Plague in the 21st century

An overview of global control strategies and WHO recommendations

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Nicolò Binello, MD MSc DTMH
Health Emergencies Preparedness and Response Programme
World Health Organization
Geneva, Switzerland

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Causative agent

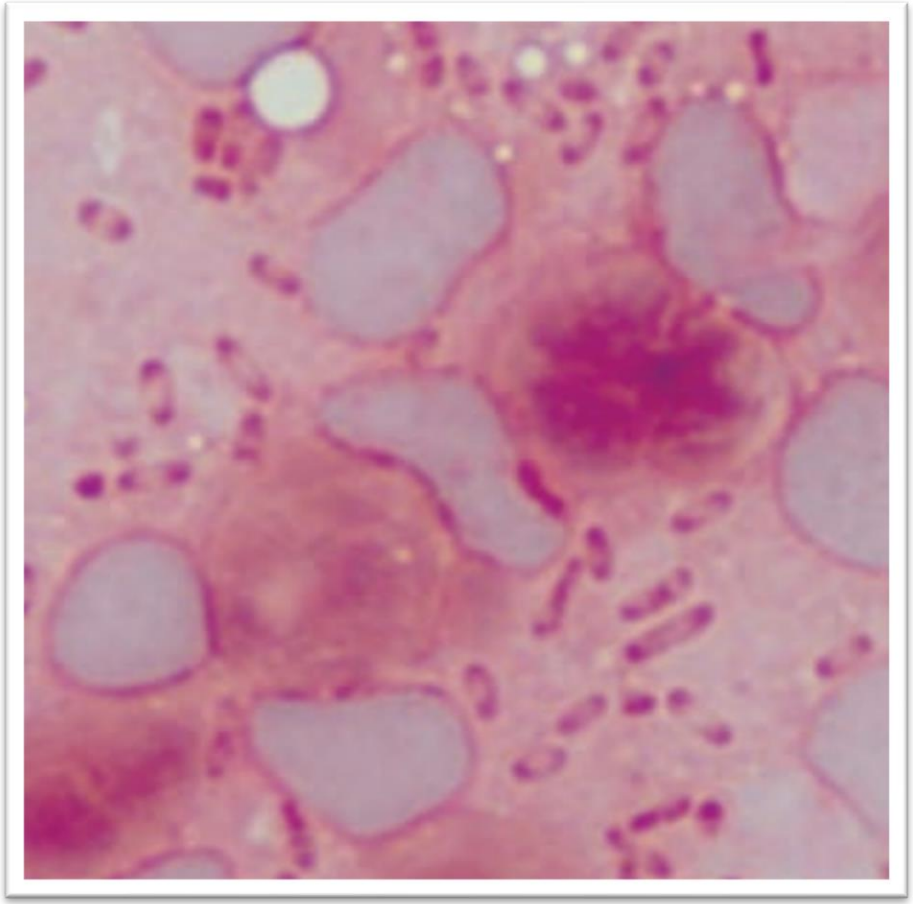
Yersinia pestis

Gram-negative coccobacillus

Capsulated, non-motile

Safety-pin appearance
(bipolar staining)

Not highly resistant
to environmental factors



Microscopic appearance of *Y. pestis* (Gram staining). Image: WHO

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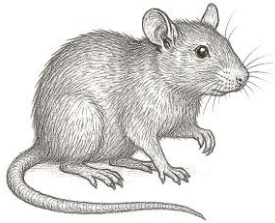
Animal reservoirs

Wild rodents	Commensal rodents (rats)
Only rarely involved in human transmission (**sylvatic cycle**)	Often involved in human transmission (**urban cycle**)
Susceptible to infection but resistant to disease	Susceptible to infection and disease ("rat falls")
Squirrels, prairie dogs, wood rats	*Rattus rattus* (roof rat) *Rattus norvegicus* (Norwegian rat)



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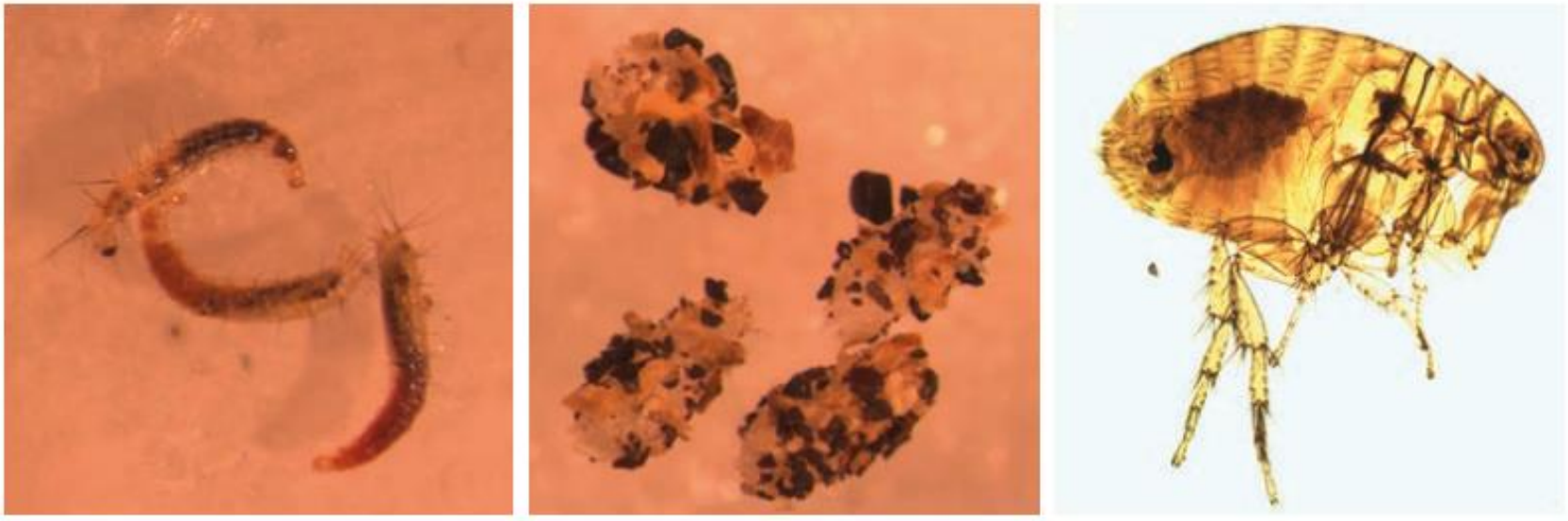
Vector

Fleas are the vectors of plague. About 30 species are proven vectors, with different flea species prevalent in different regions.

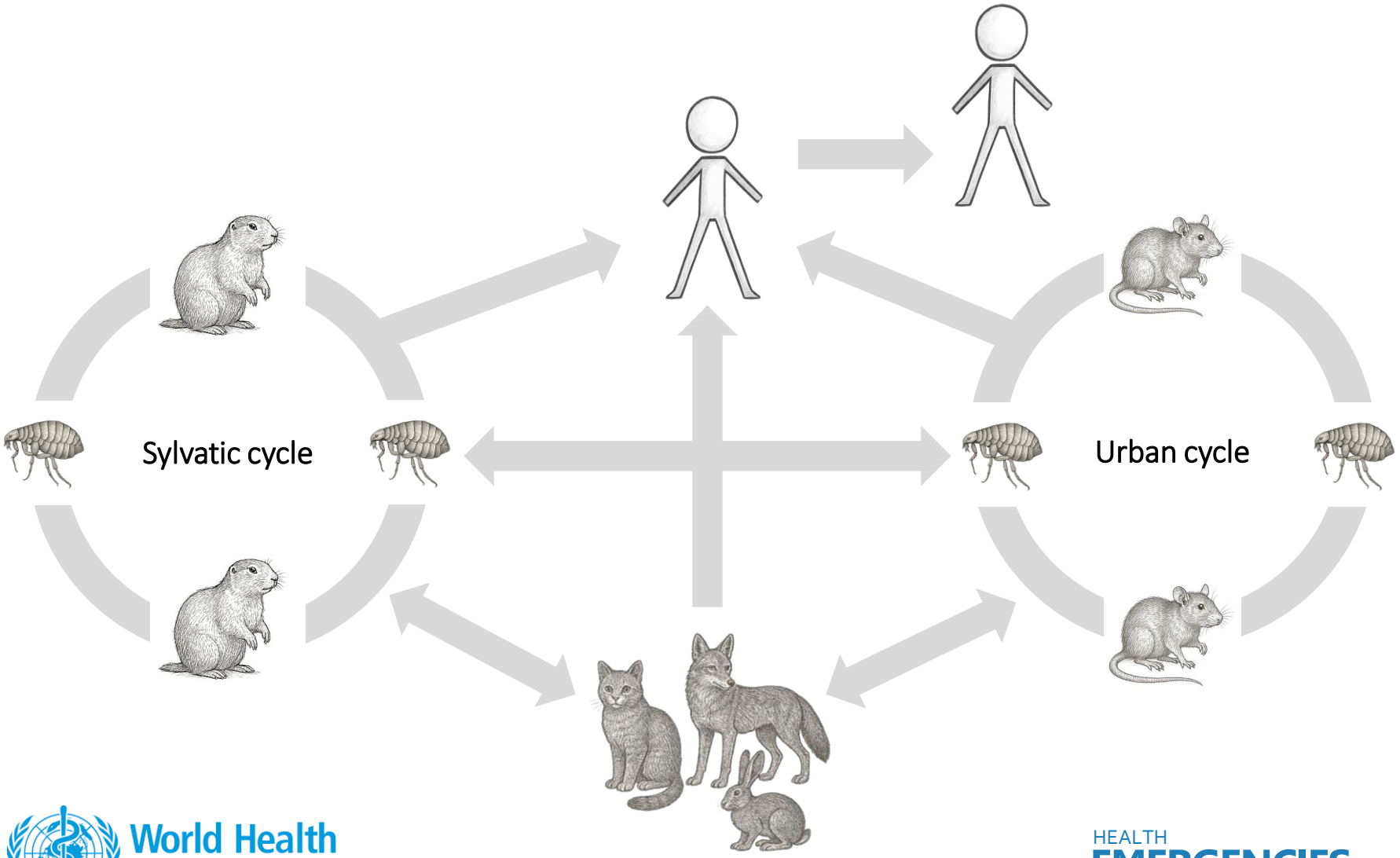
Xenopsylla cheopis (Oriental rat flea) is the most important vector, commonly infesting peridomestic rodents.



Life cycle of fleas: larva (left), pupa (middle) and adult (right).

Image credit: WHO

Transmission



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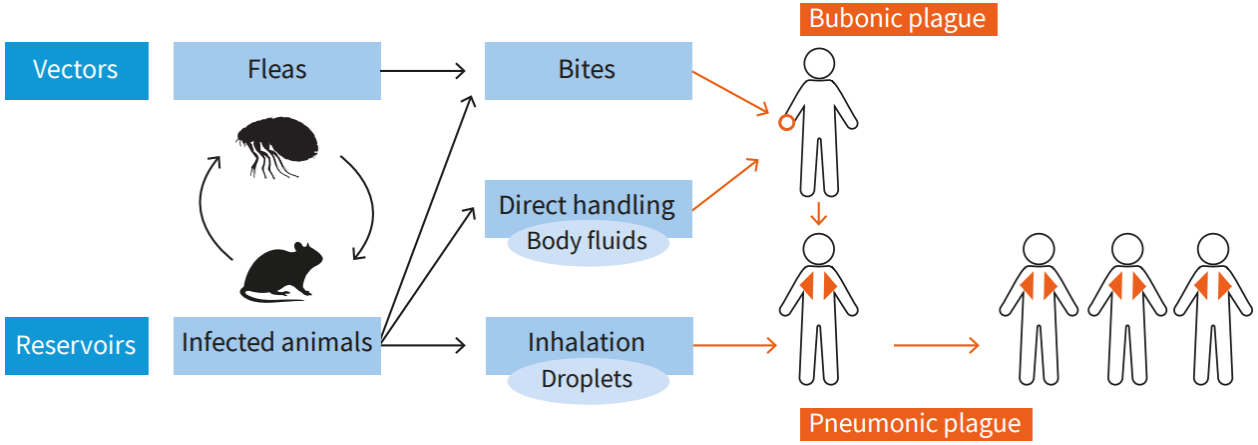
Transmission

Transmission route		Primary clinical syndrome
Flea-borne	Bite of infectious fleas (**sylvatic** vs **urban cycle**)	Bubonic and septicemic plague
Direct contact	With infected animals or animal tissues	Bubonic and septicemic plague
Droplet	From infected humans or animals	Pneumonic plague



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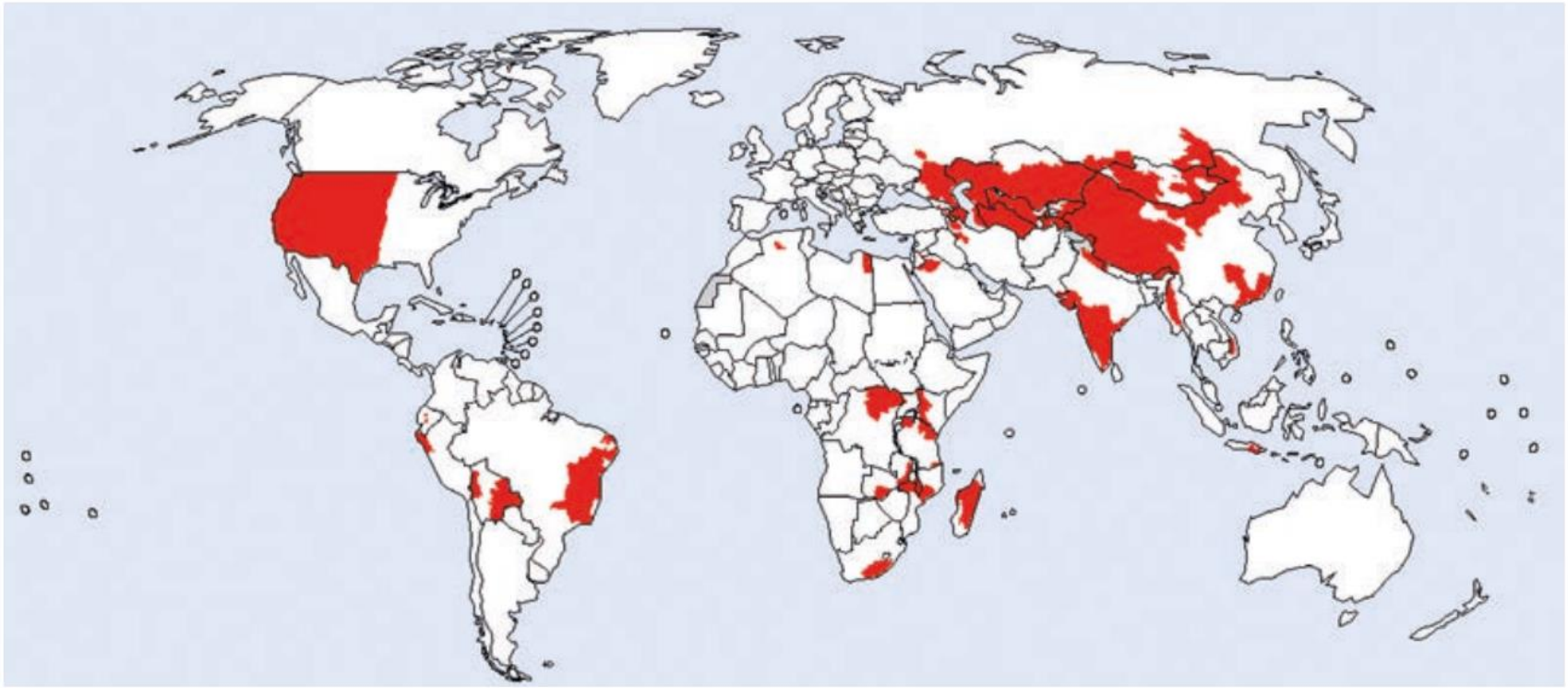
Epidemiology

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.



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

Source: WHO (2016)

Epidemiology

Plague continues to pose a **global public health threat** due to the existence of large areas with established natural foci where the disease remains endemic and enzootic.

Natural plague foci are associated with **sporadic** disease in humans and can lead to **outbreaks** (e.g., large-scale epidemic in Madagascar in 2017)

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.

Public health risk factors

Socio-economic factors

Unsanitary living conditions
Flea- or rat-infested houses, overcrowding

Lifestyle associated with animal handling
Hunting, trapping, skinning

Traditional death rituals
Body preparation and gatherings

Environmental and climatic factors

Seasonality in tropical-subtropical areas
(temperature 10-30° and high humidity)

Natural disasters
Earthquakes, flooding, drought

Ecological changes
Encroachment, deforestation and mining

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Prevention and control

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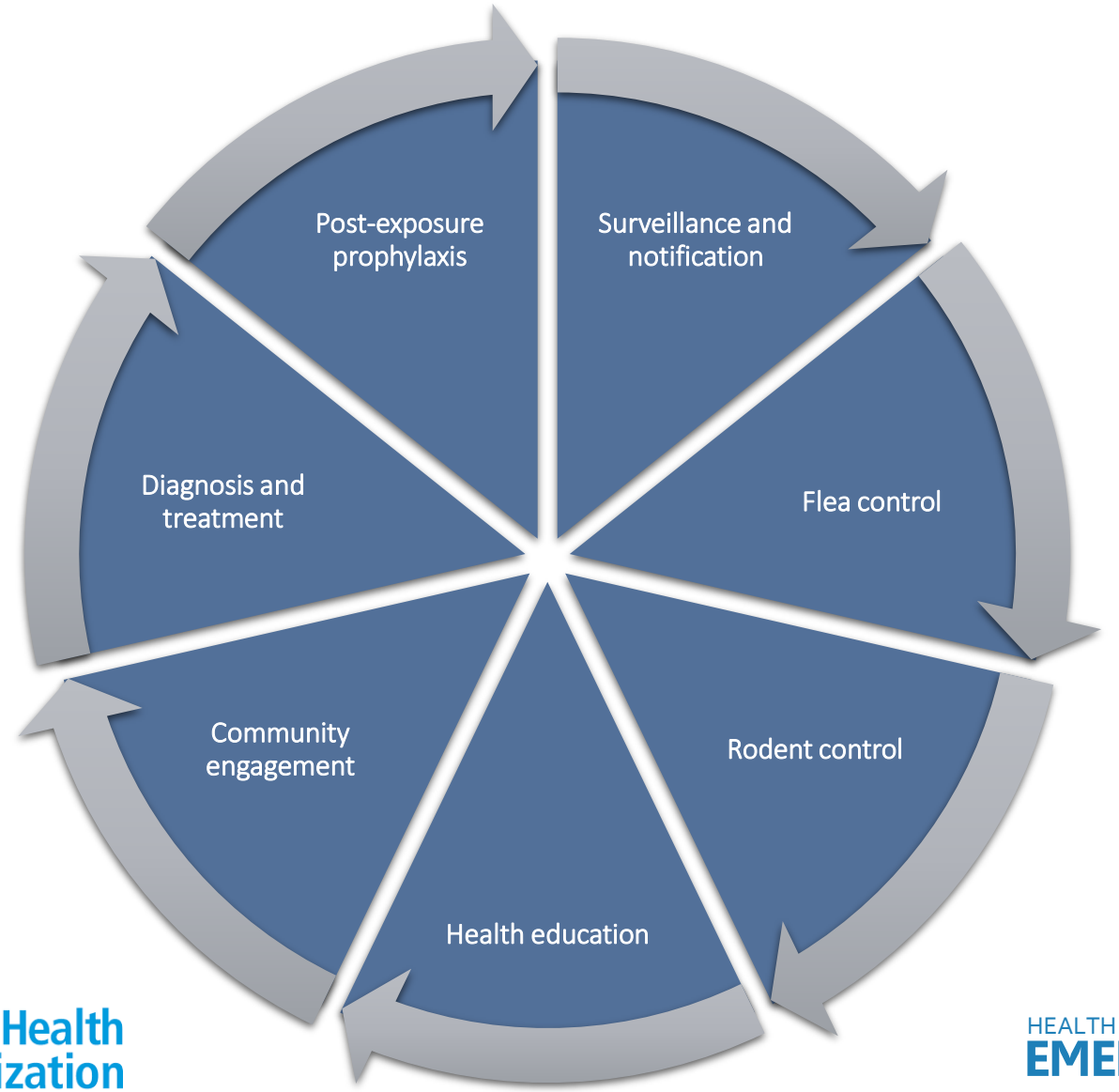
Prevention and control



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International Health Regulations (2005)

A plague event should be notified to WHO in accordance with the International Health Regulations.

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.

It is not always necessary to wait for laboratory confirmation of plague; a suspected case of plague that occurs in an area not known to be endemic should be reported as an event to WHO.

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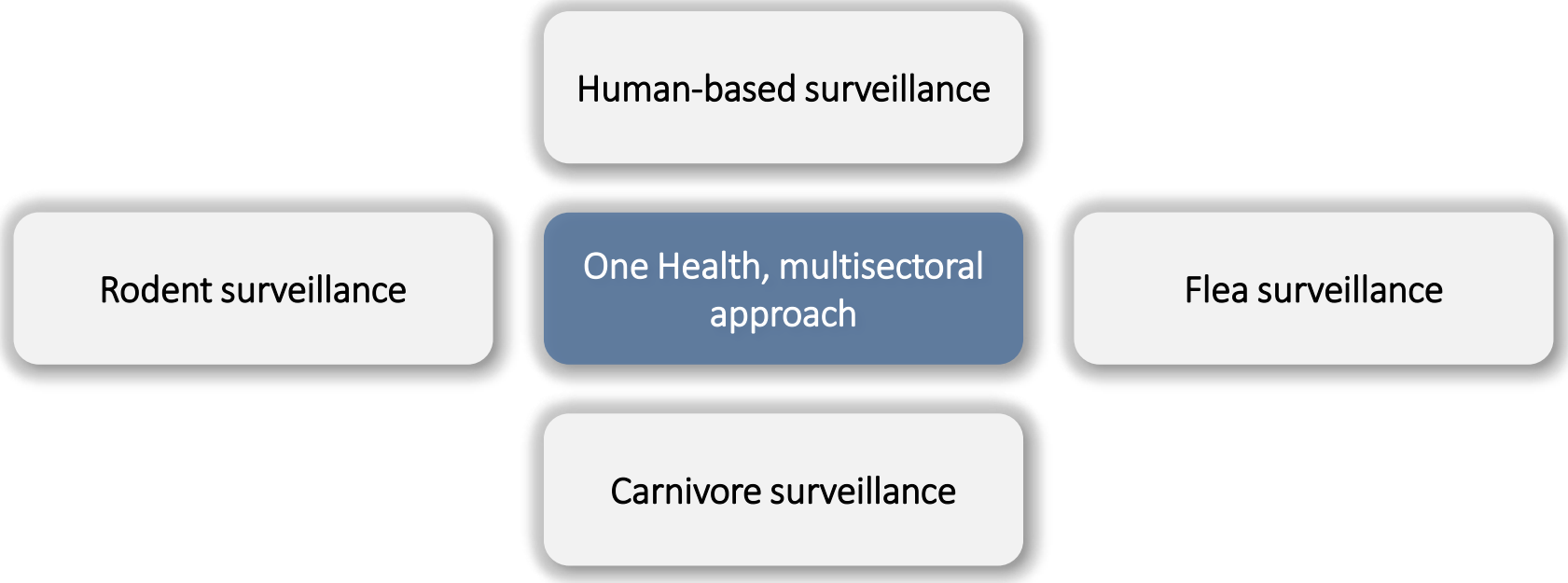
Collaborative surveillance



Close collaboration among all surveillance actors is crucial for fully understanding risks and vulnerabilities, enabling timely detection and implementing effective response efforts.

Animal-based surveillance

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 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

Human-based surveillance

Case definitions can be used as a reference for notification under the International Health Regulations framework as well as for epidemiological investigation.

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

Flea control

Flea control activities is a key intervention to interrupt ongoing transmission and should precede rodent control during outbreaks (killing rodents before vectors will cause fleas to bite new hosts).

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.

The most rapid and effective method for controlling fleas is based on the use of **insecticides** formulated as a dust or powder (insufflation) or low-volume spray (residual or non-residual).

Insecticides used for flea control should be safe for humans and include pyrethroids (e.g., deltamethrin), organochlorines (e.g., DDT), and organophosphates (e.g., malathion).

Rodent control

Rodent control should be undertaken primarily during interepidemic periods.

During outbreaks and in endemic regions, they should follow flea control measures.

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).

Rodent control requires intensive efforts and results are often short-lived, yet it remains critical for plague prevention.

Community protection and risk communication

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.

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Diagnosis and treatment

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Epidemiological assessment

High risk	Intermediate risk	Low risk
Within 10 days[a] prior to onset of the disease, any of the following occurred: • close and unprotected contact (no personal protective equipment) with a confirmed or probable[b] case of pneumonic plague; • unprotected contact with an animal infected with *Y. pestis* (e.g. a bite, contact with body fluids when skinning an animal or conducting a necropsy, eating raw meat); • accidental exposure to *Y. pestis* by puncture (e.g. in a research lab).	Any of the following occurring within 10 days[a] prior to onset of the disease: • close and unprotected contact with a suspected case of pneumonic plague; • residing in or travelling to an area where a human case of plague has recently been reported or *Y. pestis* circulation within reservoir species has been documented; • bitten by a flea in a known endemic area.	• Residing in or recent travel (within 10 days[a] prior to onset of the disease) to a known endemic area

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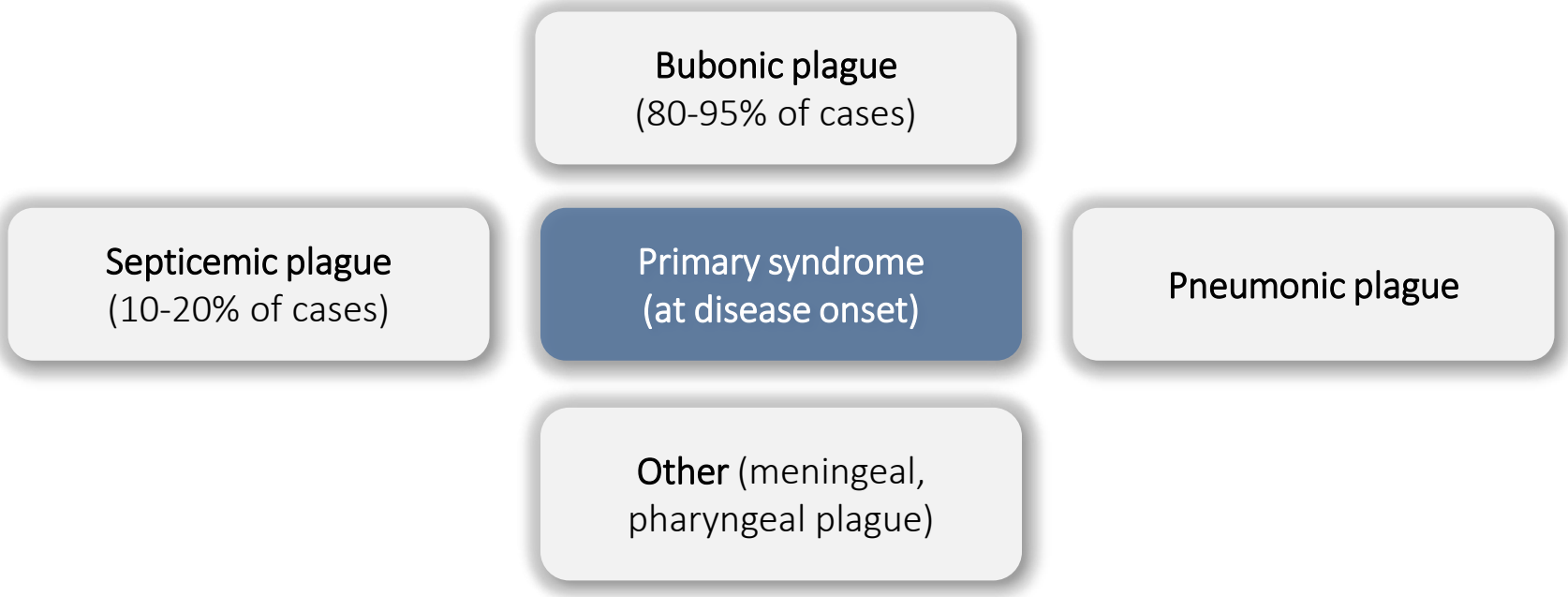
Clinical manifestations



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

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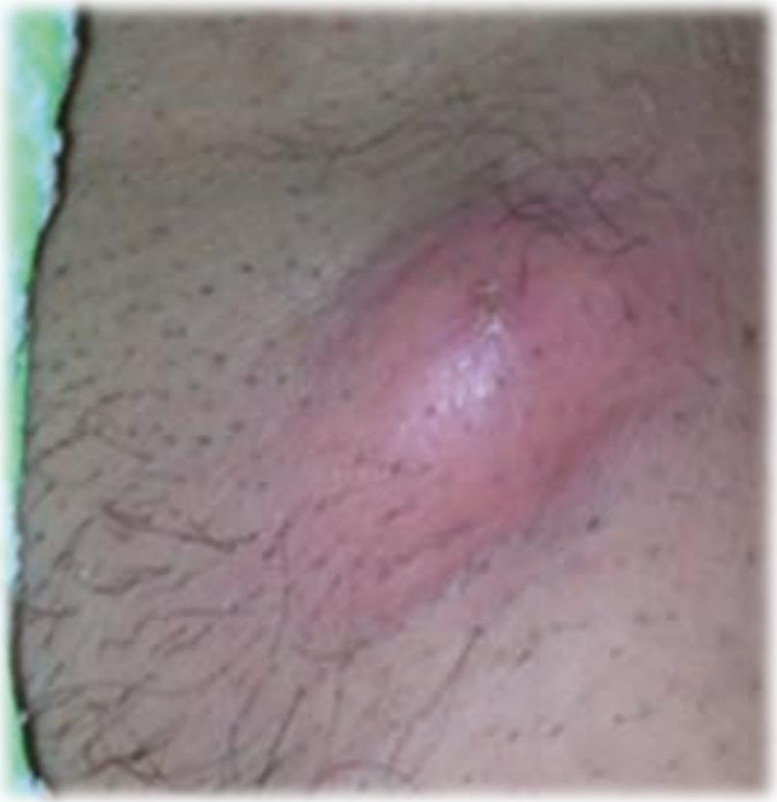
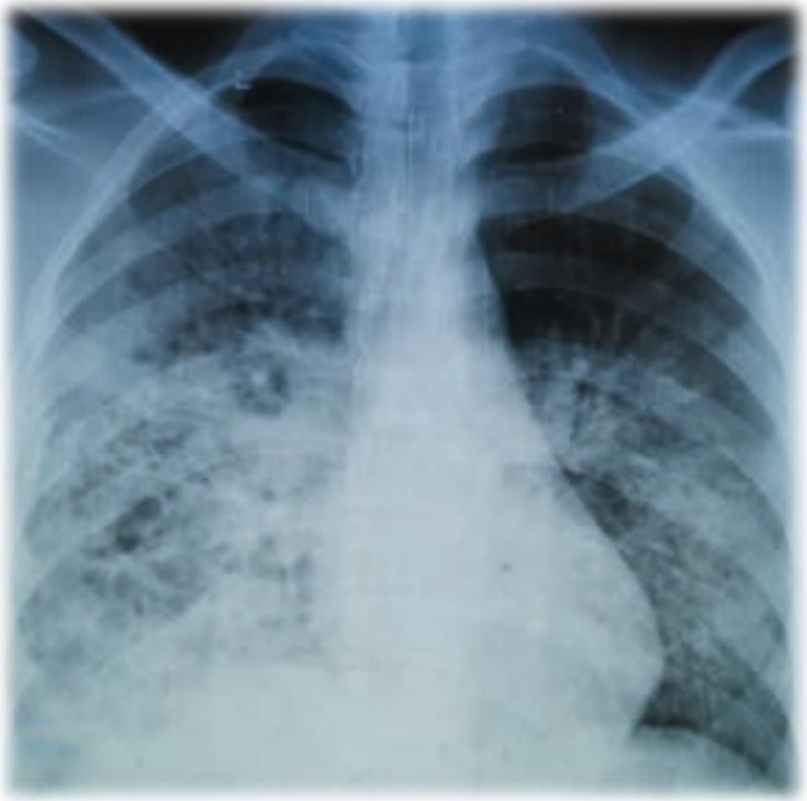
Clinical manifestations

Bubonic plague



Pneumonic plague



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Clinical manifestations

Bubonic plague	Pneumonic plague
Transmitted through flea bites or direct contact with animals	Transmitted through droplets (primary), flea bites or direct contact with animals (secondary)
Incubation period 2-6 days	Incubation period 1-3 days
Painful adenopathy (bubo) with fever	Severe pneumonia with bloody sputum
Case fatality rate ~ 15.25%	Usually fatal if untreated within 24-36 hrs

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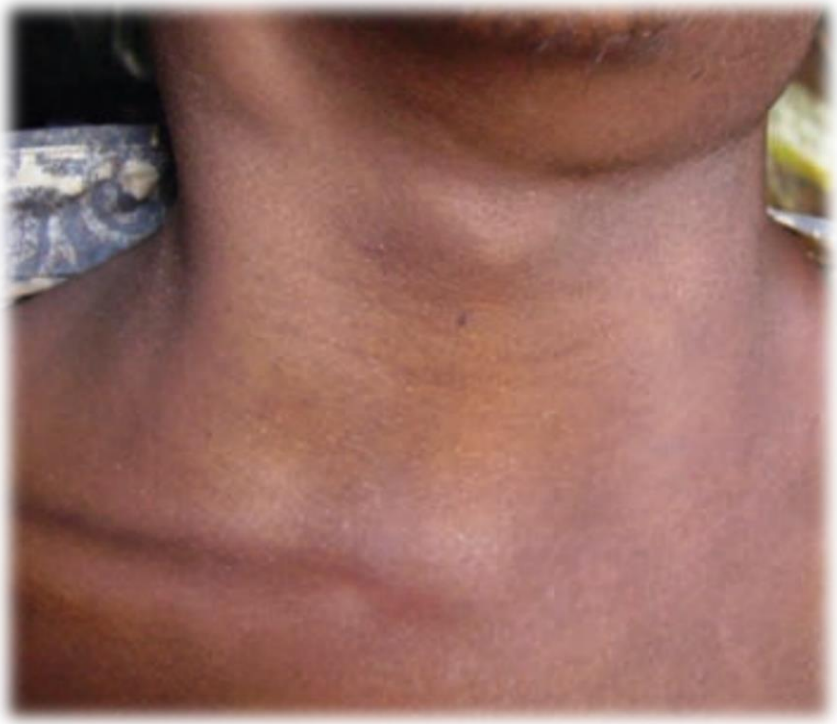
Bubonic plague

Painful lymphadenopathy (**bubo**)
(inguinal > cervical or axillary,
depending on inoculation site)

Preceded by or associated with
fever, headache and generalized weakness

Sometimes preceded by a vesicle, pustule
or ulcer at the inoculation site (**carbuncle**)

Potential to evolve to septicemic,
pneumonic or meningeal plague



A cluster of cervical buboes in a patient with plague

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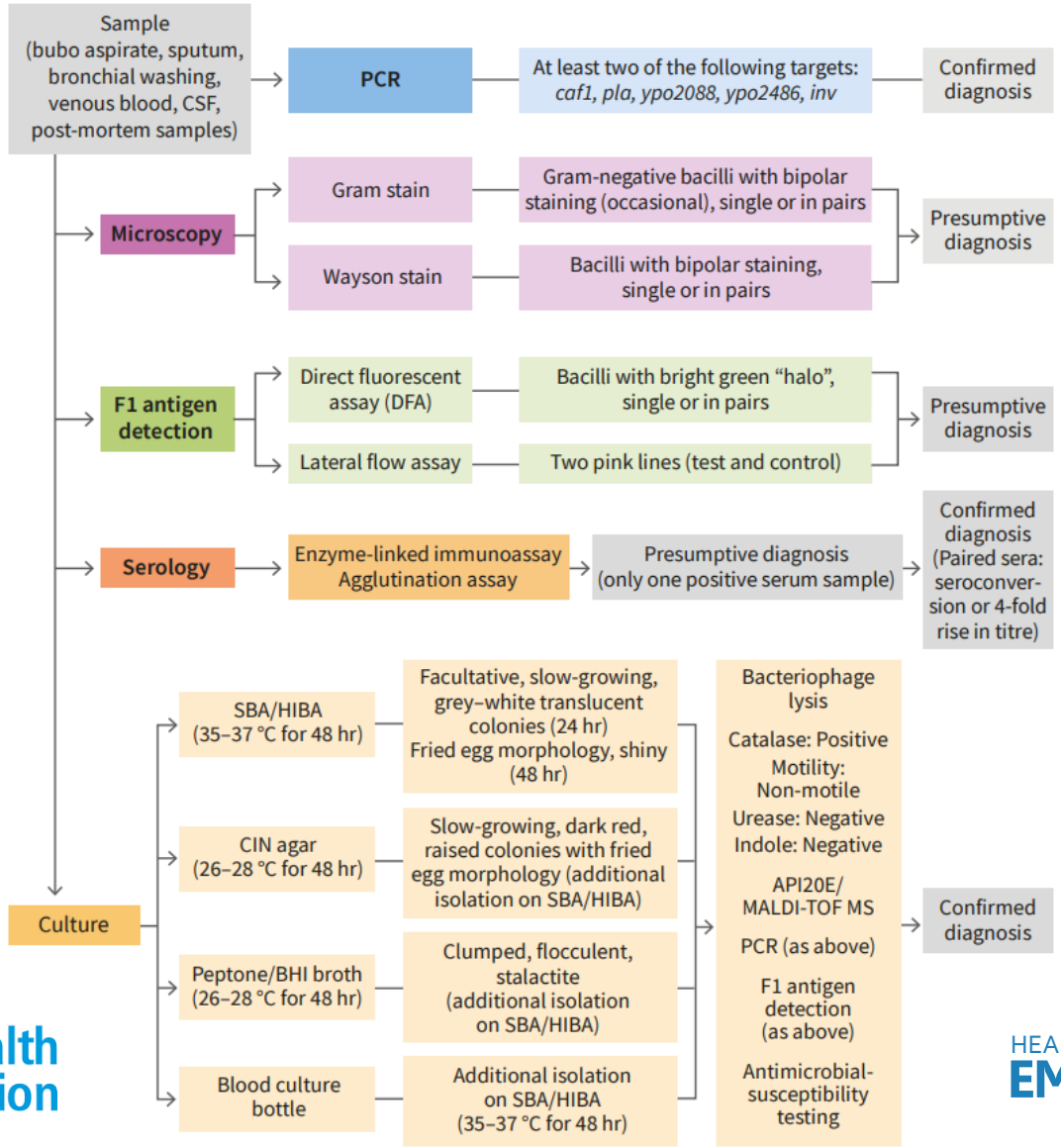
Laboratory testing

When plague is suspected, clinical specimens should be **urgently** collected and transported to the reference laboratory, and the laboratory must be informed of the shipment in advance.

Clinical syndrome	Recommended samples for diagnosis
Bubonic plague	Bubo aspirate and peripheral blood
Pneumonic plague	Sputum, bronchial or tracheal washing and peripheral blood
Septicemic plague	Peripheral blood
Meningeal plague	Cerebrospinal fluid and peripheral blood

Diagnostic assays



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Rapid diagnostic tests

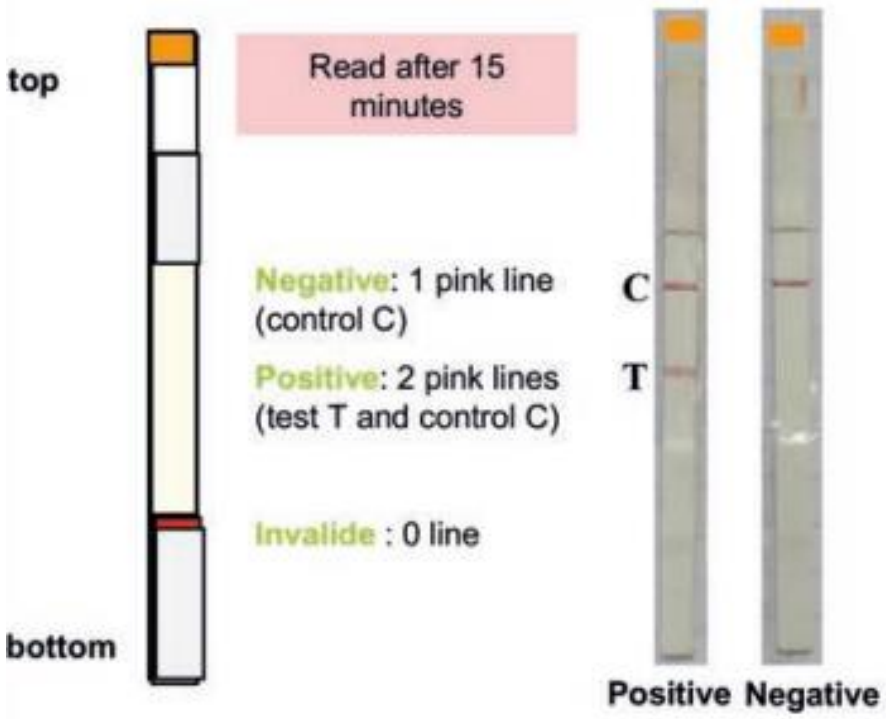

Image credit: WHO/Pasteur Institute Madagascar

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Rapid diagnostic tests – WHO recommendations (2021)

Use of F1RDTs in suspected cases	Bubonic plague	Pneumonic plague
In endemic areas **(alert tool for detection and response)**	Strong recommendation Very-low-certainty evidence	Conditional recommendation Very-low-certainty evidence
During outbreaks **(point-of-care test)**	Conditional recommendation Very-low-certainty evidence	Conditional recommendation Very-low-certainty evidence

Due to the limited specificity, a positive result should be interpreted with caution and confirmed with culture or PCR.

- While initial public health response measures may be initiated based on a positive test, it is recommended to await the results of confirmatory tests before officially declaring a confirmed plague outbreak.
- During an outbreak, if a patient presents with clinical signs consistent with any form of plague, treatment should be initiated regardless of F1RDT results.

Source: WHO

Antibiotic therapy

1. Start antibiotic therapy for all suspected cases as soon as possible. Do not wait for bacteriological confirmation.

Determine antibiotic regimen based on clinical syndrome, disease severity and bioavailability considerations.

2. Use antibiotic susceptibility testing results to tailor antibiotic treatment based on resistance patterns (if detected).

3. Complete the treatment course for a total duration of 10-14 days (or longer depending on clinical improvement).

Source: WHO

Antibiotic therapy for bubonic plague

Empiric antibiotic therapy with a **single agent** is recommended for bubonic plague.

Antibiotic	Age group	Dosing (per dose)	Interval (hours)	Route of administration
First-line options				
Ciprofloxacin	Adults	400 mg 750 mg[a]	8 12[a]	IV PO
	Children	10 mg/kg (max. 400 mg/dose) 15 mg/kg (max. 750 mg/dose)	8 or 12 12	IV PO
Levofloxacin	Adults	750 mg	24	PO or IV
	Children ≥ 6 months	< 50 kg: 8 mg/kg (max. 250 mg/dose) ≥ 50 kg: 500–750 mg	12 24	PO or IV PO or IV
Moxifloxacin[b]	Adults	400 mg	24	PO or IV
Doxycycline	Adults and children ≥ 45 kg	200 mg loading dose followed by 100 mg	12	PO or IV
	Children < 45 kg[c]	4.4 mg/kg (max. 200 mg) loading dose followed by 2.2 mg/kg (max. 100 mg)	12	PO or IV
Gentamicin	Adults	5 mg/kg	24	IM or IV
	Children	4.5–7.5 mg/kg	24	IM or IV
Streptomycin	Adults	1 g	12	IM or IV
	Children	15 mg/kg (max. 1 g/dose)	12	IM or IV

Source: WHO

Antibiotic therapy for pneumonic or septicemic plague

Empiric antibiotic therapy with **two antibiotics from distinct classes** is recommended.

Antibiotic	Age group	Dosing (per dose)	Interval (hours)	Route of administration
First-line options				
Ciprofloxacin	Adults	400 mg 750 mg[a]	8 12[a]	IV PO
	Children	10 mg/kg (max. 400 mg/dose) 15 mg/kg (max. 750 mg/dose)	8 or 12 12	IV PO
Levofloxacin	Adults	750 mg	24	PO or IV
	Children ≥ 6 months	< 50 kg: 8 mg/kg (max. 250 mg/dose) ≥ 50 kg: 500–750 mg	12 24	PO or IV PO or IV
Moxifloxacin[b]	Adults	400 mg	24	PO or IV
Gentamicin	Adults	5 mg/kg	24	PO or IV
	Children	4.5–7.5 mg/kg	24	IM or IV
Streptomycin	Adults	1 g	12	IM or IV
	Children	15 mg/kg (max. 1 g/dose)	12	IM or IV

Source: WHO

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.

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Resources

Manual for plague surveillance, diagnosis, prevention and control. Geneva: World Health Organization; 2024. https://www.who.int/publications/i/item/9789240090422

WHO guidelines for plague management: revised recommendations for the use of rapid diagnostic tests, fluoroquinolones for case management and personal protective equipment for prevention of post-mortem transmission. Geneva: World Health Organization; 2021. https://www.who.int/publications/i/item/9789240015579