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WHO Target Product Profile for Plague Vaccines

Draft 0.5

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Purpose of the document

Selected disease areas are identified as WHO priorities for product development. 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. This document aims to set out preferred and minimal characteristics for next-generation plague vaccines from a public health perspective. The target audience includes vaccine scientists, product developers, manufacturers, funding agencies and policy makers.

All the requirements contained in WHO guidelines for WHO policy recommendation and prequalification will also apply. The criteria below lay out some of the considerations that will be relevant in WHO's case-by-case assessments of plague vaccines in the future.

None of the characteristics in the tables below dominates over any other. For certain vaccine characteristics, footnotes are added to provide the rationale and assumptions made. Therefore should a vaccine's profile be sufficiently superior to the critical characteristics under one or more categories, this may

outweigh failure to meet another specific critical characteristic. Vaccines that fail to meet multiple critical characteristics are unlikely to achieve favorable outcomes from WHO's processes.

A generic description of WHO's Vaccine Prequalification process can be found at the end of this document.

Background

Plague is an infectious disease caused by the bacteria *Yersinia pestis*, a zoonotic bacteria, 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 human population co-exist. There are large plague reservoirs in African, Asian, and South American continents [1]; but since the 1990s, most human cases have occurred in Africa. Plague endemicity throughout the world has resulted in sporadic infections [2], including recent outbreaks in the 21st 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. Emergence of antibiotic-resistance strains has also been observed [1].

Plague is 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 [3].

From 2010 to 2015, 3,248 cases were reported worldwide, including 584 deaths [3]. 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 [4]. Among the 2,348 cases of plague, 1,791 cases 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.

[1] Carniel E. 6 Plague Today. *Medical History Supplement*. 2008;(27):115-122.
[2] Fernando RL et al. Plague. *Tropical Infectious Diseases: Epidemiology, Investigation, Diagnosis and Management*. Greenwich Medical Media; 2001;257.
[3] http://www.who.int/mediacentre/factsheets/fs267/en/
[4] http://www.who.int/csr/don/27-november-2017-plague-madagascar/en/

This document summarizes the desired critical qualities required for a future plague vaccine to be used effectively in either emergency-use vaccination campaigns or long-term, routine preventive vaccination in areas where disease is endemic. Although both types of vaccination programs will have overlapping benefits for target populations, the two strategies have been separately categorized as:

1. **Reactive/ emergency use** in the face of an outbreak to prevent plague in vaccinated individuals as well as to interrupt chains of transmission to terminate outbreaks. The use will be in populations experiencing an outbreak, and in populations at high risk for importation of plague cases from areas experiencing an outbreak.
2. **Preventive/ prophylactic use** to protect the populations living in areas where plague is endemic, and health care workers (HCWs) at particularly high risk of plague due to their profession (e.g. HCWs in endemic areas, laboratory personnel, deployed international HCWs).

The final version of this Target Product Profile (TPP) will be the result of an extensive consultation process with key stakeholders in public and animal health, scientific research, funding agencies, manufacturer communities and policy making bodies. It is intended that the final version will guide and prioritize the development of vaccines. As new scientific evidence is generated, this TPP may require further review and revision.

Target Product Profile

Vaccine characteristic	Reactive use		Preventive use	
	Preferred	**Critical or Minimal**	**Preferred**	**Critical or Minimal**
Indication for use	For active immunization of at-risk persons in the area of an on-going outbreak to protect against plague; to be used in conjunction with other control measures to curtail or end an outbreak.		For active immunization of persons considered potentially at risk to protect against plague. Risk groups will include communities in endemic areas and certain health care workers (HCWs) [5].	
Target population	All age groups [6,7,8] excluding infants. Suitable for administration to pregnant and lactating women and to immunodeficient persons.	All age groups [6,7,8] potentially excluding infants, pregnant and lactating women, and immunodeficient persons at the time of initial authorization based on the safety profile of the vaccine in these special populations [9].	All age groups [6,7,8]. Suitable for administration to pregnant and lactating women and to immunodeficient persons.	All age groups [6,7,8] excluding pregnant and lactating women and immunodeficient persons [10].
Safety/Reactogenicity	Safety and reactogenicity sufficient to provide a highly	Safety and reactogenicity whereby vaccine benefit	Safety and reactogenicity at least comparable to WHO-	Safety and reactogenicity whereby vaccine benefit clearly outweighs safety risks.

[5] HCWs at particularly high risk of plague due to their profession (e.g. HCWs in endemic areas, laboratory personnel, deployed international HCWs)
[6] "Plague has occurred in people of all ages (infants up to age 96)" https://www.cdc.gov/plague/maps/index.html
[7] Ju C, Liu Z, Zhang G et al. Epidemiological characteristics of human plague in different age groups in China from 1950-2012. *Zhonghua Liu Xing Bing Xue Za Zhi* 2014;35:101-103.
[8] Migliani R, Chanteau S, Rahalison L et al. Epidemiological trends for human plague in Madagascar during the second half of the 20th century: a survey of 20900 notified cases. *Tropical Medicine & International Health* 2006;11:1228-1237.
[9] This determination would rely on whether the vaccine benefit outweighs safety risks - similar to the minimal characteristics for other populations. As vaccine products are used in these populations and more data is generated on the safety profile for use in infants, pregnant and lactating women, and immunodeficient persons, the label should be updated accordingly.
[10] Post-licensure studies including the assessment of immunogenicity in pregnant and lactating women and immunocompromised individuals are expected.

Vaccine characteristic	Reactive use		Preventive use	
	Preferred	**Critical or Minimal**	**Preferred**	**Critical or Minimal**
	favorable risk-benefit profile, ideally with only mild and transient adverse events related to vaccination and no serious adverse events related to vaccination with the vaccine or vaccine-platform, including in individuals with compromised immune function or when administered in pregnancy.	clearly outweighs safety risks.	recommended routine vaccines, ideally with only mild and transient adverse events related to vaccination and no serious adverse events related to vaccination with the vaccine or vaccine platform, including in individuals with compromised immune function or when administered in pregnancy.	
Measures of Efficacy	At least 80% efficacy [11] in preventing bubonic and pneumonic forms of plague in the target population. Rapid onset of protective immunity (less than one week).	At least 70% efficacy [11] in preventing bubonic and pneumonic form of plague predicted and stop transmission in the affected population. Rapid onset of protective immunity (less than 10 days).	At least 80% efficacy [11] in preventing bubonic and pneumonic form of plague in the target population.	At least 70% efficacy [11] in preventing bubonic and pneumonic form of plague in the target population.

[11] Clinical investigation should include assessment of immunogenicity in pregnancy and among immunocompromised individuals to identify potentially clinically relevant differences. If demonstration of clinical efficacy is not feasible, immunogenicity and efficacy data generated in standardized and relevant animal models bridged with clinical immunogenicity may be considered. Passive therapy using human sera may also provide evidence of biological effect. If efficacy trials are not feasible, the predicted efficacy should be at the level specified for desired efficacy.

Vaccine characteristic	Reactive use		Preventive use	
	Preferred	**Critical or Minimal**	**Preferred**	**Critical or Minimal**
Dose regimen	Single-dose regimen highly preferred.	Primary series: no more than 2 doses, with preference for less than one-month interval between doses and good protection after the first dose.	Single-dose regimen highly preferred.	Primary series: no more than 3 doses, and with preference for less than one-month interval between doses.
Durability of protection	Confers protection of at least 2 years.	Confers protection of at least one year.	Confers long-lasting protection of 10 years or more following the primary series and can be maintained indefinitely by booster doses.	Confers protection of at least 5 years after primary series and can be maintained indefinitely by booster doses.
Route of Administration	Oral or non-parenteral route. A route enabling rapid mass administration.	A route enabling rapid mass administration. Where injection (IM, ID or SC) is required, using standard volumes for injection as specified in programmatic suitability for prequalification.	Oral or non-parenteral route. A route compatible with use in routine immunization programs.	A route compatible with use in routine immunization programs. Where injection (IM, ID or SC) is required, using standard volumes for injection as specified in programmatic suitability for prequalification.
Coverage	Coverage against all plague strains.	Coverage against the most common outbreak plague strains.	Coverage against all plague strains.	Coverage against plague strains circulating in the endemic areas.
Product Stability and	Shelf life of at least 5 years at	Shelf life of at least 12 months at -20^{o}C and one month at 2-	Ideally: stable at room temperature for 2-3 years.	Shelf life of at least 2 years at -

Vaccine characteristic	Reactive use		Preventive use	
	Preferred	**Critical or Minimal**	**Preferred**	**Critical or Minimal**
Storage	2-8°C. Preferably thermostable at higher temperatures for several days. The need for a preservative is determined and any issues are addressed including absence of toxicity. Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container. Vaccines that are not damaged by freezing temperatures (<0°C) are preferred. Vaccines stable out of cold chain are preferred. If not, vaccines that can be delivered via the Controlled	8°C. The need for a preservative is determined and any issues are addressed including absence of toxicity.	Shelf life of at least 5 years at 2-8°C. Preferably thermostable at higher temperatures for several days. The need for a preservative is determined and any issues are addressed including absence of toxicity. Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container. Vaccines that are not damaged by freezing temperatures (<0°C) are preferred. Vaccines stable out of cold chain are preferred. If not, vaccines that can be delivered	20°C and 6 months at 2-8°C. The need for a preservative is determined and any issues are addressed including absence of toxicity. Vaccine Vial Monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary distribution container.

Vaccine characteristic	Reactive use		Preventive use	
	Preferred	**Critical or Minimal**	**Preferred**	**Critical or Minimal**
	Temperature Chain are preferred [12].		via the Controlled Temperature Chain are preferred [12].	
Co-administration with other vaccines	The vaccine will be given as a stand-alone product not co-administered with other vaccines.		The vaccine can be co-administered with other vaccines.	The vaccine will be given as a stand-alone product not co-administered with other vaccines.
Presentation	If oral administration, mono-dose presentation in plastic tubes with a volume of 1-2 mL; or multi-dose (10-20) with a dropper presentation with a maximal dosage volume of 0.05 mL (1 drop) or 0.1 mL (2 drops). If injectable administration, the route is SC/IM route in 10-dose presentation with a volume of 0.5 mL. Multi-dose presentations	If oral administration, mono-dose presentation in glass vial with a volume of 1-2 mL or multi-dose container with a dropper device with 10-20 doses. If injectable administration, vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose (10-20) presentations with a volume of 0.5 mL. Multi-dose presentations	If oral administration, 2-5 doses with a volume of 1-2 mL in plastic tubes. If injectable administration, vaccine is provided as a liquid product in mono-dose or multi-dose (2) presentations with a maximal dosage volume of 0.5 mL. Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-	If oral administration, 2-5 doses with a volume of 1-2 mL in plastic tubes. If injectable administration, vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose (5-10) presentations with a maximal dosage volume of 0.5 mL. Multi-dose presentations should be formulated, managed and discarded in

[12] http://www.who.int/immunization/programmes_systems/supply_chain/resources/Controlled-Temperature-Chain-FAQ.pdf

Vaccine characteristic	Reactive use		Preventive use	
	Preferred	**Critical or Minimal**	**Preferred**	**Critical or Minimal**
	should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy.	should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy. If not supplied in a dual-barrel syringe, lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent.	dose vial policy.	compliance with WHO's multi-dose vial policy. If not supplied in a dual-barrel syringe, lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent.
Registration and Prequalification	Should be WHO pre-qualified according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies.		Should be WHO pre-qualified according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies.	

Considerations on Programmatic suitability

WHO Prequalification

Vaccines that are procured by United Nations agencies and for financing by other agencies, including Gavi, the vaccine alliance, require WHO prequalification. The WHO prequalification (PQ) process acts as an international assurance of quality, safety, efficacy and suitability for low and middle-income country immunization programs. WHO encourages vaccine developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development and to discuss the product and the regulatory requirements with the WHO prequalification staff early in the process. Licensure by a national regulatory authority (NRA), or European Medicines Agency in the case of the centralized procedure for marketing authorization in Europe, will be required prior to any consideration of prequalification. Furthermore the prequalification process requires regulatory oversight by the NRA of Record, which is usually the NRA of the country where the vaccine is manufactured or the NRA of the country of finishing and distribution, and such an NRA should have been assessed as functional by WHO. Vaccine developers should check that the planned NRA of Record for the prequalification procedure is considered functional by WHO.

The prequalification procedure is described in detail in the document Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO/BS/10.2155) available here:
http://www.who.int/immunization_standards/vaccine_quality/pq_revised_procedure_final_1may2012.pdf.

The WHO prequalification process which assesses vaccine quality, safety, efficacy and suitability for use in low and middle-income countries has developed criteria called Programmatic Suitability for Prequalification (PSPQ) criteria to review vaccines submitted for prequalification.
(http://apps.who.int/iris/bitstream/handle/10665/148168/WHO_IVB_14.10_eng.pdf)

Considerations of Programmatic Suitability for Prequalification

In addition to meeting quality, safety and efficacy requirements, it is also important that developers and manufacturers understand WHO's preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction and deployment. In addition, introduction of new vaccines that have higher volume, cold chain capacity or disposal demands have had a negative impact on existing operations of immunization programs. Therefore early stage consideration of presentation and packaging parameters is encouraged. Deferring these considerations may lead to additional costs and delays required for reformulation later in the development pathway.