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Preview

Q fever vaccine development: Challenges and progress in balancing safety and efficacy

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SUMMARY

The existing human vaccine against Q fever, a zoonotic disease of biothreat concern, is approved only in Australia. In this issue of *Cell Reports Medicine*, Gregory and colleagues describe a new vaccine candidate that overcomes specific concerns hindering wider acceptance of the commercial vaccine.[1]

Q fever is caused by the highly infectious Gram-negative bacterium *Coxiella burnetii* (*Cb*).[2] Acute Q fever in humans is often self-limiting, rarely lethal, and treatable with antibiotics once diagnosed. However, it progresses to a debilitating condition with serious long-term consequences in 10%–15% of those infected. Q fever outbreaks have occurred in several countries, including Australia and the Netherlands, and *Cb* exposure is of concern to the US and UK militaries because of high seroconversion rates among troops serving in the Middle East.[3] An effective vaccine is considered critical to the control of Q fever in occupational and biodefense settings. Q-VAX, an inactivated whole cell vaccine (WCV) used in Australia since 1989,[4] effectively prevents Q fever but has not received regulatory approval outside Australia. In this issue of *Cell Reports Medicine*, Gregory et al.[1] report the generation and initial preclinical efficacy of an experimental Q fever vaccine, a semi-defined soluble bacterial extract termed Sol II, designed to address limitations impeding wider use of Q-VAX.

Multiple countries classify *Cb* as a biothreat agent, and the associated biosafety and biosecurity requirements for manufacture from a virulent *Cb* strain contribute to limited Q-VAX availability. *Cb* virulence varies with differences in lipopolysaccharide (LPS) structure; all virulent strains (including the isolate used in Q-VAX) express full-length "phase I" LPS, while truncation to "phase II" LPS leads to a loss of virulence.[5] Sol II is derived from an avirulent phase II *Cb* strain and can be produced under lower biocontainment.[1] Although previous phase II-derived vaccine candidates demonstrated limited or no efficacy in preclinical testing,[5] Sol II vaccination conferred significant protection in mouse, guinea pig, and macaque models of *Cb* aerosol challenge, albeit with somewhat lower efficacy than did a WCV or a phase I soluble extract (Sol I) under the dosing regimens employed.[1]

A second significant hindrance to Q-VAX acceptance is that individuals with prior *Cb* infection are at increased risk for adverse reactions to Q-VAX.[4] Consequently, vaccination is contraindicated for individuals with a positive skin test for cell-mediated immune reactions to *Cb* antigen or with serologically detected circulating anti-*Cb* antibodies. Sol II did not induce the significant hypersensitivity responses seen with WCV in a sensitized guinea pig model of Q fever vaccine reactogenicity,[1] positioning Sol II as a candidate vaccine that could obviate the need for vaccination prescreening.

The encouraging preclinical results for Sol II[1] prompt a look forward along the clinical development path for a new Q fever vaccine. Although many *Cb* infections are asymptomatic or self-limiting, the extended duration of debilitating morbidity associated with acute disease and potential for long-term disabling chronic sequalae make human challenge studies inappropriate for Q fever vaccine trials.[2] Australia's approval of Q-VAX relied on field efficacy studies in abattoir workers at risk of occupational exposure to *Cb*.[6] When human challenge studies are not ethical and field trials are not feasible, the US Food and Drug Administration (FDA) may approve vaccines based on animal efficacy studies under the "Animal Rule."[7] The FDA will consider Animal Rule approval "only when the animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or the prevention of major morbidity."[7] Since acute Q fever is rarely lethal, the desired clinical outcome of Q fever vaccination is prevention of debilitating acute disease and subsequent chronic outcomes. Sterilizing immunity could be reasonably expected to protect against disease and is a common efficacy objective in vaccine studies. However, vaccination with the clinically efficacious Q-VAX, or a comparable formalin-inactivated WCV, reduced but did not prevent bacteremia in either an intraperitoneal-challenge mouse model or an aerosol-challenge macaque model.[8,9] Nevertheless, in both models, disease symptoms and pathology were abrogated or significantly attenuated in WCV-vaccinated animals compared to unvaccinated animals, consistent with the results reported by Gregory et al.[1] While sterilizing immunity may be an ideal objective in vaccine development, requiring a preclinical endpoint that is not achieved by a vaccine with proven efficacy in humans may prevent development of promising new vaccines.

In the absence of sterilizing immunity, vaccine efficacy should be reflected in improved infection control or accelerated bacterial clearance in vaccinated animals. One unambiguous endpoint demonstrating improved infection control is survival of a lethal infectious dose, and

various lethal *Cb* challenge models have been described.[10] However, these lethal preclinical models utilize high infectious doses relative to most human exposures, and although representing stringent tests of infection control, they do not reflect the typical human disease course. Reduction of fever and prevention of pneumonia following sublethal challenge in vaccinated animals compared to unvaccinated animals likely represent more relevant endpoints for disease prevention in humans.[8,10] The bacterial load reduction and attenuation of disease pathology conferred by Sol II vaccination in the sublethal aerosol challenge models used by Gregory et al. represent relevant outcomes for acute disease, though the relevance of these models for chronic disease has not been established.[1]

Successful clinical translation of preclinical vaccine studies requires that immune responses in animals and humans are sufficiently correlated to allow selection of an effective vaccine dose in humans.[7] In humans, Q-VAX vaccination induces both antibodies and cellular immune responses, but cellular immunity was a more reliable correlate of long-term protection in Australian clinical trials.[6] Consistent with a central role for cellular immunity in controlling *Cb* infection,[2,5] adoptive transfer of lymphocytes or $CD4^+$ T cells from Sol II-vaccinated mice conferred partial protection to naive animals, whereas passive transfer of immune sera did not.[1] Previous studies have demonstrated protection of naive mice by immune antibodies from WCV-vaccinated animals,[9] and whether failure of Sol II-immune sera to confer similar protection arose from differences in antibody quality or quantity remains unknown. The nature and levels of Sol II-induced antibodies were investigated,[1] but correlation of these parameters with protection in subsequently challenged animals was not examined, nor were levels of circulating antibodies following sera transfer determined. Nevertheless, these initial studies of Sol II-induced immunity against *Cb* provide an important foundation for future studies to define vaccine responses that can serve as correlates of protection bridging animal models of Q fever with human clinical responses.

DECLARATION OF INTERESTS

The authors are inventors on patent application WO 2019/183627 A1, "*Coxiella burnetii* epitopes for T cell-targeted Q fever vaccines," and are currently supported in part by grant HDTRA 1201006 from the US Defense Threat Reduction Agency, "Longitudinal Study of Immune Responses to Q-VAX in Young Healthy Adults to Support the Development of Novel Vaccines for Q Fever and Tests for Exposure Surveillance."

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