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Applying lessons from human papillomavirus vaccines to the development of vaccines against *Chlamydia trachomatis*

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Abstract

Introduction: *Chlamydia trachomatis* (*Ct*), the most common bacterial STI, leads to pelvic inflammatory disease, infertility, and ectopic pregnancy in women. In this Perspective, we discuss the successful human papillomavirus (HPV) vaccine as a case-study to inform *Ct* vaccine efforts.

Areas covered: The immunological basis of HPV vaccine-elicited protection is high-titer, long-lasting antibody responses in the genital tract which provides sterilizing immunity. These antibodies are elicited through parenteral administration of a subunit vaccine based on virus-like particles (VLPs) of HPV. We present three lessons learned from the successful HPV vaccine efforts: (1) antibodies alone can be sufficient to provide protection from STIs in the genital tract, (2) the successful generation of high antibody levels is due to the multivalent structure of HPV VLPs, (3) major challenges exist in designing vaccines that elicit appropriate effector T cells in the genital tract. We then discuss the possibility of antibody-based immunity for *Ct*.

Expert Opinion/Commentary: In this Perspective, we present a case for developing antibody-eliciting vaccines, similar to the HPV vaccine, for *Ct*. Basic research into the mechanisms of *Ct* entry into host cells will reveal new vaccine targets, which may be antigens against which antibodies are not normally elicited during natural infection.

Keywords

antibody; Chlamydia; vaccine; virus-like particles

1.0 INTRODUCTION

The estimated global prevalence of *Chlamydia trachomatis* (*Ct*) among women and men 15–49 years old is 4.2% and 2.7%, respectively, making it the most common bacterial sexually transmitted infection [1]. *Ct* has been identified by the World Health Organization (WHO) and the U.S. National Institutes of Health (NIH) as a STI for which a vaccine is needed. One vaccine candidate has entered Phase I clinical trials [2] and others are in the pipeline, although historical experience of STI vaccine trials in general, and *Ct* vaccines specifically [3], urge cautious optimism. The experience developing the human papillomavirus (HPV)

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vaccine provides important lessons for protecting against STIs. The prophylactic HPV vaccine has been remarkably successful; it elicits potent and long-lasting protection against HPV infection and markers of cervical disease (e.g. CIN 2, 3). In this Perspective, we review the immunological basis for the success of the HPV vaccine and discuss how this knowledge can be applied to *Ct* vaccine efforts.

2.0 HPV vaccines.

HPV is the most common sexually transmitted infection despite a decrease in prevalence of infection after the introduction of the HPV vaccine [4]. In the United States alone, over 6 million new HPV infections are reported each year and greater than 75 million people are estimated to be currently infected [5]. HPV infection can cause a variety of different pathologies, but the most concerning is HPV-associated cervical cancer. Persistent infection with one of the high-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can cause cervical and other mucosal cancers. These high-risk HPV types account for 5.2% of all cancers world-wide [6]. In the early 1990s, it was discovered that the HPV major capsid protein, L1, could self-assemble into virus-like particles (VLPs) [7]. VLPs structurally resemble authentic HPV virions, but are not infectious because they lack a viral genome. In subsequent studies, it was shown that parenteral administration of HPV VLPs could elicit high-titer HPV-neutralizing antibodies [8]. Clinical trials demonstrated that HPV VLP-based vaccines could effectively prevent HPV infection and disease caused by the HPV types targeted by the vaccines [9]. These studies paved the way for clinical approval of the HPV vaccines Gardasil (Merck) and Cervarix (GSK). Both Gardasil and Cervarix include VLPs derived from the L1 protein of high risk HPV types 16 and 18. Gardasil additionally includes HPV 6 and 11, low risk HPV types that cause genital warts. A next-generation HPV vaccine, Gardasil-9, was released by Merck in 2014 and includes five additional high-risk HPV types (31, 33, 45, 52, and 58).

2.1 The basis for protection mediated by HPV vaccines.

There is strong evidence that the protection provided by the VLP-based HPV vaccines is mediated by neutralizing antibodies. Immunization with HPV L1 VLPs elicits high-titer antibody responses [7], and passive transfer of immune sera (from animals or humans) can provide sterilizing protection from cervicovaginal or mucosal HPV challenge in animal models [10, 11, 12]. Vaccine-induced HPV-specific IgG and IgA responses are not only present in the serum, but are also detected in the genital tract [13]. The source of antibodies in cervico-vaginal secretions is both local antibody-producing plasma cells and antibodies that cross into the mucosal barrier from the plasma by active transcytosis or exudation at breaches in the cervicovaginal epithelium [14]. Immune sera from rabbits vaccinated with HPV VLP vaccines blocks HPV infection at two steps: binding of HPV virions to the basement membrane, and binding of HPV to the surface of epithelial cells [15]. Interestingly, in one study 10–30% of vaccinated women do not have detectable levels of antibody to HPV in cervicovaginal secretions [13]. However, in one study, mice received antibodies via intraperitoneal transfer of immune sera obtained from Gardasil immunized mice, and the amount of sera needed to see protection against genital tract challenge with HPV was less than 1/1000th of a uL of sera [10]. This, along with no evidence of

breakthrough HPV infection in vaccinated individuals, suggests that the minimum amount of antibody necessary for protection against HPV infection is exceedingly small. It remains to be seen whether such a small effective dose of antibodies is sufficient to protect against other STIs.

It is important to note that, although the HPV L1 VLPs can elicit T cell responses against L1 (the only protein component of the VLPs), the preponderance of evidence suggests that T cells are not responsible for the protection elicited by the vaccine [16]. This is due to the unique HPV replication cycle, whereby HPV gains access to basal epithelial cells (the target host cell) through microabrasions, initiate cell cycle progression through the production of viral proteins E6 and E7, and only after terminal differentiation of the infected epithelial cells produces L1 and other structural proteins that assemble into virions [17]. Thus, any T cells elicited by the vaccine would be specific for the HPV L1 protein, which is not expressed in the basal epithelial cells. Basal epithelial cells harbor persistent HPV after infection, and they are the origin of neoplastic lesions. Indeed, clinical studies of HPV vaccinated individuals showed that vaccination fails to induce regression of previously infected lesions [18], indicating that the T cells that are elicited in response to vaccination with HPV VLPs are not able to act on infected cells to provide protection against neoplastic lesions.

2.2 Challenges in developing therapeutic HPV vaccines

While the success in developing prophylactic HPV VLP-based vaccines (i.e. those vaccines that prevent HPV infection) encourages efforts to develop vaccines for other STIs, the challenges in developing therapeutic HPV vaccines (i.e. those that would treat HPV-infected lesions or cervical neoplasia) are also instructive. As mentioned above, the current HPV VLP-based vaccines are prophylactic and do not exhibit any value for therapeutic treatment of current HPV infections or cervical cancer. Attempts to develop therapeutic HPV vaccines have focused on generating cell-mediated immune responses against the HPV proteins that are expressed in the basal epithelium, particularly the viral oncoproteins E6 and E7 from high-risk HPV types. Various vaccine strategies to target E6 and/or E7 have been employed in clinical settings, including peptides [19], fusion proteins [20], vector-based strategies [21, 22], and DNA vaccines [23, 24]. There have been modest successes in phase 2 clinical studies, including a DNA vaccine targeting E6 and E7 proteins that showed efficacy against HPV-16 and HPV-18 associated CIN2/3, but was not as effective as surgical resection [24]. No therapeutic HPV vaccine has yet been evaluated in a randomized phase 3 trial.

Why have therapeutic HPV vaccines shown limited efficacy? One possibility is that most HPV therapeutic vaccines have been administered systemically or at remote mucosal sites. It is likely that vaccines that can induce local cellular immune responses in the genital tract will be advantageous for targeting HPV lesions. While the best route for eliciting strong T cell responses in the genital tract is still debated, local genital immunization [25] or topical application of an adjuvant [20] or chemokines [26] may promote local proliferation or recruitment of T cells. Even when local T cell responses are successfully induced, the breadth of T cell responses is also likely to be an important factor in determining efficacy. For example, for therapeutic HPV vaccines, inadvertent concomitant induction of regulatory

T cells has been associated with treatment failure—i.e. no regression of neoplastic lesions [20, 27]. Thus, experience with therapeutic HPV vaccines has illustrated the challenges in eliciting the appropriate protective T cell subsets to the specific location of the genital tract.

2.3 Lessons learned from HPV vaccines.

The successful production of prophylactic HPV vaccines and the challenges in developing therapeutic vaccines against HPV illustrate several lessons that can be applied generally to vaccination efforts for other sexually transmitted pathogens. First, and most importantly, the HPV vaccine has demonstrated that antibodies alone are sufficient to protect against an STI. There are several specific features of the mechanism of HPV infection that may make this virus particularly susceptible to antibody-mediated neutralization (reviewed by [28]), but, nevertheless, the HPV vaccine is capable of eliciting high enough levels of antibody in the genital tract to provide sterilizing immunity. Importantly, these levels of antibody in the genital tract can be achieved by parenteral administration rather than by using a specialized approach to elicit mucosal antibodies. Second, the successful generation of high levels of antibodies against HPV is attributed to the multivalent (a word which here means “repetitive” or “having multiple sites”) structure of HPV VLPs [16]. Third, there are major challenges in designing successful vaccines for inducing effector T cell responses against STI antigens in the genital tract. Therapeutic vaccines for HPV have appropriately targeted the viral oncoproteins. However, even when the target antigen is known, there are no straightforward techniques to direct effector T cell responses to the genital tract while, at the same time, avoiding activation of regulatory T cell subsets.

3.0 Vaccines for *Chlamydia trachomatis*.

Rather than exhaustively reviewing all historical and current *Ct* vaccine efforts, we refer the reader to three excellent recent reviews that provide a detailed discussion of *Ct* vaccine efforts [3, 29, 30]. Additionally, we refer the reader to a recent report on *Ct* vaccine strategies. This report derives from a workshop that was convened in May 2015 at the National Institute of Allergy and Infectious Diseases (NIAID) to provide an assessment of current vaccine efforts and develop recommendations for future *Ct* vaccine efforts [2]. The report provides recommendations on appropriate animal models, areas of future research that need to be investigated, and desired features of future *Ct* vaccines. The workshop concluded that a successful *Ct* vaccine would likely need to elicit both *Ct*-specific CD4+ T cell responses in the genital tract and strong antibody responses. This consensus is based on current evidence in animal models of infections, which show that CD4+ T cells are necessary for clearing primary infection and that antibody can protect against subsequent infection [2]. The workshop participants also questioned the ability of systemic immunization to be an effective mode of delivery for a vaccine capable of conferring protection in the genital tract, a viewpoint expressed previously [3]. Many of these concerns and recommendations mirror those shared by the HPV research community prior to the demonstrated success of the antibody-based HPV vaccine [31]. Given the profound success of the HPV VLP-based vaccines, we posit that a parenteral vaccine that elicits high-titer antibody may also be sufficient to induce sterilizing immunity against genital infection with *Ct*.

3.1 Can a vaccine that mediates protection through antibody effectively prevent primary *Ct* infection?

In order to consider the possibility of whether vaccine-induced antibody might be sufficient to protect against *Ct*, we must first consider the life-cycle of *Ct* in host cells in the female genital tract. Although *Ct* is a bacterium, it shares many features with HPV: namely its mode of transmission, biological niche, ability to cause long-term sequelae in the female reproductive tract, and primary site of initial host cell infection in squamocolumnar epithelial cells in the transition zone of the cervix [32] (Table 1). However, *Ct* is more antigenically complex than HPV. *Ct* exists primarily in two forms: infectious elementary bodies (EBs) and metabolically active reticulate bodies (RBs). The infectious life-cycle begins when EBs attach to the surface of host cells and gain entry. Once EBs enter into the host cell, they establish a cytoplasmic inclusion by actively preventing the fusion of the endosome with the lysosome. In the inclusion, the *Ct* EBs differentiate into the metabolically active RB form and replicate. RBs differentiate back into EBs prior to release from the cell through either lysis or extrusion of the inclusion vacuole [33].

The antibody-mediated protection provided by the HPV VLP-based vaccines is likely mediated by direct neutralization of the viral particles, which prevent adhesion and entry of the virions into the basal epithelial cells. In the case of *Ct*, antibodies could mediate protection by (1) neutralization of the EBs to prevent adhesion and/or entry and therefore prevent obligate intracellular bacterial replication and/or (2) opsonization of extracellular infectious EBs and increased opsonophagocytic clearance of *Ct*. We will consider each of these mechanisms in turn.

3.2 Antibody-mediated prevention of *Ct* EB entry into host cells.

Similar to the activity of HPV-neutralizing antibodies, antibodies that bind to and/or inactivate the function of molecules necessary for adhesion and/or entry of *Ct* EBs into the host cell could protect against *Ct* infection. Whereas HPV virions consist of two structural proteins (each of which can be targeted by neutralizing antibodies), *Ct* EBs, by one account, express 17 different proteins on their surface, and many of these proteins are extremely large [34]. Thus, unlike HPV, it is not entirely obvious which *Ct* antigens could serve as the basis for a vaccine that elicits blocking antibodies. One effective tool for vetting possible vaccine antigens is by testing monoclonal antibodies or sera for neutralizing activity by cell culture-based *Ct* neutralization assays, and then using the targets of those antibodies as vaccine antigens. This line of experimentation has identified the major outer membrane protein (MOMP), the polymorphic membrane proteins (Pmp), and others (PorB, OmcB, etc.) as possible vaccine antigens [3] [35, 36, 37] [38] [39, 40]. While many of these vaccine candidates elicit antibodies that show potent neutralizing activity in cell culture, to date no antibody-based vaccine has demonstrated protection in animal challenge models. There are several possible explanations for this observation: (1) antibody levels elicited by the immunization strategies employed so far are not of sufficient titer in the genital tract to provide measurable protection, (2) the antibodies generated are not the correct isotype to mediate protection, (3) the antibodies do not target the correct epitopes, (4) the animal model or route of infection being used is not appropriate for assessing protection, and/or (5) antibodies that are sufficient to block entry in cell culture are not sufficient in the more

complex *in vivo* environment. The relative role of each of these possibilities remains to be determined by future studies. Moreover, ongoing research into the mechanisms of host cell entry for *Ct* may reveal new and clear targets for neutralizing antibody-generating vaccines.

3.3 Opsonization and increased clearance of *Ct* EBs by phagocytes.

Antibody could also prevent *Ct* infection by serving as an opsonin, thereby enhancing clearance of extracellular bacteria by phagocytes. A recent report indicates that IFN-γ stimulated neutrophils can kill *Ct in vitro*, and this killing requires *Ct*-specific serum [41]. This suggests that vaccine-induced antibody against *Ct* might also increase opsonophagocytic killing of *Ct* by neutrophils and macrophages. Conversely, there are also reports that *Ct* can infect cultured macrophages *in vitro* [42, 43, 44]. Whether or not these phenotypes hold true *in vivo* remains to be determined. It will be important to fully investigate the activity of any antibodies elicited by vaccine candidates for their opsonization versus enhanced infection capabilities *in vitro* and *in vivo*.

4.0 Selecting protective antigens for an antibody-eliciting *Ct* vaccine.

Most *Ct* vaccine efforts have focused on eliciting antibody responses to naturally antigenic proteins. However, since natural infection with *Ct* does not confer lifelong immunity, it may be best to consider antigens that are not immunogenic during natural infection. As an example, recent efforts to generate a next generation HPV vaccine have focused on eliciting strong antibody responses to the minor HPV structural protein L2 [45]. L2 is not immunogenic during natural HPV infection, and yet antibodies to L2 are neutralizing and protective [46, 47]. L2 is considered a “cryptic epitope”, an epitope that is normally not immunogenic because it is exposed only transiently during entry into the host cell. However, if antibodies can be generated to this epitope (i.e. by displaying the L2 epitope on an immunogenic vaccine platform), then those antibodies are neutralizing and are sufficient to protect against infection [48]. Similarly, it is possible that the best antigen to target for a *Ct* vaccine that relies on an antibody-based mechanism of protection will be a similar cryptic epitope. Features to look for in a cryptic epitope are (1) the antigen or epitope is highly conserved among different types of *Ct*, (2) it is not normally immunogenic during natural infection, and (3) it is involved in an essential step in the bacterial infection process such as entry into host cells. Some possible *Ct* proteins that may have cryptic epitopes are MOMP, PorB, Pmps, and the proteins of the T3SS apparatus.

It is notable that some of the *Ct* EB surface-exposed proteins serve redundant functions. This provides a selective advantage to the pathogen, allowing it to escape antibody-mediated neutralization, but makes identifying appropriate neutralizing targets for vaccine design difficult. The Pmp proteins are a clear example, with these proteins serving redundant adhesion functions in experiments carried out in cell culture [49]. Because of this redundancy, an antibody-based approach for vaccination against *Ct* may require the inclusion of multiple targets. Some protein epitopes may also serve as “immunological decoys” [50], displaying highly variable, immunogenic domains that drive the antibody response toward non-essential regions of the protein while avoiding antibody responses that

may prevent infection. Selecting protective antigens for *Ct* will therefore require additional research into the mechanisms of adhesion and entry.

5.0 Advantages of antibody-eliciting vaccines for *Ct*

There are significant advantages of antibody-eliciting vaccines, including: (1) the possibility of single-dose vaccines, (2) multi-component vaccine formulations that target multiple antigens and serovars, (3) fine-targeting of short peptide epitopes to avoid "immunological decoy" problems or target normally non-immunogenic epitopes, (4) the possibility of a simplified pre-clinical pipeline.

Antibody-eliciting vaccines have the potential to be single-dose vaccines. Although HPV vaccines are currently administered in two or three doses, evidence is emerging that even a single dose of HPV vaccine is sufficient to provide long-lasting protection [51, 52, 53, 54]. Indeed, a randomized controlled trial of one-dose HPV vaccine is currently underway (ClinicalTrials.gov: #NCT03180034). This potent immunogenicity is unprecedented for subunit vaccines, but evidence is emerging that this strong immunogenicity is a common feature of vaccines that present antigen on a multivalent platform, such as VLPs. For example, mice immunized with a bacteriophage VLP displaying the HPV L2 epitope continued to have high titer antibodies to the displayed peptide for the life-time of the mouse [55]. This feature of antibody-eliciting vaccines is especially important when considering *Ct* vaccines that will be administered in resource-poor areas of the world, where administering multi-dose vaccines is logistically challenging.

Vaccines that mediate protection only through antibody lend themselves readily to multicomponent vaccine formulations. Gardasil-9, as the name suggests, contains 9 HPV VLPs. Other antibody-eliciting vaccines based on bacteriophage VLPs have been combined into multicomponent formulations and it appears that the only limitation to the number of individual VLPs included in one vaccine is how much protein and volume one can combine in a single injection [48]. The ease of generating a multicomponent vaccine means that vaccines can be made against pathogens for which multiple antigens must be targeted to elicit protection. This would be advantageous for *Ct* in particular, which may require multiple antigens to protect against the many bacterial serovars that can cause disease.

Vaccines that mediate protection only through antibodies generate responses that can be tailored to a specific antigen, and even to a specific epitope of that antigen. This provides a unique opportunity to elicit almost monoclonal-like responses to an epitope of interest. This is useful when targeting a so-called "cryptic epitope", which is not normally immunogenic but could be protective if antibodies are produced by vaccination. This strategy has been employed in efforts to generate a "Pan-HPV" vaccine by targeting the highly conserved HPV L2 epitope described above [48]. Displaying a short, conserved epitope of L2 on the surface of a VLP vaccine platform generates an immunogen capable of eliciting specific antibody responses that protect against a broad range of HPV types [48]. Highly specific targeting of epitopes could also be useful if the protein antigen contains epitopes that act as "immunological decoys". Avoiding targeting these epitopes could increase vaccine potency.

Vaccines developed to elicit antibodies against *Ct* present the opportunity for a simplified pre-clinical pipeline. Neutralization and opsonophagocytic killing of *Ct* can be tested without needing an animal model that fully recapitulates the pathogen-associated pathology present in humans. Indeed, HPV vaccines against L2 protein are tested in a mouse model of virus entry using a pseudovirus with a luciferase reporter system [56]. In this model, mice are vaccinated, challenged with pseudovirus, and then entry of the virus into cells *in vivo* can be assayed several days after infection with intravital imaging to detect expression of the luciferase reporter gene. Because HPV is host-species specific, similar to *Ct*, this sort of animal model is useful for assessing vaccine candidates that are only anticipated to block entry of the virus into host cells. *In vitro* assays, including neutralization assays and opsonization assays, are also relevant pre-clinical models for assessing antibody-only eliciting vaccines. We foresee the following pre-clinical pipeline for testing these types of vaccines: (1) demonstration of the ability of the vaccine to elicit high titer, long-lasting antibody responses in rodents, (2) demonstration of the elicited antibodies to either neutralize *Ct* infection *in vitro* AND/OR opsonophagocytic killing of *Ct*, (3) demonstration of prevention of early establishment of infection in an appropriate animal model, similar to the one described above for HPV, that recapitulates the early infection steps of *Ct*.

6.0 CONCLUSION

In this Perspective, we describe the immunologic basis of the successful HPV vaccine, namely that the HPV vaccine provides long-lasting, high titer, protective antibody in the genital tract, providing sterilizing immunity. We argue that the success of the VLP-based HPV vaccine and the challenges experienced by therapeutic HPV vaccine efforts, can inform *Ct* vaccine efforts. Whereas T cells play an important role in providing immunity to *Ct* during natural infection, we argue that using vaccine platforms that elicit high titer antibodies in the genital tract and eliciting antibodies to “cryptic epitopes” may be a promising vaccination strategy. Advantages of an antibody-eliciting vaccine strategy are the possibility of a single-dose vaccine, multivalent vaccine formulations to protect against multiple *Ct* serovars, and the opportunity for a simplified pre-clinical pipeline.

7.0 EXPERT COMMENTARY

The success of the HPV vaccine, in particular in inducing responses superior to those generated by natural infection, opens the door to the possibility that other sexually transmitted obligate intracellular pathogens could be targeted with a similar strategy. The key is to elicit the right antibody, in the right location, at high enough titers to protect. In the case of *Ct*, protection could be mediated by either/both (1) neutralization of the EBs such that they cannot establish a productive infection, either through prevention of adhesion or entry, and/or (2) opsonization of extracellular infectious EBs and increased clearance of the extracellular pathogen. Although natural infection or animal models of infection can provide clues to promising strategies for vaccines, as we know from HPV vaccine efforts targeting L2, it is often the case that the natural immune response is not necessarily the best response to mimic with a vaccine. This may be especially true in the case of *Ct*, for which the primary disease endpoint is caused by the cellular immune response to infection. Indeed, in animal models and humans, there is evidence of the harm caused by pathology-driving versus

protective immune responses [33, 57, 58]. We propose that HPV provides a model for other obligate intracellular sexually transmitted pathogens, such as *Ct*, and provides evidence that a successful vaccine does not necessarily need to mimic the natural protective immune response to a pathogen.

The key to generating high titer, long lasting antibodies in response to intramuscular immunization without added adjuvant is the VLP platform. When other epitopes not included in the current HPV vaccines, like L2 peptides, are displayed on the surface of VLPs, these elicit high titer, long lasting antibody responses upon intramuscular immunization and provide protection against HPV pseudovirus infection in mice [48, 55, 59]. The success of VLPs as a vaccine platform is due to two features: size and geometry. Most VLPs are between 20–100nm which is the ideal size for uptake into antigen presenting cells and trafficking to the lymph nodes[60]. Their geometry, which is highly repetitive, rigid, and multivalent, presents antigen in an optimum format for strong B cell receptor signaling, leading to robust B cell activation and long lasting, high titer antibody responses [61]. There is growing interest in using VLPs derived from a variety of viruses as platforms to display heterologous antigens for vaccines. Displaying specific *Ct* antigens on the surface of VLPs or other multivalent vaccine platforms could be one approach for eliciting high titer, long-lasting antibody responses against *Ct*.

Choosing the correct antigenic epitopes can be challenging. However, basic science research investigating the entry mechanisms of pathogens can inform antibody-eliciting vaccine efforts. Indeed, experiments that have finely mapped and investigated entry mechanisms for HPV have informed next-generation HPV vaccines targeting the L2 protein and specific L2 peptides [62]. Choosing the right antigen epitopes may require detailed knowledge about the structure/function relationship of antigens of interest. In some cases, we can be guided by epitopes recognized by monoclonal antibodies with activity of interest (i.e. with neutralizing or opsonizing activity). In other cases, bioinformatics tools (such as surface exposure prediction tools) can be used to rationally select antigens to test. In some cases, looking for highly conserved, “cryptic epitopes”, similar to the L2 peptide for HPV, can lead to successful vaccines. For a complex pathogen like *Ct*, it may be necessary to include multiple antigen epitopes in a final vaccine to achieve full protection. We imagine that a successful antibody-eliciting vaccine against *Ct* would benefit from targeting multiple antigens involved in entry, adhesion, and opsonophagocytic killing of *Ct*. It is important to note that, although experiments describing the nature of the antigenicity of the HPV vaccine have been done in retrospect, these aspects of the vaccine were not critical to the approval of the vaccine nor the decision to move into human clinical trials. These decisions were made on the basis of strong evidence of protection in animal studies, *in vitro* neutralization assays, and the human trials.

Antibody is not necessary for natural immunity to *Ct*, but, as with HPV, it may be sufficient to protect if (1) the right antigen(s) is chosen, (2) high enough titers are elicited, (3) these antibodies are in the right anatomic location, (4) they are long lasting, (5) the antibody-mediated protection mechanisms we describe in this manuscript are effective *in vivo*, and (6) the endpoint of the vaccine trial is preventing infection rather than preventing disease sequelae. The *Ct* vaccine currently in Phase I clinical trials has been shown to elicit both

strong T-cell and antibody responses to *Ct* MOMP [63, 64]. Several other experimental *Ct* vaccines that work by eliciting appropriate T-cell responses are in the pipeline [63, 64, 65, 66]. Clinical trials will inform whether these promising vaccine strategies are effective and safe. We propose a complementary approach for designing antibody-eliciting vaccines which may also prove fruitful against *Ct* given the tremendous success of the antibody-eliciting HPV vaccines at inducing sterilizing immunity in the genital tract. While we recognize that what worked for HPV may not necessarily work for *Ct*, we aim in this Perspective to encourage further discussion between HPV and *Ct* researchers about the similarities and differences between the two vaccine design efforts that might advance both fields.

8.0 FIVE-YEAR VIEW

In the next five years, we anticipate that recently developed tools for manipulating the *Ct* genome will open new opportunities to explore the role of specific *Ct* proteins in entry, establishment of infection in the host cell, pathogenesis, and immune evasion. Additionally, ongoing research investigating the immunopathology of *Ct* in animal models and humans will continue to differentiate protective versus pathology-driving immune responses. Together, this increase in our knowledge of basic *Ct* biology will provide new avenues to rationally design vaccines for *Ct*. With so much yet to understand about *Ct* pathogenesis, we are excited by the possibility that antibody-eliciting vaccines may yet play a role in protecting against this important human pathogen, just as they have for HPV.

REFERENCES

1. Newman L, Rowley J, Vander Hoorn S, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. PLoS One 2015;10(12):e0143304. doi: 10.1371/journal.pone.0143304 PubMed PMID: 26646541; PubMed Central PMCID: PMCPMC4672879. eng. [PubMed: 26646541]

2. Zhong G, Brunham RC, de la Maza LM, et al. National Institute of Allergy and Infectious Diseases workshop report: “Chlamydia vaccines: The way forward”. Vaccine 2017 10. doi: 10.1016/j.vaccine.2017.10.075 PubMed PMID: 29097007; eng. The report on a workshop held to explore issues important to Chlamydia vaccines.

3. de la Maza LM, Zhong G, Brunham RC. Update on Chlamydia trachomatis Vaccinology. Clin Vaccine Immunol 2017 4;24(4). doi: 10.1128/CVI.00543-16 PubMed PMID: 28228394; PubMed Central PMCID: PMCPMC5382834. eng.

4. McQuillan G, Kruszon-Moran D, Markowitz LE, et al. Prevalence of HPV in Adults Aged 18–69: United States, 2011–2014. NCHS Data Brief 2017 4(280):1–8. PubMed PMID: 28463105; eng.

5. Genital HPV infection - CDC fact sheet: Centers for Disease Control and Prevention; 2016 [cited 2018 January 30].

6. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006 6;118(12):3030–44. doi: 10.1002/ijc.21731 PubMed PMID: 16404738; eng. [PubMed: 16404738]

7. Kirnbauer R, Booy F, Cheng N, et al. Papillomavirus L1 major capsid protein self-assembles into virus-like particles that are highly immunogenic. Proc Natl Acad Sci U S A 1992 12;89(24):12180–4. PubMed PMID: 1334560; PubMed Central PMCID: PMCPMC50722. eng. [PubMed: 1334560]

8. Stanley M, Pinto LA, Trimble C. Human papillomavirus vaccines--immune responses. Vaccine 2012 11;30 Suppl 5:F83–7. doi: 10.1016/j.vaccine.2012.04.106 PubMed PMID: 23199968; eng. [PubMed: 23199968]

9. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012 11;30 Suppl 5:F123–38. doi: 10.1016/j.vaccine.2012.04.108

PubMed PMID: 23199956; PubMed Central PMCID: PMCPMC4636904. eng. [PubMed: 23199956]

10. Longet S, Schiller JT, Bobst M, et al. A murine genital-challenge model is a sensitive measure of protective antibodies against human papillomavirus infection. J Virol 2011 12;85(24):13253–9. doi: 10.1128/JVI.06093-11 PubMed PMID: 21976653; PubMed Central PMCID: PMCPMC3233130. eng. [PubMed: 21976653]
11. Suzich JA, Ghim SJ, Palmer-Hill FJ, et al. Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. Proc Natl Acad Sci U S A 1995 12;92(25):11553–7. PubMed PMID: 8524802; PubMed Central PMCID: PMCPMC40440. eng. [PubMed: 8524802]
12. Breitburd F, Kirnbauer R, Hubbert NL, et al. Immunization with viruslike particles from cottontail rabbit papillomavirus (CRPV) can protect against experimental CRPV infection. J Virol 1995 6;69(6):3959–63. PubMed PMID: 7745754; PubMed Central PMCID: PMCPMC189126. eng. [PubMed: 7745754]
13. Scherpenisse M, Mollers M, Schepp RM, et al. Detection of systemic and mucosal HPV-specific IgG and IgA antibodies in adolescent girls one and two years after HPV vaccination. Hum Vaccin Immunother 2013 2;9(2):314–21. PubMed PMID: 23149693; PubMed Central PMCID: PMCPMC3859753. eng. [PubMed: 23149693]
14. Mestecky J, Moldoveanu Z, Russell MW. Immunologic uniqueness of the genital tract: challenge for vaccine development. Am J Reprod Immunol 2005 5;53(5):208–14. doi: 10.1111/j.1600-0897.2005.00267.x PubMed PMID: 15833098; eng. [PubMed: 15833098]
15. Day PM, Kines RC, Thompson CD, et al. In vivo mechanisms of vaccine-induced protection against HPV infection. Cell Host Microbe 2010 9;8(3):260–70. doi: 10.1016/j.chom.2010.08.003 PubMed PMID: 20833377; PubMed Central PMCID: PMCPMC2939057. eng. [PubMed: 20833377]
16. Schiller JT, Lowy DR. Understanding and learning from the success of prophylactic human papillomavirus vaccines. Nat Rev Microbiol 2012 10;10(10):681–92. doi: 10.1038/nrmicro2872 PubMed PMID: 22961341; eng. [PubMed: 22961341]
17. Graham SV. Keratinocyte Differentiation-Dependent Human Papillomavirus Gene Regulation. Viruses 2017 8;9(9). doi: 10.3390/v9090245 PubMed PMID: 28867768; PubMed Central PMCID: PMCPMC5618011. eng.
18. Hildesheim A, Herrero R, Wacholder S, et al. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial. JAMA 2007 8;298(7):743–53. doi: 10.1001/jama.298.7.743 PubMed PMID: 17699008; eng. [PubMed: 17699008]
19. Kenter GG, Welters MJ, Valentijn AR, et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N Engl J Med 2009 11;361(19):1838–47. doi: 10.1056/NEJMoa0810097 PubMed PMID: 19890126; eng. [PubMed: 19890126]
20. Daayana S, Elkord E, Winters U, et al. Phase II trial of imiquimod and HPV therapeutic vaccination in patients with vulval intraepithelial neoplasia. Br J Cancer 2010 3;102(7):1129–36. doi: 10.1038/sj.bjc.6605611 PubMed PMID: 20234368; PubMed Central PMCID: PMCPMC2853099. eng. [PubMed: 20234368]
21. Cory L, Chu C. ADXS-HPV: a therapeutic Listeria vaccination targeting cervical cancers expressing the HPV E7 antigen. Hum Vaccin Immunother 2014;10(11):3190–5. doi: 10.4161/hv.34378 PubMed PMID: 25483687; PubMed Central PMCID: PMCPMC4514130. eng. [PubMed: 25483687]
22. Brun JL, Dalstein V, Leveque J, et al. Regression of high-grade cervical intraepithelial neoplasia with TG4001 targeted immunotherapy. Am J Obstet Gynecol 2011 2;204(2):169e1–8. doi: 10.1016/j.ajog.2010.09.020. PubMed PMID: 21284968; eng. [PubMed: 21284968]
23. Kim TJ, Jin HT, Hur SY, et al. Clearance of persistent HPV infection and cervical lesion by therapeutic DNA vaccine in CIN3 patients. Nat Commun 2014 10;5:5317. doi: 10.1038/ncomms6317. PubMed PMID: 25354725; PubMed Central PMCID: PMCPMC4220493. eng. [PubMed: 25354725]
24. Trimble CL, Morrow MP, Kraynyak KA, et al. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7

proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. Lancet 2015 11;386(10008):2078–2088. doi: 10.1016/S0140-6736(15)00239-1. PubMed PMID: 26386540; PubMed Central PMCID: PMCPMC4888059. eng. [PubMed: 26386540]

25. Rosales R, López-Contreras M, Rosales C, et al. Regression of human papillomavirus intraepithelial lesions is induced by MVA E2 therapeutic vaccine. Hum Gene Ther 2014 12;25(12):1035–49. doi: 10.1089/hum.2014.024. PubMed PMID: 25275724; PubMed Central PMCID: PMCPMC4270165. eng. [PubMed: 25275724]
26. Shin H, Iwasaki A. A vaccine strategy that protects against genital herpes by establishing local memory T cells. Nature 2012 11;491(7424):463–7. doi: 10.1038/nature11522. PubMed PMID: 23075848; PubMed Central PMCID: PMCPMC3499630. eng. [PubMed: 23075848]
27. Kojima S, Kawana K, Tomio K, et al. The prevalence of cervical regulatory T cells in HPV-related cervical intraepithelial neoplasia (CIN) correlates inversely with spontaneous regression of CIN. Am J Reprod Immunol 2013 2;69(2):134–41. doi: 10.1111/aji.12030. PubMed PMID: 23057776; eng. [PubMed: 23057776]
28. Schiller J, Lowy D Explanations for the high potency of HPV prophylactic vaccines. Vaccine 2018 1. doi: 10.1016/j.vaccine.2017.12.079. PubMed PMID: 29325819; eng.A comprehensive review examining the mechanism by which HPV prophylactic vaccines elicit protection.
29. Liang S, Bulir D, Kaushic C, et al. Considerations for the rational design of a Chlamydia vaccine. Hum Vaccin Immunother 2017 4;13(4):831–835. doi: 10.1080/21645515.2016.1252886. PubMed PMID: 27835064; PubMed Central PMCID: PMCPMC5404357. eng. [PubMed: 27835064]
30. Poston TB, Gottlieb SL, Darville T. Status of vaccine research and development of vaccines for Chlamydia trachomatis infection. Vaccine 2017 1. doi: 10.1016/j.vaccine.2017.01.023. PubMed PMID: 28111145; eng.
31. Roden R, Wu TC. How will HPV vaccines affect cervical cancer? Nat Rev Cancer 2006 10;6(10): 753–63. doi: 10.1038/nrc1973. PubMed PMID: 16990853; PubMed Central PMCID: PMCPMC3181152. eng. [PubMed: 16990853]
32. Chernesky MA. The laboratory diagnosis of Chlamydia trachomatis infections. Can J Infect Dis Med Microbiol 2005 1;16(1):39–44. PubMed PMID: 18159527; PubMed Central PMCID: PMCPMC2095010. eng. [PubMed: 18159527]
33. Elwell C, Mirrashidi K, Engel J. Chlamydia cell biology and pathogenesis. Nat Rev Microbiol 2016 06;14(6):385–400. doi: 10.1038/nrmicro.2016.30. PubMed PMID: 27108705; PubMed Central PMCID: PMCPMC4886739. eng. [PubMed: 27108705]
34. Liu X, Afrane M, Clemmer DE, et al. Identification of Chlamydia trachomatis outer membrane complex proteins by differential proteomics. J Bacteriol 2010 6;192(11):2852–60. doi: 10.1128/JB.01628-09. PubMed PMID: 20348250; PubMed Central PMCID: PMCPMC2876478. eng. [PubMed: 20348250]
35. Lucero ME, Kuo CC. Neutralization of Chlamydia trachomatis cell culture infection by serovar-specific monoclonal antibodies. Infect Immun 1985 11;50(2):595–7. PubMed PMID: 4055037; PubMed Central PMCID: PMCPMC262000. eng. [PubMed: 4055037]
36. Peterson EM, Cheng X, Markoff BA, et al. Functional and structural mapping of Chlamydia trachomatis species-specific major outer membrane protein epitopes by use of neutralizing monoclonal antibodies. Infect Immun 1991 11;59(11):4147–53. PubMed PMID: 1718870; PubMed Central PMCID: PMCPMC259009. eng. [PubMed: 1718870]
37. Qu Z, Cheng X, de la Maza LM, et al. Characterization of a neutralizing monoclonal antibody directed at variable domain I of the major outer membrane protein of Chlamydia trachomatis C-complex serovars. Infect Immun 1993 4;61(4):1365–70. PubMed PMID: 7681045; PubMed Central PMCID: PMCPMC281372. eng. [PubMed: 7681045]
38. Vasilevsky S, Stojanov M, Greub G, et al. Chlamydial polymorphic membrane proteins: regulation, function and potential vaccine candidates. Virulence 2016;7(1):11–22. doi: 10.1080/21505594.2015.1111509. PubMed PMID: 26580416; PubMed Central PMCID: PMCPMC4871649. eng. [PubMed: 26580416]
39. Sacks DL, MacDonald AB. Isolation of a type-specific antigen from Chlamydia trachomatis by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. J Immunol 1979 1;122(1):136–9. PubMed PMID: 84016; eng. [PubMed: 84016]

40. Hatch TP, Vance DW, Al-Hossainy E. Identification of a major envelope protein in Chlamydia spp. J Bacteriol 1981 4;146(1):426–9. PubMed PMID: 7217005; PubMed Central PMCID: PMCPMC217103. eng. [PubMed: 7217005]

41. Naglak EK, Morrison SG, Morrison RP. Neutrophils Are Central to Antibody-Mediated Protection against Genital Chlamydia. Infect Immun 2017 10;85(10). doi: 10.1128/IAI.00409-17. PubMed PMID: 28739831; PubMed Central PMCID: PMCPMC5607418. eng.

42. Gérard HC, Köhler L, Branigan PJ, et al. Viability and gene expression in Chlamydia trachomatis during persistent infection of cultured human monocytes. Med Microbiol Immunol 1998 10;187(2):115–20. PubMed PMID: 9832326; eng. [PubMed: 9832326]

43. Jendro MC, Deutsch T, Körber B, et al. Infection of human monocyte-derived macrophages with Chlamydia trachomatis induces apoptosis of T cells: a potential mechanism for persistent infection. Infect Immun 2000 12;68(12):6704–11. PubMed PMID: 11083785; PubMed Central PMCID: PMCPMC97770. eng. [PubMed: 11083785]

44. Koehler L, Nettelnbreker E, Hudson AP, et al. Ultrastructural and molecular analyses of the persistence of Chlamydia trachomatis (serovar K) in human monocytes. Microb Pathog 1997 3;22(3):133–42. doi: 10.1006/mpat.1996.0103. PubMed PMID: 9075216; eng. [PubMed: 9075216]

45. Jiang RT, Schellenbacher C, Chackerian B, et al. Progress and prospects for L2-based human papillomavirus vaccines. Expert Rev Vaccines 2016 7;15(7):853–62. doi: 10.1586/14760584.2016.1157479. PubMed PMID: 26901354; PubMed Central PMCID: PMCPMC4911254. eng. [PubMed: 26901354]

46. Alphs HH, Gambhira R, Karanam B, et al. Protection against heterologous human papillomavirus challenge by a synthetic lipopeptide vaccine containing a broadly cross-neutralizing epitope of L2. Proc Natl Acad Sci U S A 2008 4;105(15):5850–5. doi: 10.1073/pnas.0800868105. PubMed PMID: 18413606; PubMed Central PMCID: PMCPMC2299222. eng. [PubMed: 18413606]

*47. Roden RB, Yutzy WH, Fallon R, et al. Minor capsid protein of human genital papillomaviruses contains subdominant, cross-neutralizing epitopes. Virology 2000 5;270(2):254–7. doi: 10.1006/viro.2000.0272. PubMed PMID: 10792983; eng. [PubMed: 10792983] *Cryptic epitopes on L2 minor capsid protein of HPV are cross-protective.

48. Tumban E, Peabody J, Peabody DS, et al. A pan-HPV vaccine based on bacteriophage PP7 VLPs displaying broadly cross-neutralizing epitopes from the HPV minor capsid protein, L2. PLoS One 2011;6(8):e23310. doi: 10.1371/journal.pone.0023310. PubMed PMID: 21858066; PubMed Central PMCID: PMCPMC3157372. eng. [PubMed: 21858066]

49. Becker E, Hegemann JH. All subtypes of the Pmp adhesin family are implicated in chlamydial virulence and show species-specific function. Microbiologyopen 2014 8;3(4):544–56. doi: 10.1002/mbo3.186. PubMed PMID: 24985494; PubMed Central PMCID: PMCPMC4287181. eng. [PubMed: 24985494]

50. Crane DD, Carlson JH, Fischer ER, et al. Chlamydia trachomatis polymorphic membrane protein D is a species-common pan-neutralizing antigen. Proc Natl Acad Sci U S A 2006 2;103(6):1894–9. doi: 10.1073/pnas.0508983103. PubMed PMID: 16446444; PubMed Central PMCID: PMCPMC1413641. eng. [PubMed: 16446444]

51. Safaeian M, Porras C, Pan Y, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. Cancer Prev Res (Phila) 2013 11;6(11):1242–50. doi: 10.1158/1940-6207.CAPR-13-0203. PubMed PMID: 24189371; eng. [PubMed: 24189371]

52. Sankaranarayanan R, Prabhu PR, Pawlita M, et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. Lancet Oncol 2016 1;17(1):67–77. doi: 10.1016/S1470-2045(15)00414-3. PubMed PMID: 26652797; PubMed Central PMCID: PMCPMC5357737. eng. [PubMed: 26652797]

53. Kreimer AR, Herrero R, Sampson JN, et al. Evidence for single-dose protection by the bivalent HPV vaccine-Review of the Costa Rica HPV vaccine trial and future research studies. Vaccine 2018 1. doi: 10.1016/j.vaccine.2017.12.078. PubMed PMID: 29366703; eng.

54. Kreimer AR, Herrero R, Sampson JN, et al. Evidence for single-dose protection by the bivalent HPV vaccine-Review of the Costa Rica HPV vaccine trial and future research studies. Vaccine

2018 08;36(32 Pt A):4774–4782. doi: 10.1016/j.vaccine.2017.12.078. PubMed PMID: 29366703; PubMed Central PMCID: PMCPMC6054558. eng. [PubMed: 29366703]

55. Tumban E, Peabody J, Peabody DS, et al. A universal virus-like particle-based vaccine for human papillomavirus: longevity of protection and role of endogenous and exogenous adjuvants. Vaccine 2013 9;31(41):4647–54. doi: 10.1016/j.vaccine.2013.07.052. PubMed PMID: 23933337; PubMed Central PMCID: PMCPMC3785330. eng. [PubMed: 23933337]

56. Roberts JN, Buck CB, Thompson CD, et al. Genital transmission of HPV in a mouse model is potentiated by nonoxynol-9 and inhibited by carrageenan. Nat Med 2007 7;13(7):857–61. doi: 10.1038/nm1598. PubMed PMID: 17603495; eng. [PubMed: 17603495]

*57. Lijek RS, Helble JD, Olive AJ, et al. Pathology after Chlamydia trachomatis infection is driven by nonprotective immune cells that are distinct from protective populations. Proc Natl Acad Sci U S A 2018 2;115(9):2216–2221. doi: 10.1073/pnas.1711356115. PubMed PMID: 29440378; PubMed Central PMCID: PMCPMC5834673. eng. [PubMed: 29440378] *This study shows the importance of an inappropriate immune response in driving pathology in Chlamydia trachomatis infection.

58. Loomis WP, Starnbach MN. T cell responses to Chlamydia trachomatis. Curr Opin Microbiol 2002 2;5(1):87–91. PubMed PMID: 11834375; eng. [PubMed: 11834375]

59. Tumban E, Muttil P, Escobar CA, et al. Preclinical refinements of a broadly protective VLP-based HPV vaccine targeting the minor capsid protein, L2. Vaccine 2015 6;33(29):3346–53. doi: 10.1016/j.vaccine.2015.05.016. PubMed PMID: 26003490; PubMed Central PMCID: PMCPMC4468037. eng. [PubMed: 26003490]

**60. Bachmann MF, Jennings GT. Vaccine delivery: a matter of size, geometry, kinetics and molecular patterns. Nat Rev Immunol 2010 11;10(11):787–96. doi: 10.1038/nri2868. PubMed PMID: 20948547; eng. [PubMed: 20948547] **An excellent review that describes important considerations in the presentation of vaccine antigens.

61. Frietze KM, Peabody DS, Chackerian B. Engineering virus-like particles as vaccine platforms. Curr Opin Virol 2016 3;18:44–49. doi: 10.1016/j.coviro.2016.03.001. PubMed PMID: 27039982; ENG. [PubMed: 27039982]

62. Yang R, Day PM, Yutzy WH, et al. Cell surface-binding motifs of L2 that facilitate papillomavirus infection. J Virol 2003 3;77(6):3531–41. PubMed PMID: 12610128; PubMed Central PMCID: PMCPMC149523. eng. [PubMed: 12610128]

63. Bøje S, Olsen AW, Erneholm K, et al. A multi-subunit Chlamydia vaccine inducing neutralizing antibodies and strong IFN-γ^+ CMI responses protects against a genital infection in minipigs. Immunol Cell Biol 2016 2;94(2):185–95. doi: 10.1038/icb.2015.79. PubMed PMID: 26268662; PubMed Central PMCID: PMCPMC4748142. eng. [PubMed: 26268662]

*64. Olsen AW, Follmann F, Erneholm K, et al. Protection Against Chlamydia trachomatis Infection and Upper Genital Tract Pathological Changes by Vaccine-Promoted Neutralizing Antibodies Directed to the VD4 of the Major Outer Membrane Protein. J Infect Dis 2015 9;212(6):978–89. doi: 10.1093/infdis/jiv137. PubMed PMID: 25748320; eng. [PubMed: 25748320] *A description of the Chlamydia trachomatis vaccine currently in Phase I clinical trials.

65. Stary G, Olive A, Radovic-Moreno AF, et al. VACCINES. A mucosal vaccine against Chlamydia trachomatis generates two waves of protective memory T cells. Science 2015 6;348(6241):aaa8205. doi: 10.1126/science.aaa8205. PubMed PMID: 26089520; PubMed Central PMCID: PMCPMC4605428. eng. [PubMed: 26089520]

66. Wern JE, Sorensen MR, Olsen AW, et al. Simultaneous Subcutaneous and Intranasal Administration of a CAF01-Adjuvanted Chlamydia Vaccine Elicits Elevated IgA and Protective Th1/Th17 Responses in the Genital Tract. Front Immunol 2017;8:569. doi: 10.3389/fimmu.2017.00569. PubMed PMID: 28567043; PubMed Central PMCID: PMCPMC5434101. eng. [PubMed: 28567043]

9.0

KEY ISSUES

- *Ct* is the most common bacterial sexually transmitted infection, and infection can lead to pelvic inflammatory disease and infertility in women
- The successful HPV vaccine provides protection by eliciting high-titer, long-lasting antibody responses that neutralize viral infection.
- HPV vaccines provide three lessons that can be applied to *Ct* vaccine efforts: (1) HPV vaccine has demonstrated that antibodies alone are sufficient to protect against an STI, (2) the successful generation of high levels of antibodies against HPV is attributed to the multivalent structure of HPV VLPs, and (3) there are major challenges in designing successful vaccines for inducing effector T cell responses against STI antigens in the genital tract.
- Although antibody is not necessary for natural immunity to *Ct*, antibody may be sufficient to protect if the right antigens are chosen, high enough titers are elicited, these antibodies are in the right anatomic location, the antibody is long-lasting, the antibody is functional *in vivo,* and if preventing infection is sufficient to prevent long-term sequelae.

Table 1.

Features of HPV and *Ct* relevant to vaccine design

Feature	HPV	*Chlamydia trachomatis*
Transmission route	Sexual	Sexual
Site of initial infection in female genital tract[1]	Squamocolumnar epithelial cells in the transition zone of the cervix	Cervical epithelial cells
Disease sequelae	Cervical intraepithelial neoplasia, cervical cancer,	Pelvic Inflammatory Disease, ectopic pregnancy, infertility
Size of proteome	8 proteins (2 structural)	~903 predicted proteins (17 predicted EB surface expressed)
Pre-clinical animal models	Mice, rabbits, non-human primates	Mice, minipigs, non-human primates
Mechanism of protection after natural infection	Unknown	IFNγ producing CD4+ T cells in humans and mouse models
Strength of evidence for antibody-mediated protection after natural infection in humans	Weak	Weak
Strength of evidence for antibody-mediated protection after vaccination in humans	Strong	No human vaccine yet available

[1]The site of initial infection in the female genital tract is thought to be the squamocolumnar epithelial cells in the transition zone of the cervix for both HPV and *Ct*. For HPV, this is supported by the origin of precancers and cervical intraepithelial neoplasias near the ectoendocervical squamocolumnar junction of the cervix. However, for Ct we have not seen definitive evidence of the particular cell type that is a site for initial infection.