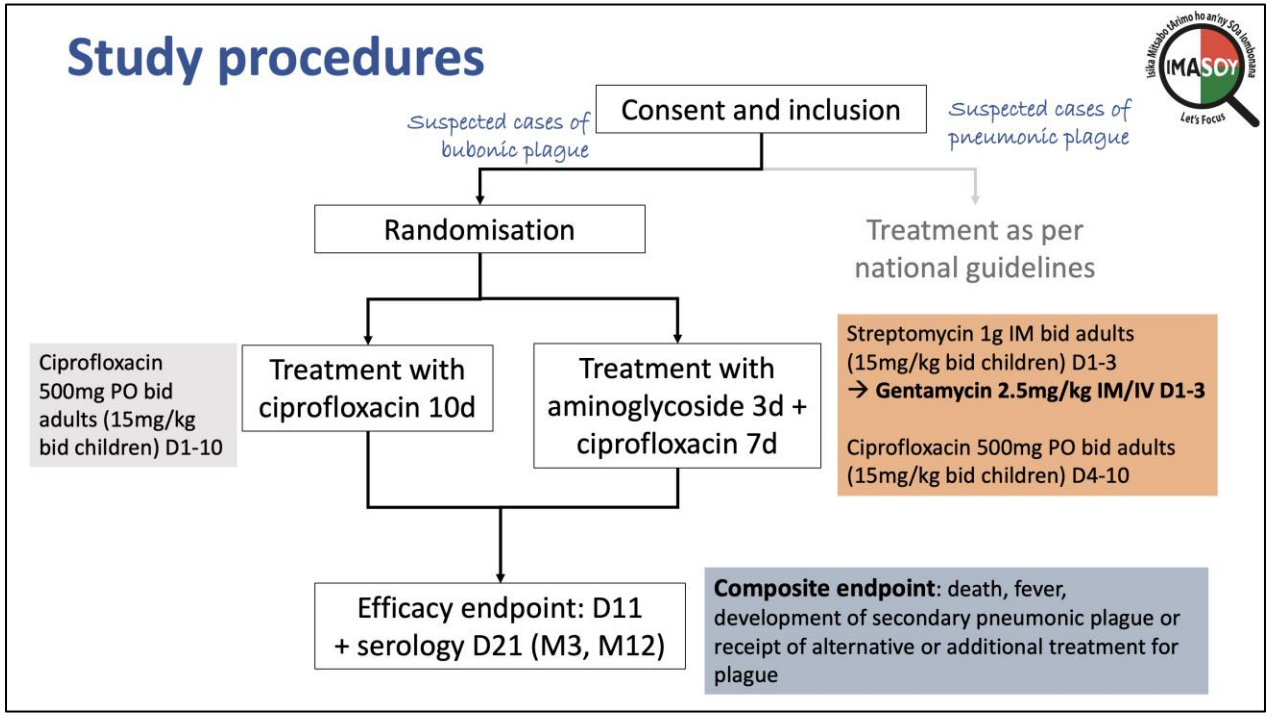
- Start antibiotic therapy for all suspected cases as soon as possible. Do not wait for bacteriological confirmation.
- Use antibiotic susceptibility testing results to tailor antibiotic treatment based on resistance patterns (if detected).
- Complete the treatment course for a total duration of 10-14 days (or longer depending on clinical improvement).

Infection prevention and control

- **Standard precautions** should be used to manage all patients with suspected plague.
- **Droplet precautions and isolation** should be used for all patients with suspected pneumonic plague.
- **Source control** should be implemented for patients with pneumonic plague, including by applying a medical mask to the patient when possible and tolerated.
- **Safe body handling and burial practices** should be ensured.

IMASOY

- A randomised, open-label controlled non-inferiority trial comparing 10-day ciprofloxacin to three-day aminoglycoside followed by seven-day ciprofloxacin for treating bubonic plague in Madagascar
- 82 sites activated in 12 districts over 5 transmission seasons – including during covid-19 pandemic.
- Trial embedded in public healthcare system from most peripheral dispensary to hospital
- Conclusion: Both gentamicin + ciprofloxacin and ciprofloxacin alone >90% effective; Ciprofloxacin non-inferior (from 7.8% worse to 6% better)
- IMASOY is the first RCT powered to produce conclusive results on treatment of bubonic plague



Collaborative partners: INSTITUT PASTEUR de Madagascar, PASTEUR NETWORK; ISARIC; PANDEMIC SCIENCES INSTITUTE; UNIVERSITY OF OXFORD; LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Funded by: UK International Development, Partnership | Progress | Prosperity; wellcome

World Health Organization

EPI-WIN webinar

- View webinar “Plague in the 21st century: New evidence to control a re-emerging zoonotic disease”
- Speakers
  - Maria Van Kerkhove, WHO HQ
  - Lorenzo Pezzoli, WHO Health Eemergencies (WHE), WHO HQ
  - Nicolo Binelo, WHE, WHO HQ
  - Piero Olliaro, University of Oxford
  - Rindra Vatosoa Randremanana, Institut Pasteur de Madagascar
  - Mihaja Raberahona, Centre Hospitalier Universitaire
  - Joseph Raseta ,Befelatanana, Madagascar