



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



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ISBN 978-92-4-001557-9 (electronic version)

ISBN 978-92-4-001558-6 (print version)

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Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

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Design and layout by Sophie Guetaneh Aguetant



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Acknowledgements

The World Health Organization (WHO) Department of Infectious Hazards Management produced these guidelines under the direction of the responsible technical officer, Eric Bertherat. They were prepared by Sophie Jullien, in consultation with the methodologist, Paul Garner.

WHO acknowledges the many professionals from all over the world who committed their time and expertise to the process of developing these guidelines.

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Funding sources

Funding for these guidelines was provided by the Australian Department of Foreign Affairs and Trade.



Abbreviations

CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
ELISA	enzyme-linked immunosorbent assay
F1RDT	rapid diagnostic test based on the F1 antigen
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PICO	participants, intervention, comparison, outcome
PCR	polymerase chain reaction
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RDT	rapid diagnostic test
WHO	World Health Organization



Executive summary

Plague has killed millions of people during the past 25 centuries (1), and the disease reappeared in several countries during the 1990s. Consequently, plague was categorized as a re-emerging disease (2). Human plague outbreaks continue to be reported, including an outbreak of pneumonic plague in Madagascar in 2017 (2–4).

Plague is an acute bacterial infection caused by *Yersinia pestis*. Although effective antimicrobials are available, plague still has high mortality because most outbreaks take place in remote places, where proper diagnosis and treatment remain challenging (2). Early identification of the disease is crucial to ensure prompt treatment and better outcomes. Pneumonic plague is highly contagious and of particular concern because of the high risk of triggering epidemics. Thus, plague is both a medical and a public health emergency.

These guidelines were developed in accordance with the *WHO handbook for guideline development* (5). A WHO Steering Group, led by the responsible technical officer, developed the draft scope of the guidelines and the key questions to be addressed. The Steering Group selected the members of the Guideline Development Group (GDG) to ensure diverse areas of expertise were represented, including clinicians, microbiologists, public health professionals, researchers and an anthropologist. The Steering Group also commissioned technical advisers to lead the Evidence Review Team and provide methodological support. The GDG assisted with developing the final scope of the guideline and defining the key areas to be addressed, and also formulated the recommendations.

Three key areas were selected to be addressed: (i) the use of rapid diagnostic tests (RDTs) for diagnosing plague in different contexts; (ii) the choice of antimicrobials for treating the different forms of plague, including whether fluoroquinolones should be introduced as a first-line medicine of choice; and (iii) the use of personal protective equipment in case of exposure to the dead body of a person who was infected with plague. The Evidence Review Team conducted systematic reviews to address each of the three key areas.

At a meeting in Antananarivo, Madagascar, on 20–21 September 2019, the GDG interpreted the main findings of the systematic reviews as they applied to each key question and formulated evidence-based recommendations following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. For each key question, there was discussion about the certainty of the evidence, desirable and undesirable effects, values and preferences, cost, acceptability, equity, feasibility and barriers to implementation. The GRADE evidence-to-decision tables were used to facilitate consensus and record the decision of the GDG. The GDG developed final recommendations where possible and graded each of them as strong or conditional (Table 1). The final guidelines were written by the Evidence Review Team

lead and reviewed by the responsible technical officer, the methodologist, the members of the GDG and the external reviewers before submission to the WHO Guidelines Review Committee.

These guidelines supplement the existing WHO guidelines on plague surveillance, diagnosis, prevention and control, published in 2009 (2).

Table 1. WHO recommendations on using RDTs and fluoroquinolones for early diagnosis and treatment of plague, and on the appropriate use of personal protective equipment, 2019

Recommendations	Strength of the recommendation	Quality of the evidence
<i>Use of F1RDT for plague</i>		
In areas where plague is known to occur, the GDG suggests using F1RDT in people with suspected pneumonic plague to rapidly detect the disease and implement an immediate public health response (alert tool). While the initial public health response is being implemented, a confirmatory test (such as culture or molecular testing) should be carried out before declaring a confirmed plague outbreak, because F1RDT has limited specificity.	Conditional	Very low
During an outbreak, the GDG suggests using F1RDT in people with suspected pneumonic plague to provide rapid diagnosis at the point of care. A negative result helps rule out the disease and encourages consideration of an alternative diagnosis. A confirmatory test (such as culture or molecular testing) should be carried out at the same time.	Conditional	Very low
In areas where plague is known to occur, the GDG recommends using F1RDT in people with suspected bubonic plague to rapidly detect plague and implement an immediate public health response (alert tool). While the initial public health response is being implemented, a confirmatory test (such as culture or molecular testing) should be carried out before declaring a confirmed plague outbreak, because F1RDT has limited specificity.	Strong	Very low
During an outbreak, the GDG suggests using F1RDT in people with suspected bubonic plague to provide rapid diagnosis at the point of care. A confirmatory test (such as culture or molecular testing) should be carried out at the same time.	Conditional	Very low
<i>Antibiotics for treating plague</i>		
The GDG suggests adding fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) to the first-line medicines recommended for treating pneumonic or septicemic plague (streptomycin and gentamicin).	Conditional	Very low
The GDG suggests adding fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) to the first-line medicine recommended for treating bubonic plague (streptomycin, doxycycline and gentamicin).	Conditional	Very low
The GDG suggests adding fluoroquinolones (moxifloxacin and ofloxacin) to the first-line medicine recommended for treating plague meningitis (chloramphenicol).	Conditional	Very low
The GDG suggests adding fluoroquinolones (ciprofloxacin) to the first-line medicines recommended for postexposure presumptive treatment (doxycycline and sulfamethoxazole + trimethoprim).	Conditional	Very low

Use of personal protective equipment

The GDG suggests using personal protective equipment when handling the dead body of a person who was infected with plague. The minimum required equipment includes a gown, goggles, an N95 mask and gloves.

Conditional

Very low

GDG: Guideline Development Group; F1RDT: rapid diagnostic test based on the F1 antigen.



CHAPTER 1

Introduction

1.1 Background

Plague reappeared in several countries during the 1990s and, consequently, was categorized as a re-emerging disease (2). This severe disease has caused major outbreaks, such as the one in Madagascar in 2017 (6) and remains endemic in many natural foci around the world, including several countries in Africa, the Americas and Asia.

Plague has killed millions of people over the last 25 centuries (1). While often considered a disease of the past, it is far from being eradicated and remains a threat in many parts of the world (7). Between 1989 and 2003, a total of 38 310 human cases of plague, including 2845 deaths, were reported from 25 countries (4). Since 2000, more than 95% of the global disease burden has been concentrated in Africa, with the Democratic Republic of the Congo, Madagascar, Uganda and the United Republic of Tanzania being the countries most affected (3,4). In the Americas, Peru and the United States of America regularly report cases. While Asia is the area with the largest natural foci, outbreaks occur sporadically there because the reservoir consists of gerbils and marmots, and few people are in contact with these animals (3). As of 2017, the Democratic Republic of the Congo, Madagascar and Peru were the countries with the highest incidence of the disease. However, the disease is re-emerging in places where it had disappeared and emerging in other places where it had never occurred because the natural foci of the disease are expanding. Globally, human plague outbreaks are regularly reported to WHO, for example, from India in 2004, Indonesia in 2007, the Democratic Republic of the Congo and the United Republic of Tanzania in 2014, and the outbreak of pneumonic plague reported in Madagascar in 2017 (2–4).

Plague is an acute bacterial infection caused by *Yersinia pestis*. It is a zoonosis affecting wild and domestic animals, particularly rodents. Humans mainly become infected after being bitten by infected fleas from rodents. Other routes of transmission include being bitten by infected domestic cats, direct handling of tissues or fluids from a plague-infected animal, handling infected samples in a laboratory or during their transport, inhaling respiratory secretions from infected animals or aerosolized droplets from humans with pneumonic plague, and being exposed during a post-mortem examination (8,9).

Human plague presents in several forms, with three major clinical syndromes. Bubonic plague is characterized by swollen lymph nodes that have necrotic areas, called buboes. Bubonic plague is the most common form worldwide and accounts for approximately 80% to 95% of all cases, with case-fatality rates of 10% to 20% (10). Septicaemic plague occurs when the infection spreads to the circulatory system, and it accounts for around 10% to 20% of cases. Pneumonic plague is a fulminant form that affects the lungs and presents with cough and bloody sputum.

Pneumonic plague is rare, but has the highest case-fatality rate, close to 100% if left untreated. Although efficient antimicrobials are available, plague still has high mortality because most outbreaks take place in remote areas, where access to proper diagnosis and treatment is limited (2). Pneumonic plague is highly contagious and of particular concern due to its epidemic potential. This risk makes the disease both a medical and a public health emergency.

1.2 Rationale for these guidelines

With the re-emergence of plague guidance is needed on detecting and treating the disease. Corpses are a significant source of plague infections and therefore clear, evidence-based risk analyses of their infectivity are needed to gauge the right level of protection required during procedures or handling of the body that is proportional to the estimated risk.

The WHO guidelines on plague surveillance, diagnosis, prevention and control were published in 2009 by the WHO Regional Office for South-East Asia (2). In 2014, a scientific meeting was convened to revise these guidelines. However, the deliberations were general and were not formalized in a published document. Moreover, uncertainties remain regarding the best practices for managing this disease. There is no guidance regarding the use of the relatively new RDT for plague, which could allow for faster identification of cases and prompt treatment, especially in remote areas without laboratory facilities to perform microbiological diagnosis. Although streptomycin has been used for decades with good results, it causes significant adverse effects and requires parenteral administration. Other antibiotics have been used to treat plague infections, such as fluoroquinolones, but in the absence of a consensus about first-line treatments. Because plague is highly contagious, strict, empirically based measures have been recommended for handling the bodies of humans who were infected with the disease, including the use of full personal protective equipment. However, these measures are complex, difficult to implement in resource-constrained settings and culturally inappropriate in others; meanwhile, there has been a lack of scientific evidence endorsing such practices.

Following the most recent Ebola virus disease outbreaks, there was a call for WHO and partners to designate 2019 as a year of action on preparedness for health emergencies. Although *Y. pestis* was not included in the WHO R&D Blueprint list of diseases and pathogens for priority research and development, plague has the potential to trigger large outbreaks with high mortality. WHO-endorsed guidelines are needed that have clear and evidence-based recommendations for managing the disease. The decision to develop this set of simplified guidelines was taken in order to clarify key technical questions before the next plague epidemic season in the countries that are most affected.

1.3 Target audience

These guidelines were developed for clinicians practising in primary and secondary care, and public health professionals preparing for or responding to plague outbreaks.

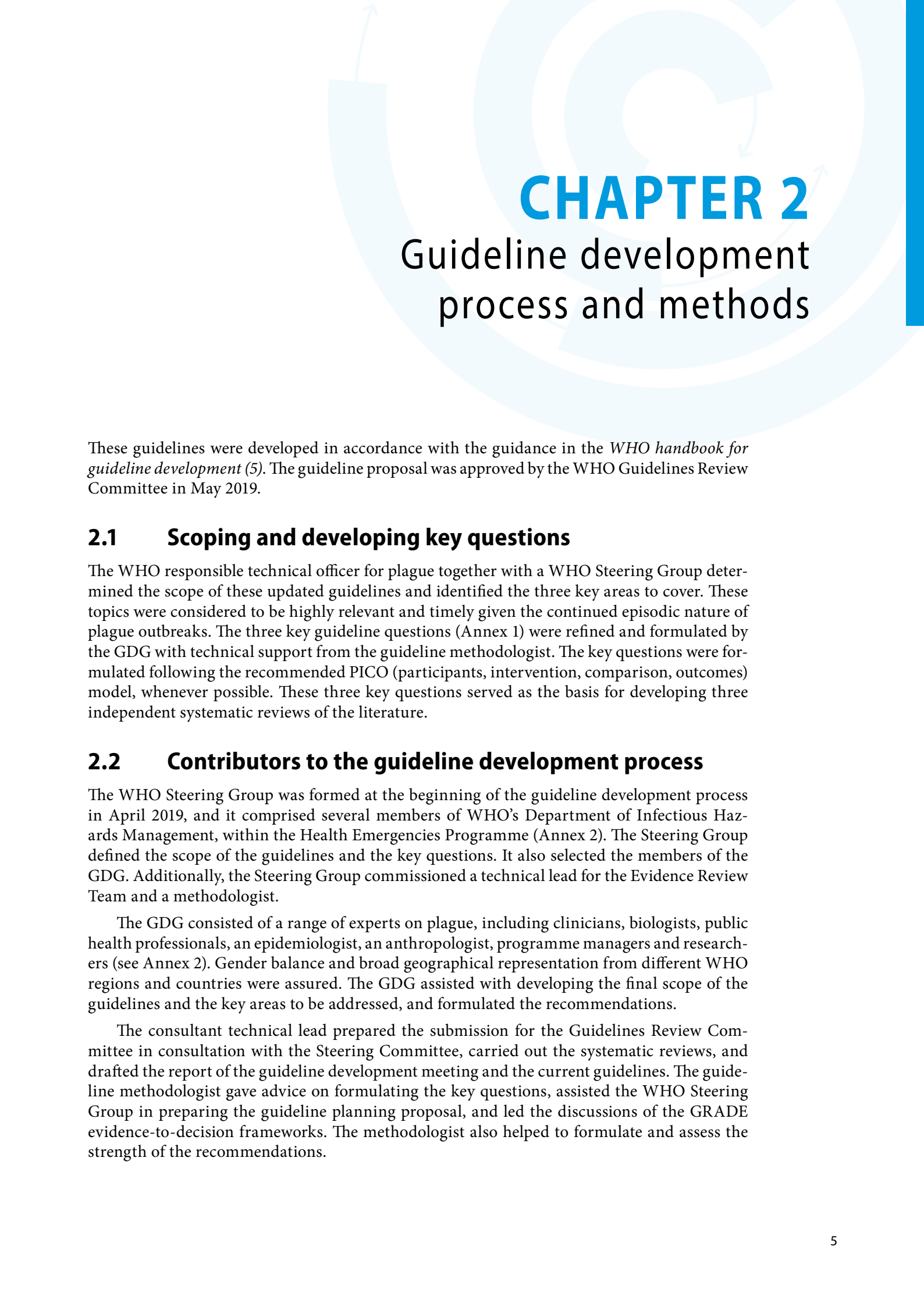
These guidelines were also developed to inform policy- and decision-makers responsible for developing national policies and guideline documents, as well as for procuring drugs and implementing training programmes.

1.4 Aim and objective

The aim of these guidelines is to provide up-to-date guidance on the diagnosis, case management, prevention and control of the different forms of plague, both for sporadic cases and during outbreaks. They are also intended to serve as the basis for developing national guidelines, taking into account the available resources and other determinants in each country.

The objective of these guidelines is to provide recommendations on:

- the use of RDTs for the various forms of plague in plague-endemic areas and during outbreaks;
- the choice of antimicrobial medicines for the various forms of plague, including whether fluoroquinolones should be introduced as a first-line medicine of choice; and
- the use of personal protective equipment for the safe handling of potentially infectious human remains.



CHAPTER 2

Guideline development process and methods

These guidelines were developed in accordance with the guidance in the *WHO handbook for guideline development* (5). The guideline proposal was approved by the WHO Guidelines Review Committee in May 2019.

2.1 Scoping and developing key questions

The WHO responsible technical officer for plague together with a WHO Steering Group determined the scope of these updated guidelines and identified the three key areas to cover. These topics were considered to be highly relevant and timely given the continued episodic nature of plague outbreaks. The three key guideline questions (Annex 1) were refined and formulated by the GDG with technical support from the guideline methodologist. The key questions were formulated following the recommended PICO (participants, intervention, comparison, outcomes) model, whenever possible. These three key questions served as the basis for developing three independent systematic reviews of the literature.

2.2 Contributors to the guideline development process

The WHO Steering Group was formed at the beginning of the guideline development process in April 2019, and it comprised several members of WHO's Department of Infectious Hazards Management, within the Health Emergencies Programme (Annex 2). The Steering Group defined the scope of the guidelines and the key questions. It also selected the members of the GDG. Additionally, the Steering Group commissioned a technical lead for the Evidence Review Team and a methodologist.

The GDG consisted of a range of experts on plague, including clinicians, biologists, public health professionals, an epidemiologist, an anthropologist, programme managers and researchers (see Annex 2). Gender balance and broad geographical representation from different WHO regions and countries were assured. The GDG assisted with developing the final scope of the guidelines and the key areas to be addressed, and formulated the recommendations.

The consultant technical lead prepared the submission for the Guidelines Review Committee in consultation with the Steering Committee, carried out the systematic reviews, and drafted the report of the guideline development meeting and the current guidelines. The guideline methodologist gave advice on formulating the key questions, assisted the WHO Steering Group in preparing the guideline planning proposal, and led the discussions of the GRADE evidence-to-decision frameworks. The methodologist also helped to formulate and assess the strength of the recommendations.

The GDG held a guideline development meeting in Antananarivo, Madagascar, on 20–21 September 2019 to interpret the main findings of the systematic reviews for each key question and to formulate evidence-based recommendations.

2.3 Declarations of interests

All members of the GDG, the technical advisers and the external peer reviewers were required to complete and submit a WHO Declaration of Interests form. Together with each member's curriculum vitae, their statements were reviewed and assessed by WHO. The final decision regarding participation in the guideline development process was taken by consensus. In addition, at the beginning of the guideline development meeting, all participating members presented orally their declarations of interests (see Annex 3).

After reviewing the declarations, it was concluded that no member had financial or commercial conflicts of interest and that there were no significant academic or intellectual conflicts of interest that would exclude any member from participating in the guideline development process. Two members were academically involved in the development of RDTs, and although this was not considered a conflict of interest, it was decided that the members in question would not chair the session on developing recommendations for tests. Moreover, these two members declared their academic involvement prior to the discussions and did not participate in the discussion and decision-making related to that session.

2.4 Identifying, appraising and synthesizing evidence

A rigorous systematic review was conducted by teams identified by the Cochrane Infectious Diseases Group for each of the three key topics. For RDTs, the Evidence Review Team conducted a systematic review following the methods described in the Cochrane handbook for reviews of diagnostic test accuracy, which uses the GRADE methodology (11). The methodological quality of each study included in the review was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The QUADAS-2 tool allows for transparent rating of the biases and applicability of primary studies of diagnostic accuracy by assessing four domains: patient selection, index test, reference standard, and flow and timing.

These methods were adapted to conduct the two reviews addressing the key topics of antimicrobial medicines for treating plague and the infectiousness of the bodies of people who died from plague. For the review on antimicrobial medicines for treating plague, evidence was gathered from data on humans and animals. For data on humans, the findings of an extensive systematic review conducted by CDC were used (12,13). For data on animals, a systematic review of evidence from studies in monkeys and rodents was conducted. See Annex 4 for a detailed description of the process and methods used for development of these guidelines.

The final drafts of these reviews were circulated to the GDG prior to the guideline development meeting.

2.5 Formulating recommendations

2.5.1 Evidence-to-decision considerations

The GDG formulated the recommendations during the 2-day meeting in September 2019 using the GRADE evidence-to-decision frameworks. Following the presentation of the results of the reviews and a summary of the findings, the GDG addressed each question with a full discus-

sion that included consideration of the certainty of the evidence, the desirable and undesirable effects, values and preferences, cost, acceptability, equity, feasibility and barriers to implementation. The GRADE evidence-to-decision tables were used to facilitate consensus and record the decisions of the GDG. The GDG developed final recommendations when possible and graded each of them as strong or conditional, using the criteria outlined in Annex 4.

2.5.2 Group decision-making

All of the recommendations were developed by the GDG and based on consensus. There was no need to proceed with a vote on any of the recommendations.

2.6 Peer review

The report of the guideline development meeting was circulated to all GDG members for feedback and comments; it comprised information about the evidence synthesis, the GRADE evidence-to-decision tables, the formulated recommendations and the methodology.

As a measure of quality assurance, the full report was peer reviewed by external reviewers with diverse areas of expertise (see Annex 2). The consultant in charge of developing the guideline assessed and incorporated comments into the final version before it was submitted to the WHO Guidelines Review Committee.

2.7 Stakeholders and the public

The GDG comprised members from key stakeholder groups, including clinicians, biologists, public health professionals, programme managers, researchers, an epidemiologist and an anthropologist. Representatives from Malagasy civil society were invited to be part of the guideline development meeting, but none attended.

2.8 Guiding principles

WHO's vision is of a world in which all people attain the highest possible level of health. These guidelines have been developed taking into account the values established in WHO's Constitution, which reflect the principles of human rights, universality and equity (14).

Plague is associated with poverty. People affected by plague may also suffer from discrimination and stigma. This may influence detection of the disease; the willingness to come forward for treatment; public health follow-up; and for those dying, the wish of relatives not to disclose the cause of death. However, health workers may indeed discriminate against individuals with plague and their communities. Therefore, the indicator framework based on the criteria of availability, accessibility, acceptability and quality must be considered in order to ensure equity in terms of economic, social and cultural rights when developing recommendations related to plague and when considering their implementation (15). In addition, all of the recommendations should be implemented while ensuring that adequate information is provided to the patient or caregiver in regard to the intervention (use of a diagnostic test, choice of an antibiotic), and care should be provided only after obtaining informed consent. Special consideration needs to be given to ensure that the implementation of the recommendations, especially those for the use of RDTs and personal protective equipment, does not put vulnerable people, families or communities at risk of discrimination and stigma related to the disease. Unintentional consequences and harms were considered at both the societal and individual levels.

The above factors were considered when developing recommendations at the evidence-to-decision stage. Decision-makers in countries where plague is endemic are urged to ensure that the policies derived from these guidelines uphold basic human rights.



CHAPTER 3

Recommendations

3.1 Use of F1RDT for plague

3.1.1 Background

Patients progress to an advanced stage of plague when diagnosis is delayed, resulting in poor outcomes and increased risk of further transmission of the disease. RDTs detect pathogen-specific antigens in a small quantity of different body fluids through lateral flow immunochromatography. In the case of plague, the F1RDT detects the F1 capsular antigen of *Y. pestis*, which is present in large amounts in buboes, blood and sputum from infected patients. The test is performed on sputum from patients with suspected pneumonic plague and on bubo aspirate from patients with suspected bubonic plague.

F1RDT can easily be used and interpreted by health workers without advanced training. Within 15 minutes, the test gives a semi-quantitative result that is interpreted according to the intensity of the line (from 1+ to 4+), although it is most commonly used as a qualitative test (positive or negative result) in which positivity is interpreted as soon as the line is visible. Therefore, F1RDT is a diagnostic tool that could help to establish a prompt diagnosis of plague, especially at the community level and in low-resource settings. Thus its use would improve patient care and help guide an appropriate public health response.

3.1.2 Use of F1RDT to detect pneumonic plague in plague-endemic areas

Recommendation

In areas where plague is known to occur, the GDG suggests using F1RDT in people with suspected pneumonic plague to rapidly detect the disease and implement an immediate public health response (alert tool).

While the initial public health response is being implemented, a confirmatory test (such as culture or molecular testing) should be carried out before declaring a confirmed plague outbreak, because F1RDT has limited specificity.

(Conditional recommendation, very low-certainty evidence)

3.1.2.1 Rationale for the recommendation

The evidence was derived from a limited number of patients in case series and was of very low certainty.

F1RDT seems highly sensitive for detecting pneumonic plague, but it showed a specificity of 70.6%. Therefore, a negative F1RDT helps rule out the disease, but a positive F1RDT needs to be combined with other laboratory evaluations to confirm the diagnosis. The test was compared only with culture, which might be an imperfect reference standard that leads to a high level of false positives. The high level of false positives is of concern, as it can have serious consequences, such as unnecessary social alarm and economic repercussions.

3.1.2.2 Supporting evidence

A systematic review was conducted to elucidate the role of F1RDT in diagnosing plague (16). The review included studies in which individuals clinically suspected of having plague were tested with both F1RDT and at least one reference standard: isolation of *Y. pestis* by culture, polymerase chain reaction (PCR) or paired serology.

Three studies that reported data about using F1RDT to detect pneumonic plague were identified. Two studies were conducted in Madagascar (one during an outbreak and the other based on 17 years of national surveillance data that included data from outbreaks) and one in the Democratic Republic of the Congo (with data from two outbreaks). The overall risk of bias in relation to patient selection was high on QUADAS-2, reflecting the circumstances in which the test was being used.

Compared with culture, the sensitivity of F1RDT appeared high (100%), but in a meta-analysis of 56 participants, 3 patients in a small outbreak tested negative, which resulted in very wide confidence intervals [CIs] (0% to 100%). The specificity was 70.6% (95% CI: 59.3 to 79.8). However, the evidence was of very low certainty, and there were insufficient data to make any estimates comparing F1RDT with either PCR or paired serology.

The findings indicate that if F1RDT was used in a population of 1000 people in a plague-endemic area with an indicative prevalence rate of 4% (pre-test probability) and the results were compared with those obtained using culture, F1RDT would correctly diagnose all 40 patients (with wide confidence intervals) and would not miss any with plague, but it would also diagnose 278 patients as having plague who were culture negative.

3.1.2.3 Evidence-to-decision considerations

The GDG agreed that F1RDT is an important part of public health programmes addressing plague. The GDG noted the difficulty of obtaining good-quality samples from sputum in the field, which reduces the sensitivity of the reference standard.

The GDG discussed the problem of culture being an imperfect reference standard. The apparent high level of false positives with F1RDT when culture is the reference standard may be due to a false-negative result on culture (people have plague but test culture negative), for example, due to poor sampling or prior antibiotic use. The GDG concluded that for negative F1RDTs, the test helps rule out the disease. For positive F1RDTs, the test needs to be combined with other laboratory evaluations to confirm the diagnosis.

In considering the desirable effects, clearly the test provides early alerts of an outbreak; it is easy to perform; and it makes testing possible in remote and resource-constrained areas. Early detection will ensure prompt treatment and reduce the risk of transmission. However, the GDG considered the societal and individual consequences of using the test: false positives can have serious consequences, including false alarms and economic repercussions. The GDG recommended that the test be used only where there is capacity for patients to undergo further investigations, so that false alarms are mitigated. This may challenge health equity: although the

ease of access and performance of F1RDT is beneficial to communities in remote and resource-constrained areas, the need for confirmatory investigations may have negative consequences for these populations. Communities value the rapid result from the F1RDT, but adequate information about the test should be provided to the patient, ensuring informed consent, and delays in confirmatory testing need to be carefully managed by using risk communication strategies and approaches. WHO's guiding principles for risk communication include: (i) create and maintain trust; (ii) acknowledge and communicate, even in uncertainty; (iii) coordinate with partners before, during and after an emergency; (iv) be transparent and rapid with the initial and all subsequent communications; (v) be proactive in public communication; (vi) involve and engage those affected; (vii) use integrated approaches; and (viii) build national capacity and support national ownership (17).

3.1.2.4 Implementation considerations

The GDG noted that the test would be used only for people who can produce sputum. The GDG also noted the importance of the test being administered by properly trained health care workers and in accordance with the manufacturer's instructions. Consent should be obtained before performing the test, and the information presented to obtain consent should be non-stigmatizing and clear about the expected consequences of a positive or negative test result. The result of the test needs to be disclosed to the patient in a manner that ensures confidentiality.

3.1.3 Use of F1RDT to diagnose pneumonic plague in patients in areas where an outbreak is in progress

Recommendation

During an outbreak, the GDG suggests using F1RDT in people with suspected pneumonic plague to provide rapid diagnosis at the point of care. A negative result helps rule out the disease and encourages consideration of an alternative diagnosis. A confirmatory test (such as culture or molecular testing) should be carried out at the same time.

(Conditional recommendation, very low-certainty evidence)

3.1.3.1 Rationale for the recommendation

The evidence was derived from a limited number of patients in case series and was of very low certainty.

F1RDT seems highly sensitive for detecting pneumonic plague, but it showed a specificity of 70.6%. Therefore, a negative F1RDT helps rule out the disease and encourages consideration of alternative diagnoses. A positive F1RDT might not help in the acute management of the disease because in the context of an outbreak treatment will be started based on clinical suspicion, and a positive F1RDT needs to be combined with other laboratory evaluations to confirm the diagnosis. The test was compared only with culture, which might be an imperfect reference standard that leads to a high level of false positives. In this scenario, the high level of false positives raises concern about the implications it may have for delaying treatment of the true underlying condition.

3.1.3.2 Supporting evidence

Evidence was provided by the findings of a systematic review examining the accuracy of F1RDT for diagnosing plague (16).

The main findings relevant to pneumonic plague are presented in the recommendation. They indicate that if F1RDT was used in a population of 1000 people in a plague-endemic area where an outbreak is in progress, with an indicative prevalence rate of 20% (pre-test probability), the test would correctly diagnose all 200 patients (with wide confidence intervals) and would not miss any with plague, but it would also diagnose 232 patients as having plague who were culture negative.

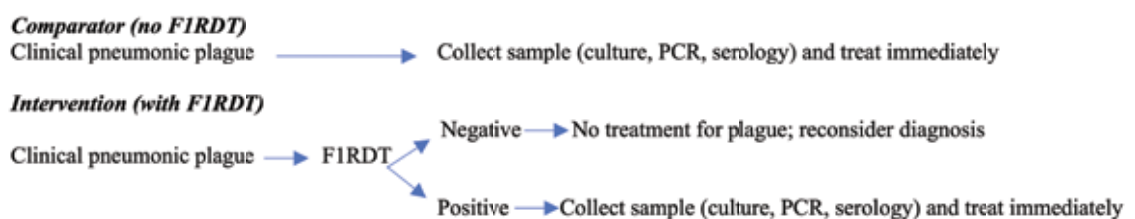
3.1.3.3 Evidence-to-decision considerations

The GDG evaluated how F1RDT would be useful in clinical management in the context of an epidemic when used in patients with clinical symptoms and signs; in particular, the GDG considered whether it contributed to ensuring better quality care and better outcomes. Fig. 1 shows the two clinical scenarios considered by the GDG: one with F1RDT and one without.

The GDG discussed the problem of culture being an imperfect reference standard. The apparent high level of false positives with F1-RDT when culture is the reference standard may be due to a false-negative result on culture (people have plague but test culture negative), for example, due to poor sampling or prior antibiotic use. Therefore, the GDG concluded that a negative F1RDT result helps rule out the disease. A positive F1RDT result needs to be combined with other laboratory evaluations to confirm the diagnosis, but treatment can be started prior to confirmation. The uncertainty of the evidence around false positives may have a negative impact on patient care because the false-positive test is taken to indicate plague and this may delay or prevent investigation into and treatment of the true underlying condition.

The GDG also pointed out that the availability of and access to F1RDT are likely to improve clinical detection and treatment of the poorest people (which is particularly relevant for plague because it occurs in remote areas in resource-constrained settings). The use of F1RDT has potential cost savings in ruling out pneumonic plague, but costs may be incurred for false-positive cases.

Fig. 1. Two clinical scenarios considered by the GDG for the use of F1RDT for plague in the context of an epidemic



F1RDT: rapid diagnostic test based on the F1 antigen; PCR: polymerase chain reaction.

3.1.3.4 Implementation considerations

The GDG specified that F1RDT might best be used for patients with a clinical presentation compatible with plague **and** who are able to produce sputum. In this way, treatment can be started in endemic settings independently of test findings and does not rely on a positive test. The GDG specified that the test is most useful in indicating the need to investigate alternative diagnoses in the case of a negative result. The GDG also noted the importance of the test being administered by properly trained health care workers and in accordance with the manufacturer's instructions. Consent should be obtained before performing the test, and the information presented to obtain consent should be non-stigmatizing and clear about the expected consequences of a positive or negative test. The result of the test needs to be disclosed to the patient in a manner that ensures confidentiality.

3.1.4 Use of F1RDT to detect bubonic plague in plague-endemic areas

Recommendation

In areas where plague is known to occur, the GDG recommends using F1RDT in people with suspected bubonic plague to rapidly detect plague and implement an immediate public health response (alert tool).

While the initial public health response is being implemented, a confirmatory test (such as culture or molecular testing) should be carried out before declaring a confirmed plague outbreak, because F1RDT has limited specificity.

(Strong recommendation, very low-certainty evidence)

3.1.4.1 Rationale for the recommendation

Although the evidence was derived from a limited number of patients in case series and was of very low certainty, the GDG judged that the desirable effects of using F1RDT in this scenario far outweighed the undesirable effects. F1RDT showed high sensitivity for detecting bubonic plague and high specificity when compared with PCR for some of the genes targeted. The concern about missing an outbreak was lower than for the case of pneumonic plague due to the higher likelihood of the diagnosis of bubonic plague in a person with a painful bubo compared with the likelihood of diagnosing pneumonic plague in a person presenting with respiratory symptoms, such as cough and fever. There were limited concerns about the level of false positives, and F1RDT was valued as a useful tool to detect bubonic plague.

3.1.4.2 Supporting evidence

The accuracy of F1RDT for detecting bubonic plague was assessed in the systematic review (16).

Two studies that reported data about using F1RDT to detect bubonic plague were identified, both from Madagascar (one conducted during a period of almost 2 years and the other based on 17 years of national surveillance data that included data from outbreaks). The overall risk of bias in relation to patient selection was high on QUADAS-2, reflecting the circumstances in which the test was used.

Compared with culture results, the sensitivity of F1RDT appeared high (100%). The specificity was 67% (95% CI: 65 to 70). However, the evidence for sensitivity was of low certainty and that for specificity was of very low certainty. One study compared F1RDT with PCR for three genes (*caf1*, *pla*, *ymt*). In that study, sensitivity ranged from 72% to 95%, and specificity ranged

from 77% to 93%. When compared with PCR targeting the *cafI* gene, the sensitivity was 95% (95% CI: 89 to 99) and the specificity was 93% (95% CI: 84 to 98). Neither of the two studies compared F1RDT with paired serology.

The findings indicated that if F1RDT was used in a population of 1000 people in a plague-endemic area with an indicative prevalence rate of 4% (pre-test probability) and the results were compared with those obtained using culture, the test would correctly diagnose all 40 patients (confidence intervals not calculable) and would not miss any with plague, but it would also diagnose 317 patients as having plague who were culture negative. If the results were compared with those obtained using PCR targeting *cafI*, F1RDT would correctly diagnose 38 patients (with narrow confidence intervals) and would miss 2 patients with plague; it would also diagnose 67 patients as having plague who were PCR negative.

3.1.4.3 Evidence-to-decision considerations

The GDG agreed that F1RDT is an important part of public health programmes addressing plague.

The GDG discussed the difference in the specificity of F1RDT when compared with culture and with PCR. The lower false-positive rate when comparing F1RDT with PCR rather than culture highlighted again that culture is an imperfect reference standard. Therefore, the GDG was less concerned about the high false-positive rate when culture is used as the reference standard.

Negative F1RDTs help rule out the disease. Positive F1RDTs need to be combined with other laboratory evaluations to confirm the diagnosis, but the presence of a painful bubo makes the likelihood of the diagnosis very high, regardless of the test results.

In considering the desirable effects, it is clear the test provides a rapid means of detecting an outbreak, it is easy to perform, and it can be used in remote and resource-constrained areas. Early detection will ensure prompt alerts of outbreaks and treatment of patients and also provides a signal to implement rodent- and flea-control activities. The GDG recognized that the consequences of missing an outbreak (false negative) would be substantial, but considered this was of low concern due to the high sensitivity of the test and the high likelihood of the diagnosis in the presence of a painful bubo. The GDG was less concerned about false positives, acknowledging the more reassuring results of F1RDT when compared with those obtained using PCR. The GDG also noted the usefulness of F1RDT in countries considered to be at risk because they share borders with a country where an outbreak is in progress, and agreed that F1RDT was a valuable and cost-effective tool for communities in these countries.

Communities value the benefit of an early alert from F1RDT. Although delays in confirmatory tests need to be carefully managed, delays in receiving an alert would additionally be present if F1RDT was not available, and any intervention that provides rapid notification of an outbreak was considered to be helpful.

3.1.4.4 Implementation considerations

The GDG emphasized the importance of using F1RDT according to the indications for its use in patients fulfilling the clinical case definition of bubonic plague. The test must be administered by properly trained healthcare workers and in accordance with the manufacturer's instructions. Consent should be obtained before performing the test, and the information presented to obtain consent should be non-stigmatizing and clear about the expected consequences of a positive or negative test. The result of the test needs to be disclosed to the patient in a manner that ensures confidentiality.

3.1.5 Use of F1RDT to diagnose bubonic plague in patients in areas where an outbreak is in progress

Recommendation

During an outbreak, the GDG suggests using F1RDT in people with suspected bubonic plague to provide rapid diagnosis at the point of care. A confirmatory test (such as culture or molecular testing) should be carried out at the same time.

(Conditional recommendation, very low-certainty evidence)

3.1.5.1 Rationale for the recommendation

The evidence was derived from a limited number of patients in case series and was of very low certainty.

F1RDT showed high sensitivity for detecting bubonic plague and high specificity when compared with PCR for some of the genes targeted. Although the test might be useful in some cases and scenarios, there was uncertainty about how much the use of F1RDT would contribute to case management in a patient with a painful swollen lymph node when an outbreak is in progress.

3.1.5.2 Supporting evidence

The findings of the systematic review on the accuracy of F1RDT for diagnosing bubonic plague are summarized in the recommendation (16). They indicate that if F1RDT was used in a population of 1000 people in an area where an outbreak is in progress, with an indicative prevalence rate of 50% (pre-test probability), and the results were compared with those obtained using culture, F1RDT would correctly diagnose all 500 patients (confidence intervals not calculable) and would not miss any with plague, but it would also diagnose 165 patients as having plague who were culture negative. If the same indicative prevalence rate of 50% was used and the results were compared with those obtained using PCR (*caf1*), F1RDT would correctly diagnose 475 patients (with narrow confidence intervals) and would miss 25 patients with plague; it would also diagnose 35 patients as having plague who were PCR negative.

3.1.5.3 Evidence-to-decision considerations

The GDG discussed how much F1RDT would contribute to care when an outbreak was in progress and a patient had a typical bubo. The GDG recognized the difficulties in obtaining samples, especially from small buboes.

The GDG debated extensively about whether the test actually made a difference to the initiation of treatment during an outbreak. When assessing how much F1RDT would contribute to case management in a patient with a painful swollen lymph node during an outbreak, some members considered that in these circumstances, a clinician would simply begin treatment and send bubo aspirate for confirmatory diagnosis, without the need for F1RDT due to the high clinical certainty of plague. In addition, if there was local epidemiological evidence that this was a case (for example, if others living nearby had the disease), then F1RDT would not be particularly useful because clinicians would in any case treat the patient.

However, the GDG noted that there were some circumstances in which the test might be useful, such as when there is no obvious evidence of transmission in the community (for exam-

ple, in a particular village or household, although an outbreak is in progress in surrounding areas) or the clinical manifestations are less obvious. In these circumstances, a negative test might help clinicians consider other underlying causes.

The GDG agreed that a positive FIRDТ would help to confirm the diagnosis of bubonic plague. If the test is negative, it may prompt the clinician to seek other diagnoses in order to provide appropriate treatment (in the case of a true negative). However, it is important that the clinician interprets the result in light of the clinical presentation of the patient and the epidemiological context (in the case of a false-negative result, which is associated with a small risk of evolution of the disease to pneumonic plague, potentially leading not only to spread of the disease but also to a fatal outcome).

On balance, the use of the test was considered to be helpful in terms of informing both the clinician and the patient by providing an early result. However, the use of an early result to inform patients about their unconfirmed diagnosis needs to be managed cautiously by the health care workers performing the test; thus appropriate risk communication strategies should be used and the patient's confidentiality must be ensured.

3.1.5.4 Implementation considerations

The likelihood of diagnosing bubonic plague in a person with a painful bubo during a previously declared outbreak of bubonic plague is high, and antibiotics are likely to be prescribed based on clinical diagnosis. Therefore, the GDG noted that the usefulness of the test is not to provide a basis for treatment initiation (because treatment might be started independently of the test findings), but rather to encourage the consideration of other diagnoses in patients with a negative test. Consent should be obtained before performing the test, and the information presented to obtain consent should be non-stigmatizing and clear about the expected consequences of a positive or negative test. The result of the test needs to be disclosed to the patient in a manner that ensures confidentiality.

3.2 Antibiotics for treating plague

3.2.1 Background

If detected and treated early with appropriate antibiotics, the cure rate among confirmed cases of plague is high.

In 2009, the guidelines published by the WHO Regional Office for South-East Asia recommended treatment of suspected or confirmed cases with streptomycin, gentamicin, doxycycline, oxytetracycline, ciprofloxacin or chloramphenicol for at least 10 days, without ranking the antibiotics or commenting on the particular suitability of any specific class for the various clinical forms of plague (2). For postexposure presumptive treatment, the 2009 guidelines state that the preferred antibiotics are tetracyclines, chloramphenicol or one of the effective sulfonamides for 7 days. For chemoprophylaxis prior to exposure, the options given are tetracycline, doxycycline, sulfamethoxazole + trimethoprim, or ciprofloxacin.

Globally, countries generally follow the 2009 WHO guidelines. However, fluoroquinolones have also been used for treating people with plague, and streptomycin and chloramphenicol are becoming less available worldwide due to reduced production.

Fluoroquinolones are or can be made easily available and accessible in all settings (including remote areas), and they do not present challenges in terms of storage and administration. They have a safe profile and are usually well accepted by patients and health professionals.

3.2.2 Development of recommendations on antibiotics for treating plague

The methodologist proposed that the GDG consider all classes of currently used antibiotics for all types of plague treatment, including postexposure presumptive treatment and pre-exposure chemoprophylaxis, and carefully appraise options for making changes to the 2009 WHO guidelines.

The GDG reviewed the evidence and formulated recommendations based on the effectiveness of antibiotics in people with confirmed plague. The GDG agreed not to use a syndromic approach, which would consider choosing an antibiotic based on a patient's symptoms, such as fever and cough, in a particular epidemiological context.

3.2.3 Supporting evidence

As only one randomized controlled trial evaluating treatments for plague in humans was available, the Evidence Review Team systematically summarized a range of relevant data to help inform decision-making. This included drawing on the systematic review of case series conducted by CDC and other observational data in humans, referred to in Web Annex A.

The Evidence Review Team generated a series of therapeutic questions and used systematic methods to assemble data from multiple sources, such as information about pharmacological properties and safety characteristics from a variety of standard clinical pharmacology texts, summaries of human data from the systematic review conducted by CDC, and summaries of animal data (see Web Annex A). See Table 2 for a summary of recommendations on the use of antibiotics for treatment or prevention of plague.

Table 2. Summary of recommendations on the use of antibiotics to treat or prevent plague

Indication	Form of plague	Antibiotic	Recommendation	New recommendation?
Treatment	Pneumonic or septicaemic	Fluoroquinolones	The GDG suggests adding fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) to the first-line medicines recommended for treating pneumonic or septicaemic plague (streptomycin and gentamicin) (Conditional recommendation, very low-certainty evidence)	Yes
		Streptomycin or gentamicin	First-line choice	No ^a
	Bubonic	Fluoroquinolones	The GDG suggests adding fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) to the first-line medicines recommended for treating bubonic plague (streptomycin, doxycycline and gentamicin) (Conditional recommendation, very low-certainty evidence)	Yes
		Streptomycin, doxycycline or gentamicin	First-line choice	No ^a
	Meningitis	Fluoroquinolones	The GDG suggests adding fluoroquinolones (moxifloxacin and ofloxacin) to the first-line medicine recommended for treating plague meningitis (chloramphenicol) (Conditional recommendation, very low-certainty evidence)	Yes
		Chloramphenicol	First-line choice	No ^a
Postexposure presumptive treatment	NA	Fluoroquinolones	The GDG suggests adding fluoroquinolones (ciprofloxacin) to the first-line medicines recommended for postexposure presumptive treatment (doxycycline and sulfamethoxazole + trimethoprim) (Conditional recommendation for either the intervention or the comparison, very low-certainty evidence)	Yes
		Doxycycline or sulfamethoxazole+ trimethoprim	First-line choice	No ^a
Pre-exposure chemoprophylaxis	NA	Tetracycline, doxycycline, sulfamethoxazole + trimethoprim or ciprofloxacin	First-line choice	No ^a

GDG: Guidelines Development Group; NA: not applicable.

^a Recommended in the WHO *Operational guidelines on plague surveillance, diagnosis, prevention and control* (2).

3.2.4 Use of fluoroquinolones for treating pneumonic or septicaemic plague

Recommendation

The GDG suggests adding fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) to the first-line medicines recommended for treating pneumonic or septicaemic plague (streptomycin and gentamicin).
(Conditional recommendation, very low-certainty evidence)

3.2.4.1 Rationale for the recommendation

There are no human data from comparative studies. The evidence comes from observational studies in humans and from data on animals. Although the certainty of the evidence is very low, the GDG expressed confidence in using fluoroquinolones as a first-line choice for treating pneumonic plague. However, there are no cost-effectiveness studies, and several implementation considerations may need to be taken into account.

3.2.4.2 Supporting evidence

Mortality is close to 100% from pneumonic and septicaemic plague without prompt, effective treatment. Streptomycin has been available for many years and became the standard treatment based on retrospective studies from the late 1940s and on the successful treatment of thousands of cases of plague in Viet Nam during the 1960s. The current therapeutic question is whether fluoroquinolones can be used for treatment. Therefore, the GDG formally considered fluoroquinolones, comparing them with streptomycin, drawing on the evidence summary in Web Annex A and following the framework detailed in Web Annex B.

For fluoroquinolones, the data on pharmacological properties and from animal models and case series in humans indicate that fluoroquinolones are effective in treating plague, but the data to compare their effectiveness with that of streptomycin are insufficient. The advantages of fluoroquinolones when compared with streptomycin are that they can be administered orally, have fewer side effects and patients do not need biological monitoring.

3.2.4.3 Evidence-to-decision considerations

The GDG acknowledged the effectiveness of fluoroquinolones for treating pneumonic plague, although this comes from very low-certainty evidence. In addition, fluoroquinolones have been used, with successful outcomes, as one of the options for first-line treatment in a few countries. Fluoroquinolones are efficacious for treating other bacterial lung infections, which provides further indirect support for their use in pneumonic plague.

The GDG also acknowledged the above-mentioned advantages of fluoroquinolones and noted that their oral formulation makes them more acceptable, and this will improve equity of access to treatment among populations that are poor and/or isolated (18,19).

The GDG noted that the cost of fluoroquinolones varies greatly between the individual medicines in this class and between countries. No cost-effectiveness studies have been performed, although a randomized controlled trial planned to assess the effectiveness of streptomycin versus ciprofloxacin for treating bubonic plague in Madagascar will include this as a component.

3.2.4.4 Implementation considerations

Patients with severe plague might need parenteral antibiotics until the oral route is tolerated and not contraindicated. The GDG noted that health care staff familiar with giving streptomycin intramuscularly might be unfamiliar with giving fluoroquinolones intravenously, and thus there might be a need for training. In addition, health care staff are used to giving streptomycin, so the move to fluoroquinolones would require training to ensure that the change in first-line treatment takes place.

3.2.5 Use of doxycycline for treating pneumonic or septicaemic plague

Doxycycline is currently an option for treating pneumonic and septicaemic plague, although some clinicians consider that it is less effective than other medicines.

The GDG noted that data in the evidence summary are limited (Web Annex A). The GDG recognized that doxycycline is used as first-line treatment in some settings for milder forms of pneumonic or septicaemic plague, but clinicians would probably not use doxycycline to treat more severe forms.

The GDG agreed that no new recommendation was required.

3.2.6 Use of fluoroquinolones for treating bubonic plague

Recommendation

The GDG suggests adding fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) to the first-line medicines recommended for treating bubonic plague (streptomycin, doxycycline and gentamicin). (Conditional recommendation, very low-certainty evidence)

3.2.6.1 Rationale for the recommendation

There are no human data from comparative studies. The evidence comes from observational studies in humans and from data in animals. Although the certainty of the evidence is very low, and although oral tetracyclines are well accepted as the main treatment for bubonic plague, fluoroquinolones could be used as a first-line option for treating bubonic plague.

3.2.6.2 Supporting evidence

The current therapeutic question is whether fluoroquinolones can be used for treating bubonic plague. Therefore, the GDG formally considered fluoroquinolones, comparing them with doxycycline, drawing on the evidence summary in Web Annex A and following the framework detailed in Web Annex B.

The pharmacological properties of fluoroquinolones and findings from animal models and case series in humans indicate that fluoroquinolones are effective in treating plague, but there are insufficient data to compare their effectiveness with that of doxycycline.

3.2.6.3 Evidence-to-decision considerations

For the antibiotic treatment of bubonic plague, the GDG considered the case of patients who had bubonic plague without any signs or symptoms indicative of septicaemic, pneumonic or any other severe form of plague.

The GDG noted that countries mainly use oral doxycycline for treating bubonic plague. The GDG noted the evidence summary comparing doxycycline with streptomycin (Web Annex A) and agreed that doxycycline is accepted as the main treatment for bubonic plague.

The GDG agreed that fluoroquinolones have fewer side effects than doxycycline and do not present additional undesirable effects. Both fluoroquinolones and doxycycline can be administered orally, and the GDG did not raise any concern regarding the acceptability, equity or feasibility of introducing fluoroquinolones as an option for treating bubonic plague.

3.2.6.4 Implementation considerations

No implementation considerations were reported.

3.2.7 Use of fluoroquinolones for treating plague meningitis

Recommendation

The GDG suggests adding fluoroquinolones (moxifloxacin and ofloxacin) to the first-line medicine recommended for treating plague meningitis (chloramphenicol).
(Conditional recommendation, very low-certainty evidence)

3.2.7.1 Rationale for the recommendation

There are no comparative data from human studies. The evidence comes from observational studies of pneumonic and bubonic plague. Despite the uncertainty, the GDG was confident in recommending fluoroquinolones as a first-line medicine of choice for plague meningitis, considering the side effects of the alternative (chloramphenicol).

3.2.7.2 Supporting evidence

The GDG formally compared fluoroquinolones with chloramphenicol for treating plague meningitis, drawing on the evidence summary in Web Annex A and following the framework detailed in Web Annex B.

As already discussed for the pneumonic, septicaemic and bubonic forms, fluoroquinolones are considered effective for treating plague based on indirect comparisons. For plague meningitis, there are insufficient data comparing their effectiveness with that of chloramphenicol.

3.2.7.3 Evidence-to-decision considerations

The 2009 WHO guidelines do not provide any specific recommendations for treating plague meningitis (2).

Chloramphenicol has been widely used for treating plague meningitis because it is more able to cross the blood–brain barrier than are other antibiotics. However, it has potentially severe adverse effects, is not widely available and is becoming less available worldwide.

The GDG acknowledged the lack of direct supportive evidence for using fluoroquinolones to treat plague meningitis and considered an indirect approach based on the effectiveness of fluoroquinolones for pneumonic and bubonic plague. Selected fluoroquinolones have good cerebrospinal fluid penetration and are efficacious for treating bacterial meningitis, which provides further indirect support for this indication. The GDG considered that fluoroquinolones present considerable advantages because they have fewer side effects than chloramphenicol and are still widely available.

3.2.7.4 Implementation considerations

Clinicians need to select a fluoroquinolone with good cerebrospinal fluid penetration, for example moxifloxacin or ofloxacin.

3.2.8 Use of fluoroquinolones for postexposure presumptive treatment

Recommendation

The GDG suggests adding fluoroquinolones (ciprofloxacin) to the first-line medicines recommended for postexposure presumptive treatment (doxycycline and sulfamethoxazole + trimethoprim).
(Conditional recommendation for either the intervention or the comparison, very low-certainty evidence)

3.2.8.1 Rationale for the recommendation

There are no comparative data from human studies. The evidence comes from observational studies of pneumonic and bubonic plague. Overall, fluoroquinolones could be used as an option for postexposure presumptive treatment, but there is uncertainty about how this would be beneficial or prejudicial when compared with the alternative (doxycycline).

3.2.8.2 Supporting evidence

The GDG formally compared the use of fluoroquinolones with doxycycline for postexposure presumptive treatment, drawing on the evidence summary in Web Annex A and following the framework detailed in Web Annex B.

Fluoroquinolones are effective for treating plague based on indirect comparisons and observational data. There are insufficient data from studies assessing the use of fluoroquinolones compared with doxycycline for postexposure presumptive treatment.

3.2.8.3 Evidence-to-decision considerations

The 2009 WHO guidelines recommend postexposure presumptive treatment for all persons who within the previous 7 days have been in close contact with patients who have pneumonic plague, have been in contact with contaminated body fluids or tissues, have been exposed to infectious samples during a laboratory accident or have been exposed to infected fleas (2). The GDG emphasized that in these scenarios, the exposed persons must be presumed to be infected with plague, even if they are asymptomatic. Therefore, postexposure presumptive treatment aims to avoid the possible evolution from infection to disease.

For postexposure presumptive treatment, the 2009 WHO guidelines state that the preferred antibiotics for 7-day treatment are tetracyclines, chloramphenicol or one of the effective sulfonamides. All members of the GDG agreed that doxycycline or one of the effective sulfonamides, such as sulfamethoxazole + trimethoprim, should be used for postexposure presumptive treatment, although chloramphenicol was not mentioned during the discussion. The GDG agreed that there was no need for further discussion about this. This applies to postexposure presumptive treatment for any type of exposure to *Y. pestis* as long as the person is asymptomatic.

The GDG acknowledged that fluoroquinolones are effective for treating plague (as discussed in previous sections), based on their pharmacological properties and data from animals and human case reports. There were insufficient data both on their effectiveness compared with doxycycline and on the use of fluoroquinolones for postexposure presumptive treatment. However, the GDG noted that their effectiveness should not differ from that of doxycycline for treating plague, and had already agreed that fluoroquinolones could be used as an option for treating all forms of plague. Nonetheless, it was noted that if fluoroquinolones were available in major cities and not in rural areas, a recommendation in favour of fluoroquinolones could (temporarily) disadvantage poor, rural communities.

The GDG considered the use of fluoroquinolones as alternatives for patients who have adverse effects from doxycycline. However, the GDG expressed concern about using ciprofloxacin in situations where a considerable number of persons need to receive postexposure treatment (such as in a large outbreak) due to the possibility of resistance developing.

3.2.8.4 Implementation considerations

No implementation considerations were reported.

3.2.9 Antibiotics for pre-exposure chemoprophylaxis

The 2009 WHO guidelines list tetracycline, doxycycline, sulfamethoxazole + trimethoprim and ciprofloxacin as options for chemoprophylaxis prior to exposure (2). The GDG acknowledged that there was no need for further discussion of this recommendation with respect to any type of exposure to *Y. pestis*. The GDG highlighted the general consensus based on expert opinion that the duration of chemoprophylaxis should last until 7 days after the end of the exposure. The GDG agreed that no new recommendation was required.

3.3 Use of personal protective equipment

3.3.1 Background

The level and duration of infectiousness of the body of someone who was infected with plague is a long-standing issue, the resolution of which has practical consequences for the management of cases of plague. A set of preventive measures was established in Madagascar during the 2017 outbreak, but there was uncertainty about the level of personal protective measures, if any, required for people handling the bodies of those who had died of plague.

The 2009 WHO guidelines recommend the use of “masks, protective clothing, boots and thick rubber gloves” for undertakers involved in the disposal of the bodies of plague victims (2). Chemoprophylaxis is also recommended for professionals handling bodies.

The GDG recognized the need to look at the evidence around the contagiousness of the dead bodies of people who were infected with plague in order to revisit the existing recommendations.

Recommendation

The GDG suggests using personal protective equipment when handling the dead body of a person who was infected with plague. The minimum required equipment includes a gown, goggles, an N95 mask and gloves.

(Conditional recommendation, very low-certainty evidence)

3.3.1.1 Rationale for the recommendation

Plague can be acquired from the remains of someone who was infected with plague. However, there is uncertainty about the conditions under which transmission may occur and about which body fluids are infectious, as well as the duration of infectiousness. Due to the severity of the disease, some personal protective equipment should be used when people are exposed to the remains of someone who was infected with plague, but the level of protection required remains undetermined.

3.3.1.2 Supporting evidence

There is no direct evidence that examines the contagiousness of the remains of someone who was infected with plague. The Evidence Review Team separated the questions and systematically examined: (i) evidence of the infectiousness of different body fluids in people who are ill with plague; (ii) reported cases of plague acquired from human or animal remains; and (iii) evidence of body fluid infectiousness in animal and human remains, including the duration of infectiousness (20). The main findings of this systematic review are summarized below.

- The evidence shows that direct transmission through infective cough droplets may occur, but some of the reports indicate that this occurs only after close and prolonged exposure.
- Handling the remains of someone who has been infected with plague can lead to bubonic plague. Some studies have described people who developed axillary bubonic plague after handling the remains of humans or animals infected with plague with bare hands that had open skin lesions, while persons with intact skin exposed to the same remains were not infected. However, some studies that reported infection in people who handled human remains did not specify whether those who became infected had any skin abrasions or cuts. The low certainty of the evidence means that it is not clear whether infection occurs only in people with skin abrasions or cuts.
- It is possible that pneumonic plague could be transmitted by actions that provoke aerosolization of infected body fluids, but these actions would require considerable manipulation of a corpse.
- The infectiousness of body fluids other than sputum and blood (i.e. urine, faeces, sweat or bubo pus) remains unknown.
- It is not known for how long *Y. pestis* can survive in the body fluids of people who die from plague, and thus for how long the remains are infectious. One case reported infection from an animal 35 hours after its death, which means that whatever the size of the risk, it may extend well beyond 24 hours.

3.3.1.3 Evidence-to-decision considerations

The GDG considered two questions: (i) whether full personal protective equipment is required by health staff, mortuary workers or family members to avoid infection; and (ii) whether infectiousness changes between the time immediately after death and up to 24 hours after death.

The GDG affirmed by consensus that the duration of the risk of infectivity is unknown. The GDG considered that it had no evidence of a decline in transmission over time and, therefore, the use of personal protective equipment should be standardized and remain until burial.

The GDG noted that *Y. pestis* can be isolated from the cerebrospinal fluid of a patient with plague meningitis, but did not come to a consensus on whether *Y. pestis* is present in other body fluids, such as sweat or tears.

Although difficult to quantify, the GDG acknowledged the risk of infection from the remains of people who have died from plague and that some personal protective equipment is required, but the necessary level of protection remains undetermined.

The GDG recommended that anyone handling the remains of someone who was infected with plague should take at least minimum precautions by using personal protective equipment comprising a gown, goggles, an N95 mask and gloves. More basic levels of personal protective equipment were discussed but were not considered to provide sufficient protection.

The GDG agreed with the existing WHO recommendation from 2009 that chemoprophylaxis could be an option, but that it should not replace the use of personal protective equipment (2).

3.3.1.4 Implementation considerations

The availability and adequate quality of personal protective equipment should be ensured in all settings so that people have access to the appropriate standard of such equipment and adequate information on its use. The GDG acknowledged that although these preventive measures are likely to be accepted by many relatives preparing human remains, there are settings or circumstances in which the preparation of a dead body and funeral rites are culturally important, and in these situations the use of personal protective equipment might interfere with rituals, thus decreasing the acceptability of these measures. The GDG recommended using communication interventions to address the risks to communities related to certain practices involving the handling of a body both at home and during funeral rites. The potential unintentional consequences of implementing this recommendation need to be minimized by maintaining confidentiality regarding the cause of death to protect the affected families. Care should be taken to ensure that the dignity of the deceased and surviving family members is respected.

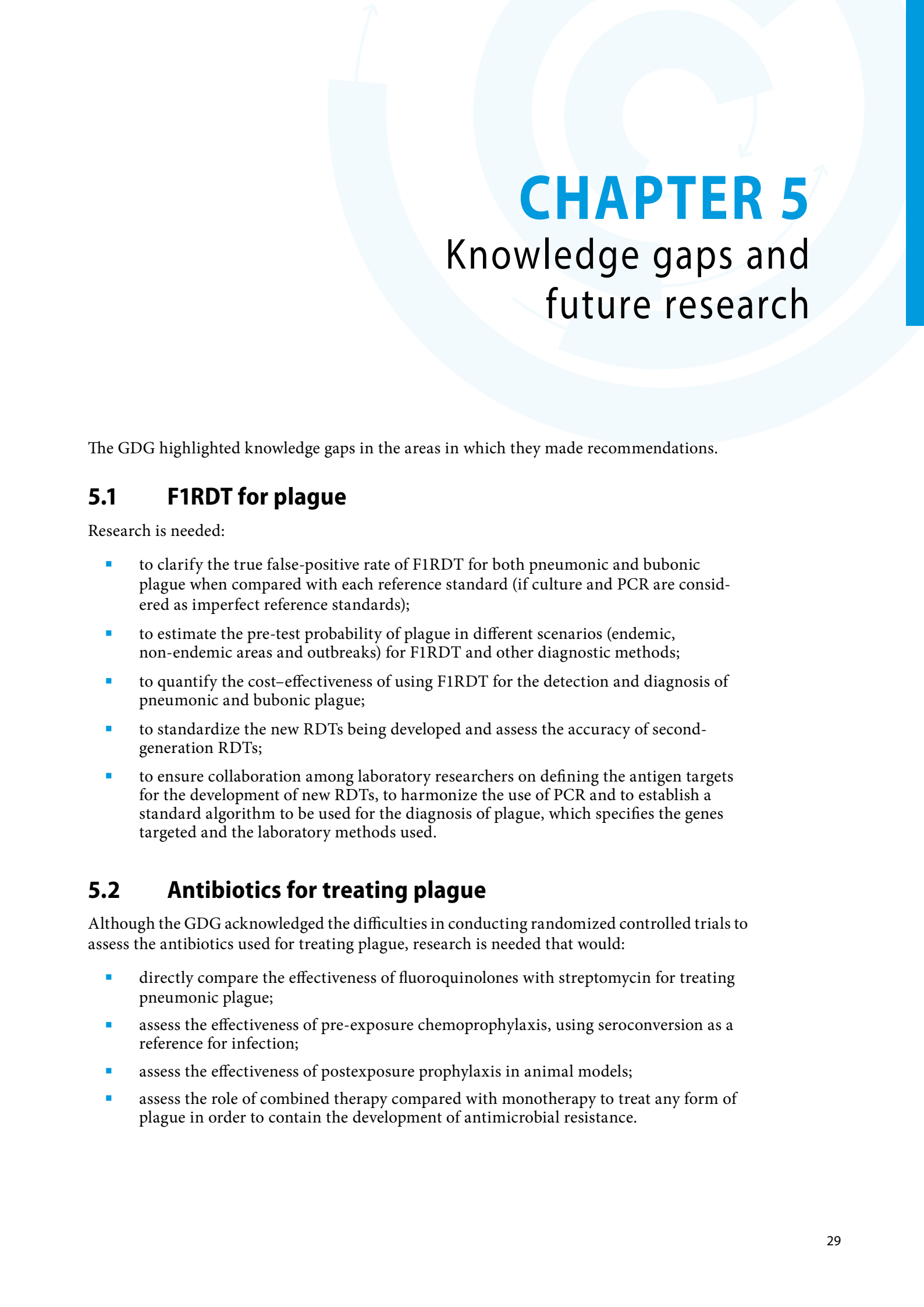


CHAPTER 4

Monitoring and evaluation

The GDG recommended monitoring *Y. pestis* resistance to fluoroquinolones at the national level. The reason for this is that resistance to this class of antimicrobials develops quickly in a range of organisms when these medicines are used to treat other conditions.

Other activities for monitoring and evaluation should follow previous guidelines and national policies (2).



CHAPTER 5

Knowledge gaps and future research

The GDG highlighted knowledge gaps in the areas in which they made recommendations.

5.1 F1RDT for plague

Research is needed:

- to clarify the true false-positive rate of F1RDT for both pneumonic and bubonic plague when compared with each reference standard (if culture and PCR are considered as imperfect reference standards);
- to estimate the pre-test probability of plague in different scenarios (endemic, non-endemic areas and outbreaks) for F1RDT and other diagnostic methods;
- to quantify the cost-effectiveness of using F1RDT for the detection and diagnosis of pneumonic and bubonic plague;
- to standardize the new RDTs being developed and assess the accuracy of second-generation RDTs;
- to ensure collaboration among laboratory researchers on defining the antigen targets for the development of new RDTs, to harmonize the use of PCR and to establish a standard algorithm to be used for the diagnosis of plague, which specifies the genes targeted and the laboratory methods used.

5.2 Antibiotics for treating plague

Although the GDG acknowledged the difficulties in conducting randomized controlled trials to assess the antibiotics used for treating plague, research is needed that would:

- directly compare the effectiveness of fluoroquinolones with streptomycin for treating pneumonic plague;
- assess the effectiveness of pre-exposure chemoprophylaxis, using seroconversion as a reference for infection;
- assess the effectiveness of postexposure prophylaxis in animal models;
- assess the role of combined therapy compared with monotherapy to treat any form of plague in order to contain the development of antimicrobial resistance.

5.3 Risk of transmission from the dead body of a person who was infected with plague

The GDG identified the need for research:

- to determine the persistence of the viability and infectiousness of *Y. pestis* in the body fluids of a person who was infected with plague;
- to understand the risk of plague transmission associated with funeral rites for different population subgroups, including pregnant women, stillbirths, twins and traditional leaders.

The proposed research on the persistence of *Y. pestis* should include consideration of the effect of antimicrobial therapy received by the person before death. Studies in animal models may be informative.

5.4 Recommendations for additional guidance

The GDG recommended developing clinical guidance and algorithms based on a syndromic approach to case management for patients presenting with signs and symptoms of plague that would include both diagnosis and treatment. This guidance may require a further guideline development process, after which it could be adapted at the country level; however, this was considered beyond the scope of this particular GDG.



CHAPTER 6

Updating

This document will be revised if necessary, based on the results of an impact survey and comments provided by ministries of health and reference laboratories. Between 2 and 3 years after publication, WHO will collate information on responses to the survey and other comments. After 3 years, WHO will formally appraise emergent evidence on all three topics (use of F1RDT for diagnosis, choice of antibiotics and use of personal protective equipment), including on feasibility issues and new medicines and technologies, downloads and references to the guideline, and stakeholders' views. All of this information will help in developing new topics for the guidelines and evaluating whether the current recommendations and evidence summaries need to be updated.



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Annex 1. Analytical framework and key questions

The analytical framework and key questions are represented in Fig. A1.1.

— Key question 1. Among individuals with clinical suspicion of plague, does F1RDT accurately detect plague compared with isolation of *Yersinia pestis* by culture, PCR or paired serology?

Participants Adults and children suspected to have plague

Intervention F1RDT

Comparison Isolation of *Y. pestis* by culture, PCR or paired serology

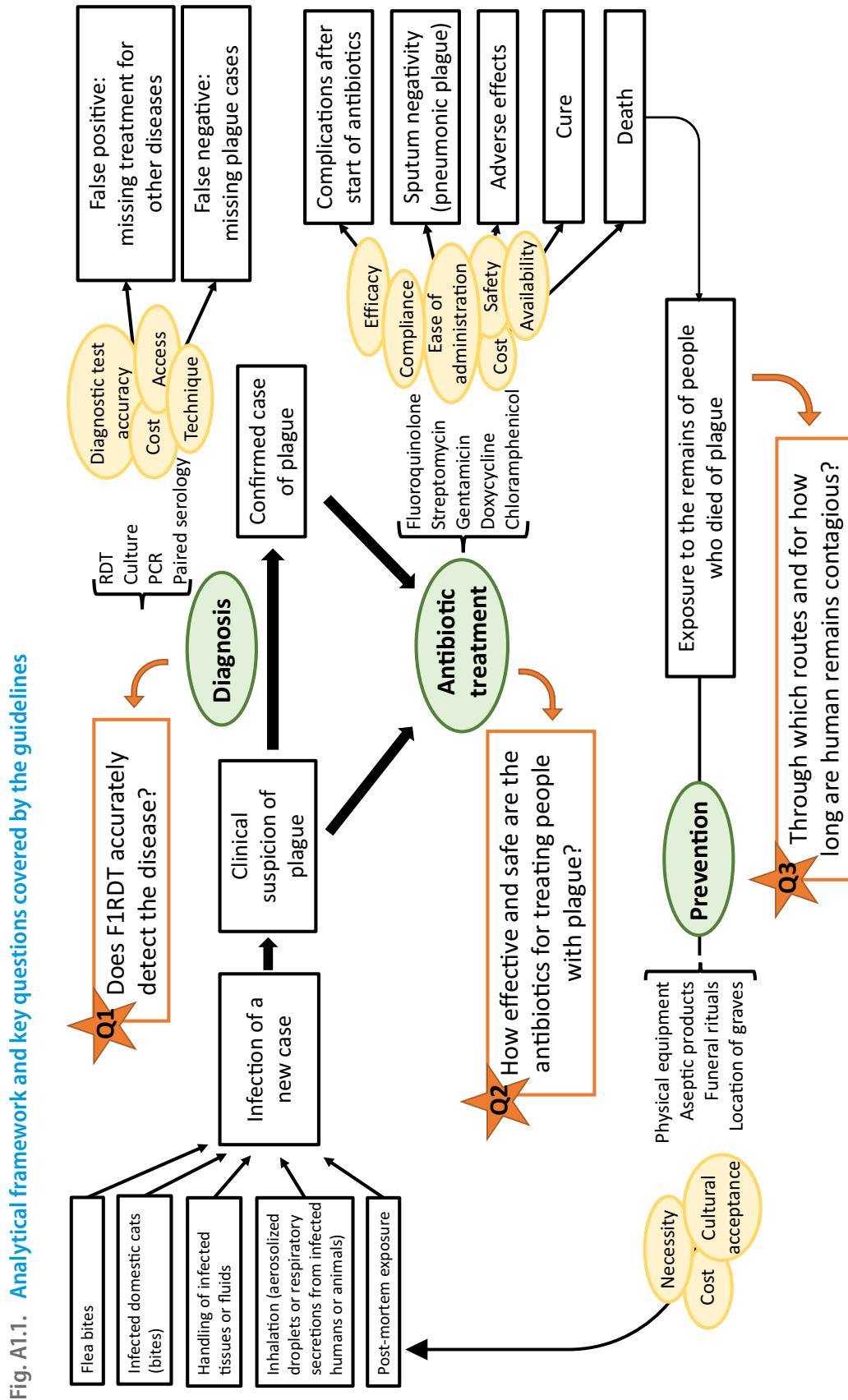
Outcomes Test accuracy: sensitivity, specificity

We explored heterogeneity between study results by looking at findings for the following subgroups:

- different forms of plague – bubonic, septicaemic and pneumonic;
- type of reference standard – bacterial isolation by culture, PCR and enzyme-linked immunosorbent assay (ELISA);
- context – plague-endemic areas, areas where an outbreak is in progress.

Therefore, the four main questions that derived from the first key question were the following.

- Should an RDT be used to detect pneumonic plague in plague-endemic areas?
- Should an RDT be used to diagnose pneumonic plague in patients in areas where an outbreak is in progress?
- Should an RDT be used to detect bubonic plague in plague-endemic areas?
- Should an RDT be used to diagnose bubonic plague in patients in areas where an outbreak is in progress?



F1RDT: rapid diagnostic test based on the F1 antigen; RDT: rapid diagnostic test; PCR: polymerase chain reaction.

▶ **Key question 2. Among individuals with plague, how effective and safe are the following antibiotics?**

Participants	Adults and children with confirmed or suspected plague
Intervention	Any fluoroquinolone
Comparison	Streptomycin Gentamicin Tetracyclines, doxycycline Chloramphenicol
Outcomes	<ul style="list-style-type: none"> – Death – Cure (defined as resolution of fever and painful bubo swelling and, if initially present, recovery from pneumonia or any other symptoms of plague) – Complications after the initiation of antimicrobial therapy (including systemic inflammatory response syndrome, meningitis and secondary pneumonia)^a – Defervescence time (number of days with fever) – Sputum negativity (for pneumonic plague) – Relapse (defined as the return of bubo tenderness, fever or other symptoms within 1 to 2 weeks after the end of therapy)^a – Adverse effects

^a Mwengee W, Butler T, Mgema S, Mhina G, Almasi Y, Bradley C et al. Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. *Clin Infect Dis.* 2006;42:614–21. doi:10.1086/500137.

We first gathered all the evidence from direct comparisons between any of the following antibiotics: any fluoroquinolone and streptomycin, gentamicin, doxycycline or chloramphenicol. As we anticipated that there were limited studies that directly compared one antibiotic with another, we then summarized the outcomes for each of the above antibiotics from single-arm studies and case reports.

These antibiotics were selected by the GDG members in consultation with the responsible technical officer.

Whenever possible, we aimed to examine the evidence of possible effect modifiers, including:

- forms of plague – bubonic, septicaemic and pneumonic plague, and plague meningitis;
- certainty of diagnosis – confirmed and probable or presumptive plague;
- subgroup populations – adults, children.

▶ **Key question 3. What is the risk of plague transmission from exposure to the remains of people who died of plague?**

We formulated a broad question because we anticipated that there was limited literature describing this topic. For this question, we aimed to answer, clarify and summarize the responses to a series of questions.

- How contagious are the body fluids of people with bubonic, septicæmic or pneumonic plague?
- How many studies described fluid or aerosol transmission among people?
- How many cases of plague transmitted by human body fluid or other human remains have been documented? Was the possible route of transmission described?
- How many cases of plague transmitted during the manipulation of contaminated material in a laboratory have been documented? Was the possible route of transmission described?
- How many cases of plague transmitted by animal remains have been documented? Was the possible route of transmission described?
- For how long can *Y. pestis* survive in a dead body and be infectious to a human?

We aimed to describe and summarize all reported cases of plague infection occurring during post-mortem exposure to human and animal remains. We collected data on the possible mode of transmission (inhalation, contact with blood or other body fluids and secretions, contact with infected tissues), duration of exposure and length of time since death.

Annex 2. Contributors

Contributors to the guideline development process are listed in Tables A2.1 to A2.5.

Table A2.1. Members of the WHO Steering Group for the development of the guidelines on plague control

Name	Affiliation
Yahaya Ali Ahmed	WHO Health Emergencies Programme, WHO Regional Office for Africa, Brazzaville, Congo
Eric Bertherat ^a	Department of Infectious Hazards Management, WHO Health Emergencies Programme, WHO headquarters, Geneva, Switzerland
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Gyanendra Gongal	Country Preparedness and International Health Regulations Programme, WHO Health Emergencies Programme, WHO Regional Office for South-East Asia, New Delhi, India
Stéphane Hugonnet	WHO Health Emergencies Programme, WHO headquarters, Geneva, Switzerland

^aResponsible technical officer.

Table A2.2. Members of the Guideline Development Group for plague control

Name	Affiliation	Gender	Expertise
Julienne Ngoundoung Anoko	Department of Infectious Hazards Management, WHO Health Emergencies Programme, Dakar, Senegal	Female	Anthropologist
Oswaldo Cabanillas	Centro Nacional de Epidemiología Prevención y Control de Enfermedades, Ministry of Health, Lima, Peru	Male	Public health
Vladimir Markovich Dubyanskiy	Stavropol Plague Control Research Institute, Stavropol, Russian Federation	Male	Biologist
Arum Sih Joharina ^a	National Institute of Health Research and Development, Yogyakarta, Indonesia	Female	Biologist
Rakotonjanabelo Lamina Arthur	Ministry of Health, Antananarivo, Madagascar	Male	Public health

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Name	Affiliation	Gender	Expertise
Paul Mead ^{b,c}	CDC, Atlanta, GA, USA	Male	Clinician, epidemiologist
Mihaja Raberahona	Infectious Diseases Unit, University Hospital Joseph Raseta Befelatanana, Antananarivo, Madagascar	Male	Clinician
Minoarisoa Rajerison ^c	Pasteur Institute, Antananarivo, Madagascar	Female	Biologist
Bertrand Renaud ^b	Faculté de Médecine, Université Paris Descartes, Paris, France	Male	Clinician
Jenny Rossouw ^d	National Institute for Communicable Diseases, Johannesburg, South Africa	Female	Biologist
Jean-Christophe Shako	Ministry of Health, Kinshasa, Democratic Republic of the Congo	Male	Biologist
Xin Wang ^d	National Institute for Communicable Disease Control and Prevention, Beijing, China	Female	Public health

^a Arum Sih Joharina was present for only part of the guideline development meeting. She did not contribute to the development of recommendations on antibiotics for plague (key question 1) and the use of personal protective equipment (key question 3).

^b Co-chairs for key question 2.

^c Co-chairs for key question 3.

^d Co-chairs for key question 1.

Table A2.3. Observers at the guideline development meeting for plague control, 2019

Name	Affiliation	Gender	Expertise
Laurence Baril	Pasteur Institute, Antananarivo, Madagascar	Female	Epidemiologist
Salatiga Ristiyanto	National Institute of Health Research and Development, Yogyakarta, Indonesia	Male	Epidemiologist

Table A2.4. Technical advisers on the development of the guidelines for plague control

Name	Affiliation	Role
Sophie Jullien	Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom	Evidence Review Team lead; consultant for development of the guidelines
Paul Garner	Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom	Methodologist

Table A2.5. External reviewers of the guidelines on plague control

Name	Affiliation	Expertise	Interests declared
Manuel Céspedes Zambrano	Instituto Nacional de Salud, Lima, Peru	Public health, microbiology	None
Farida Handayani	Institute for Vector and Reservoir Control Research and Development, National Institute of Health Research and Development, Salatiga, Indonesia	Microbiology, molecular biology	None

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Name	Affiliation	Expertise	Interests declared
Rebecca Thomas	Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom	Integration of equality, rights, gender and social determinants into the global health guideline development process; evidence synthesis; clinician	None

Annex 3. Declarations of interests

Table A3.1. Summary of declarations of interests from members present at the guideline development meeting for plague control, 2019

Name	Affiliation	Declarations of interests related to the topic of the guideline
Julienne Ngoundoung Anoko	Department of Infectious Hazards Management, WHO Health Emergencies Programme, Dakar, Senegal	None
Oswaldo Cabanillas	Centro Nacional de Epidemiología Prevención y Control de Enfermedades, Ministry of Health, Lima, Peru	None
Vladimir Markovich Dubyanskiy	Stavropol Plague Control Research Institute, Stavropol, Russian Federation	None
Paul Garner	Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom	Direction of a UKAID-funded research and development programme that aims to increase the number of health sector decisions in low- and middle-income countries that are based on systematic reviews and reliable evidence
Arum Sih Joharina	National Institute of Health Research and Development, Yogyakarta, Indonesia	None
Sophie Jullien	Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom	None
Rakotonjanabelo Lamina Arthur	Ministry of Health, Antananarivo, Madagascar	None
Paul Mead	CDC, Atlanta, GA, USA	Oversees a laboratory involved in the development of RDTs for plague, but not the RDT under discussion during the meeting
Mihaja Raberahona	Infectious Diseases Unit, University Hospital Joseph Raseta Befelatanana, Antananarivo, Madagascar	Involved in a randomized controlled trial to assess streptomycin versus ciprofloxacin for treating bubonic plague in Madagascar that is funded by the Wellcome Trust ^a
Minoarisoa Rajerison	Pasteur Institute, Antananarivo, Madagascar	Involved in the development of RDTs for plague
Bertrand Renaud	Faculté de Médecine, Université Paris Descartes, Paris, France	None
Jenny Rossouw	National Institute for Communicable Diseases, Johannesburg, South Africa	None

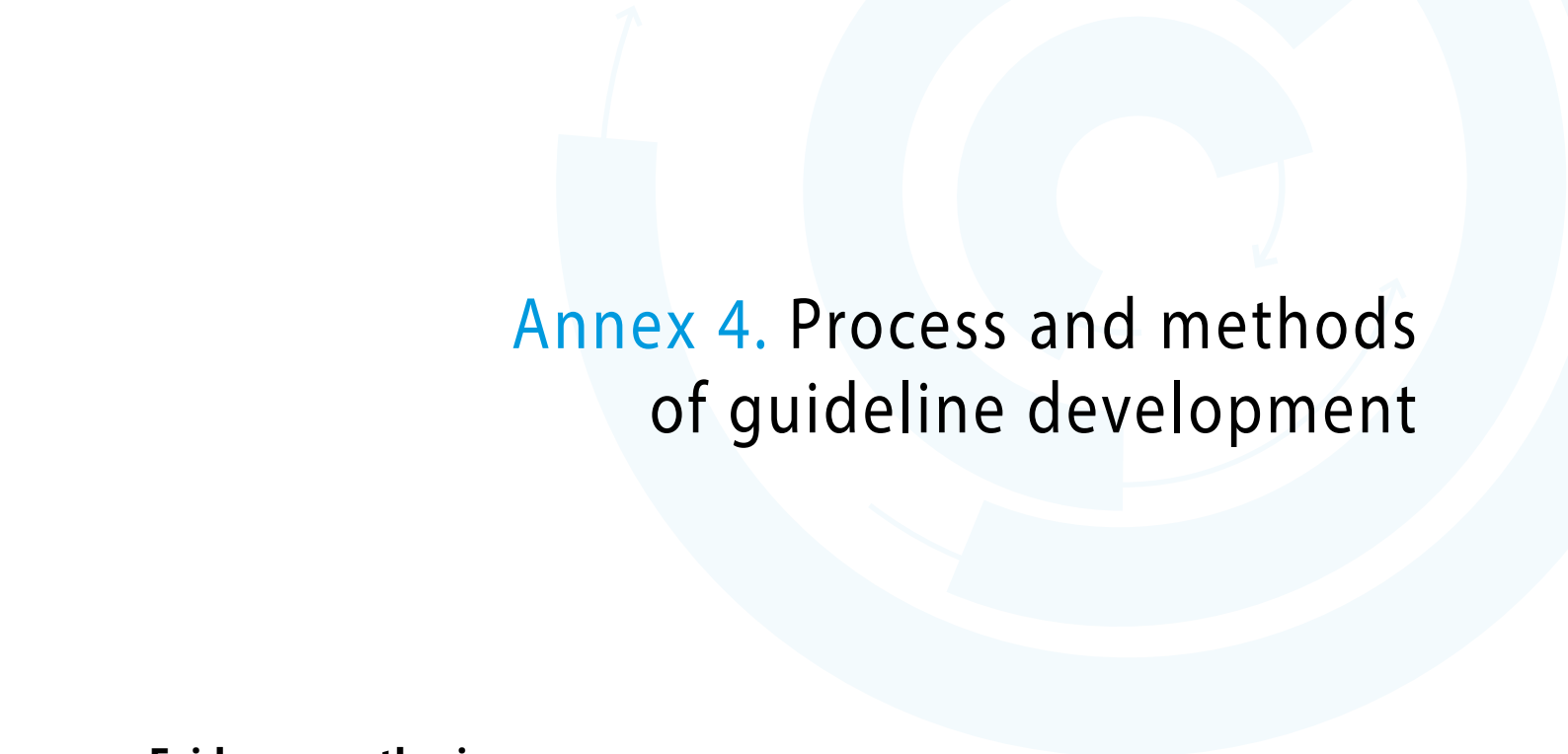
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Name	Affiliation	Declarations of interests related to the topic of the guideline
Jean Christophe Shako	Ministry of Health, Kinshasa, Democratic Republic of the Congo	None
Xin Wang	National Institute for Communicable Disease Control and Prevention, Beijing, China	None

RDT: rapid diagnostic test.

^a Ciprofloxacin versus streptomycin and ciprofloxacin for bubonic plague [website]. Bethesda (MD): United States National Library of Medicine, ClinicalTrials.gov; 2019 (<https://clinicaltrials.gov/ct2/show/NCT04110340?term=NCT04110340&draw=2&rank=1>, accessed 23 October 2019).



Annex 4. Process and methods of guideline development

Evidence synthesis

The Evidence Review Team lead carried out the evidence synthesis for each of the three key areas. These are described in the methods section of each review and summarized below.

For RDTs, the Evidence Review Team conducted a systematic review following the rigorous and transparent methods of the Cochrane handbook for reviews of diagnostic test accuracy (1). The review included studies of adults and children living in or visiting areas where plague is endemic, with clinical suspicion of any form of plague, who were tested for plague with both the F1RDT and at least one of the reference standards (culture, PCR or paired serology). A literature search was conducted using several databases, including the Cochrane Central Register of Controlled Trials, MEDLINE (PubMed), Embase and the Science Citation Index (Web of Science). Two review authors independently screened all abstracts retrieved using the search strategy, selected the eligible studies following the predefined inclusion criteria and extracted data from the included studies. Two review authors independently assessed the methodological quality of each included study using the QUADAS-2 tool, which addresses four domains: patient selection, index test, reference standard, and flow and timing. Pooled estimates for sensitivity and specificity were calculated by meta-analysis when possible and the findings were stratified by the reference standard used and the form of plague. The systematic review was peer reviewed and is available to the public in the Cochrane Library (2).

For treatment, direct head-to-head comparisons in humans were available only in one small trial, and the synthesis group was aware that other information – such as data on safety, route of administration, results from animal studies – would be used by the group to inform their decisions. Thus, synthesis tables were prepared summarizing a variety of information from these different sources. For human data, the findings from an extensive systematic review conducted by CDC were used. For animal data, a systematic review was conducted following rigorous and transparent methods to gather evidence from studies in monkeys. The methods for each step are described in Web Annex A.

For the evaluation of the use of personal protective equipment, a systematic review was conducted to assess the risk of plague transmission from human remains. Owing to a lack of direct evidence, an indirect approach was used, which involved collecting and summarizing evidence on: (i) the infectiousness of different body fluids in people who are ill with plague; (ii) reported cases of plague transmitted from human and animal remains; and (iii) the infectiousness of body fluids in animals or humans who have died from plague, including how long such infectiousness may last. Clear inclusion criteria were established for each of the three objectives. A literature search was conducted using several databases, including MEDLINE (PubMed), Embase, Web

of Science (Science Citation Index) and Scopus. Two review authors independently screened the abstracts and selected full-text studies for inclusion in the review. The risk of bias for each included study was assessed using a simple appraisal tool comprising six questions. Statistical analysis was not possible due to the heterogeneity of the data. The findings were presented narratively and in tables. The protocol was published in Prospero (CRD42019133786) (3).

Quality of the evidence

For RDTs, the certainty of the evidence from the systematic review was assessed using GRADE for the sensitivity and specificity for each subgroup of plague (stratified by reference standard) and rated on a four-point scale (high, moderate, low, very low) after consideration of five aspects: risk of bias in included studies, publication bias, and the directness, consistency and precision of the estimates. The terms used to rate the certainty of the evidence are as follows.

- High: the group is very confident in the estimates of effect and considers that further research is very unlikely to change this confidence.
- Moderate: the group has moderate confidence in the estimate of effect but considers that further research is likely to have an important impact on their confidence and may change the estimate.
- Low: the group has low confidence in the estimate of effect and considers that further research is very likely to have an important impact on their confidence and is likely to change the estimate.
- Very low: the group is very uncertain about the estimate of effect.

It was not possible to apply this GRADE approach to the findings from the two other reviews (antibiotics for plague and use of personal protective equipment) because statistical analysis was not possible, and so findings were presented narratively and in tables.

Making recommendations

The GDG held a 2-day meeting in September 2019, in Antananarivo, Madagascar, to develop and finalize the recommendations. Final drafts of the three reviews together with the assessments of the quality of the evidence, when applicable, were circulated to the GDG prior to the meeting.

For each question, the GDG considered the certainty of the evidence, the desirable and undesirable effects, values and preferences, cost, acceptability, equity, feasibility and barriers to implementation. The GRADE evidence-to-decision tables were used to facilitate consensus and record the decision of the GDG (Web Annex B). The GDG then formulated a recommendation based on consensus decision-making. Each recommendation was finally graded as strong or conditional, based on the level of certainty of the evidence and on the degree of concordance among the GDG. Areas of disagreement were extensively discussed, and a final consensus was reached without the need for a vote. The criteria used for grading each recommendation and the meaning of the strength of a recommendation are outlined in Tables A4.1 and A4.2, respectively.

Table A4.1. Factors that affect the strength of a recommendation

Factor	Rationale
Certainty of the evidence	The higher the certainty of the evidence, the more likely it is that a strong recommendation will be made. When there is very low certainty about the evidence, a conditional recommendation is more likely.
Balance of benefits and harms	The more the expected benefits (desirable effects) outweigh the expected risks (undesirable effects), the more likely it is that a strong recommendation will be made. When the balance of benefits and harms is likely to vary by setting or is finely poised, a conditional recommendation is more likely.
Values and preferences	If the recommendation is likely to be widely accepted or highly valued, a strong recommendation is more likely.
Feasibility	If an intervention is achievable in the settings in which the greatest impact is expected, a strong recommendation is more likely.

Table A4.2. The meaning of strong and conditional recommendations for different groups

Group	Strong	Conditional
Patients	Most people would want the recommended test or treatment and only a small proportion would not.	Most people would want the recommended test or treatment, but many would not.
Clinicians	Most patients should receive the recommended test or treatment.	Clinicians need to be prepared to help patients make a decision that is consistent with their own values because the test or treatment might not be right for everybody.
Policy-makers	The recommendation can be adopted as standard policy and practice in most situations.	There is need for substantial debate and involvement of stakeholders when considering adopting this policy or practice.

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ISBN 978-92-4-001557-9

