

# **“Efficacy trials of Plague Vaccines: endpoints, trial design, site selection”**

## **WHO Workshop**

### **Meeting Report**

April 23, 2018  
INSERM, Paris, France

## Table of contents

<b>TABLE OF CONTENTS</b>	<b>1</b>
<b>1. INTRODUCTION</b>	<b>2</b>
<b>2. EPIDEMIOLOGY OF PLAGUE, OUTBREAK CONDITIONS, AND PLAGUE CANDIDATE VACCINES</b>	<b>4</b>
<b>3. TRIAL DESIGN CONSIDERATIONS</b>	<b>7</b>
3.1 CLINICAL ENDPOINTS SELECTION (BOTH REACTIVE AND PREVENTIVE)	7
3.2 STUDY POPULATION AND SITE SELECTION (BOTH REACTIVE AND PREVENTIVE)	8
3.3 RANDOMIZATION AND COMPARATOR (BOTH REACTIVE AND PREVENTIVE)	9
3.4 STATISTICAL ANALYSIS	10
<b>4. ESTABLISHING A TRANSPARENT FRAMEWORK FOR SELECTING VACCINES TO BE EVALUATED IN PHASE 2B/PHASE 3 TRIALS</b>	<b>10</b>
<b>5. NEXT STEPS</b>	<b>11</b>

## 1. Introduction

Plague is an infectious disease caused by *Yersinia pestis*, a zoonotic bacterium, usually found in small mammals and their fleas. As an animal disease, plague is found in all continents, except Oceania. There is a risk of human plague wherever the presence of plague natural foci (the bacteria, an animal reservoir and a vector), and the human population co-exist. There are large plague reservoirs in African, Asian, and South American continents; but since the 1990s, most human cases have occurred in Africa. Plague endemicity throughout the world has resulted in sporadic infections, including recent outbreaks in the 21<sup>st</sup> century. The three countries with most reported cases in recent years are the Democratic Republic of Congo, Madagascar, and Peru. In 2017, there was a large plague outbreak in Madagascar. There are effective therapeutics to treat plague although evidence of antibiotic-resistance has been observed in *Y. pestis* strains naturally or those deliberately developed to serve as a biothreat agent. Antibiotic treatment and post-exposure prophylaxis are generally initiated on plague suspected cases (i.e., before laboratory confirmation of plague infection), given the extremely short incubation and infectious period of plague infection.

Plague is usually associated with two major forms of infection: bubonic and pneumonic. Bubonic plague is transmitted to humans through flea bites and direct contact with infected rodents. Domestic cats and dogs that have been in contact with rodents can transport the infected fleas. Pneumonic plague, the most deadly form, occurs when bacteria infect the lungs either through direct inhalation or through secondary spread of bacteria from septicaemic or bubonic infection. Pneumonic plague infection can be transmitted from person to person by respiratory droplets, and can be fatal within 24 hours of disease onset, if left untreated.

From 2010 to 2015, 3,248 cases were reported worldwide, including 584 deaths. In 2017, a total of 2,348 confirmed, probable and suspected cases of plague, including 202 deaths (case fatality rate: 8.6%), were reported by the Ministry of Health of Madagascar to WHO. Among the 2,348 cases of plague, 1,791 were pneumonic plague (76.3%), one case of septicaemic plague (<0.1%), 341 cases of bubonic plague (14.5%), and 215 cases of unspecified plague (9.2%). Of the 1,791 cases of pneumonic plague, 22% were confirmed, 34% were probable, and 44% were suspected. A WHO confirmed case definition was defined in 2006 to account for a universal plague definition in the context of the International Health Regulations.

Currently, WHO does not recommend immunization with old-generation plague vaccines<sup>1</sup>. The recrudescence of plague outbreaks, the availability of new vaccine technologies, and biodefense concerns, have triggered renewed interest towards the development of new-generation plague vaccines. Furthermore, the need for a plague vaccine is also underscored in areas where plague infections may occur but where timely access to diagnosis and treatment is not guaranteed (e.g., remote rural areas, resources-limited settings, conflict areas, etc.). The WHO mapping tool currently registers 17 plague vaccine candidates under development, by private and public-sector laboratories. Two of these candidates have completed a Phase 2 clinical trial, and several candidates have plans to enter clinical trials in 2019. A WHO Plague vaccine Target Product Profile (TPP) was developed to provide aspirational guidance to vaccine developers. The TPP is informed by regulatory

---

<sup>1</sup> except for high-risk groups (such as laboratory personnel who are constantly exposed to the risk of contamination, and health care workers).

expectations, by technological feasibility and to consider both a preventive and a reactive scenario when using a Plague vaccine.

On April 23, 2018, WHO convened a group of about 30 experts in epidemiology, regulatory, preclinical and clinical vaccine trials, and mathematical modelling, in a workshop on planning for plague vaccine efficacy trials. The workshop aimed to define generic principles on how to best design, conduct and analyse vaccine trials against plague, based on the available scientific evidence as well as on lessons learned from the public health response to plague outbreaks.

Participants reviewed available evidence on plague epidemiology and vaccine candidates, identified and discussed methodological options to evaluate vaccines, regardless of vaccine products, and agreed on some preliminary recommendations. The WHO Plague vaccine TPP was expected to help inform vaccine evaluation decisions during the workshop.

It was recognised that the preliminary recommendations are likely to evolve as new evidence is generated, and also, they must be tailored to the social and cultural context of affected communities.

## 2. Epidemiology of plague, outbreak conditions, and plague candidate vaccines

### **The population at-risk of plague infection is globally increasing.**

There is a risk of human plague wherever the presence of plague natural foci (the bacteria, an animal reservoir and a vector), and the human population co-exist. A global expansion of the geographic distribution of the natural foci, notably in urban settings, has been observed, although the geographic distribution of the foci remains patchy resulting in heterogeneous bubonic plague transmission in humans. Because the risk of pneumonic plague depends on the occurrence of bubonic plague, it is also expected that the at-risk population to pneumonic plague increases as well as the risk of plague outbreak in unexpected areas, particularly in urban settings.

For instance, the 2017 plague outbreak in Madagascar has occurred in areas and time of the year (August to November) that differed from the usually observed seasonal occurrence (October to April) of plague cases in the endemic areas of the Central Plateau. The 2017 plague outbreak occurred unexpectedly in urban areas, and has been associated with an unusual ratio of pneumonic versus bubonic cases, suggesting that human to human aerosol transmission contributed significantly to the spread of the bacterium. The basic reproduction number (i.e., the average number of secondary cases generated in a fully susceptible population) of the 2017 Madagascar outbreak was estimated to be about 1.70.

Several knowledge gaps remain: the role of factors such as age, socio-economic status, and other demographic factors as risk factors requires further investigation to identify at-risk populations and to understand what might potentially influence transmission rates. In particular, it is unclear whether the risk of pneumonic cases is due to the importation of human cases from rural to urban setting or due to the geographic expansion of the natural foci in urban settings, or both of these two reasons. In addition, it remains unclear whether plague infection confers lifelong immunity, although there is some evidence of a durable antibody response following immunization with old-generation live-attenuated plague vaccines. Asymptomatic and mild plague infections may also occur and there are uncertainties associated with the real burden of plague. Sero-prevalence studies and enhanced surveillance in Madagascar and other affected countries are needed to help inform the above gaps and a thorough analysis of the 2017 Madagascar plague outbreak data must be conducted to better estimate secondary attack rates and other epidemiological parameters.

### **Outbreak circumstances provide challenging conditions to the conduct of a vaccine trial.**

The WHO TPP for plague vaccines notably considers a scenario for the reactive use of a plague vaccine associated with a public health emergency. Generating evidence to support a broader use of a plague vaccine under that scenario may necessitate a vaccine trial during a plague outbreak setting. Research has increasingly been a norm in responding to outbreaks of infectious diseases. The research response must be fully integrated in the broader control efforts and cannot be performed at the expense of the control efforts.

For instance, during the 2017 Madagascar outbreak, a series of outbreak control measures were implemented, including enhanced epidemiological surveillance, rapid detection, isolation and treatment of plague cases, contact tracing, and community engagement strategies. Also, an uncontrolled consumption of antibiotics used as a chemoprophylaxis has

been observed among contacts of suspected pneumonic cases and less frequently among contacts of suspected bubonic cases. It is expected that the above public health response elements should be considered in the design of a vaccine trial in the context of an outbreak. Lastly, anthropological studies are needed to assess the acceptability of a vaccine trial from affected communities in such conditions.

**There is currently no licensed vaccine recommended by WHO for use and there are at least 17 vaccine candidates currently identified in the pipeline.**

The WHO TPP for plague vaccines considers both a preventive and a reactive use. The preventive use of a plague vaccine aims to protect the populations living in endemic areas or health workers related to plague investigation or surveillance, and the reactive use of a plague vaccine aims to protect individuals in the areas of an outbreak and help interrupt chains of transmission. In terms of protective immunity, a vaccine suitable for preventive use requires a long-lasting immune response, while a vaccine suitable for reactive use requires a rapid ramp-up in protective immunity after the first dose, especially given the very short incubation period of plague.

New-generation of plague vaccines' approaches include subunit (F1/V based with adjuvant), bacterial vector-based (e.g., OMV drug delivery, salmonella-expressed), viral vector-based (e.g., Ad5-based, Chad-based), *E. coli* T4 bacteriophage-based, and live-attenuated (e.g., *Y. pseudotuberculosis*-based or *Y. pestis*-based) vaccine expressing one or several antigens representative of *Y. pestis* (e.g., F1 capsular protein antigen, V or LcrV antigen, YscF antigen, PLA (pesticin coagulase)), which have been tested in a variety of mice, rats, and non-human primates immunogenicity and challenge models. Subunit plague vaccines are the most advanced candidate vaccines and two of them have completed Phase 2 studies in humans. Likewise, live-attenuated *Y. pestis* vaccines deleted for virulence factor-encoding genes have been tested in mouse and rat models of pneumonic plague. These vaccines generated protective and long-term immune responses in animals.

Various vaccine designs may be suitable for different uses. Subunit vaccines generally have an acceptable safety profile but typically require several doses to confer protective immunity, except for some vector-based vaccines. Given the potential interval to confer protection compared to the serial interval of plague cases, subunit approaches may be considered to protect populations for preventive use. Bacterial and viral live-attenuated approaches typically require a single-dose and may confer rapid protection (around 10 days post immunization) which could be notably suitable for a reactive use of a plague vaccine, although the safety profiles of such vaccines requires further studies. However, bacterial live-attenuated vaccines may experience biological interference with the use of antibiotics and interfere with current diagnostics tools may significantly challenge their evaluation. Viral live-attenuated vaccines may not experience this interference as they are not affected by antibiotics and usually have specific *Y. pestis* antigenic composition. Another approach, using OMVs produced in bacteria, eliminates the compulsory temperature chain requirements of live vaccines (since they are sterile and thermostable) and do not represent a risk from interference due to antibiotic treatment of the patient. Other vaccine design approaches may target a combination of both preventive and reactive uses.

Some candidate vaccines are designed for non-invasive delivery (e.g., oral or intranasal in the form of a fine mist), the preferred option according to the WHO TPP, and have shown to elicit both a mucosal, humoral, and cell-mediated immune responses, although other type of vaccine administration delivery (e.g., intramuscular) are also acceptable from a public health perspective.

Vaccine efficacy against bubonic and pneumonic plague infection may be different and a higher efficacy against pneumonic form is generally sought given the higher virulence and the potential for human-to-human transmission associated with the pneumonic form. Furthermore, vaccine developers tend to set the evaluation bar for pneumonic plague, because it is expected – although not proven - that if a plague vaccine protects pneumonic plague will also protect against bubonic plague.

**The demonstration of benefit based on a clinical endpoint is the optimal way to evaluate a plague vaccine but, if this is not feasible, other approaches may be necessary.**

Licensure of vaccines generally requires the demonstration of benefit based on a clinical endpoint or based on a scientifically well-established marker of protection, using evidence generated by well-controlled clinical studies. In a context where there is no established immune marker of protection against plague, clinical trials to evaluate vaccine efficacy are preferred, and these trials may also help define a correlate of protection by looking at relationships between the level of immunity and the level of protection in trial participants. However, if the demonstration of clinical efficacy is not feasible, pre-clinical immunogenicity and efficacy in a standardized and relevant animal model together with clinical immunogenicity may be considered. If regulatory authorization is provided without clinical efficacy data, effectiveness of data are to be generated during use in a future outbreak to the extent possible.

There is no well-established immunological surrogates of protection. Defining correlates of risk and immunological surrogates of protection are needed to help evaluate and compare plague candidate vaccines. Protection against plague has been demonstrated by several vaccine approaches in various animal models. However, mechanisms of protective immunity are complex and may vary depending on the vaccine design and the route of administration. Furthermore, it is unclear whether we can define universally accepted immunological surrogates of protection: mucosal immunity may be required to protect against pneumonic plague while systemic humoral immunity may be required to protect against bubonic plague. Cellular immunity is not preferentially elicited by all vaccine approaches but its role in protection may be important too. Live-attenuated vaccines as well as those which are based on viral vectors trigger both arms of the immune response. Finally, it is unclear whether immunological surrogates and bridging levels identified in animal models translate into protection in humans. Defining appropriate immunological surrogates of protection rely on functional and standardized assays. International standard strains and reagents must be defined and made available to authorised entities to allow the comparison of the immune responses elicited by different vaccines. Sharing of such strains and reagents clearly represent a hurdle and must be overcome expeditiously to make meaningful progress.

### 3. Trial design considerations

It was expected that the WHO draft TPP for plague vaccines would inform workshop participants in the rationale of defining trial design elements.

**Vaccine trials should be designed to generate evidence in an effort to support a broader use of a vaccine defined under one of the two (or both) scenarios as mentioned in the plague vaccine TPP.**

Trial designed to support a preventive use of a plague vaccine may be challenged by expected low cumulative attack rates while trial designed to support a reactive use of a plague vaccine may be challenged by conducting a trial in outbreak conditions.

As ways of example, a vaccine with 70% expected efficacy would require to observe 62 events on average. This corresponds to a sample size of about 15 000 trial participants<sup>2</sup> for cumulative attack rates representative of outbreak conditions (about 1% in the comparator arm). Sample sizes are expected to rise to at least ten fold higher for trials designed for the preventive use. In the light of those preliminary numbers, the question of the feasibility of trials designed for preventive use was raised, given the very low and unpredictable incidence of Plague infections. A better understanding of Plague incidence is needed to help refine sample size calculations. Lastly, it is expected that the implementation of a vaccine trial would come along with a strengthened surveillance system in order to increase endpoint detections.

Given the low plague incidence, a reactive trial design may be more achievable than a preventive trial design. However, it was recognized that outbreak conditions (e.g., public health measures, behavioural change) may significantly interfere with the conduct of a trial design. Reactive trial designs should take notably into account the prophylaxis treatment given to exposed or at-risk populations. Lessons learned from outbreaks management of other infectious diseases demonstrated that is nevertheless feasible to test a vaccine in outbreak conditions.

One may also imagine trials designed to generate evidence in an effort to support both a preventive and reactive use of a vaccine, or one could evaluate a vaccine in the most feasible context that may differ from the targeted intended use of the vaccine and later on verify clinical benefit in other studies.

#### 3.1 Clinical endpoints selection (both reactive and preventive)

**Laboratory-confirmed plague clinical illness, regardless of the form of plague, should be the primary endpoint of a Phase 2b/3 plague vaccine trial.**

It was agreed that the definition of endpoints should be closely linked to the WHO case definition for confirmed cases and to the surveillance system of a given country. Primary endpoint should also be supportive of the public health objectives outlined in the TPP for plague vaccines.

---

<sup>2</sup> Assuming a 2:1 randomization, with a one-sided hypothesis test, a lower efficacy bound of 0.3, and 20% loss-to-follow-up.

The diagnostic algorithm used in a surveillance system for confirmation may challenge the confirmation of endpoints of a vaccine trial. Plague vaccines could interfere with certain tests, such as lateral flow assays. For instance, the WHO confirmed case definition has been tailored to the 2017 Madagascar outbreak, whereby confirmation of cases was performed using a RDT detecting F1 antigen on suspected cases with subsequent PCR confirmation. In this context, RDTs may not be able to distinguish between vaccine antigens and wild-type antigens.

For all vaccine design approaches, except for some live-attenuated vaccines, confirmation of cases by PCR – that targets genes that are not included in the vaccine design of interest - provides an appropriate method for case ascertainment and primary endpoint measurement in the context of a vaccine trial. Collection and transport methods should be validated prior to use.

**Laboratory-confirmed bubonic plague, laboratory-confirmed pneumonic plague, plague-caused mortality and immunological correlates of risk and surrogates of protection should be secondary endpoints of a Phase 2b/3 plague vaccine trial.**

Mortality should be also investigated as various plague cases could not get treated on time.

In the absence of well-established surrogates of protection, phase 2b/3 vaccine trials may provide an opportunity to help identify immunological surrogates of protection for a given vaccine design, which would reasonably likely predict clinical benefit.

Baseline samples are needed to be collected from trial participants to help account for prior immunity to plague in the trial analysis for both primary and immunological endpoints and because there may be mild or asymptomatic plague infection. Humoral, mucosal and cellular immunity seem to play a role in protection. However, their relative contributions to immune protection remain unclear and additional sample collections points after the last dose are needed to help analyse per-protocol what immunological markers correlates with protection.

Standardized, validated assays, with agreed units of measurement will be critical to quantitate and compare protection among vaccine candidates. Lastly, tests sensitivity may be challenged by the collection and transport conditions of samples unless adherence to collection protocols and the cold chain can be assured.

### **3.2 Study population and site selection (both reactive and preventive)**

**Healthy adults and children should be the study population of a Phase 2b/3 plague vaccine trial**

Plague affects the general population at all ages and considerations should also be given to the inclusion of pregnant and lactating women, and other special populations depending on the further risk-benefit analysis on a given plague candidate vaccine in those populations and depending on where the trial is planned. One should also distinguish the risk-benefit analysis on special populations for preventive and reactive scenarios. Currently, there is no safety data for any plague vaccines in under 18 years old. Dose-escalation Phase 1 and Phase 2 studies are needed to assess the safety profile in children and other special populations (above the age of 18 first). For vaccine candidates that would be expected to have a favourable profile for pregnancy, pregnant women could be included in the trial at some stage. The intended use of a preventive plague vaccine is expected to cover the general population, so clinical benefit to the populations excluded from the trial, must be verified in post-licensure studies.

### **The need for a multi-site approach**

Given the low incidence of plague, there is a risk that incomplete results from underpowered trials may be misleading to decision-makers. A multi-site international approach under a “Master Protocol” may be required to increase the chance of including groups with a high incidence of plague, as well as providing an opportunity to evaluate vaccine efficacy across different populations and different strains. Multiple seasons may be required to accumulate enough evidence as well. If the trial does not achieve the targeted number of events in the first season, the study must remain blinded to allow for further data collection.

Although plague occurs regularly in the same areas, it is difficult to anticipate where and when the next plague outbreak will occur. Planning of a plague vaccine trial will rely on good surveillance and epidemiological data. More research is needed to assess the true incidence of plague as well as to identify the geographical units, where enough transmission occurs, to define sites. Sero-prevalence surveys and longitudinal cohorts could help inform site selection for vaccine trials. A multi-site trial requires standardization of concepts (e.g., same protocol, plague case definition), fit-for-purpose instruments and assay (e.g., laboratory equipment and reagents) used in the trial.

### **3.3 Randomization and comparator (both reactive and preventive)**

**A double-blind placebo-controlled individually-randomized trial is the optimal design to evaluate the efficacy of one or several plague vaccine candidate(s).**

**Individual level of randomization is preferred** – Individual level randomization would occur in areas mapped to have plague transmission. Individual level randomization is preferred to a cluster-randomised trial design because of the patchiness of plague infection from area to area, which mitigates against a cluster-randomised design. However, indirect effects that would give a sense of herd immunity due to a plague vaccine (essentially for pneumonic plague), would not be possible. A 2:1 randomization scheme could be used in order to learn more on the plague candidate vaccine (e.g., safety profile). Careful analysis of plague transmission is needed to help define the size of relevant clusters or areas in which individual randomization would be performed.

Using individual randomisation, multiple vaccines could potentially be tested simultaneously within the same trial through a two-times 2:1 (vaccine 1 or 2:placebo) randomization scheme. When testing multiple vaccines, a Phase 2b screening trials would realistically likely be required given the sample size calculations of a full Phase 3 trial with multiple vaccines and would help by dropping any unsuccessful vaccines.

**Masking procedures: placebo is preferred** - A placebo-controlled trial would be ethically acceptable. A vaccine against another disease (which the trial population would not normally receive and that does not affect the incidence of the primary and secondary endpoints) might also be considered. However, assessment of the reactogenicity of the plague vaccine may be hampered if the comparator vaccine is highly reactogenic (which might also compromise

blinding). Furthermore, blinding of trial participants is essential as we expect a significant behavioural response from the population to the occurrence of plague transmission (e.g., auto-medication).

### 3.4 Statistical Analysis

**Define a statistical analysis plan *a priori*** - A statistical analysis plan should be prepared prior to the start of a trial. This should include consideration of any interim analyses, with specification of the circumstances in which the trial would be halted for overwhelming efficacy or for futility. The analysis would likely involve combining data across sites and/or outbreaks. Adaptive elements are acceptable (for example, dropping a poorly performing vaccine early, if several are being tested in the same trial), but all go/no go decisions need to be established in advance. Both Per-Protocol and Intention-To-Treat analysis should be performed. For the Per-Protocol analysis of a reactive design, caution should be taken at the start of an analysis period, based on the incubation period and the ramp-up immunity of the vaccine.

In the context of the proposed individually-randomized placebo-controlled trial, the primary analysis will be the estimated vaccine efficacy against confirmed plague illness, based on the ratio between the estimated hazard of illness for individuals who receive vaccine and those who receive placebo. Because the vaccine TPP suggests that only highly effective vaccines would be acceptable from a public health perspective, the primary outcome for the hypothesis test could be one-sided with a null hypothesis based on a lower efficacy boundary of 30% (i.e., the test should be formulated such that one would reject the null hypothesis that the plague vaccine efficacy is below 30%). Lower boundaries could be considered to lower the sample size depending on how confident developers were (evidence to be submitted to WHO) that their vaccine could induce high protective efficacy.

## 4. Establishing a transparent framework for selecting vaccines to be evaluated in Phase 2b/Phase 3 trials

It is hoped that the availability of a transparent framework to review various candidates' attributes will help inform the selection of those to be taken into clinical trials. In this way, WHO intends to ensure resources are utilized most efficiently, and aimed at evaluating and licensing efficacious vaccines.

Given the number of candidate vaccines under development and the challenges of identifying and establishing trial sites, it was discussed that there may be merit for a transparent and evidence based approach for selection of candidate vaccines for trials. Some initial considerations were discussed.

It was recognized that the decision to move forward a plague vaccine candidate to Phase 2b/Phase 3 should be based on how good the plague vaccine characteristics matches with the characteristics of the WHO vaccine TPP and how likely it is expected to demonstrate efficacy values that are close to the target measured efficacy as described in the TPP, provided an acceptable safety profile.

## 5. Next Steps

A series of collaborative steps to continue to advance the discussions were outlined and agreed upon. It is anticipated that the steps will be implemented in close collaboration with the workshop participants and other experts in the community as appropriate.

**a) Finalizing the WHO draft TPP for plague vaccines**

The WHO TPP for plague vaccines will undergo an extensive online consultation in June 2018. WHO will consider comments received from various partners and will prepare a final consensus TPP to be shared to the plague community.

**b) Developing an annotated generic protocol for plague vaccine efficacy trials, based on preliminary design consensus.** The generic protocol will be developed with inputs from all participants, and it will be published on the WHO website for public consultation by Fall 2018. It is anticipated that candidate vaccine developers and industrial representatives will be informed of the consultation process and invited to provide their perspectives.

**c) Clarify the role of RDT and other diagnostics tools in a plague surveillance system for endemic and outbreak conditions.** Confirmation of cases in a surveillance system is critical for trial endpoint measurement. WHO will organize a meeting in summer 2018 to review the current WHO case definitions in the light of the available diagnostics tools and in order to discuss their role as screening or confirmatory tools as part of a surveillance system.

**d) Promote enhanced surveillance and epidemiological studies to better understand the plague burden and its evolution.** Sero-prevalence surveys and modelling studies are crucial to better understand the distribution of susceptible population and to anticipate patterns of transmission in the future, and to inform the planning of vaccine evaluation studies. Retrospective analysis of the 2017 Madagascar outbreak is essential to understand transmission patterns (e.g., cluster of cases) and estimate attack rates in outbreak situations.

**e) Establish collaborations with countries and research sites and plan for clinical trials.** WHO will continue to promote collaboration with relevant groups, to gain knowledge of plague transmission, and prepare for a multi-country approach for plague vaccine evaluation in concert with the national regulatory authorities and ethics committees of the affected countries. Efforts towards the use of WHO standard case definition will be encouraged, and WHO will promote standardization efforts towards the development of international standards reagents and material.

**f) Establishing a transparent framework for selecting vaccines to be evaluated in Phase 2b/Phase 3 trials.** There are 17 plague vaccine candidates in various stages of development and there would be benefit from establishing a framework for vaccine selection to ensure resources are utilized for development of candidates that demonstrate the highest likelihood of success.

**g) Further develop a mathematical model for transmission and control of plague.** This model will be used to refine the development of Phase 2b/Phase 3 vaccine trials in terms of optimal design and sample size calculation. The model can also be used to explore the best control strategies once a vaccine is shown to be efficacious.