© 2022 Journal of Pharmacy & Pharmacognosy Research, 10 (5), 875-887, 2022
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres22.1430_10.5.875

Review

Technology surveillance in veterinary vaccine adjuvants (2015-2022): University-industry interaction

[Vigilancia tecnológica en adyuvantes de vacunas veterinarias (2015-2022): Interacción universidad-industria]

Aníbal Domínguez-Odio[1], Oliver Pérez[2], Alexander Batista-Duharte[3], Daniel Leonardo Cala-Delgado[4*]

[1]Dirección de Investigación e Innovación. Grupo Empresarial LABIOFAM. Avenida Independencia Km 16 ½ Boyeros, La Habana, Cuba.
[2] Instituto de Ciencias Básicas y Preclínicas "Victoria de Girón", Universidad de Ciencias Médicas de La Habana, La Habana, Cuba.
[3]Laboratório de Imunología Clínica. Dpto Analises Clinicas. Faculdade de Ciências Farmacêuticas. Univesidade Estadual Paulista (UNESP). Rod. Araraquara-Jaú, Km 1, Campus Ville Arara-quara, São Paulo, Brazil.
[4]Animal Science Research Group Universidad Cooperativa de Colombia sede Bucaramanga. Carrera 33 N°. 30A–05. Zip Code 68000, Bucaramanga, Colombia.
*E-mail: daniel.cala@campusucc.edu.co

Abstract

Context: The new generation of immunoenhancers will have to offer solutions to each clinical and technological limitation that currently exists. This innovative context requires periodic technological surveillance by the veterinary biopharmaceutical industry to anticipate technological changes and predict future competitive advantages.

Aims: To evaluate the current status, scientific trends, and technological projections in the use of veterinary immunological adjuvants for productive and companion species in the period 2015 and 2021.

Methods: The bibliometric analysis included scientific articles on adjuvants in veterinary medicine published in English in 2015–2021 and indexed on the Scopus and Web of Science platforms. All relevant records retrieved between 2015 and 2022 were grouped using the EndNote bibliographic manager, while the analysis of the relational metric indicator was performed and viewed by VOSviewer®. Instead, data on the main commercial veterinary vaccine adjuvants in 2022 were collected from the official websites of 20 veterinary vaccine manufacturers with experience in the market.

Results: The academy dedicated 68.2% of its production to disseminating articles with original experimental results with 73.6% being novel notifications about adjuvants of natural, microbial and nanotechnological origin. Industrial production mainly used monoadjuvation (86.9%), inorganic salts adjuvants (48.1%), particularly aluminum hydroxide (43.0%), and classical technology (89.2%) to produce their commercial formulations. Ruminants, swines, and poultry dominated both sectors, with ruminants being the main protagonist.

Conclusions: The new scientific knowledge will not have a significant impact on the veterinary pharmaceutical industry in the short term and the hegemonic continuity of traditional adjuvants, in particular aluminum hydroxide, is expected.

Keywords: adjuvant; immunoprophylaxis; technological surveillance; veterinary vaccine.

Resumen

Contexto: La nueva generación de inmunopotenciadores deberá ofrecer soluciones a cada limitación clínica y tecnológica que existe en la actualidad. Este contexto innovador requiere una vigilancia tecnológica periódica por parte de la industria biofarmacéutica veterinaria para anticipar cambios tecnológicos y predecir futuras ventajas competitivas.

Objetivos: Evaluar el estado actual, tendencias científicas, y proyecciones tecnológicas en el uso de adyuvantes inmunológicos veterinarios para especies productivas y de compañía en el periodo 2015 y 2021.

Métodos: El análisis bibliométrico incluyó artículos científicos sobre adyuvantes en medicina veterinaria publicados en inglés en 2015-2021 indexados en las plataformas Scopus y Web of Science. Todos los registros relevantes recuperados entre 2015 y 2022 se agruparon utilizando el administrador bibliográfico EndNote, mientras que el análisis del indicador métrico relacional se realizó y visualizó mediante VOSviewer®. Los datos sobre los principales adyuvantes de vacunas veterinarias comerciales en 2022 se recopilaron de los sitios web oficiales de 20 fabricantes de vacunas veterinarias con experiencia en el mercado.

Resultados: El sector académico dedicó el 68,2% de su producción a difundir artículos con resultados experimentales originales siendo el 73,6% notificaciones novedosas sobre adyuvantes de origen natural, microbiano y nanotecnológico. La producción industrial utilizó principalmente monoadyuvación (86,9 %), adyuvantes de sales inorgánicas (48,1 %), en particular hidróxido de aluminio (43,0 %) y tecnología clásica (89,2 %) para producir sus formulaciones comerciales. Los rumiantes, porcinos y aves dominaron ambos sectores siendo los rumiantes los principales protagonistas.

Conclusiones: El nuevo conocimiento científico no tendrá un impacto significativo en la industria farmacéutica veterinaria en el corto plazo y se espera la continuidad hegemónica de los adyuvantes tradicionales, particularmente el hidróxido de aluminio.

Palabras Clave: adyuvante; immunoprofilaxis; vacuna veterinaria; vigilancia tecnológica.

ARTICLE INFO
Received: June 8, 2022.
Accepted: July 24, 2022.
Available Online: August 21, 2022.

AUTHOR INFO
ORCID: 0000-0003-2243-7150 (ADO)
0000-0002-8117-4939 (OP)
0000-0002-1875-0518 (ABD)
0000-0003-4639-5952 (DLCD)

INTRODUCTION

Veterinary vaccines are fundamentally used to mitigate the effects of emerging, re-emerging, and zoonotic infections, improve animal productivity and promote food safety (Woodland, 2019). The health, social, environmental, and economic success achieved by these vaccines in control programs or emergencies (Sander et al., 2020; Warimwe et al., 2020) would not have been possible without the inclusion of adjuvants in their formulation.

An adjuvant is a substance added to a vaccine to improve the immunogenicity of antigens, and it can induce stronger immune responses and reduce the dosage and production cost of the vaccine. They include a broad variety of molecules, some of which have been used widely for many years, and they have many different mechanisms of action (Nicholls et al., 2010). Available evidence suggests that adjuvants employ one or more of the following mechanisms to elicit immune responses: sustained release of antigen at the site of injection (depot effect), up-regulation of cytokines and chemokines, cellular recruitment at the site of injection, increase antigen uptake and presentation to antigen presenting cells, activation and maturation of antigen presenting cells and activation of inflammasomes (Gerdts, 2015; Marciani, 2003; Nicholls et al., 2010).

Despite these achievements, the use of these molecules in terrestrial and aquatic animals currently faces a complex scenario from a health and scientific-technological point of view. The field of veterinary vaccines needs new solutions to address the current challenges and increased animal production (Entrican and Francis, 2022). The progressive global emergence of multiple pathogens with the ability to evade the immune system makes it necessary to search for adjuvants that combine protective humoral and cellular responses through different mechanisms tailored to each organism and animal species to be protected (Brito and O'Hagan, 2014; Garg et al., 2017). The new generation of immunoenhancers will have to offer solutions to each clinical and technological limitation that currently exists. Unwanted adverse effects with emphasis on companion animals and fish, unspecified mechanisms of action (Adams, 2019; Hoare et al., 2019), low structural stability of the formulations, degradation *in vivo*, rapid excretion, and high manufacturing cost (Brito and O'Hagan, 2014) are some challenges that must be urgently resolved.

Nowadays, innovation in adjuvant technology is driven by rapidly expanding knowledge in immunology and other areas, including systems biology, biotechnology, materials sciences, chemistry, and regulatory requirements for the vaccine product's quality, safety, and efficacy. This innovative context requires periodic technological surveillance by the veterinary biopharmaceutical industry to anticipate technological changes and predict future competitive advantages. On this basis, a study was performed to evaluate the current status, scientific trends, and technological projections in the use of veterinary immunological adjuvants for productive and companion species in 2015 and 2021.

MATERIAL AND METHODS

Information sources

The bibliometric analysis included scientific articles on adjuvants in veterinary medicine, published in English in 2015–2022 by typology (research or review, among others), refereed by pairs, and indexed and available on the Scopus and Web of Science platforms. Instead, data on the main commercial veterinary vaccine adjuvants in 2022 were collected from the official websites of 20 veterinary vaccine manufacturers with experience in the market (Table 1).

Search strategy

Title, abstract, and keyword fields were used, and specific search terms in English were combined: Adjuvant (mineral salts, microbial products, emulsions, saponins, polymers, vitamin E, vegetable, mineral or animal oils, microbial products, cytokines, microparticles, and others), and species of domestic animals (productive and companion animals) were stratified, and the combinations of terms that are frequently used to denominate them were also selected (Table 2).

Studied variables

In general terms, the databases took into account the following parameters: type of scientific articles, co-occurrence of keywords indexed in the literature (at least five matches in one keyword), type of adjuvant, type of technology to manufacture vaccines (classic, modern, and combined), and animal species–productive animals (bovine, equine, swine, sheep–goat, chicken, rabbit and fish) and companion animals (dog and cat).

Data collection process

All relevant records retrieved between 2015 and 2022 were grouped using the EndNote bibliographic manager, while the analysis of the relational metric indicator (co-occurrence of keywords) was performed and viewed by VOSviewer® version 14.0. To refine and increase the precision of the database, additional

Table 1. Veterinary vaccine manufacturers with experience in the market.

Pharmaceutical companies	Websites
BioChemiq	www.biochemiq.com
Biogénesis Bagó S. A	www.biogenesisbago.com
Bioveta Ltd	www.bioveta.eu
BioZoo	www.biozoo.com
Boehringer Ingelheim	www.boehringer-ingelheim.com
CEVA Santé Animale	www.ceva.com
Elanco	www.elanco.com
Finmark Laboratorios S. A	www.finlab.com.co/
Institute for Veterinary Research & Development of Vietnam	www.vinoda.vn; www.hanvetsg.com
Instituto Rosenbusch S. A	www.rosenbusch.com
James Brown Farma	www.jamesbrownpharma.com
Kenya Veterinary Vaccines Production Institute	www.kevevapi.or.ke
Laboratorios HIPRA, S. A.	www.hipra.com
Laboratorios Microsules	www.laboratoriosmicrosules.com
Laboratorios Ovejero, S. A	www.labovejero.es
Lavet	www.grupolavet.com
Lohmann Animal Health	www.lohmann-breeders.com
Merck Sharp & Dohme Animal Health, S.L.	www.msd-animal-health.com
Qilu Animal Health	www.en.qiludb.com/
Vecol	www.vecol.com.co

Table 2. Keywords and synonyms to use in the search strategy.

Keywords	Synonyms
Adjuvant	Adjuvant veterinary vaccine, immunepotentiator, costimulators, immunological adjuvant, immunomodulator
Bovine	Cattle, ruminant, calf, cow, calves, livestock
Equine	Horse
Swine	Pig, hog, porcine, piglets, livestock
Sheep–goat	Ruminant, small ruminant, ovine, sheep, caprine, goat, goatish, livestock
Chicken	Poultry, bird, avian
Rabbit	Cunicular
Fish	Aquaculture, aquafarming, fish farming
Dog	Canine, pets
Cats	Feline, pets

filters were designed and applied to eliminate non-specific terms and neighboring topics: live or attenuated vaccines and parasitic diseases in humans, flying mammals, captive animals, and wild aquatic birds from freshwater, marine, migratory, and predatory regions, such as swamps, wetlands, and urban environments. The data relating to the adjuvanted veterinary vaccines, marketed during January to August 2021, were organized and analyzed using Microsoft Office® in Excel format. Descriptive statistics were performed using the SPSS version 12.0 program.

RESULTS

A total of 6078 indexed publications on adjuvants in the veterinary sector were found from 2015 to 2022,

of which 4145 (68.2%) were original contributions, 1549 (25.5%) constituted reviews, and 384 (6.3%) were other modalities. Particularly, the production of original articles was characterized by concentrating its efforts on the development of new adjuvants individually (Table 3) with emphasis on those of natural, microbial, and nanotechnological origin (73.6%), followed at a distance by the immunological evaluation of new formulations of adjuvants (26.4%).

Table 3. List of selected studies analyzing the use of new adjuvants (research and development) for animal vaccination.

Origin/Molecules	Study	References
Saponins		
Quillaja saponaria (extract)	Bovine	El Fadeel et al., 2021
Q. saponaria QS-21	Feline	Zhu and Tuo, 2016
Q. saponaria GPI-0100	Mice, monkeys	Fleck et al., 2019
Q. brasiliensis (extract)	Mice	Cibulski, 2018b; Yendo et al., 2016
Q. brasiliensis QB-80	Mice	Cibulski, 2018b
Q. brasiliensis QB-90	Mice	Cibulski, 2018a; Yendo et al., 2016
Panax notoginseng (extract)	Pig	Yi et al., 2022
P. ginseng Rg1	Rabbit	Chenwen et al., 2021
P. ginseng E515-D	Chicken	Yuan et al., 2020a
Polymers		
Chitosan	Chicken	Burakova, 2018; Ibe et al., 2019
Carbomer	Guinea pigs, equine	Burakova, 2018; Warda et al., 2021
Polyphosphazene	Bovine, pig	Chand et al., 2021
Polysaccharide (GPS-1)	Chicken	Wu et al., 2022
Achyranthes bidentata polysaccharide	Guinea pigs	Yang et al., 2022
Microbial		
Glycolipids	Mice	Stark et al., 2019
β-glucan	Mice, chicken	Shi et al., 2022
Enterotoxin B	Chicken	Nandre and Lee, 2015
Flagellin	Chicken	Burakova, 2018
CpG-ODNs[†]	Chicken	Ishaq et al., 2018
Nano/microparticles		
Chitosan nanoparticle	Chicken, bovine	Acevedo et al., 2021; Fawzy et al., 2021
Peptide nanofibers	Mice	Burak et al., 2020
Protein-nanoparticles	Mice	Dong et al., 2021; Wang et al., 2022
Silica nanoparticles	Sheep, chicken	Mahony et al., 2015; Mohamed et al., 2022
Golden nanoparticles	Cell lines (PK-15, BHK-21 and F81)	Teng et al., 2018
Calcium phosphate nanoparticles	Mice	Sadeghi et al., 2020
Poly(diaminosulfide) microparticles	Bovine	Wilson-Welder et al., 2021
Formulations		
Glycine max (oil)+ *P. ginseng* (extract)	Mice	Zhang et al., 2018
Helianthus annuus (oil)+ *P. ginseng*	Chicken	Yuan et al., 2020a
H. annuus (oil)+ E515-D	Chicken	Yuan et al., 2020b
PLGA[††] nanoparticle+ cytokine	Guinea pig	Yang et al., 2021
Liposomes+ CpG-ODNs	Bovine	Novoa et al., 2021

[†]CpG-ODNs: CpG oligodeoxynucleotides; [††]PLGA: Poly D, l-lactide-co-glycolic acid.

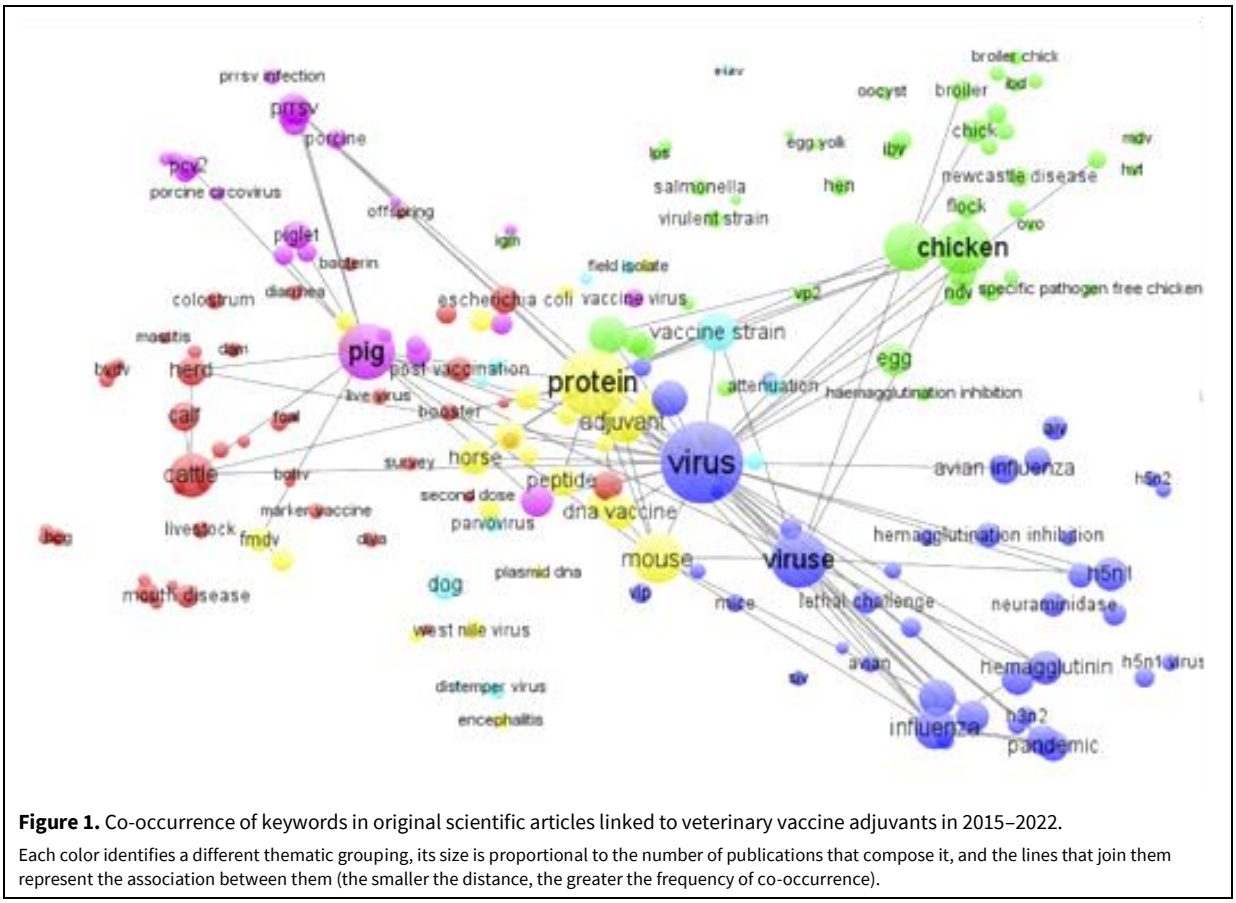

Figure 1. Co-occurrence of keywords in original scientific articles linked to veterinary vaccine adjuvants in 2015–2022.

Each color identifies a different thematic grouping, its size is proportional to the number of publications that compose it, and the lines that join them represent the association between them (the smaller the distance, the greater the frequency of co-occurrence).

The co-occurrence analysis performed with the highest frequency expressions in the field of adjuvants obtained a complex data matrix. The visualized network consisted of 83 nodes and a bithematic central nucleus (protein/adjuvant), all with several matches equal to or greater than five. The bird, pig, bovine (animals for human consumption), and virus clusters also constituted strategic areas of research, and as a whole, they have strong links with the nucleus, the same not occurring with equines and canines (Fig. 1).

Concerning the current commercial use of vaccine adjuvants in 2022, Table 4 details some aspects that characterized it. The catalog of immunological costimulators used by selected pharmaceutical companies consisted of approximately 18 products, of which three were classified by their frequency of use as essential (aluminum hydroxide, emulsions and mineral oil), as they were present in 69.5% (244/351) of all formulations marketed in the period analyzed. Regarding current business adjuvant strategies (Table 3), 86.9% of the 351 commercial vaccines added a single type of adjuvant in the formulation. The remaining 13.1% (46/351) included several types (polyadjuvation) to generate robust immune responses, mostly using combinations of up to four adjuvants (8.3%, 29/351).

The segment of the market corresponding to adjuvanted vaccines was dominated by inorganic salts (aluminum hydroxide, aluminum phosphate, and aluminum hydroxyphosphate) with 48.1% (169/351), followed to a lesser extent by emulsions (20.5%, 72/351) and oil-based adjuvants (liquid paraffin, vitamin E and mineral oil) with 14.5%, (51/351). In particular, aluminum hydroxide was the most commonly used at 43.0% (151/351).

Other features that characterized this market segment were the solid positioning of the classical production technology to obtain antigens (89.2%, 313/351), modern technologies (8.5%, 30/351), and the combination of both platforms in the same product (2.3%, 8/351). Similarly, it was identified that 100% of the formulations available on the market had a prophylactic and parenteral clinical indication (intramuscular and/or subcutaneous).

It was also known that there was polarized use of licensed immunological adjuvants by animal species in 2022 (Fig. 2). At one extreme were poultry, swine and ruminants (cattle, sheep, and goats), which accounted for 86.3% (303/351) of all manufactured adjuvanted vaccines, while equines, rabbits, fish, and companion animals (dog and cat) only consisted of 13.7% (48/351) of the market. The asymmetry detect-

ed in general terms was conserved among the leading species. In comparison with poultry and swine, the ruminant was the main protagonist, having 1.56 and 1.37 times more commercial adjuvanted vaccines than both separately.

All species (livestock animals and companion animals), except fish, used the aluminum adjuvant to increase the quality of the vaccine response. The descriptive statistics confirmed that ruminants were the leading species with 104 formulations, representing 81.3% (104/128) of all vaccines designed to immunize them. On the contrary, polymers, and saponins (3.7%, 13/351) were used in a restricted way in the commercialized formulations during the study period and only for the swine and equine species.

DISCUSSION

The increasing effect of veterinary infectious diseases in causing serious economic and health damage is well known. Preventing and controlling its enormous negative effects by vaccination requires establishing strategic alliances between the university and the veterinary biopharmaceutical industry (Gutiérrez et al., 2012; Heldens et al., 2008). Addressing the collaborative relationships that link both sectors is relevant to predicting future business development strategies (Mascarenhas et al., 2018).

Table 4. Main immunological adjuvants and their combinations, used in commercial veterinary formulations in 2022.

Adjuvants	Formulations
Single use (1 component)	**305 (86.9%)**
Aluminum hydroxide†	151
Aluminum phosphate	12
Aluminum hydroxyphosphate	6
Liquid paraffin	19
Vitamin E	11
Mineral oil†	21
Saponin	3
Polymers	10
Emulsions† (water/oil, oil/water and water/oil/water)	72
Adjuvant combination (2 or 3 components)	**17 (4.8%)**
Water/oil emulsion + MFL-A††	1
Oil/water emulsion + liquid paraffin	1
Aluminum hydroxide + saponin	1
Aluminum hydroxide + DEAE-D†††	6
Aluminum hydroxide + mineral oil	3
Aluminum hydroxide + liquid paraffin	3
Liquid paraffin + vitamin E	2
(≥4 components)	**29 (8.3%)**
Microsol Diluvac Forte®	8
Fortazol Microsol	3
MetaStim®	5
Diluvac Forte®	5
Emunade® + aluminum hydroxide	3
SPUR®	1
Retigen®	4
	351 (100%)

†Classified by their frequncy of use as essential; ††MPL-A: monophosphoryl lipid A; †††DE-AE-D, diethylaminoethyl-dextran.

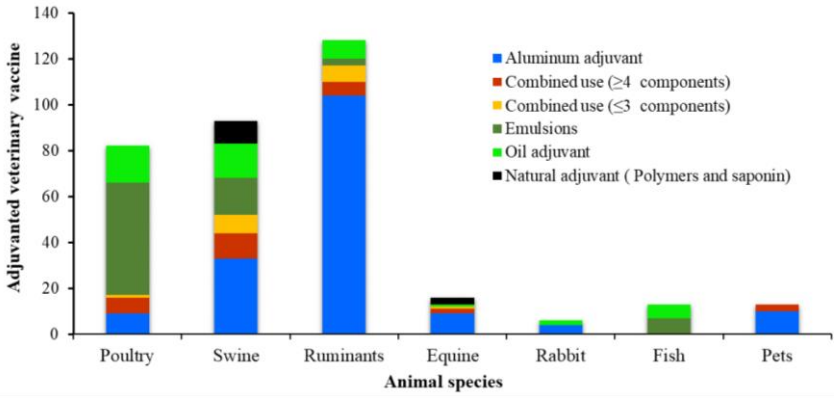

Figure 2. Use of adjuvants in commercial vaccines by animal species in 2022

Regarding public research on adjuvants in veterinary medicine, the high percentage of original scientific articles (new knowledge) indexed compared with other publication modalities confirms the value of this resource for veterinary vaccinology (Burakova et al., 2018; Heegaard et al., 2011). The intensity of research on adjuvants in a general sense is not accidental. It occurs when working with intact pathogens is avoided and new purified, synthetic or recombinant antigens are used, which are specific and well-characterized but not very immunogenic (Batista-Duharte et al., 2014; Pérez et al., 2013). This is encouraged by the successes achieved in the informatics, molecular, immunological, toxicological and biomaterials fields (Batista-Duharte et al., 2018; Brito and O'Hagan, 2014; Nnamdi et al., 2020).

Another key factor that contributes to the creation of a favorable environment for the research of new adjuvants is the emergence and re-emergence of infectious diseases in multiple species, some of them zoonotic, which is hoped to be controlled in the future by vaccination, such as foot-and-mouth and Newcastle (Warimwe et al., 2020; Yuan et al., 2020a; Zhang et al., 2018). Expansion and intensification of pig, cattle, and poultry productions have resulted in significant changes to traditional husbandry practices leading to an environment conducive to increased emergence and spread of infectious diseases. These include several zoonotic viruses, including avian influenza, Japanese encephalitis, Nipah and coronaviruses, and others (McLean and Graham, 2022; Rathore et al., 2022; Thomas et al., 2022).

The search for new adjuvants as the mainline of research is in line with the veterinary biopharmaceutical industry need for new molecules that induce rapid, long-lasting, robust protective immunity without booster doses and reduce the amount of antigen per dose (Heegaard et al., 2011; Heldens et al., 2008; Sun et al., 2020). However, in the period studied, the new knowledge from universities and scientific institutions worldwide have not yet reached the vaccine producer. Much research on natural, microbial, and nanotechnological adjuvants is left only for academic demonstrations (Fawzy et al., 2021); Heegaard et al., 2011). The results are still very far from benefiting the industry because the development of stable, reproducible, robust, scalable formulations that comply with good production practices remained in the background. The identified thematic imbalance reinforces the need to plan rational pharmaceutical development, focused on encouraging the advancement of the veterinary biopharmaceutical industry toward the use of modern adjuvant formulations and technologies with minimal risks of failure (Brito et al., 2013; Brito and O'Hagan, 2014; Mascarenhas et al., 2018).

The centrality and high interrelation visualized between the protein and adjuvant nodes in the co-occurrence network (Fig. 1) show that the international scientific interest in proteins expanded, from their traditional use as antigens to the area of immunoadjuvants. This thematic opening reflects the progress obtained in relation to promising molecules and biomaterials, such as saponins, polysaccharides, nano/microparticles, and others (Byoung et al., 2019; Cerbu et al., 2021; Chand et al., 2021; Ji et al., 2020), all with an acceptable efficacy and safety profile, biocompatibility, and biodegradability (Table 3).

Under these circumstances, a strong relationship was also observed between the aforementioned bithematic nucleus and the bovine, chicken, and pig domains. This scenario was expected if each species establishes complex and specific relationships with its pathogens, which makes it necessary to investigate specific strategies of survival in each species (Cambronero et al., 2017). The strength of this association originates from the importance of these species in human nutrition and, therefore, in the world market for meat and derivatives (Ali, 2015; Bavyko and Bondarchuk, 2019). According to the opinion of some authors, the privileged position occupied by these animals encourages the allocation of financial resources to develop a wide range of investigations,

which includes pathogens that impair their productive and reproductive performance, vaccines, and adjuvants (Domínguez-Odio et al., 2014; Ducrot et al., 2016; Rodríguez et al., 2021).

The increase in thematic weight and close relationship observed between protein-adjuvant and virus is not surprising either (Fig. 1). The visualized oversizing may be associated with the enormous scientific and editorial activity unleashed by the outbreaks of avian influenza in multiple species and their respective strains of high and medium pathogenicity. Such suspicion is based on analogous bibliometric interference identified by Ducrot et al. (2016), in a study on veterinary infectious diseases between 2006 and 2013, which showed an increase of 13% in articles published on this topic.

Although the comprehensive analysis of the results allows observing a marked divergence between what is researched and commercialized, it should not be interpreted as a contradiction between university and industry. The delayed arrival of many adjuvants to marketable status is due to biological, economic, and regulatory reasons (Heldens et al., 2008; Jones et al., 2007). Many adjuvant candidates show little clinical evidence on efficacy and mechanisms of action, unacceptable local or systemic toxicity, poor stability and prohibitive cost have an unfavorable cost-benefit ratio, or do not meet good production practice standards (Awate et al., 2013; Spickler and Roth, 2003). Many of these mechanisms are now becoming known in sufficient detail to allow the tailored design of molecularly defined adjuvants, in principle allowing control of the induced innate immune activation, and thereby the type of obtained adaptive immune response, aiming at adaptive responses providing optimal protection and with memory towards the infection in question (Heegaard et al., 2011).

One of the main problems university–veterinary biopharmaceutical industry cooperation is the time lag between research projects and the industrial use of results. The variety and particularities of the animals to which immunostimulation is a factor that contributes to this fact and consequently slows down the generalization of adjuvants. Although terrestrial and aquatic vertebrates share similarities, they also have immunological differences that complicate extrapolations (Cambronero et al., 2017). Consequently, evaluating each species' biological effects requires time, financial resources, experimental models, challenge methods, and different biomarkers of effectiveness (Brito and O'Hagan, 2014). Fish are the best example; multiple and complex factors converge on them, such as the diversity of species, production cycle, diseases, farming technology (handling and mechanization), environment (temperature and salinity), stress factors, and cost-benefits (Adams, 2019).

In the industrial order, the predominance of inactivated monoadjuvanted vaccines in the veterinary market (Fig. 2) shows that profitability is a determining factor in this sector, and its influence is greater than any benefit that attractive molecules or modern production technologies can provide (Byoung et al., 2019; Jorge and Dellagostin, 2017). This business strategy is associated with financial limitations derived from the low average sales prices for veterinary vaccines in the world market, which generates 30 times lower income than human vaccines (Knight-Jones et al., 2014). The use of monoadjuvants with inorganic, oil-based adjuvants, and emulsions (Table 4) is an excellent example that supports it. The respective inclusions of these costimulators in most veterinary vaccines produced are due to their low prices, simplicity of the acquisition, and common history of safety and efficiency (Del Giudice et al., 2018; Siel et al., 2014), which translates into shorter terms for the development of inexpensive vaccines and pathways for official approval of their commercialization.

In this context, aluminum adjuvants deserve a special mention. Such distinction is due to its long years of use, beginning in 1926 (Glenny et al., 1926); its proven ability to combine with numerous viral and bacterial antigens (Baylor et al., 2002), high degree of safety, stability, known chemical structure, easy preparation and, above all, low cost (Ghimire 2015; Moyer et al., 2020). For these reasons, the inclusion of these compounds in veterinary vaccines ensures the manufacturer, from the regulatory point of view, lower registration costs and shorter times for the return on investment (Del Giudice et al., 2018).

The immunological base that sustains the current and future hegemony of these compounds in the market is progressively strengthened. Although not all the elements involved in its mechanism of action are known, there is sufficient evidence to affirm that the depot and cytolytic effects at the injection site are key to its performance (Awate et al., 2013). Both processes are explained by the non-biodegradable nature of these compounds, particle sizes greater than 10 µm, and by the ability to adsorb and internalize the antigen (strong electrostatic interaction) without modifying it, to later release it gradually over prolonged periods (stimulation of the immune system) (Batista-Duharte et al., 2014; He et al., 2015; Kuroda et al., 2013; Matheis et al., 2001). In general, the use of these compounds is linked to a powerful Th2-type immune response, differentiation of B lymphocytes, production of cytokines IL-1β, IL-4, IL-5, IL-10, and IL-18, and activation of the innate immune system. More specifically, they are associated with robust endoge-

nous DNA-induced immunoglobulin (IgG1 and IgE) production, and rapid recruitment of various polymorphonuclear cells, including eosinophils, monocytes, neutrophils, dendritic cells, and natural killer cells at the site of injection (Awate et al., 2013; He et al., 2015; Kooijman et al., 2018; Marichal et al., 2011).

All these aspects (biological, practical, and economic) as a whole cause aluminum adjuvant and hydroxide in particular to be the most widely used worldwide and, therefore, a reference for developing new adjuvants (Cárdenas-Vargas et al., 2016). The advantages described above compensate for its weak capacity to stimulate immune responses against antigens with a polysaccharide structure and cytotoxic CD8+ T lymphocytes necessary to combat intracellular pathogens (Ghimire, 2015).

Fish are the only animals of economic interest that deviate from this generality. Aluminum hydroxide, despite having potential in this species (D'Angosto et al., 2018), was displaced by oil-based adjuvants. The latter has the ability to generate sustained and robust pro-inflammatory responses, effective humoral immunity, strong innate immune responses and are excellent platforms for formulating multivalent vaccines (Brudeseth et al., 2013; Miccoli et al., 2019; Xu et al., 2019). However, its parenteral by use, like other adjuvants, generates local side effects, including tissue inflammation, adherence, and necrosis (Embregts and Forlenza, 2016). The limited number of vaccines approved for use in aquatic organisms clearly demonstrates how much work remains to be done. Achieving better results involves facing some challenges, including the undetermined optimal route of administration (intraperitoneal, intramuscular, immersion and oral), lack of effective adjuvants and basic knowledge about an immune response for both pathogens and vaccines, absence of a single experimental model and high cost to inject fish (Adams, 2019; Embregts and Forlenza, 2016).

In the coming years, the hegemony of inorganic adjuvants in the veterinary market is not synonymous with the industry's disinterest in modern adjuvants. The development achieved in the research and production of vaccines in this sector is years ahead of human vaccines, and the use of adjuvants is no exception (Aida et al., 2021). As reflected in this study, the swine is the main exponent of this still incipient advancement but not the only one. The use of formulations, such as MetaStim®, Diluvac Forte® or Impran-FLEX® (Gutiérrez et al., 2015; Horohov et al., 2015; Martelli et al., 2011), mark the beginning of the journey with a long way to go.

The overwhelming dominance of productive species observed in the scientific and commercial areas (Fig. 2), far from being exclusive to the adjuvanted vaccine market, is a behavior that distinguishes the veterinary sector. The popularity of poultry, swine, and ruminants is proportional to the weight these species have in producing meat, egg, milk, cheese, and leather. The husbandry of polygastric animals is essential both for household survival and for increasing economic capital and social prestige in pastoralist and peasant societies in developing countries (McGaw et al., 2020; Tilahun et al., 2019). A similar fact is identified by other authors when analyzing topics as diverse as infectious disease research, vaccine development, and commercialization of herbal products (Bavyko and Bondarchuk, 2019; Rodríguez et al., 2021).

Other reasons that determine it are diverse in this case. The one that exerts the greatest pressure is the need for farmers to control or eradicate infectious diseases to access lucrative benefits provided by international markets for the export of animals and their products (Byoung et al., 2019; Dybowski and Bugała, 2016). The second, no less important, is the urgency of increasing the inventory of healthy edible animals with minimum expenses and economic losses. Both reasons converge at times when the demand for animal protein is associated with the sustained growth of the world population and consumption patterns are increasingly demanding in terms of food safety (Hoelzer et al., 2018). These same economic reasons explain, in part, why veterinary vaccines intended for low-incidence diseases or species that remain in small numbers are scarce on the market (Heldens et al., 2008; Meeusen et al., 2007).

Limitations of evidence

The available articles are limited to *in vivo/in vitro* research models and 20 veterinary vaccine manufacturers with experience in the international market, so the level of evidence provided is limited.

CONCLUSION

The acquisition and global accumulation of knowledge on new adjuvants will not significantly impact the veterinary pharmaceutical industry in the short term. This is because the development of stable, reproducible, robust, and scalable formulations took a back seat. Traditional adjuvants (aluminum-based mineral salts, emulsions, and oil-based adjuvants), particularly aluminum hydroxide, will maintain their commercial hegemony in the coming years despite the existence of attractive costimulating molecules in the immune system. Monoadjuvant, classical technologies for producing vaccines, parenteral administration, and productive animals will continuously receive priority attention from science and industry.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors thank Dirección Nacional de Investigación de la Universidad Cooperativa de Colombia (DINAI) for their assistance. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

Acevedo K, Renu S, Gourapura R, Selvaraj R (2021) Efficacy of a nanoparticle vaccine administered *in-ovo* against *Salmonella* in broilers. PloS One 16(4): e0247938.

Adams A (2019) Progress challenges and opportunities in fish vaccine development. Fish Shellfish Immunol 90: 210–214.

Aida V, Pliasas V, Neasham P, North J, McWhorter K, Glover S, Kyriakis C (2021) Novel vaccine technologies in veterinary medicine: A herald to human medicine vaccines. Front Vet Sci 8: 654289.

Ali J (2015) Global meat market: Structural changes across geographical regions. South Asia Res 35(2): 143–157.

Awate S, Babiuk L, Mutwiri G, Awate S, Babiuk L, Mutwiri G (2013) Mechanisms of action of adjuvants. Front Immunol 4: 114–120.

Batista-Duharte A, Lastreb M, Pérez O (2014) Adyuvantes inmunológicos. Determinantes en el balance eficacia-toxicidad de las vacunas contemporáneas. Enferm Infecc Microbiol Clin 32(2): 106–114.

Batista-Duharte A, Téllez-Martínez D, Portuondo-Fuentes F, Carlos I (2018) Molecular adjuvants that modulate regulatory T cell function in vaccination: A critical appraisal. Pharmacol Res 129: 237–250.

Bavyko O, Bondarchuk M (2019) Trends in the development of the world food market. Mod Sci 6(3): 5–13.

Baylor N, Egan W, Richman P (2002) Aluminum salts in vaccines-US perspective. Vaccine 20(suppl. 3): S18–S23.

Brito L, Malyala P, O'Hagan D (2013) Vaccine adjuvant formulations: a pharmaceutical perspective. Semin Immunol 25(2): 130–145.

Brito L, O'Hagan D (2014) Designing and building the next generation of improved vaccine adjuvants. J Control Release 2819(190): 563–579.

Brudeseth B, Wiulsrod R, Fredriksen B, Lindmo K, Lokling K, Bordevik M, Steine N, Klevan A, Gravningen K (2013) Status and future perspectives of vaccines for industrialised fin-fish farming. Fish Shellfish Immunol 35(6): 1759–1768.

Burak D, Tohumeken S, Gunduz N, Aref K, Tekinay T, Guler M, Tekinay A (2020) Biotin functionalized self-assembled peptide nanofiber as an adjuvant for immunomodulatory response. Biotechnol J 15(12): e2000100.

Burakova Y, Madera R, McVey S, Schlup J, Shi J (2018) Adjuvants for animal vaccines. Viral Immunol 31(1): 11–22.

Byoung S, Kee J, Puna M, Sunghwa C (2019) Plant factory: new resource for the productivity and diversity of human and veterinary vaccines. Clin Exp Vaccine Res 8(2): 136–139.

Cambronero M, Prado-Cohrs D, López S (2017) Conceptos inmunológicos básicos aplicados a la vacunología. Vacunas 18(2): 49–58.

Cárdenas-Vargas A, Pedroza-Roldán C, Elizondo-Quiroga D (2016) Adyuvantes para vacunas: tipos aplicaciones y modos de acción. Rev Mex Cienc Farm 47(3): 29–47.

Cerbu C, Kah M, White J, Astete C, Sabliov C (2021) Fate of biodegradable engineered nanoparticles used in veterinary medicine as delivery systems from a one health perspective. Molecules 26(3): 523.

Chand D, Magiri B, Wilson H, Mutwiri G (2021) Polyphosphazenes as adjuvants for animal vaccines and other medical applications. Front Bioeng Biotechnol 9: 625482.

Chenwen X, Quanan J, Yee H, Yan L, Jiaoyu W, Qiang W, Guolian B (2021) Efficacy of Rg1-oil adjuvant on inducing immune responses against *Bordetella bronchiseptica* in rabbits. J Immunol Res 2021: 8835919.

Cibulski S, Rivera-Patron M, Mourglia-Ettlin G, Casaravilla C, Yendo A, Fett-Neto A, Silveira F (2018a) *Quillaja brasiliensis* saponin-based nanoparticulate adjuvants are capable of triggering early immune responses. Sci Rep 8: 13582.

Cibulski S, Rivera-Patron M, Suárez N, Pirez M, Rossi S, Yendo A, Silveira F (2018b) Leaf saponins of *Quillaja brasiliensis* enhance long-term specific immune responses and promote dose-sparing effect in BVDV experimental vaccines. Vaccine 36(1): 55–65.

D'Angosto A, López-Muñoz A, García-Alcazar J, Meseguer M, Sepulcre V (2018) Aluminum is a powerful adjuvant in teleost fish despite failing to induce interleukin-1β release. Dev Comp Immunol 85: 18–24.

Del Giudice G, Rappuoli R, Didierlaurent A (2018) Correlates of adjuvanticity: A review on adjuvants in licensed vaccines. Semin Immunol 39: 14–21.

Domínguez-Odio A, Polanco R, Cossío G, Morejón Y, Riquenes Y (2014) Current trends and perspectives in veterinary vaccine production. Biotec Apl 31: 196–203.

Dong J, Chen Y, Shi L, Shen B, Sun X, Ruan K, Feng N (2021) Nanoparticles of conformation-stabilized canine distemper virus hemagglutinin are highly immunogenic and induce robust immunity. Virol J 18: 229.

Ducrot C, Gautret M, Pineau T, Jestin A (2016) Scientifc literature on infectious diseases acting livestock animals longitudinal worldwide bibliometric analysis. Vet Res 47: 42.

Dybowski G, Bugała A (2016) Global food market–new factors influencing development Agrofor Inter J 1(2): 13–19.

El Fadeel M, El Dakhly A, Farag T, Allam A, Ali N, El Koly A (2021) Protective value of freeze-dried inactivated bovine viral respiratory combined vaccine stabilized by carbomer and adjuvanted with saponin. Adv Anim Vet Sci 9(4): 525–532.

Embregts C, Forlenza M (2016) Oral vaccination of fish: Lessons from humans and veterinary species. Dev Comp Immunol 64: 118–137.

Entrican G, Francis M (2022) Applications of platform technologies in veterinary vaccinology and the benefits for one health. Vaccine 40(20): 2833–2840.

Fawzy M, Khairy G M, Hesham A, Rabaan A, El-Shamy A, Nagy A (2021) Nanoparticles as a novel and promising antiviral platform in veterinary medicine. Arch Virol 166(10): 2673–2682.

Fleck J, Betti A, Da Silva F, Troian E, Olivaro C, Ferreira F, Verza S (2019) Saponins from *Quillaja saponaria* and *Quillaja brasiliensis*: particular chemical characteristics and biological activities. Molecules 24(1): 171–200.

Garg R, Babiuk L, van Drunen L, Gerdts V, Ravendra G, Lorne B, Sylviavan D, Volker G (2017) A novel combination adjuvant platform for human and animal vaccines. Vaccine 35(35): 4486–4489.

Gerdts V (2015) Adjuvants for veterinary vaccines-types and modes of action. Berl Munch Tierarztl Wochenschr 128(11-12): 456–463.

Ghimire T (2015) The mechanisms of actions of vaccine containing aluminum adjuvants: an *in vitro* vs *in vivo* paradigm. SpringerPlus 4: 181.

Glenny A, Pope C, Waddington H, Wallace V (1926) The antigenic value of toxoid precipitated by potassium-alum. J Path Bact 29: 38–45.

Gutiérrez A, Spero D, Gay C, Zimic M, D`Groot A (2012) New vaccines needed for pathogens infecting animals and humans: one health. Hum Vaccin Immunother 8(7): 971–978.

Gutiérrez C, González F, Araya A, Gadicke P, Ruiz A (2015) Evaluación productiva de un programa de inyección sin aguja para la administración de vacunas contra Circovirus porcino tipo 2 y *Mycoplasma hyopneumoniae* en un plantel porcino intensivo tipo destete-venta. Arch Med Vet 47(2): 147–153.

He P, Zou Y, Hu Z (2015) Advances in aluminum hydroxide-based adjuvant research and its mechanism. Hum Vaccin Immunother 11(2): 477–488.

Heegaard P, Dedieu L, Johnson N, Potier M, Mockey M, Mutinelli F, Vahlenkamp T, Vascellari M, Sorensen N (2011) Adjuvants and delivery systems in veterinary vaccinology: current state and future developments. Arch Virol 156: 183–202.

Heldens J, Patel J, Chanter N, Thij G, Gravendijck M, Schijns V, Langen A, Schetters T (2008) Veterinry vaccine development from an industrial perspective. Vet J 178(1): 7–20.

Hoare R, Jung S, Ngo T, Bartie K, Bailey J, Thompson K, Adams A (2019) Efficacy and safety of a non-mineral oil adjuvanted injectable vaccine for the protection of Atlantic salmon (*Salmo salar* L.) against *Flavobacterium psychrophilum*. Fish Shellfish Immunol 85: 44–51.

Hoelzer K, Bielke L, Blake D, Cox E, Cutting S, Devriendt B, Erlacher-Vindel E, Goossens E (2018) Vaccines as alternatives to antibiotics for food producing animals Part 1: challenges and needs. Vet Res 49(1): 64–74.

Horohov D, Dunham J, Liu C, Betancourt A, Stewart J, Page A, Chambers T (2015) Characterization of the *in situ* immunological responses to vaccine adjuvants. Vet Immunol Immunopathol 164(1-2): 24–29.

Ibe M, Odimegwu D, Onuigbo E (2019) Alginate-coated chitosan microparticles encapsulating an oral plasmid-cured live *Salmonella enterica* serovar Gallinarum vaccine cause a higher expression of interferon-gamma in chickens compared to the parenteral live vaccine. Avian Pathol 48(5): 423–428.

Ishaq MU, Rafique A, Cheema HM, Ashraf MU, Rahman SU, Abbas RZ, Mahmood MS. (2018) Role of cytosine-phosphate-guanosine-oligodeoxynucleotides (CpG ODNs) as adjuvant in poultry vaccines. Worlds Poult Sci J 74(3): 453–462.

Ji Q, Wang S, Ma J, Liu Q (2020) A review: Progress in the development of fish *Vibrio* spp vaccines. Immunol Lett 226: 46–54.

Jones P, Cowan G, Gravendyck M, Nagaa T, Robnson S, Waits M (2007) Regulatory requirements for vaccine authorization. Rev Sci Tech 26(2): 379–393.

Jorge S, Dellagostin O (2017) The development of veterinary vaccines: A review of traditional methods and modern biotechnology approaches. Biotechnol Res Innov 1(1): 3–6.

Knight-Jones T, Edmond K, Gubbins S, Paton D (2014) Veterinary and human vaccine evaluation methods. Proc Biol Sci 281(1784): 2013–2839.

Kooijman S, Brummelman J, van Els C, Marino F, Heck A, Mommen G, Metz B, Kersten G, Pennings J, Meiring H (2018) Novel identified aluminum hydroxide-induced pathways prove monocyte activation and pro-inflammatory preparedness. J Proteomics 175: 144–155.

Kuroda E, Coban C, Ishii K (2013) Particulate adjuvant and innate immunity: past achievements present findings and future prospects. Int Rev Immunol 32: 209–220.

Mahony, D, Mody K, Cavallaro A, Hu Q, Mahony T, Qiao S, Mitter N (2015) Immunisation of sheep with bovine viral diarrhoea virus, E2 protein using a freeze-dried hollow silica mesoporous nanoparticle formulation. PloS One 10(11): e0141870.

Marciani J (2003) Vaccine adjuvants: role and mechanisms of action in vaccine immunogenicity. Drug Discov Today 8(3): 934–943.

Marichal T, Ohata K, Bedoret D, Mesnil C, Sabatel C, Kobiyama K, Lekeux P, Coban C, Akira S, Ishii K (2011) DNA released from dying host cells mediates aluminum adjuvant activity. Nat Med 17: 996–1002.

Martelli P, Ferrari L, Morganti M, D`Angelis E, Bonilauri P, Guazzetti S, Caleffi A, Borghetti P (2011) One dose of a porcine circovirus 2 subunit vaccine induces humoral and cell-mediated immunity and protects against porcine circovirus-associated disease under field conditions. Vet Microbiol 149(3-4): 339–351.

Mascarenhas C, Ferreira J, Marques C (2018) University–industry cooperation: A systematic literature review and research agenda. Sci Pub Poli 45(5): 708–718.

Matheis W, Zott A, Schwanig M (2001) The role of the adsorption process for production and control combined adsorbed vaccines. Vaccine 20: 67–73.

McGaw L, Famuyide I, Khunoana E, Aremu A (2020) Ethnoveterinary botanical medicine in South Africa: Review of research from the last decade (2009 to 2019). J Ethnopharmacol 257: 112864.

McLean R, Graham S (2022) The pig as an amplifying host for new and emerging zoonotic viruses. Int JOne Health 14: 100384.

Meeusen E, Walker J, Peters A, Pastoret P, Jungersen G (2007) Current status of veterinary vaccines. Clin Microbiol Rev 20(3): 489–510.

Miccoli A, Saraceni P, Scapigliati G (2019) Vaccines and immune protection of principal Mediterranean marine fish species Fish Shellfish Immunol 94: 800–809.

Mohamed A, El Naggar H, El-Dek S, Farghali A, Fekry El Kersh M (2022) using a novel nanoparticle as an adjuvant for inactivated avian influenza vaccine. J Appl Anim Res 7(1): 31–37.

Moyer T, Kato Y, Abraham W, Chang J, Kulp D, Watson N, Turner H, Menis S, Abbott R (2020) Engineered immunogen binding to alum adjuvant enhances humoral immunity. Nat Med 26: 430–440.

Nandre R, Lee J (2015) Generation of a safe *Salmonella gallinarum* vaccine candidate that secretes an adjuvant protein with immunogenicity and protective efficacy against fowl typhoid. Avian Pathol 2(43): 164–171.

Nicholls E, Madera L, Hancock R (2010) Immunomodulators as adjuvants for vaccines and antimicrobial therapy. Ann N Y Acad Sci 1213: 46–61.

Nnamdi O, Okechukwu O, Ositadimma I, Chukwu O, Nnaemeka O, Ogonna E, Adedeji A, Ibeanu G (2020) Immunoinformatics and vaccine development: an overview. Immunotargets Ther 9: 13–30.

Novoa MB, Sarli M, Reidel IG, Veaute C, Valentini B, Primo ME (2021) *Neospora caninum* truncated recombinant proteins formulated with liposomes and CpG-ODNs triggered a humoral immune response in cattle after immunisation and challenge. Vet Immunol Immunopathol 238: 110285.

Pérez O, Romeu B, Cabrera O, González E, Batista-Duharte A, Labrada A, Pérez R, ReyesL, Ramírez W, Sifontes S, Fernández N, Lastre M (2013) Adjuvants are key factors for the development of future vaccines: Lessons from the Finlay adjuvant. Platform Front Immunol 4: 407.

Rathore S, Gehlot H, Prakash G, Nandi J (2022) Epizootic, endemic and pandemic zoonotic viral infections. J Biosci Med 10(3): 90–96.

Rodríguez C, Domínguez-Odio A, Mena A, Toirac P, González M, Cala D (2021) Global market for veterinary herbal products during the 2018-2019 period. Braz J Ve t Res Anim Sci 58: e181002.

Sadeghi Z, Fasihi-Ramandi M, Bouzari S (2020) Nanoparticle-based vaccines for brucellosis: calcium phosphate nanoparticles-adsorbed antigens induce cross protective response in mice. Int J Nanomedicine 15: 3877–3886.

Sander V, Sánchez L, Mendoza M, Ramos D, Corigliano M, Clemente M (2020) Use of veterinary vaccines for livestock as a strategy to control foodborne parasitic diseases. Front Cell Infect Microbiol 10: 288.

Shi S, Yin L, Shen X, Dai Y, Wang J, Yin D, Pan X (2022) β-Glucans from *Trametes versicolor* (L.) Lloyd is effective for prevention of influenza virus infection. Viruses 14(2): 237.

Siel D, Vidal S, Sáenz L (2014) Principales sistemas de entrega de antígenos en medicina veterinaria y humana. Av Cienc Vet 29(1): 50–69.

Spickler R, Roth A (2003) Adjuvants in veterinary vaccines: modes of action and adverse effects. J Vet Intern Med 17(3): 273–281.

Stark F, Akache B, Ponce A (2019) Archaeal glycolipid adjuvanted vaccines induce strong influenza-specific immune responses through direct immunization in young and aged mice or through passive maternal immunization. Vaccine 37: 7108–7116.

Sun X, Jin P, Liu Q, Wang Q, Zhang Y, Liu X (2020) A CpG-riched plasmid as vaccine adjuvant reduce antigen dose of an inactivated *Vibrio anguillarum* vaccine in turbot (*Scophthalmus maximus* L.). Fish Shellfish Immunol 98: 312–317.

Teng Z, Sun S, Chen H, Huang J, Du P, Dong H, Xu X, Mu S, Zhang Z, Guo H (2018) Golden-star nanoparticles as adjuvant effectively promotes immune response to foot-and-mouth disease virus-like particles vaccine. Vaccine 36: 6752–6760.

Thomas S, Abraham A, Rodríguez-Mallon A, Unajak S, Bannantine J (2022) Challenges in veterinary vaccine development. In: Thomas, S. (eds) Vaccine Design. Methods in Molecular Biology, vol 2411. New York, NY: Humana, pp. 3–34.

Tilahun M, Etifu M, Shewage T (2019) Plant diversity and ethnoveterinary practices of Ethiopia: A systematic review. Evid Based Complement Alternat Med 2019: 5276824.

Wang B, Li S, Qiao Y, Fu Y, Nie J, Jiang S, Shan Y (2022) Self-assembling ferritin nanoparticles coupled with linear sequences from canine distemper virus haemagglutinin protein elicit robust immune responses. J Nanobiotechnol 20: 32.

Warda S, Ali N, Warda, F, Farouk E, Farahat L (2021) Improvement of inactivated equine herpes virus-1 vaccine using carbomer. J Appl Vet Sci 6(1): 21–27.

Warimwe G, Francis M, Bowden T, Thumbi S, Charleston B (2020) Using cross-species vaccination approaches to counter emerging infectious diseases. Nat Rev Immunol 21: 815–822.

Wilson-Welder J, Alt D, Nally J, Olsen S (2021) Bovine immune response to vaccination and infection with *Leptospira borgpetersenii* serovar Hardjo. Msphere 6(2): e00988-20.

Woodland D (2019) Veterinary vaccines. Viral Immunol 32(9): 361.

Wu Y, Li N, Zhang T, Che Y, Duan K, Wang Y, Wang D (2022) Glycyrrhiza polysaccharides can improve and prolong the response of chickens to the Newcastle disease vaccine. Poult Sci 101(1): 101549.

Xu W, Jiao C, Bao P, Liu Q, Wang P, Zhang R, Liu X, Zhang Y (2019) Efficacy of Montanide™ ISA 763 A VG as aquatic adjuvant administrated with an inactivated *Vibrio harveyi* vaccine in turbot *(Scophthalmus maximus* L.). Fish Shellfish Immunol 84: 56–61.

Yang K, Song H, Shi X, Ru J, Tan S, Teng Z, Sun S (2022) Preparation of a polysaccharide adjuvant and its application in the production of a Foot-and-Mouth disease virus-like particles vaccine. Biochem Eng J 184: 108479.

Yang Y, Teng Z, Lu Y, Luo X, Mu S, Ru J, Sun S (2021) Enhanced immunogenicity of foot and mouth disease DNA vaccine delivered by PLGA nanoparticles combined with cytokine adjuvants. Res Vet Sci 136: 89–96.

Yendo C, de Costa F, Cibulski S (2016) A rabies vaccine adjuvanted with saponins from leaves of the soap tree (*Quillaja brasiliensis*) induces specific immune responses and protects against lethal challenge. Vaccine 34(20): 2305–2311.

Yi H, Yu Z, Wang Q, Sun Y, Peng J, Cai Y, Wang H (2022) *Panax notoginseng* saponins suppress type 2 porcine reproductive and respiratory syndrome virus replication *in vitro* and enhance the immune effect of the live vaccine JXA1-R in piglets. Front Vet Sci 9: 886058.

Yuan L, Wang Y, Li Z, Ma X, Cui X, Chi X, Xu W, Hu S (2020b) Sunflower seed oil containing ginseng stem–leaf saponins (E515-D) is a safe adjuvant for Newcastle disease vaccine. Poult Sci 99(10): 4795–803.

Yuan L, Wang Y, Ma X, Cui X, Lu M, Guan R, Hu S (2020a) Sunflower seed oil combined with ginseng stem-leaf saponins as an adjuvant to enhance the immune response elicited by Newcastle disease vaccine in chickens. Vaccine 38(33): 5343–5354.

Zhang C, Xu W, Chen J, Guan R, Bi S, Jin H, Cui X, Shi F, Hu S (2018) Soybean oil containing ginseng saponins as adjuvants promotes production of cytokines and enhances immune responses to foot-and-mouth disease vaccine. Microbiol Immunol 62(3): 187–194.

Zhu D, Tuo W (2016) QS-21: A potent vaccine adjuvant. Nat Prod Res 3(4): e113.

AUTHOR CONTRIBUTION:

Contribution	Domínguez-Odio A	Pérez O	Batista-Duharte A	Cala-Delgado DL
Concepts or ideas	x	x	x	x
Design	x	x	x	x
Definition of intellectual content	x	x	x	x
Literature search	x	x	x	x
Experimental studies	x	x	x	x
Data acquisition	x	x	x	x
Data analysis	x	x	x	x
Statistical analysis	x	x	x	x
Manuscript preparation	x	x	x	x
Manuscript editing	x	x	x	x
Manuscript review	x	x	x	x

Citation Format: Domínguez-Odio A, Pérez O, Batista-Duharte A, Cala-Delgado DL (2022) Technology surveillance in veterinary vaccine adjuvants (2015-2022): University-industry interaction. J Pharm Pharmacogn Res 10(5): 875–887. https://doi.org/10.56499/jppres22.1430_10.5.875