International Journal of Infectious Diseases 154 (2025) 107861

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

Innovative approach for the clinical development of a *Chlamydia trachomatis* vaccine through a human challenge model in women

Craig R. Cohen*

Department of Obstetrics, Gynecology & Reproductive Sciences, University of California San Francisco, San Francisco, CA, USA

ARTICLE INFO

Article history:
Received 26 November 2024
Revised 20 February 2025
Accepted 21 February 2025

Keywords:
Chlamydia trachomatis
Vaccine
Clinical trial
Human challenge model

ABSTRACT

Chlamydia trachomatis remains the most common sexually transmitted bacterial infection worldwide. Recent phase I trials of the *C. trachomatis* vaccine candidate CTH522 in women and men have shown that the adjuvanted and non-adjuvanted formulations are safe and elicit systemic (immunoglobulin G) and mucosal (immunoglobulin A) antibodies, as well as vaccine-specific cell-mediated immunity. In advance of a standard phase II randomized controlled trial to determine the vaccine's efficacy, this perspective advocates for a carefully and ethically designed human challenge model as an innovative approach to assess a vaccine's ability to prevent infection and its impact on tubal immunopathogenesis in breakthrough infections. Such models could accelerate vaccine development by providing critical insights, making it essential for stakeholders to consider this approach and expedite the long-awaited chlamydia vaccine.

© 2025 The Author. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Chlamydia trachomatis is the most prevalent sexually transmitted bacterial infection worldwide. Although antibiotic treatment is highly effective, most infections go undetected and untreated because they are often asymptomatic. *C. trachomatis* can ascend to the upper female genital tract, causing pelvic inflammatory disease, tubal factor infertility, ectopic pregnancy, and chronic pelvic pain [1]. In fact, about 40% of cervical *C. trachomatis* infections are associated with plasma cell endometritis and about 15% of cervical infections are associated with symptomatic pelvic inflammatory disease [2,3]. These sequelae are more common in repeat infections and are associated with a T helper (Th)2 clusters of differentiation 4+ T-cell response, whereas a Th1 immunoregulatory phenotype is associated with clearance of infection [2,4]. Current screening and treatment programs have failed to control this epidemic, highlighting the urgent need for a vaccine to prevent transmission and disease [1].

Data from animal models and human epidemiologic data suggest that natural immunity to chlamydia exists because immune responses after initial infection can provide partial or short-term complete immunity to repeat exposure. These insights have guided the preclinical rational design of vaccines, and the first phase I clinical trials have recently been completed [5,6]. These trials tested the *C. trachomatis* vaccine candidate CTH522 in women and men, finding the adjuvanted and non-adjuvanted vaccines to be safe and to elicit systemic (immunoglobulin G) and mucosal (immunoglobulin A) antibodies, as well as a vaccine-specific cell-mediated immune response indicated by interferon-γ enzyme-linked immunosorbent spot of peripheral blood mononuclear cells. The investigators concluded that the next step in clinical development is a phase II trial to test the hypothesis that the vaccine will reduce the incidence of chlamydia infection. Estimates suggest that such a trial would require around 2000 participants to detect a >50% reduction in incidence (A. Borges, personal communication), necessitating significant investment in time and resources before determining the vaccine's potential efficacy.

Furthermore, this traditional clinical trial design primarily measures safety by comparing adverse events between the active and placebo groups. However, if the true purpose of a vaccine is to reduce the sequelae of chlamydia infection, this approach may not answer whether the vaccine impacts the immunopathogenic pathway, leading to tubal scarring [7]. Previous research in non-human primate models and clinical studies have demonstrated that tubal scarring results from a Th2-directed pathway [8], with immunoregulation mediated by genetic factors that increase some individuals' risk of disease [9].

As an alternative, a human challenge model could test a vaccine's efficacy in preventing infection and, for breakthrough infections, its impact on tubal immunopathogenesis. Human challenge models have historically improved our understanding of multiple infectious diseases, including *Neisseria gonorrhoeae* in men [10,11]. This highly controlled and efficient clinical trial design offers several strengths: the ability to study infection risk and tubal pathology after breakthrough infections, relatively small sample sizes to

* Corresponding author. Tel.: +1 415 290 7085.
E-mail address: craig.cohen@ucsf.edu

https://doi.org/10.1016/j.ijid.2025.107861
1201-9712/© 2025 The Author. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

test efficacy, and obtaining tissue at risk of infection and pathology, such as the Fallopian tubes and endometrium. The risk of upper genital tract involvement, including tissue fibrosis in the Fallopian tubes, after natural infection can be used to estimate the required sample size for the human challenge trial. Potential challenges include the risk of breakthrough infection potentially outweighing the benefits to research participants and their sexual partners and increased scrutiny of the study protocol by regulatory authorities, including the US Food and Drug Administration and local institutional review boards.

To reduce the risk of chlamydia infection sequelae and maximize safety and efficacy data on the vaccine's effect on the female upper genital tract, I propose that women who are seeking female sterilization performed by bilateral salpingectomy be offered participation into the human challenge clinical trials. Bilateral salpingectomy is an accepted procedure for patients desiring sterilization, and patients often agree to delay the procedure for several months if using long-acting reversible contraception. Owing to the greater risk of recurrent *C. trachomatis* infection compared with primary infection in causing sequelae [2], an initial trial may consider limiting enrollment to participants who are *C. trachomatis* antibody–negative, with subsequent trials enrolling those who are antibody-negative and -positive. Women willing to participate in the human challenge experiment would have the clinical trial, including risks and benefits, explained in detail. Those who provide informed consent would be enrolled and randomized to receive either a chlamydia vaccine or a placebo. After completion of the vaccination dosing regimen, participants would be vaginally inoculated with a *C. trachomatis* strain highly susceptible to doxycycline and closely monitored for 6-8 weeks for any signs or symptoms of infection. This length of follow-up is based on data from *C. trachomatis* non-human primate models [1,2]. Symptomatic participants would be treated immediately with doxycycline. Participants would be encouraged to remain abstinent or use condoms, and male partners would need to be consented and closely monitored for chlamydia infection, potentially taking doxycycline pre-exposure prophylaxis or doxycycline post-exposure prophylaxis to reduce infection risk. At the conclusion of the observation period, female participants would undergo laparoscopic bilateral salpingectomy, with specimens evaluated histopathologically and using multiomics to assess immunologic factors associated with infection risk. All participants would be treated with doxycycline immediately after the procedure.

Although this approach has many potential challenges, they may be overcome by early engagement with community advisory boards, ethics boards, regulators, and research sponsors and commitment to open discussions as represented by this "perspective." The development of a *C. trachomatis* vaccine has taken far too long. Preclinical work on several chlamydia vaccines has accelerated [1], necessitating novel and efficient approaches to test their efficacy and safety, including the prevention of infection and disease. In addition, a human challenge model could provide valuable insights about chlamydia immunopathogenesis, specifically, identifying corelates of upper genital tract infection and scarring—both of which are difficult to ascertain under standard clinical trial conditions. Finally, I recommend that as a next step, researchers, companies, regulators, and potential funders should convene to consider a human challenge approach for testing chlamydia vaccines and work out the details required to maximize benefits and reduce risks.

Declarations of competing interest

The author is an Editor-in-Chief for Advances *in Global Health* and was not involved in the editorial review or the decision to publish this article. The author declares the following financial interests/personal relationships which may be considered as potential competing interests: the author is on advisory boards for Evvy Inc. and Osel Inc. and has received stock options. These companies were not involved in the development of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval statement

None required for this manuscript.

Author contributions

The author is the sole author of this perspective.

References

[1] Poston TB. Advances in vaccine development for Chlamydia trachomatis. *Pathog Dis* 2024;**82** ftae017. doi:10.1093/femspd/ftae017.
[2] Cohen CR, Brunham RC. Pathogenesis of Chlamydia induced pelvic inflammatory disease. *Sex Transm Infect* 1999;**75**:21–4. doi:10.1136/sti.75.1.21.
[3] den Heijer CDJ, Hoebe CJPA, Driessen JHM, Wolffs P, van den Broek IVF, Hoenderboom BM, et al. Chlamydia trachomatis and the risk of pelvic inflammatory disease, ectopic pregnancy, and female infertility: a retrospective cohort study among primary care patients. Clin Infect Dis 2019;69:1517–25. https://doi.org/10.1093/cid/ciz429. Erratum in: Clin Infect Dis 2020;70:2459. https://doi.org/10.1093/cid/ciz897.
[4] Ondondo BO, Brunham RC, Harrison WG, Kinyari T, Sheth PM, Mugo NR, Cohen CR. Frequency and magnitude of Chlamydia trachomatis elementary body- and heat shock protein 60-stimulated interferon gamma responses in peripheral blood mononuclear cells and endometrial biopsy samples from women with high exposure to infection. *J Infect Dis* 2009;**199**:1771–9. doi:10.1086/599095.
[5] Abraham S, Juel HB, Bang P, Cheeseman HM, Dohn RB, Cole T, et al. Safety and immunogenicity of the chlamydia vaccine candidate CTH522 adjuvanted with CAF01 liposomes or aluminium hydroxide: a first-in-human, randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet Infect Dis* 2019;**19**:1091–100. doi:10.1016/S1473-3099(19)30279-8.
[6] Pollock KM, Borges ÁH, Cheeseman HM, Rosenkrands I, Schmidt KL, Søndergaard RE, et al. An investigation of trachoma vaccine regimens by the chlamydia vaccine CTH522 administered with cationic liposomes in healthy adults (CHLM-02): a phase 1, double-blind trial. *Lancet Infect Dis* 2024;**24**:829–44. doi:10.1016/S1473-3099(24)00147-6.
[7] Poston TB, Darville T. First genital chlamydia vaccine enters in-human clinical trial. *Lancet Infect Dis* 2019;**19**:1039–40. doi:10.1016/S1473-3099(19)30290-7.
[8] Hafner LM. Pathogenesis of fallopian tube damage caused by Chlamydia trachomatis infections. *Contraception* 2015;**92**:108–15. doi:10.1016/j.contraception.2015.01.004.
[9] Cohen CR, Gichui J, Rukaria R, Sinei SS, Gaur LK, Brunham RC. Immunogenetic correlates for Chlamydia trachomatis-associated tubal infertility. *Obstet Gynecol* 2003;**101**:438–44. doi:10.1016/s0029-7844(02)03077-6.
[10] Hobbs MM, Sparling PF, Cohen MS, Shafer WM, Deal CD, Jerse AE. Experimental gonococcal infection in male volunteers: cumulative experience with Neisseria gonorrhoeae Strains FA1090 and MS11mkC. *Front Microbiol* 2011;**2**:123. doi:10.3389/fmicb.2011.00123.
[11] Choy RKM, Bourgeois AL, Ockenhouse CF, Walker RI, Sheets RL, Flores J. Controlled human infection models to accelerate vaccine development. *Clin Microbiol Rev* 2022;**35**:e0000821. doi:10.1128/cmr.00008-21.