



New challenges for vaccination to prevent chlamydial abortion in sheep

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ABSTRACT

Ovine enzootic abortion (OEA) is caused by the obligate intracellular Gram-negative bacterium *Chlamydia abortus*. OEA remains a common cause of infectious abortion in many sheep-rearing countries despite the existence of commercially available vaccines that protect against the disease. There are a number of confounding factors that influence the uptake and use of these vaccines, which includes an inability to discriminate between infected and vaccinated animals (DIVA) using conventional serological diagnostic techniques. This suggests that the immunity elicited by current vaccines is similar to that observed in convalescent, immune sheep that have experienced OEA. The existence of these vaccines provides an opportunity to understand how protection against OEA is elicited and also to understand why vaccines can occasionally appear to fail, as has been reported recently for OEA. Interferon-gamma (IFN- γ), the cytokine that classically defines Th1-type adaptive immunity, is a strong correlate of protection against OEA in sheep and has been shown to inhibit the growth of *C. abortus* *in vitro*. Humoral immunity to *C. abortus* is observed in both vaccinated and naturally infected sheep, but antibody responses tend to be used more as diagnostic markers than targets for strategic vaccine design. A future successful DIVA vaccine against OEA should aim to elicit the immunological correlate of protection (IFN- γ) concomitantly with an antibody profile that is distinct from that of the natural infection. Such an approach requires careful selection of protective components of *C. abortus* combined with an effective delivery system that elicits IFN- γ -producing CD4+ve memory T cells.

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1. Introduction

The strategic development of safe and effective vaccines is dependent on the identification of the immunological correlates of protection against disease and reproducing these correlates by delivering suitable pathogen antigens in an appropriate manner. The multiple phases of industrial vaccine development for human or veterinary diseases begin with proof-of-concept studies based on robust academic exploration of fundamental science [1]. Optimal vaccine efficacy is achieved by initiating immune responses

by targeting the components of the innate immune system that then direct and modulate the adaptive immune response in a manner that generates long-lasting immunological memory to protect against the pathogen in question. For vaccines to be both effective and safe it is essential that neither the pathogen components, nor the adjuvant used to deliver them, cause inappropriate inflammation or induce ineffective immune responses. Hence, evaluation of the efficacy and safety of experimental vaccines depends on the capability to identify not only the immunological correlates of protection but also the immunological correlates of disease.

It is particularly important to separate these aspects of the immune response for chlamydial vaccines since pathogen persistence, inflammation and tissue damage are

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common features of chlamydial infections in both humans and animals [2]. Despite the impact of chlamydial infections on human health, there are no chlamydial vaccines currently licensed for use in humans [3,4]. In contrast, veterinary chlamydial vaccines have been licensed for use in sheep and cats for several years [2]. These veterinary vaccines have been evaluated for protection and safety in their target host species, but there is little or no information on the immunological responses they elicit [5,6]. This is due in part to the reduced capability to study immunology, particularly cellular immunology in the host species at the time these vaccines were first developed. This lack of capability in comparison to rodent laboratory models and humans stemming from a dearth of appropriate immunological reagents is being redressed, but nevertheless still remains a barrier to veterinary disease research [7]. However, it is also reflective of the less stringent regulatory requirements for licensing a vaccine for use in veterinary species as opposed to humans [1]. This represents a lost opportunity for understanding chlamydial vaccine efficacy. Such knowledge not only has cross-species relevance for new vaccine design but can also help explain why vaccine strategies fail. Here we discuss the challenges of implementing a vaccine control strategy in sheep and how immunology and disease pathogenesis studies combine to support strategic vaccine design.

2. Chlamydia diversity

Chlamydial abortion in sheep, also known as ovine enzootic abortion (OEA) and enzootic abortion in ewes (EAE), has a worldwide prevalence, with the exception of Australia and New Zealand [8]. The causative agent is the obligate intracellular Gram-negative bacterium *Chlamydia abortus*. This organism was known until very recently as *Chlamydophila abortus*, and previous to 1999 as *Chlamydia psittaci* serotype 1. The change in both genus and species name was proposed in 1999 as part of a re-classification of the family Chlamydiaceae into two genera (*Chlamydia* and *Chlamydophila*) and nine species (*trachomatis*, *suis*, *muridarum*, *pneumoniae*, *abortus*, *psittaci*, *felis*, *caviae* and *pecorum*), which until then comprised one genus (*Chlamydia*) and four species (*trachomatis*, *psittaci*, *pneumoniae* and *pecorum*) [9]. These organisms all share a distinctive biphasic developmental cycle comprising of two forms, an extracellular, non-multiplying infectious form known as an elementary body (EB) and an intracellular, multiplying non-infectious body known as a reticulate body (RB) [10]. While there was wide recognition that the re-classification of the original four species into nine was reflective of the diversity of the organisms, the creation of two genera was controversial and the proposed re-classification was not universally adopted [11]. This has led to confusion, particularly for the organisms previously classified as *C. psittaci*, which were reclassified into four species (*psittaci*, *abortus*, *caviae* and *felis*) of which one retained the original species name but a new genus name (*C. psittaci*). Additionally, the change in genus name for the human pathogen *Chlamydophila pneumoniae* was not accepted by those working in the human field and has been consequently been referred to as

Chlamydophila pneumoniae since the reclassification, causing further confusion. Thus, a subcommittee on the taxonomy of the *Chlamydiae* met at the International Committee on Systematics of Prokaryotes in 2010 to review the genome data with a view to returning to a single genus classification (*Chlamydia*) with nine species [12]. This has subsequently been adopted and will be used throughout this review [13].

3. Features of ovine enzootic abortion (OEA)

OEA typically presents in late gestation, most commonly as a result of a persistent infection with *C. abortus* acquired prior to pregnancy. These persistently infected sheep are very difficult to identify through traditional diagnostic methods since the site of persistence of the organism remains unknown and the sheep do not typically exhibit clinical signs prior to abortion [14] or antibodies detectable using current serodiagnostic tests [15]. Consequently, infected sheep can be introduced unknowingly into a flock and by the time that the infection clinically manifests itself it is often too late to implement an effective control strategy within that lambing season [16]. There are a number of farm management strategies for controlling OEA that include maintenance of a closed flock and other biosecurity measures. Since OEA has a bacterial aetiology, treatment with antibiotics is possible, but is not considered a sustainable strategy for long-term control and prevention of OEA [2].

4. Antibiotic control of OEA

There is a range of antibiotics and regimes available for treating chlamydial infections, the therapy of choice depending on the type of *Chlamydia*, the site of infection and the species of host infected. However, treatment of disease is different from prevention of infection, and while antibiotics can prevent infection by reducing transmission within populations, there are several issues that caution against an over-reliance on their use either prophylactically or therapeutically. Tetracycline is used in pregnant sheep flocks to reduce the incidence of abortion and lamb losses when signs of OEA are first observed or if there is perceived threat of OEA [17]. This combined therapeutic/prophylactic approach is not guaranteed to prevent abortion or to prevent the shedding of infectious bacteria from infected ewes at parturition [8]. The risk of employing a prophylactic strategy is the development of antibiotic resistance. While tetracycline resistance has not been reported in *C. abortus*, it has been found in *Chlamydia suis* strains isolated from pigs [18,19]. Although antibiotic resistance in *Chlamydiae* remains a relatively rare clinical occurrence *in vivo*, the potential to evolve resistance through the accumulation of point mutations under selective antibiotic pressure has been shown to occur *in vitro* [20]. Furthermore, tetracycline resistance can be transferred horizontally, suggesting that maintained pressure could drive the spread of resistance [21]. The prolonged use of antibiotics in livestock is also a consumer issue due to public concerns over residues in the food chain.

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