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# Vaccine Issues Revisited

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Even before Edward Jenner developed the first scientifically proven small pox vaccine by using cox pox as the inoculum in 1796, it was used privately by Benjamin Jesty in 1774 to protect his family from small pox [1]. Presently, for nearly 100 years, vaccines have been used commercially and for research in humans and animals to elicit protective immunity to specific infectious agents [2-11].

Despite these longstanding efforts and focus on vaccine-related issues, this subject is perhaps the most contentious of all human and animal medical safety and efficacy procedures [2-5,8,10,12-20]. No doubt, new approaches and research tools are still needed to effect worldwide protection from current and emerging infectious diseases, such as virulent Ebola virus epidemic of 2014 on the African continent, not only for humans, but also for companion animals, pocket pets, birds, laboratory animals, livestock, and wildlife [3,7-11,20].

With respect to veterinary medicine, annual vaccination has been and remains the single most important reason why most owners bring their pets for an annual "wellness visit". Reluctance to change current vaccination programs is fueled by the lack of understanding of the principles of applied vaccinal immunity, which is rarely taught even at the post-graduate level [3]. The accumulated evidence indicates that vaccination protocols for pets should not be driven by a "one size fits all" program, as vaccine volume needs for protection have been shown to differ from small to large breeds [3,4]. Today, only an estimated 40% of veterinarians follow the latest vaccine policy guidelines, as they have no regulatory authority [3]. Many pet caregivers receive written or telephone reminders that their pet is "due" for vaccinations or is "up-to-date" on vaccinations.

Regardless, the debate and controversies surrounding human and animal vaccines and vaccination policy is not likely to be resolved in the foreseeable future. So, what does our collective experience tell us and what promising new technologies are on the horizon?

## EFFICACY ISSUES

All commercial vaccines, before being licensed, are tested first in experimental animals (e.g. rodents, rabbits, guinea pigs) and then in clinical trials typically done in phases I, II, III and IV for humans, and experimental species-targeted animals followed by clinical trials in the intended species for veterinary vaccines [3,4,11].

A recent, novel approach used electron-microscopy to determine if there were solid particulate contaminants in vaccines [16]. They found micro- and nano-sized particulates composed of inorganic elements in 43 of 44 vaccines studied; this was inexplicable and they were not declared among the components. Curiously, the only vaccine without these particles was a feline 3-way vaccine; all the others were human vaccines made by a variety of manufacturers and for various diseases, including those for typhoid, tetanus, diphtheria, pertussis, hepatitis B, polio, Hemophilus influenza, measles, mumps and rubella, chicken pox, yellow fever, pneumococcus, and meningococcus [16].

The latest concept, termed "reverse vaccinology" is a promising candidate approach of vaccine development to induce innate, non-specific immunity for long periods [20]. It is computer data-based to identify candidate vaccine antigens; highly sensitive, but not specific and not hypothesis driven. To date, it has been used in studies of meningococci and tuberculosis organisms and was made possible once the whole genome sequencing technology of population biology was identified. The future for these "trained-immunity based vaccines" would be to replace today's vaccine adjuvants and non-toxic derivatives of toxins [20].

## SAFETY ISSUES

Literally many millions of individual people and animals have received vaccinations in early and later life with relatively few serious, proven adverse events. However,

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vaccines still carry an inherent, albeit small risk, which is encompassed by the term 'vaccine pharmacovigilance' [4].

## KILLED, INACTIVATED VERSUS MODIFIED-LIVE VACCINES

The late Dr. Jonas Salk indicated that killed inactivated vaccines are always preferable to those of modified live virus origin because they are safer [3]. The hotly debated costs, convenience and risks concerning live (Sabin) versus inactivated (Salk) human polio vaccines are but one example. However, in the case of veterinary biologicals, 15% of those licensed and used are of the killed, inactivated type and yet they account for 85% of the reported post-vaccinal adverse reactions [4]. This discordancy is believed to be due to the adverse effects of the various adjuvants and other excipients (cell tissue culture remnants, egg protein, fetal calf serum, human and bovine serum albumin, yeast proteins, squalene, formaldehyde, antibiotics like neomycin and gentamicin, as well as other proprietary additives) used in vaccines for humans and other species [5,12-15]. So, what is truly considered to be "acceptable harm" in vaccine pharmacovigilance? As vaccines are generally viewed by the medical community and public as inherently safe, toxicity studies may have been excluded from regulatory safety assessments [4].

## ARE VACCINES INNOCUOUS?

Vaccines are not innocuous products, so the benefit/risk equation needs to be assessed before vaccination. The side effects of vaccines appear to be increasing lately in frequency and severity, particularly in children. The diphtheria-tetanus-pertussis vaccine has been linked to cases of sudden infant death syndrome; measles-mumps-rubella vaccine with autism; high-titer measles vaccines with childhood mortality; multiple immunizations with immune disorders; hepatitis B vaccines with multiple sclerosis, and the recent serious local or systemic adverse effects from human papillomavirus vaccine [3,10,16,18]. These adverse effects can no longer be denied but appear to happen on a random and stochastic basis [16].

For animals, in 2003, the American Animal Hospital Association importantly stated that "no vaccine is always safe, no vaccine is always protective and no vaccine is always indicated. Misunderstanding, misinformation and the conservative nature of our profession have largely slowed adoption of protocols advocating decreased frequency of vaccination". Prof. Michael Day of the United Kingdom stated in the 2015-2017 World Small Animal Veterinary Association guidelines "Vaccination is an act of veterinary science that should be considered as individualized medicine, tailored for the needs of the individual pet and delivered as one part of a preventive medicine program in an annual health check visit".

Further, those who experience these adverse events are believed to be genetically predisposed, rather than have reactions that are unexpected and idiosyncratic [3,4,17]. To some veterinarians, canine and feline vaccination programs have been "practice management tools" rather than medical procedures. It is not surprising, therefore, that attempts to change vaccination programs based on scientific information have created significant controversy and, a "more is better" philosophy still prevails with regard to pet vaccines.

The adjuvants added to killed, inactivated vaccines are intended to enhance their degree and duration of immunogenicity in order to compete favorably with the typical longer immunity induced by modified-live virus vaccines. These adjuvants generate a more robust and sustained humoral antibody-mediated immune response to many viral and other infectious agents [2,4].

## OTHER VACCINE ADVERSE EVENT ISSUES

Vaccines clearly are not innocuous products, so the benefit/risk equation needs to be assessed before vaccination, even for the legally mandated rabies vaccine given to dogs and cats, if the pet is unhealthy [6]. Young individuals (infants, toddlers, adolescents; puppies, kittens, foals, young livestock and wildlife) and young animals are especially at risk as they are more vulnerable to all forms of toxicity than adults [3,14,16].

## SIZE, AGE AND HEAVY METALS

In contrast to animal vaccine use and the potential for volume reduction for smaller pets [3], body weight is ignored with respect to human vaccines, as the heavy metals are included to enhance immune efficacy [14,15]. Most disturbing is the fact that neonates currently receive 17 times more aluminum from vaccines than would be allowed if the doses were adjusted for body weight. Some experts now urge that aluminum and mercury not be given in vaccines until after brain maturation (no earlier than 6-7 months of age but preferably not before 12 months) [5,14,15]. Suitable alternatives to these heavy metals are calcium phosphate, approved by the World Health Organization, and zinc [4,5]. Infants and young children throughout the world receive multiple inoculations that include high quantities of mercury and aluminum. Incremental changes to the recommended vaccination schedule, along with the introduction of new aluminum-containing vaccines for pneumococcus and influenza, have significantly increased the quantity of metals in childhood immunizations despite the federal United States phase-out of the use of mercury-based vaccine adjuvants between 2000 and 2002 [5]. Hopefully, future vaccines will utilize calcium phosphate or other, safer alternatives to aluminum or other metals.

In pets, the type of allergy or immune response induced by these metals is typically a delayed-type hypersensitivity that begins around three days but can occur up to 45 days after vaccination. Heavy metals can cross the blood-brain barrier and remain there indefinitely [5,12,13]. Ultra-trace minerals, including chromium, nickel, molybdenum, silica and

aluminum, are not regulated in the United States by the National Research Council (NRC) or the American Association of Feed Control Officials (AAFCO) and there are currently no set safe upper limits. It often manifests as contact dermatitis (skin inflammation), liver or joint damage, seizures, aggression, phobias, or an attack on the red blood cells and/or platelets [5,12-14].

## ALUMINUM ADJUVANTS IN SHEEP

Vaccines containing aluminum are commonly used in sheep herd management [19]. Results showed behavioral changes, aggression, stereotypic and excitatory responses, compulsive eating and reduced sociability in both the adjuvant alone and adjuvanted vaccine groups but not in the controls.

## AUTOIMMUNE INFLAMMATORY SYNDROME INDUCED BY ADJUVANTS (ASIA SYNDROME)

This ASIA syndrome was first defined in 2011 [12]. Presently, it includes four conditions that share similar signs and symptoms, one of which is from the effects of vaccination. The common denominator in these syndromes is the triggering effect of adjuvants, in combination with other environmental factors along with genetic predisposition. When combined, these factors cause the failure of self-tolerance, which equates to autoimmunity [4].

Vaccine-induced sarcomas in cats, although uncommon, have most often been found to occur with feline rabies and leukemia virus vaccines [3]. Inflammation caused by these adjuvanted vaccines appears to encourage neoplastic transformation, by a mechanism that remains unclear. It occurs in an estimated 1 to 10 out of 10,000 cats and locally invasive metastasis has been found to 10% to 28% of them. To minimize risk of tumor development in cats, vaccines should be given only when truly needed and use non-adjuvanted, modified live or recombinant vaccines. Further, these vaccines should be given as distally on the limb as possible or in areas to allow for future surgery, as radical, complete incision is required to prevent tumor recurrence. Radiotherapy or immunotherapy is recommended following surgical excision.

## REDUCING EXPOSURE RISK

The epidemiological goal of disease control is to reduce the exposure risk of susceptible human and animal populations to known infectious agents. For animals, the typically recommended annual vaccine boosters are not necessary and may be unwise in most cases, since the clinically important so-called “core” vaccines have a much longer duration of immunity than previously thought [3]. Boosters should be given only when absolutely necessary (such as with inadequate serum titer immunity to a “core” vaccine).

Non-adjuvanted, recombinant, subunit, synthetic (or the DNA/RNA vaccines under development), should be used whenever possible [2,3,10]. However, all rabies vaccines given to animals, as well as vaccines for canine leptospirosis, Lyme, canine influenza, and the injectable form of Bordetella are killed adjuvanted vaccines. Cats have more vaccine options in comparison to dogs. For example, a non-adjuvanted feline rabies vaccine is available [3,6]. Studies to improve vaccinal immunity generally have paid little attention to the immune competence and efficacy of the host’s response to the immune challenge. A recent study in dogs addressed the potential immune modulating effect(s) of stimulating specific acupuncture points along the body’s meridian system, GV-14, as practiced in Traditional Chinese Medicine [11]. This randomized trial used canine distemper virus (CDV) vaccine in 100 healthy client-owned dogs, ages 1-10 years, and quantitated the immune response after vaccination in both control and acupuncture groups. No significant differences were found between groups in age, weight, or sex and both groups had highly significant increases of CDV serum neutralization titer post-vaccination. The mean serum titer increase in the acupuncture group, however, was significantly greater than that of the control group. Thus, acupoint vaccination has the potential to enhance the immune response to this immunological challenge.

## OTHER POTENTIAL ADVERSE EVENTS AND TOXICITY

### Human Occupational Illness from use of veterinary vaccines [15]

Veterinarians, veterinary technicians, livestock handlers exposed to brucellosis, animal rescue and shelter organizations are at occupational risk for accidental vaccine-related illness. Even vaccines such as intranasal canine Bordetella can spray vaccine aerosol around the face and eyes of the vaccinate and those close by.

### Gender [17]

Sex differences of humans and animals include the physiological and metabolic traits that affect important immune system functions, thereby predisposing males and females to respond differently to infectious diseases. Females are predisposed because of their higher estrogen content and their differential responses can involve all three arms of immune function, namely, the innate, humoral, and cellular immune systems. Thus, we need to take both sexes into account as we implement appropriately created and implemented preventive vaccines and immunologically targeted therapies. The goal would be to design sex-specific vaccines, adjuvants and vaccine strategies beginning with infants, to reduce adverse reactions in females and increase immunogenicity in males.

### Herd Immunity Concept [3,4]

When a significant portion of a human or animal population (70-95%, depending upon the vaccine) is vaccinated for a particular infectious agent, those unvaccinated within the group will benefit by protection from what is called “herd

immunity". For varicella vaccine in people, herd immunity has been shown to be effective [4]. But, not all vaccines create herd immunity.

**Vaccine Protection Breakthrough with aging [4]**

Examples of vaccine protection breakthroughs include: The herpes varicella-zoster vaccine for chicken pox and shingles in the elderly, where the breakthrough rate in children is 2-34% and is 4-20 times higher for those that are immunocompromised; and , the recent breakthrough of vaccinates getting mild cases of polio in the 6-7th decade of life.

**Epitope Vaccines (biological carriers) [7]**

The newer epitope vaccines exhibit substantial advantages over conventional vaccines, although they typically provide only limited immunity, unless conjugated with built-in adjuvants (e.g., some carrier proteins or new biomaterials) with special properties, including immunologic specificity, good biosecurity and biocompatibility. These include: pattern recognition receptor ligands (toll-like receptors); virus-like particle carrier platforms; bacterial toxin proteins; and novel potential delivery systems (nanoparticles, lipid core peptides).

## CONCLUSION

For the last 100 years, vaccines have proven their importance in providing protective immunity for human and animal populations. Despite these earlier, current and new advances in vaccination development and technology, adverse events still occur in a small cohort of vaccinates. This had led to an ongoing worldwide contentious debate that is unlikely to be resolved in the foreseeable future.

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