



World Health
Organization

Meeting Summary

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Plague vaccines

What R&D progress has been achieved and how can we accelerate development of a vaccine?

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R&D Blueprint

Powering research
to prevent epidemics

Plague epidemiology

Transmission from fleas, some H2H. Global cases estimated 1-3K per yr. Bubonic untreated CFR 30-60%, pneumonic 100%, septicemic 20-35%. >90% of cases in Africa, Madagascar & DRC account for most cases, which are likely underreported. Transmission is seasonal with November peak in Madagascar. Median age 11-13 (higher for pneumonic). African outbreaks/epidemics range from 1-2676 cases (238 deaths in Madagascar 2017). 94 cases in Ituri this yr so far (non-seasonal). BOL, BRA, ECU, PER in SA. 2013-2018 5-28 cases per yr in Americas. Agricultural areas, large markets associated with outbreaks. 16 Eastern Med countries historically reported with focus on Iran. Rodents identified throughout Pakistan. Recent outbreak in Libya 2009 (5 cases), 2007 Afghanistan 83 cases with acute gastroenteritis symptoms (17 deaths) from camel meat ingestion. 1 Bubonic case in Europe (Kyrgistan) 2013 but >150 cases during 20th century. Kazakhstan 19 cases 1990-2002. Recently cases in Asia are rare, possibly due to low surveillance– but continued cases e.g., Mongolia 3 cases 8/23 and reported cases each year, often assoc. with marmot hunting.

Animal reservoirs make plague difficult to eradicate

Plague vaccines

Heat-inactivated Haffkine vaccine in India given to 26 million with reported 50-85% efficacy v.s. mortality 1897-1935, severely reactogenic. Formalin inactivated vaccine (3+ doses) studied 1939-99. EV-76 LA vaccine (1+ doses) used 1936-present (humoral & cellular responses).

Next gen live-attenuated vaccines with deletions in key genes induce both cellular and humoral responses. 1-3 doses depending on vaccine protect animals v.s. pneumonic plague.

Numerous adjuvanted subunit vaccines, mostly based on F1-V. Mostly 2 doses, but some studied as 1 dose. Most induce humoral responses, but some strategies (e.g., OMV, nanoparticles) can also induce cellular responses. YscF may also be considered as an antigen.

Nucleic acid (DNA, SA-RNA, and mRNA) and vectored vaccines induce both cellular & humoral responses. Vectors include Ad, phage, bacterial vectors. F1 mRNA investigated as single dose. AGM challenge model seems more stringent than cynos.

Dynavax rF1V/CpG vaccine planned animal rule evaluation. High immunogenicity. 2 doses 1 month apart yield immune response better than legacy alum-adjuvanted 3-dose vaccine, which provided 71% efficacy against lethal aerosol challenge in NHPs. Passive immunization of mice was protective. Dynavax believes T cell responses will be induced by CpG, but doesn't intend to measure CMI directly in animals or humans.

Plague vaccines

Lanzhou Institute F1 rV Alum adjuvanted vaccine. 3-dose (0,1,6 or 0,2,6). Passive transfer of high titer serum can protect mice from lethal infection.

Mongolia live vaccine EV76NIEG and EV (Kazakhstan) annual campaigns since 2002. 5.6% of plague cases received vaccine, in population where ~25% get vaccine (with more vaccine given in places with higher plague case counts).

Cell-mediated responses may be important for vaccine efficacy, especially against intracellular pathogen like plague, and should be considered in immunogenicity-based decision-making.

TPP considers preventive and reactive use. For reactive use, rapid onset of protection is critically important, while for preventive use, duration of efficacy is a key consideration. We desire 70+% protection.

Plague vaccines: animal models and immunity

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Pneumonic plague disease model has been used for animal rule approval of antibiotics. Lethal doses in animals similar to infective dose in humans and disease is similar. Cyno preferred due to better protection with vaccines. Treated animals develop immune responses. Data on relative importance of CMI for vaccines and specific animal models are lacking. Antigen capture assays can be species independent.

High immune response (e.g., with Δ nlpD vaccine) did not correlate with protection. Human responses to plague vaccines can be variable and different vaccines induce different types of immune responses. Measuring both humoral and cellular responses may be important. NHPs are closest to human disease, but additional animal models can be considered: baboons, humanized mice (though not for live-attenuated). Unusual pathogenesis of plague suggests importance of very high humoral responses for antibody-mediated protection which can be different for bubonic vs pneumonic plague.

Serological markers are essential and reference standard will be very useful. Assays of humoral and cellular responses (including immune markers). Quantitative ELISA targets will depend on vaccines. Can functional antibodies be measured, e.g., by competitive ELISA? Candidate standard to cover range of human Ab responses will be evaluated in international collaborative study in 2024. Assays that address binding to known protective epitopes (including displacement of monoclonal binding) can be useful. Can levels from survivors be used to identify correlates of protection? How to generate and measure mucosal immune response?

Plague vaccines: Clinical evaluation

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Consider a prospective randomized trial with reactive vaccination in outbreak areas. Madagascar 2017 outbreak was focused over 6-8 week time period. Consider trial across multiple outbreaks/areas. If 1% placebo attack rate, sample size would be around 15K. Need to do where an outbreak is expected and pre-position vaccines and protocols. Can high risk areas be identified in advance of outbreaks? Single dose vaccines could be very useful in outbreaks. For reactive use may need to sacrifice lower bound or expected efficacy (based on single dose). Consider Bayesian approaches. Other treatments could interfere with trial. Endpoint definition may be difficult to implement.

Gaps between epidemics. Resources have been diverted to pressing needs. Need improved surveillance and diagnostics. Endemic areas are still large with need to identify areas of highest risk. Security issues can be important. Few cases in Uganda but infected rodents are present. 2017 Madagascar outbreak was very unusual. 27 cases of pneumonic plague. Madagascar currently studying cipro for bubonic plague. 52 sites. Could get 190 confirmed cases in past 5 yrs of Abx trial. Optimism within Africa that a trial could be conducted in endemic areas. Labs and diagnostic capability already exist in key areas.

Plague vaccines: Additional considerations for evaluation

Independent technical advisory group considers data about candidate vaccines in context of target product profile

Regulators would consider accelerated pathways, if they are based on very good science, validated assays, and there is a potential to conduct a confirmatory study. Animal efficacy studies could support indication for pneumonic plague especially where trials are less feasible.

Knowledge gaps and research priorities

Improved/reinstated surveillance with more data about true plague infection rates and how outbreaks evolve. This will depend on availability of lab capacity and diagnostic tools, which are available in some places and not in others.

Address role of cell-mediated and mucosal responses in short and long-term protection and consider developing assays to measure these. Work on functional Ab responses could identify more reliable correlates of protection. Need to be practical in thinking about what assays can be implemented to support specific goals.

Consider approaches to confirm vaccine efficacy if vaccines are made available e.g., for limited indications based on animal data.