

## Adjuvants in Veterinary Vaccines: Modes of Action and Adverse Effects

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Vaccine adjuvants are chemicals, microbial components, or mammalian proteins that enhance the immune response to vaccine antigens. Interest in reducing vaccine-related adverse effects and inducing specific types of immunity has led to the development of numerous new adjuvants. Adjuvants in development or in experimental and commercial vaccines include aluminum salts (alum), oil emulsions, saponins, immune-stimulating complexes (ISCOMs), liposomes, microparticles, nonionic block copolymers, derivatized polysaccharides, cytokines, and a wide variety of bacterial derivatives. The mechanisms of action of these diverse compounds vary, as does their induction of cell-mediated and antibody responses. Factors influencing the selection of an adjuvant include animal species, specific pathogen, vaccine antigen, route of immunization, and type of immunity needed.

**Key words:** Enhancement of immunity; Immunization; Immunomodulation.

The advent of vaccination in the 1800s had unprecedented benefits for both human and veterinary medicine. Vaccines now control or prevent numerous human and animal diseases, including scourges such as poliomyelitis, smallpox, distemper, and parvovirus enteritis. The contributions of pioneer vaccine researchers such as Pasteur and Jenner are well known. Less often noted are parallel discoveries that made vaccination more powerful and, indeed, in some cases, even feasible. In the 1920s, Ramon<sup>1,2</sup> discovered that horses that developed abscesses at the injection site had higher antibody titers after vaccination. Subsequently, he and others found that titers could be enhanced by injections of tapioca, agar, lecithin, saponin, and aluminum compounds.<sup>2,3</sup> In the 1930s, Freund et al<sup>4</sup> invented a particularly effective combination of mineral oil, water, and killed mycobacteria. These discoveries were the basis for the development of adjuvants, vaccine additives that boost immunity and alter immune responses to coadministered antigens.

A protective immune response must enhance those aspects of immunity that will be effective against specific pathogens. Vaccines against extracellular bacteria should induce immunoglobulin G (IgG) to opsonize the bacteria for phagocytosis, to activate complement, and to neutralize toxins. On mucosal surfaces, IgA prevents attachment, and IgE arms mast cells under the mucosal surface to react if the pathogen invades. Other pathogens are effectively destroyed only by cell-mediated immune reactions. For facultative intracellular bacteria (eg, *Mycobacteria*, *Brucella*, and some *Salmonella*), activated macrophages are required. If a pathogen such as a virus, *Listeria*, or some protozoan

parasite begins to replicate in the cytoplasm of a cell, a cytotoxic T-lymphocyte (CTL) response is needed to destroy the infected cell. Often, a combination of immune mechanisms may be the most effective defense: for example, an IgA response to inhibit viruses from invading through a mucosal surface, an IgG response to neutralize viruses that do invade, and a cytotoxic T-cell response to destroy cells that the virus manages to infect.

Infection with a virulent pathogen usually provides the necessary signals to induce the correct type or types of immune response. By mimicking the virulent organism, modified live vaccines also can provide these signals. Although they often are very effective, these vaccines have several potential disadvantages and are undesirable for some diseases.<sup>5</sup> The main alternative at present is a killed vaccine. However, killed vaccine antigens administered by an unnatural route of exposure (ie, injection) may not provide the signals necessary to induce protective immunity. Less purified killed vaccines sometimes contain bacterial or viral components that can serve as "built-in" adjuvants, but more purified antigens usually do not stimulate a strong and lasting immune response.<sup>6</sup> This is particularly true for highly purified peptides or carbohydrates. In the absence of adjuvants, such killed antigens may even result in tolerance.<sup>7</sup> Adjuvants can provide artificial signals to the immune system to initiate the immune response. By doing so, adjuvants minimize the number of immunizations necessary for a good immune response. They also may decrease the amount of antigen needed, making the vaccine more cost-effective. Some but not all adjuvants also can shift responses toward the more effective form or forms of immunity.

When developing a vaccine, it is essential to know what type of immune response will provide optimal protection and then select an adjuvant that will help induce that type of immune response without unacceptable adverse effects. Considerable trial and error often is needed to find a safe and effective adjuvant for a particular pathogen in a given species. Induction of the wrong type of immune response actually can enhance disease pathogenesis after the animal becomes exposed to the pathogen. Early attempts to develop a vaccine against infectious peritonitis virus in cats are an example of this response.<sup>8</sup> Host factors also influence the effectiveness of the adjuvant. Whereas young, healthy

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