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Review

Vaccines against sexually transmitted diseases

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Introduction

Human sexually transmitted infections are prevalent throughout the world. Several have been associated with adverse pregnancy outcome and increased susceptibility to HIV infection, in addition to the discomfort of inflammation of the genital tract. Yet vaccines to protect against the infection at the genital mucosa are not available. Hepatitis B is an exception, but this virus becomes systemic and protection may be at the systemic level. Sexually transmitted diseases (STDs) have long been associated with reproductive failure in cattle. These infections cause considerable economic loss, which has been a stimulus to investigation. Consequently, vaccines and mechanisms of immune protection have been studied quite thoroughly. The results obtained with two commercially available vaccines will be used to illustrate principles of protective immunity against STDs. Both *Campylobacter fetus subsp. venerealis* and *Tritrichomonas foetus* are only transmitted sexually and both cause reproductive failure in cattle.

Campylobacter fetus subsp. venerealis Vaccines

Although the work on *C. fetus* was done several decades ago, a brief review is included here because several important principles were first defined with this vaccine. *Campylobacter fetus subsp. venerealis* (formerly *Vibrio fetus*) is a microaerophilic gram negative motile curved bacterium. The organism is an extracellular noninvasive pathogen so antibody is critical to protection. This was demonstrated by Berg et al. [1], who passively protected heifers against experimental intravaginal infection with *C. fetus* by systemic administration of immune serum. Since antibody

was protective, little research has been done on cell mediated immunity (CMI). Sexual transmission results in genital campylobacteriosis, a chronic infection of the female reproductive tract which lasts several months. Clinical signs are minimal, with the exception of fetal loss or apparent infertility (perhaps due to early embryonic loss). The male is an asymptomatic carrier and thus is a constant source of transmission. In female cattle, convalescent immunity is partially protective. Cows becoming reinfected within 2 years of clearing the infection are protected against reproductive failure, but do become vaginal carriers. This partial immune protection was seen as evidence that enhancement of immunity may result in total clearance of infection. Studies of mechanisms of convalescent immunity were undertaken as a basis for designing vaccines [2,3]. Infected animals had early and long lasting surface specific IgA antibody responses in vaginal secretions [4]. These antibodies remained at high levels until the end of the experiment (20–30 weeks after vaginal cultures were negative for *C. fetus*). IgG antibody responses were detectable later and waned much earlier. Although IgA antibodies predominated in vaginal secretions throughout infection, antibodies in uterine secretions (collected at necropsy at 7–9 months post-infection) were primarily of the IgG1 subclass [4,5]. Since the uterus is usually cleared of the infection before the vagina [2], it appeared that IgG1 was more protective than IgA antibody to surface antigen. Therefore, heifers (sexually mature animals which had never been with a bull, so were not exposed to STDs) were systemically immunized with whole formalized cells of *C. fetus* in (complete Freund's

Table 1: Summary of key information on protective immunity in bovine genital campylobacteriosis and trichomoniasis.

| Characteristic | Campylobacteriosis | Trichomoniasis |
|---|--|---|
| Etiologic Agent | <i>C. fetus</i> (Gram negative bacteria) | <i>T. foetus</i> (Protozoa) |
| Parasitic Type | Extracellular noninvasive | Extracellular noninvasive |
| Passive Protection by Antibody | Reference 1 | ND* |
| Specificity of Protective Antibody | Heat labile surface antigen (S-Layer – Reference 33) | Lipophosphoglycan surface antigen |
| Predominant Ig Class of Protective Antibody | Uterus IgG1 or IgG2 Vagina IgA or IgG1 | Uterus IgG1 Vagina IgA or IgG1 |
| Most Protective Immunization | Systemic | Systemic or Systemic priming and local boosting |
| Cure of Infection by Vaccination | Male and Female | Male (Female?) |
| Evasion of Host Responses | Antigenic Variation | Proteinase cleavage of Ig Nonspecific binding of Ig |
| Vaccines Available Commercially | Whole killed cells Systemic route | Whole killed cells Systemic route |

*ND = Not Done

Adjuvant (CFA). Only IgG1 and IgG2 antibodies to *C. fetus* were detected in vaginal and uterine secretions [2]. Since animals immunized with this procedure were resistant to colonization by *C. fetus* [2], the IgG response elicited by systemic immunization appeared to be more protective than convalescent immunity. *In vitro* functional studies [5] showed that neither IgG nor IgA antibodies to surface antigens mediated killing of the virulent strain by bovine complement, although a rough strain was killed (positive complement control). IgA antibodies immobilized *C. fetus* better than IgG antibodies at a standardized agglutination titer. Conversely, IgG antibodies mediated opsonization and intracellular killing of *C. fetus* by macrophages [5] and neutrophils [6], whereas IgA antibodies did not.

Interestingly, in experimentally infected heifers, the infection lasts from 4 to 10 months in the face of a robust antibody response [2,3]. Mechanisms of evasion of this immune response were addressed by infecting heifers intravaginally with a *C. fetus* inoculum that had been cloned by limiting dilution. Isolates from periodic samplings over the course of infection (120 to 219 days) exhibited marked antigenic variation [7]. This evasive mechanism was thought to account for the chronicity of the infection. Even with effective antigenic variation, systemic vaccination with formalized *C. fetus* in CFA, 14 and 24 days after experimental infection was shown to cure the infection [8]. Antigenic variation was detected before the infection was cleared, but the high antibody levels in genital secretions were correlated with termination of infection shortly after the second vaccination in most heifers. This illustrates the dynamic interaction between the microbe's evasive mechanism and the protective immune responses of the host. Antigenic variation results in evasion until the host response catches up with the specificity and magnitude necessary to clear infection. The studies of immunity to *C. fetus* provide the basis for understanding the mechanisms by which vaccines for this sexually transmitted bovine infection protect. These vaccines have been

available for several decades and have controlled the disease in parts of the world where they are used.

Tritrichomonas foetus Vaccines

Trichomoniasis is a human and bovine sexually transmitted disease. Other animal species do not have STDs caused by trichomonads, as far as is known. Human trichomoniasis is caused by *Trichomonas vaginalis* and bovine trichomoniasis is caused by *Tritrichomonas foetus*. Both are motile anaerobic protozoan pathogens which colonize the epithelial surface in the genital tract. Like *C. fetus*, *T. foetus* is an extracellular pathogen, so antibody on the mucosal surface should be most critical for protection. Undoubtedly CMI plays a role also, but this has not been well studied. Bovine trichomoniasis, like the *C. fetus* infection, results in reproductive failure. Fetal loss occurs most often late in the first trimester or early in second trimester, although late term abortions are also seen. Since this is the only known animal to have a naturally occurring STD due to trichomonads, it serves as a model of human trichomoniasis. The human infection is also associated with adverse outcome of pregnancy, including preterm birth, premature rupture of the membranes and low birth weight infants [9-12]. Little information is available on the role of *T. vaginalis* in human pregnancy loss at the end of the first/beginning of the second trimester (spontaneous abortion). Human trichomoniasis is similar to the bovine infection in that only sexual transmission occurs, the chronic infection is limited to the mucosal surface, and asymptomatic carriers occur among females and predominate among males. Vaccines protective against the bovine infection may provide clues for protection against human trichomoniasis and other STDs.

Protective antigen(s)

In order to identify virulence factors of *T. foetus* which may be targets for protective immune responses, we first prepared a bank of monoclonal antibodies (mAbs) [13]. Two surface reactive mAbs (TF1.15 and TF1.17) were shown to have functions which correlate with protection (agglutination, immobilization, inhibition of adherence

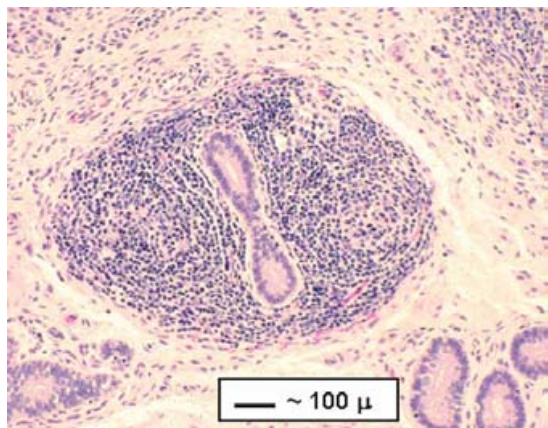


Figure 1

Histopathologic section of the endometrium of a heifer 12 weeks after experimental infection with 10^6 *T. foetus* at estrus. Note the periglandular lymphoid nodule with apparent germinal centers. Stained with haematoxylin and eosin.

to vaginal epithelial cells and complement mediated killing). These mAbs recognize different epitopes on the same highly glycosylated antigen, which was conserved among all isolates tested [14]. The antigen was then immunoaffinity purified with TF1.17 mAb and designated TF1.17 antigen. Further studies showed it to be a lipophosphoglycan (LPG)/protein complex [15]. A soluble form of the antigen is released from the surface (soluble glycosylated antigen or SGA). Both *T. foetus* and *T. vaginalis* have $\sim 10^6$ molecules of LPG per cell [16], so it is a major antigen of both pathogens.

Protective immune responses

Convalescent immunity is partially protective against *T. foetus* as with *C. fetus*. We studied this response in order to understand how to enhance protection by vaccination. Skirrow and BonDurant [17] showed that clearance of vaginal infection occurred when antibodies to whole trichomonads increased in vaginal secretions. There was little detectable systemic antibody response. Later studies showed that IgG1 and IgA antibodies correlated with clearance of the vaginal infection [18]. Only IgG1 and IgA antibody to TF1.17 antigen (LPG/protein complex) were detected in uterine secretions also [19]. IgG1 is a Th2 type response in cattle [20], so it may be that this antigen induces a very skewed response. The production of any local immune response to genital tract infection raised a question since a mucosally associated lymphoid tissue is

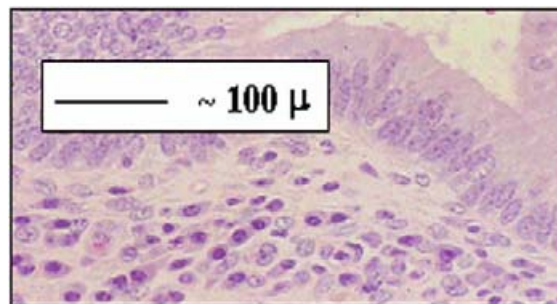


Figure 2

Higher magnification of Figure 1, showing plasma cells below the uterine glandular epithelium.

not seen in histologic sections, especially in the uterus. Histopathologic studies of reproductive tracts of experimentally infected heifers, however, showed lymphoid accumulations under the uterine surface and glandular epithelium [19,21,22]. This was especially true around infected glands. Some lymphoid nodules even had germinal centers (Figure 1). Plasma cells below the glandular epithelium (Figure 2) were consistent with secretion of antibodies across the uterine epithelium. Subsequent immunohistochemical studies, with mAbs specific for *T. foetus* LPG, demonstrated antigen uptake by uterine epithelial cells (Figure 3). This figure also demonstrates abundant intraepithelial and subepithelial lymphocytes, suggesting recruitment of immune cells. We have detected similar lymphoid nodules and antigen uptake in the vaginal mucosa of heifers (Rhyan, BonDurant and Corbeil, unpublished data) and the preputial epithelium of bulls [25] infected with *T. foetus*. Both bulls and heifers had IgA responses in genital secretions [18,19,21,22,25]. Others [23] have shown that both human uterine epithelial and stromal cells can present antigen to T cells. This same research group has also demonstrated lymphoid nodules in human uterine epithelium [24]. Therefore, it can be concluded that cells taking up antigen likely present that antigen to T helper cells, that antigenic stimulation leads to the formation of mucosally associated lymphoid tissue in the genital tract and that IgA responses result.

The association of mucosal IgA and IgG1 antibody responses to TF1.17 antigen indicated that it was a candidate for a subunit vaccine. Several studies showed that systemic immunization with immunoaffinity purified TF1.17 antigen cleared the infection, usually before 7 weeks [18,19,21,22]. Controls cleared several weeks later. Earlier Parsonson et. al. [26] had shown that before 8

weeks of infection there was no fetal loss and little inflammation in the reproductive tract or placenta of *T. foetus* infected pregnant heifers. Heifers aborted if they had not cleared the infection by 8 weeks. Thus, in this chronic infection, clearance before 8 weeks should protect against disease (reproductive failure). Studies with whole cell vaccines have demonstrated that immunized heifers and cows do have higher pregnancy rates [27]. The role of IgA vs. IgG1 in protection was not clear from these studies, however. IgA is usually thought to be the major Ig class in protection of mucosal surfaces, but both IgA and IgG1 pathogen specific antibodies were found in vaginal secretions in both the local immune response of infected heifers and after systemic immunization [18]. To determine which was more protective, we first immunized mice using several different routes and adjuvants to enrich for either IgA or IgG antibodies to TF1.17 antigen in genital secretions [21]. Systemic priming with TF1.17 antigen and local vaginal boosting with whole trichomonads gave the greatest IgA anti-TF1.17 levels in genital secretions whereas systemic priming and boosting with these antigens in the same adjuvant (Quil A) greatly enriched for IgG antibodies. These two regimens then were used in virgin heifers, followed by challenge with the standard dose of *T. foetus* intravaginally to test protection. The vaginally boosted group did have primarily IgA antibodies to TF1.17 antigen in vaginal secretions and the systemically boosted group had primarily IgG1 antibodies. Both groups cleared the infection earlier than controls ($p < 0.05$), mostly before 7 weeks, as in earlier studies. There was no significant difference between the two immunized groups. Since the specificity of both Ig classes was the same, this indicates that IgG1 and IgA antibodies are both protective. To determine whether the common mucosal immune system could be employed to protect the genital tract in this infection, we then repeated the experiment, but with local intranasal boosting rather than intravaginal boosting [22]. Again, IgA antibodies predominated in vaginal secretions of the locally boosted groups and IgG1 antibodies predominate in the systemically boosted group. Both were cleared faster than nonimmunized controls ($p < 0.05$) but there was no significant difference between locally and systemically boosted immunized groups [22]. It is apparent that both intranasal and intravaginal immunization results in secretion of IgA antibodies into vaginal secretions and that either IgA or IgG1 specific TF1.17 antibodies is equally protective. In addition to successful immunization of cows against trichomoniasis, it has been shown that systemic vaccination of bulls with whole trichomonads or partially pacified glycosylated membrane antigens also protects against chronic infection [31]. Notably, systemic vaccination with these antigens has been reported to cure infected bulls [32]. Thus, systemic immunization can protect against *T. foetus* induced disease and can cure long term infection.

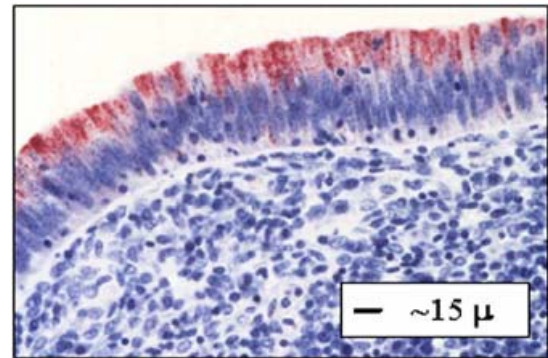


Figure 3

Immunohistochemistry of the surface endometrial epithelium of a heifer 6 weeks after experimental infection with 10^6 *T. foetus* at estrus. Stained with mAb TF1.15 (specific for TF 1.17 antigen) and developed with peroxidase conjugate. Note the antigen uptake by epithelial cells with intense staining at the apical surface. Intraepithelial plus subepithelial lymphocytes are also detected.

Mechanisms of transport of immunoglobulins

The mechanism of transport of antibodies into the genital secretions is of some interest. It has been known for some time that IgA is transported across the epithelium via the Poly-Ig receptor. However, the mechanism of transport of IgG1 across the epithelium is not well understood. Preliminary data from our lab indicates that mast cells and IgE antibody responses to TF 1.17 antigen may be involved (Corbeil LB, BonDurant RH, Campero CM and Gerswin LJ, unpublished data). The need for an IgE response to allow IgG1 antibodies to be transported to genital secretions may be partially responsible for the delay in appearance of IgG1 antibodies in these secretions.

Mechanisms of immune evasion

Trichomonas foetus, like *C. fetus*, has mechanisms to evade the host response. The parasite binds IgG to its surface nonspecifically [28], which provides a means of self-recognition. This may be a factor in the delayed inflammation and local immunity by masking of antigens to evade stimulation of responses. Furthermore, *T. foetus* (like *T. vaginalis*) secretes cysteine proteinase which cleaves IgG1, IgG2, fibronectin, fibrinogen and lactoferrin [29] as well as C3 [30]. The first mechanism (Ig binding) may avoid stimulation of immune responses and the second (proteinase digestion) likely destroys potentially protective innate and acquired responses. In spite of this,

however, local immunity eventually clears the infection and local or systemic vaccination with appropriate antigens and adjuvants can enhance the response enough to clear infection before inflammation and reproductive failure result.

Conclusions

In both *C. fetus* and *T. foetus* infection of the bovine female genital tract, convalescent immunity associated with mucosal IgA antibody is partially protective. Systemic immunization clears the chronic infection early enough to prevent adverse outcome of pregnancy in both infections. Studies with trichomoniasis showed that antigen uptake by the genital epithelium is followed by formation of mucosally associated lymphoid tissue. A local IgA and IgG1 response results. Either IgA or IgG1 antibodies are equally protective. Mechanisms of transport of IgG1 antibodies into mucosal secretions needs to be defined. Since systemic immunization protects in both bovine trichomoniasis and genital campylobacteriosis, it may be protective against other extracellular pathogens causing STDs in other animal species and in humans. It may be even more protective against pathogens which invade across the genital mucosa becoming more accessible to systemic immune responses.

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