



## Commentary: Important features of modified live virus vaccines -A comment

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### Article Info

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Prior to and since publication of my original commentary on this topic in 2014, numerous articles have appeared that address issues raised concerning vaccine safety and efficacy primarily in companion animals and humans, but also in livestock<sup>1-11</sup>. In livestock animals, earlier and recent studies have identified the adverse effects on reproduction (necrotic oophoritis, infertility, abortion and neonatal pancytopenia) from vaccinating heifers during estrus, and pregnant cows with MLV bovine herpesvirus-1 (for bovine rhinotracheitis) and bovine viral diarrhea virus<sup>3,8,9</sup>. Another study in sheep attributed the acute and chronic autoimmune/autoinflammatory (ASIA) syndrome to repetitive administration of aluminum-containing adjuvanted ovine blue tongue virus vaccines<sup>4</sup>. These issues, while mostly discussed with regard to companion animals, transcend those related to the modified live virus (MLV) vaccines discussed previously, with recent focus being on the safety of adjuvants used in killed, inactivated vaccines to accelerate, prolong, or enhance antigen-specific immune responses<sup>1-15</sup>.

While inactivated vaccines do not multiply in the host, thereby making them inherently safer than those of MLV type, they are usually less effective in initiating a complete and sustained immune protective response unless potent adjuvants are included<sup>6,7,13</sup>. Further, incorporating these adjuvants increases the risk of immediate and even delayed adverse autoimmune and inflammatory effects from the vaccine<sup>6,7,12-14</sup>.

Adjuvants have been used safely in human and veterinary medicine for decades, especially those containing aluminum salts and monophosphoryl lipid A in human and animal vaccines, and squalene in animal vaccines. But, these adjuvants may also induce adverse effects<sup>2-6,12-26</sup>.

A landmark review for its time addressed the vehicles used as immunomodifiers in vaccines<sup>16</sup>. Today, these include: aluminum salts, water-in-oil emulsions, biodegradable oil vehicles, oil-in-water emulsions, biodegradable microcapsules, nano- and micro-particles, immune-stimulating complexes, organic oils like squalene, liposomes and lipid A, oral vaccines, and virosomes<sup>12-35</sup>. The more recent availability and popularity of sub-unit, recombinant, intranasal and oral vaccines is tempered by the fact that they also need adjuvants to elicit an optimum immune response<sup>13,14,16,17,28,29</sup>. Since then, the literature and vaccine industry has exploded with new types of adjuvants and numerous studies describing the

safety and efficacy of adjuvants in human and animal vaccines<sup>4,6,13-15,36</sup>. Biodegradable polymeric nanoparticles are newer vaccine vehicle adjuvants that have entrapped antigens such as proteins, peptides, or DNA. The goal of these novel adjuvants is to selectively target the host's antigen-presenting cells by controlling the release of vaccinal antigens and thus promoting the desired immune response<sup>19-21,36</sup>. The use of dendritic cells in efficiently delivering vaccinal antigens to a host has been an important approach in vaccine technology research<sup>36</sup>. While the currently available vaccine adjuvants can successfully generate humoral antibody-mediated protection, other diseases such as tuberculosis and malaria require a cell-mediated immune response for adequate protection<sup>17-19,22</sup>.

Interesting experimental findings have shown that giving just two or three adjuvants simultaneously can overcome the genetic resistance to autoimmunity<sup>23</sup>. However, the dilemma emanating from concerns about vaccine safety is confounded by the fact that developmental, reproductive and whole animal toxicity studies in the target species are often excluded from the regulatory safety assessment of vaccines, because they historically have been viewed as inherently safe and non-toxic<sup>37,38</sup>. For example, MLV bovine herpesvirus vaccine is still used in pregnant cattle despite published concerns for the increased risk of infertility, abortion and neonatal pancytopenia<sup>8,9</sup>. Further, children and young animals with their more vulnerable immune system and higher risk of toxicity than adults, have the extra challenge of receiving more vaccines and adjuvants at that age<sup>8-11,26,27,37,38</sup>. Adjuvants also have the capacity to change individual gene expression which can adversely impact the central nervous system, brain development, and overall immune function<sup>23-27</sup>.

The ASIA autoimmune (auto-inflammatory) syndrome induced by adjuvants was first defined in 2011<sup>24-26</sup>. Presently, it includes four conditions that share similar signs and symptoms and result from hyperactive immune responses: silicosis, macrophagic myofasciitis syndrome, Gulf War syndrome and post-vaccination phenomena<sup>4,13,24,26</sup>.

Heavy metals such as the mercury and aluminum used as adjuvants and preservatives in vaccines as well as nickel, chromium, silver and gold are believed to be triggers of the ASIA syndrome<sup>23-27</sup>. The mechanism involved mainly evokes toxic and immunological reactions in the body that then present as hypersensitivity or autoimmunity. Metals can be a risk factor in a variety of autoimmune disease including autoimmune thyroiditis, multiple sclerosis, and kidney disease, and nonspecific symptoms such as chronic fatigue and myalgia<sup>22,24-26</sup>. The type of allergy induced by metals is delayed-type hypersensitivity and manifests often as a contact dermatitis<sup>12,22</sup>.

In humans, causality questions about the adverse events

associated with childhood vaccines are categorized by: Can It (Potential Causality)? Did It (Retrodictive Causality)? and Will It (Predictive Causality)?<sup>10</sup>. This publication from 1994, was updated in 2011 by the Institute of Medicine, National Academy of Sciences, which agreed that a causal relationship was present between some vaccines and adverse events<sup>10,11</sup>. Even though convincing evidence was presented for adverse events from mumps-measles-rubella (MMR), varicella zoster (herpes virus), influenza, hepatitis B, meningococcal, and tetanus-containing vaccines, the group's conclusion was that "while no vaccine is 100 percent safe, very few adverse events are shown to be caused by vaccines"<sup>11</sup>.

A multifaceted approach is necessary to foster the recognition not only of the benefits but also of the risks of vaccines given to humans, companion animals and livestock. Further, the goal should be focused on seeking improved vaccination strategies and alternative means to prevent and control the spread of infectious diseases and their environmental impact<sup>3-5, 8,9,11,37,38</sup>. As a beginning for the companion animals, the periodicity between adult booster vaccinations for the so-called "core" vaccines given to healthy individuals should be increased to three or more years, and regular monitoring of serum antibody levels (as an indirect assessment of protection against the clinically important infectious agents) should be implemented<sup>1,7,39,40</sup>.

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