A Systematic Review of the Efficacy, Safety, and Immunogenicity of Plague Vaccines

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BACKGROUND

- Plague is an infectious disease caused by the Yersinia pestis bacterium, which is still endemic in many countries.
- Currently, there is no licensed plague vaccine, and efficacy and safety evidence for those currently produced is scarce.
- Antibiotics are used for early prophylaxis and treatment of plague because vaccine protection is delayed after immunization for at least 1 week.[1] However, bacterial resistance to antibiotics is becoming a challenge, and two strains of plague bacterium have already been identified as antibiotic resistant.[2,3]
- Given the rising levels of antibiotic resistance to bacterial infectious diseases, it is important to identify and develop alternative prevention strategies.

OBJECTIVE

- To evaluate evidence from randomized controlled trials of the efficacy, safety, and immunogenicity of vaccines to prevent bubonic and/or pneumonic plague.

METHODS

- A systematic literature review of randomized controlled trials (RCTs) was conducted to identify studies that assessed a live or attenuated plague vaccine compared with either placebo, no intervention, or other plague vaccines.
- MEDLINE, Embase, and the Cochrane Library were searched from inception to November 2020. Clinical trial registers, conference proceedings, and bibliographies of relevant studies were also searched.
- Studies were screened by two independent researchers, and risk of bias of included studies was assessed using the Cochrane Collaborations tool.
- Primary outcomes were efficacy (number of cases avoided by vaccination), safety (including adverse events [AEs]), and immunologic outcomes (a rise in antibody titers).

RESULTS

- Figure 1 present the PRISMA diagram of study inclusion and exclusion.
- Of the 73 publications screened, 4 publications relating to 2 RCTs were identified which met the predefined inclusion criteria.
- Table 1 shows the trial characteristics.
- Given the heterogeneity between the trials in design, interventions, and timepoints, no quantitative synthesis for outcomes could be conducted.
- Among the 2 trials, no data were available on the efficacy of either plague vaccine.
- The limited evidence for safety showed both vaccines were well tolerated with only mild to moderate AEs. Frey et al.[4] reported no severe solicited AEs 28 days after each dose of the vaccine, and most AEs reported were mild. Only the Flagellin 6 mg arm showed a higher proportion of solicited systemic AEs (80%) when compared with placebo (75%).
- For Chu et al.[5], no serious AEs were reported between day 56 and 6 months, and only 1 serious AE was reported between 6 months and 12 months, but this was not related to vaccination. For solicited systemic AEs within 7 days of vaccination, none of the treatment arms reported grade 3 fever, muscle pain, fatigue, or headaches.
- Both vaccines reported an immune response. For Chu et al.,[5] both treatment arms showed an increase from baseline in antibodies to the F1 antigen at all timepoints, but GMTs were higher at all timepoints after vaccination for the 30-mcg group compared with the 15-mcg group.
- For the rV antigen, a decrease in antibodies between baseline and all timepoints after vaccination was found for both doses of plague vaccine. In Chu et al.,[5] GMTs were similar between both vaccine doses at 56 days (P = 0.3387). However, GMTs were numerically higher at both month 6 and month 12 for the 30-mcg group compared with the 15-mcg group.
- For Frey et al.,[6] postvaccination fourfold increases in responses to the F1 antigen were higher in all Flagellin treatment arms compared with placebo (10.0 %, 20.0%, 55.6%, and 60.0% vs. 0.0%). This was also the case for fourfold increases in the V antigen after vaccination (20.0 %, 30.0%, 88.9%, and 70.0% vs. 0.0%).
- Risk of bias assessment showed both studies with at least 1 domain classified as having an unclear risk of bias. However, the overall risk of bias in these trials was low.
- Figure 2 shows a risk of bias summary.

RESULTS CONTINUED

Figure 1. PRISMA Diagram

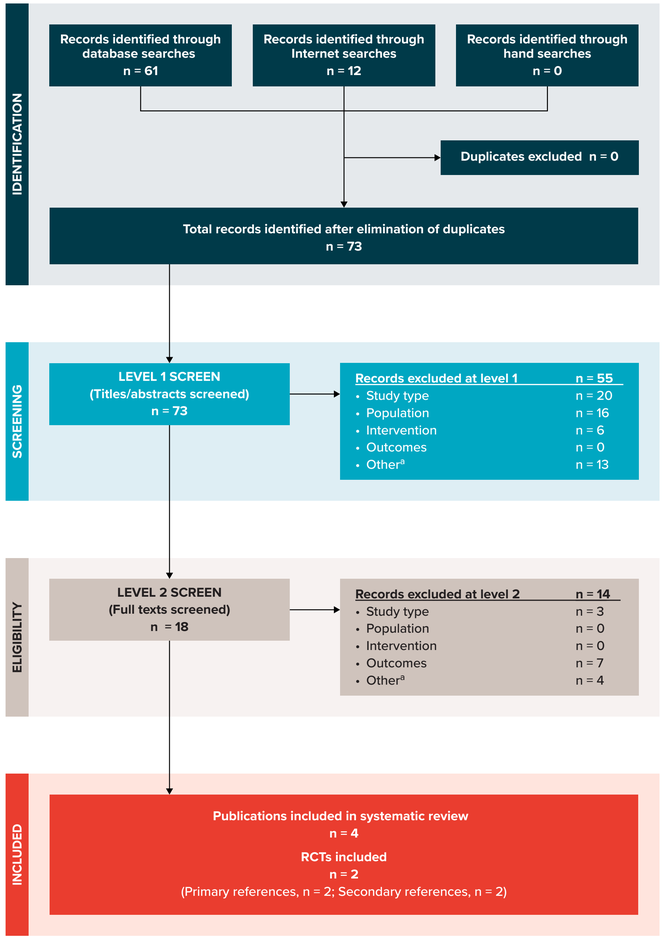
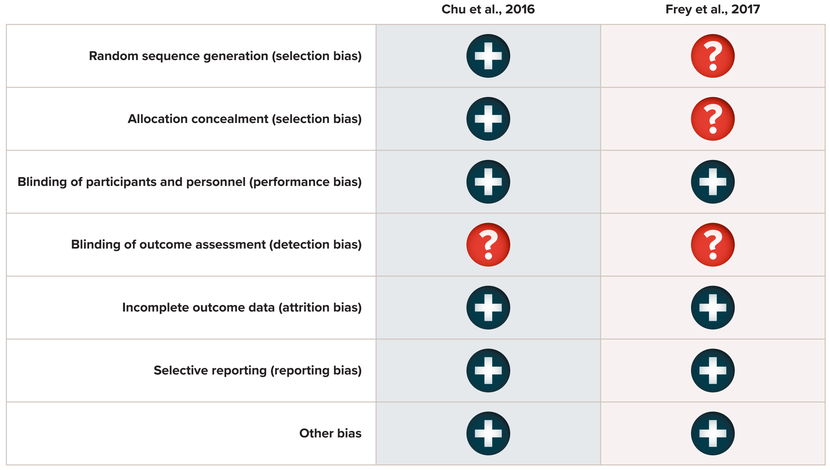


Table 1. Trial Characteristics

First Author, Year	Trial Registry Identifier	Study Design	Study Location	Study Length	Outcomes Reported	Patient Characteristics	Trial Arms
Chu et al. (2016)[5]	NCT02596308	RCT Phase 2	China	3 months	Immunogenicity (GMT for F1 antigen and rV antigen) Safety (solicited local AEs within 7 days of vaccination; solicited systemic AEs within 7 days of vaccination and unsolicited AEs within 28 days of vaccination)	Healthy adults (n = 240)	1. Plague vaccine of F1 and rV antigens 15 mcg (2 doses given at 28-day interval between doses) 2. Plague vaccine 30 mcg (2 doses given at 28-day interval between doses)
Frey et al. (2017)[4]	NCT01381744	RCT Phase 1	US	13 months	Immunogenicity Safety (solicited systemic AEs and solicited local AEs)	Healthy adults (n = 60)	1. Flagellin/F1/V 1 mg (intramuscular injection of 1 mcg/dose on days 0 and 20; delivered in a volume of 100 mL) 2. Flagellin/F1/V 3 mg (intramuscular injection of 3 mcg/dose on days 0 and 28; delivered in a volume of 300 mL [1 mcg/100 mL]) 3. Flagellin/F1/V 6 mg (intramuscular injection of 6 mcg/dose on days 0 and 28; delivered in a volume of 600 mL [1 mcg/100 mL]) 4. Flagellin/F1/V 10 mg (intramuscular injection of 10 mcg/dose on days 0 and 28; delivered in a volume of 100 mL) 5. Placebo (the volume of placebo given was the same volume as the vaccine in the respective dose group)

GMT = geometric mean titer; US = United States.

Figure 2. Risk of Bias Summary



DISCUSSION

- **No evidence as to the efficacy of plague vaccines was identified. However, the limited evidence of safety showed both vaccines to be well tolerated, and both produced an immune response.**

CONCLUSIONS

- **Given the limited trials identified in this systematic review, we are unable to conclude as to the efficacy, safety, and immunogenicity of vaccines to prevent plague. This systematic review highlights that more trials of plague vaccines are needed with further evidence of their long-term effects. This is imperative given the high mortality from plague, the emergence of antibiotic resistance, and given that early antibiotic treatment may not be viable in rural areas during an outbreak.**

REFERENCES

1. Anisimov AP, Amoako KK. Treatment of plague: promising alternatives to antibiotics. J Med Microbiol. 2006 Nov;55(Pt 11):1461-1475. doi: 10.1099/jmm.0.46697-0. PMID: 17030904.
2. Galimand M, Carniel E, Courvalin P. Resistance of Yersinia pestis to antimicrobial agents. Antimicrob Agents Chemother. 2006 Sep;50(10):3233-323. doi: 10.1128/AAC.00306-06.
3. Ditchburn JL, Hodgkins R. Yersinia pestis, a problem of the past and a re-emerging threat. Biosafety Health. 2019;1(2) 65-70.
4. Frey SE, Lottenbach K, Graham I, Anderson E, Bajwa K, May RC, et al. A phase I safety and immunogenicity dose escalation trial of plague vaccine, Flagellin/F1/V, in healthy adult volunteers (DMID 08-0066). Vaccine. 2017;35(48):6759-65.
5. Chu K, Hu J, Meng F, Li J, Luo L, Xu J, et al. Immunogenicity and safety of subunit plague vaccine: A randomized phase 2a clinical trial. Hum Vaccin Immunother.. 2016;12(9):2334-40.

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