First ever phase 1 trial of genital chlamydia vaccine finds it is safe and provokes immune response

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Chlamydia is the most common sexually transmitted bacterial infection worldwide, but national screening programmes and antibiotic treatment have failed to decrease infection incidences.

The first ever chlamydia vaccine to reach phase 1 clinical trial has been found to be safe and able to provoke an immune response, according to a study published in *The Lancet Infectious Diseases* journal. The randomised controlled trial of 35 healthy women demonstrates promising early signs of what could be an effective vaccine, but further trials are required to determine whether the immune response it provokes effectively protects against chlamydia infection.

Chlamydia, caused by the bacterium *Chlamydia trachomatis*, presents a major global health burden—with 131 million new cases occurring annually. However, as three out of four infections are symptomless, the number of cases is likely to be underestimated. The highest number of new cases are found in teenagers and young adults.

Vaccination may be the best way to tackle the epidemic, as national treatment programmes have largely failed to curb the epidemic, despite availability of diagnostic tests and effective antibiotic treatment. Previous studies have suggested that people infected with chlamydia develop either partial or temporary natural immunity to the pathogen, but no previous vaccines for genital chlamydia have reached clinical trials.

"Given the impact of the chlamydia epidemic on women's health, reproductive health, infant health through vertical transmission, and increased susceptibility to other sexually transmitted diseases, a global unmet medical need exists for a vaccine against genital chlamydia," says study author, Professor Peter Andersen, from Statens Serum Institut, Denmark.

For one in every six women infected with chlamydia, the infection travels up from the cervix and causes pelvic inflammatory disease. This can result in chronic pelvic pain and even infertility or ectopic pregnancy, especially in the developing world, where access to treatment and screening is limited. In addition, chlamydia is strongly associated with susceptibility to other sexually transmitted infections, particularly gonorrhoea and HIV, and chlamydia infection during pregnancy can increase the risk of adverse outcomes such as miscarriage, stillbirth, and preterm birth.

In the trial, the authors aimed to assess the safety and ability to provoke an immune response, in humans, of a new chlamydia vaccine CTH522 based on the major outer membrane protein of the C trachomatis bacterium. The researchers compared two different formulations—one with added CAF01 liposomes designed to aid cellular immunity and one with aluminium hydroxide known for its ability to help produce antibodies—to examine which formulation would perform better.

The 35 women not infected with chlamydia included in the trial were randomly assigned to three different groups: two with the new vaccine, CTH522, and one to placebo (five participants received saline). Of those receiving the vaccine, 15 participants received the vaccine combined with CAF01 liposomes (CTH522:CAF01), and the other 15 received the vaccine with aluminium hydroxide (CTH522:AH).

The vaccination was given to participants in three intramuscular injections in the arm administered on day 0, 28, and 112 and two intranasal boosts

administered on day 126 and 140. 32 participants received all five vaccinations.

Both formulations of the vaccine provoked an immune response in 15 out of 15 (100%) participants, whereas no participants in the placebo group achieved an immune response.

While both formulations of the vaccines were found to provoke an immune response, CTH522:CAF01 consistently performed better (producing 5.6 times more antibodies), so the authors suggest this formulation should be pursued for further clinical development. CTH522:CAF01 showed additional signs of better performance compared with CTH522:AH including an enhanced mucosal antibody profile that serves as first line of defence against the infection, and a more consistent cell-mediated immune response profile that is associated with long-lived immunity.

Although the vaccine provokes an immune response, whether this translates into protective immunity remains unclear. First author Helene B Juel, Statens Serum Institut, Denmark says: "Studies of antibodies in mice have found that antibodies in the vagina are the first line of defence against chlamydia infection, which suggests they are key to how effective the new vaccine may be. In our trial, significantly increased concentrations of these antibodies were found in both CTH522:CAF01 and CTH522:AH-vaccinated individuals. Although many more years of research are needed before this vaccine is marketed, we are planning the next stage of research—a phase 2a study of CTH522:CAF01."

CTH522 with either CAF01 or aluminium hydroxide appeared to be safe and well tolerated. There were no related serious adverse events reported. The most frequent adverse events were mild local injection-site reactions (all 15 participants in the two vaccine treatment groups had a mild reaction, which seemed to occur more frequently than in the placebo group [three out of five participants affected]). The most common local reactions were injection-site pain, tenderness, and movement impairment, with 88-93% of events being reported as mild in each of the groups, lasting a median of 2-4 days in all groups.

The authors note that the main limitation of the study is its sample size. As with other phase I trials, the small sample size limits its ability to pick up rarer adverse reactions to the vaccine or provide robust evidence on its ability to provoke an immune reaction.

Writing in a linked Comment, Professor Toni Darville from University of North Carolina, USA, notes: "A vaccine for prevention of C trachomatis infection would have enormous public health and economic impact. Although clinical vaccine testing for chlamydia is in its infancy, this trial suggests optimism for the future."

More information: Sonya Abraham 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, *The Lancet Infectious Diseases* (2019). DOI: 10.1016/S1473-3099(19)30279-8

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