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Review Article

Current Scenario and Potential Challenges to Vaccination Approach in Animals: An Insight into Animal Immunization

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Abstract

Infectious diseases are responsible for debilitating livestock production causing substantial economic losses to agricultural sector throughout the globe. Conventional disease control strategies being fruitful, have managed the situation to a larger extent however, limitations to traditional control methods paved way for advancing techniques as alternative strategies. As advancement in medical field, immunization remains a developing sphere responsible for alleviation of negative effects of fatal diseases. The formulations containing pathogenic substances are capable of providing immunity for lifetime that has revolutionized the concept of immunization. Vaccination has emerged as a standard method for controlling disease and further turned out to be an essential approach to deter disease development. It has been reported to be responsible for high production of livestock which would not have been achieved otherwise. Nonetheless, these approaches still have significant disadvantages, providing a window to include advanced techniques in this area thereby directing the search for vaccine production grounded on a protective recombinant protein. The development of recombinant subunit vaccine is one of the approaches marked as an innovative control strategy alternative to conventional vaccines receiving support from growing scientific studies. To further, their effectiveness is yet to be explored so the need of an hour is to investigate additional strategies for enhancing recombinant vaccine efficacy in commercial settings.

INTRODUCTION

Livestock production plays a pivotal role in the socioeconomic development of an agrarian province and provides livelihood to a huge population of the globe. This vibrant sector generates 40% of agricultural output globally, supporting livelihoods and food security of nearly 1.3 billion people, according to Food and Agriculture Organization [1]. The global demand for value-added livestock products is increasing in line with the growing human population worldwide [2]. It is estimated that there is significant opportunity to enhance livestock practices for sustainability, equity, and reduced risk to animal and human health. Furthermore, diseases have a profound impact on this economically significant sector, leading to substantial losses and impeding progress thereby need to be tackled for sustainable productivity of this major agricultural sub-sector.

Animal health and welfare are seriously threatened by infectious diseases, which must be effectively controlled to protect agronomic health, ensure food security, and reduce poverty in rural areas. Although disease control strategies have advanced with advancement in novel techniques; however, limitations follow the technological development like a shadow [3]. The global livestock industry would not have reached the stage that it is holding today without the use of chemical drugs made available to curb the spread of fatal diseases. Nonetheless, emergence of drug resistance along with drug residue issues have generated concerns about their continuity and paved way for more advanced approaches in the field of disease prevention [4]. Immunization approach is a gold standard in animal production through enhancement of the productivity via immunity stimulation as there occurs the generation of specific antibodies responsible for deterring parasite development. Vaccination, being carried out for centuries has emerged as an essential cost-effective medical technology, and immunization of birds by using live vaccines has turned out to be a standard method for disease control [5].

Conventional vaccines comprise of two types of live vaccines; attenuated and unattenuated with attenuated vaccines having reduced pathogenicity requiring multiple administrations, and unattenuated being potentially pathogenic while inducing long-lasting protective

immunity [6]. The complex interactions between the immune system and the components of a particular vaccine result in an immune response crucial for understanding the effectiveness and safety of the vaccine. The administration of vaccine leads to a series of responses involving at first the presentation of specific vaccine molecules, the antigens to immune cells such as macrophages and dendritic cells that detect the presence of antigens in the vaccine. These immune cells represent innate immune system, the first line of defense, activated immediately after vaccination and are involved in producing signaling molecules termed cytokines. Although the introduction of vaccines to control diseases is a truly landmark contribution to animal science, however live vaccines have significant troubles associated with their production, application and efficiency. To combat diseases, administration of live vaccines is one of the most feasible and sustainable strategies inducing both cellular and humoral immune responses [7], however; some practical disadvantages still exist including the substantial risk of reactivation of the attenuated form of microorganism along with production of medical complications following the development of severe reaction in recipient animals. Additionally, development of live attenuated vaccines is expensive and raises concerns along cost-benefit lines; moreover, conventional vaccines require multiple administrations in order to induce basic immunity [8]. Yet another aspect of modern technology that somehow eliminated the glitches associated with traditional vaccines are DNA vaccines, containing the gene for specific protective proteins responsible for eliciting an immune response against particular disease-causing entity. Following the discovery of parasite life-cycle stages capable of inducing protective immunity, recombinant vaccines represent a more modern approach to immunization strategy [4].

Trends and Advances in vaccination approach

The prevalence of diseases in animals varies widely, encompassing bacterial infections such as Brucellosis, viral diseases like Foot-and-Mouth Disease (FMD), and protozoal infections such as Coccidiosis. Historically, these diseases have raised significant concerns, profoundly impacting livestock, wildlife, and companion animals alike. The implementation of vaccination strategies has proven essential in managing the spread of infectious diseases within animal populations. A paradigm shift towards disease prevention as opposed to solely treatment has led to the eradication of several diseases, with immunization serving as a proactive approach to mitigate the occurrence of various animal ailments. Vaccines play a crucial role in reducing the severity of illnesses and limiting their transmission, particularly in cases where outbreaks have already begun. Furthermore, the effectiveness of vaccination programs is heavily dependent on the type and quality of available vaccines. The development of vaccines utilizes various methods grounded in a comprehensive understanding of parasite biology and pathology.

Vaccine development for bacteria-causing disease

Brucellosis, a zoonotic disease, caused by facultative intracellular bacterial species belonging to genus Brucella, is a hindrance to animal production worldwide [9]. Brucellosis continues to pose a significant challenge for both livestock and human health on a global scale. There is a pressing need for the development of improved vaccines to enhance protection and diminish the incidence of this disease. The vaccines formulated for the prevention of this infectious disease are primarily live attenuated vaccines, generated through the modification of wild-type bacteria. It is critical to emphasize that these vaccines are contraindicated for administration to pregnant females due to the potential risk of abortion. Furthermore, there exist significant safety concerns, as vaccinated animals may serve as a vector for the transmission of the infection to humans upon consumption [10].

At present, three vaccines are employed worldwide for the prevention of brucellosis. The rough B. abortus mutant, designated RB51, is administered to cattle. Additionally, the smooth vaccine B. abortus S19 is also utilized for immunization in cattle. Furthermore, the smooth vaccine B. melitensis Rev. 1 is specifically designated for use in goats and sheep [11]. Subunit vaccines for brucellosis have not consistently achieved the levels of immunity that live vaccines provide. Nevertheless, subunit vaccines offer notable advantages, including the reduction of side effects commonly associated with live vaccines and the enhancement of serological surveillance in vaccinated livestock. Furthermore, these vaccines have the potential to address multiple Brucella species due to the high conservation of their proteins. Despite extensive research and development efforts, a successful subunit vaccine for brucellosis has yet to be realized.

Current vaccinations for livestock demonstrate an efficacy of approximately 70%. As such, there exists a pressing necessity for the formulation of more effective vaccines to comprehensively address brucellosis in livestock, which serves as the principal reservoir of infection. The advancement of such vaccines is reliant on a more profound understanding of the pathogenesis of Brucella, particularly in animal species that exhibit natural susceptibility to these infections [12].

Vaccine development for virus-causing diseases

In the early 19th century, one of the foremost advancements in veterinary medicine was the development of a vaccine for Foot-and-Mouth Disease (FMD), a highly contagious viral disease of considerable economic significance that affects both domestic and wild ruminants [13-15]. This disease is attributed to a virus classified within the genus Aphthovirus of the Picornaviridae family, which encompasses seven genetically and antigenically distinct serotypes: O, A, C, Asia 1, and the Southern African Territories (SAT) 1, 2, and 3. The inactivated whole virus vaccine for FMD has been widely implemented on a global scale. This whole-organism vaccination approach is particularly prominent in contexts where the pathogen can be cultivated via in vitro methodologies. The vaccine is produced through the processes of viral culture and subsequent chemical inactivation, with the incorporation of adjuvants to augment its efficacy [14]. Recognizing that the immune response elicited by each serotype is specific, vaccine formulations typically include a combination of various serotypes, meticulously adapted to the prevailing epidemiological conditions; thus, diverse combinations of serotypes are employed worldwide [15,16].

Despite the global advancements in these vaccine formulations, certain limitations pertaining to multivalent vaccines have been delineated. These limitations include the requirement for a biosafety level III facility for the large-scale synthesis of viral antigens, challenges associated with thermolability, and a constrained duration of immunity [17]. In response to the challenges associated with inactivated whole virus vaccines, a range of alternative strategies has been explored. Notably, the production of modified viruses presents potential solutions; however, this method continues to exhibit certain inadequacies that necessitate further examination of viable alternatives [15].

DNA Vaccines

The DNA vaccine strategy employs a plasmid incorporating viral genes that are transcribed into mRNA, which subsequently undergoes translation into proteins that elicit both cellular and humoral immune responses following recognition by the host's immune system. The method of naked DNA immunization in animals utilizing protective viral antigens constitutes a profoundly promising avenue for the advancement of viral vaccines. This approach mitigates safety concerns while facilitating the induction of cytotoxic T cells through intracellular antigen expression [18,19]. DNA vaccines, which encompass sequences derived from the FMD virus, have exhibited efficacy in generating protective immunity and confer numerous advantages, including the integration of marker genes, enhanced thermostability, substantial stability for extended storage durations, the rapid incorporation of multiple viral strain or serotype gene sequences, and the capability for production without the necessity of a biosafety level III containment facility.

Nevertheless, it is essential to recognize several shortcomings associated with DNA vaccines. These vaccines generally elicit a short-term and limited antibody response, necessitating multiple doses along with the incorporation of adjuvants and cytokines to effectively stimulate the immune response [15].

Vaccine development for protozoan-causing diseases

Coccidiosis has been reported as the second most prevalent major livestock diseases in 2018 after Foot & Mouth Disease (FMD) and third disease with higher mortality rate after Ranikhet Disease (NCD) and Chronic Respiratory Disease (CRD) in India [20]. Anticoccidial products have attained global approval for application in the management of poultry health. Preventive measures predominantly involve the prolonged and continuous administration of compounds exhibiting coccidiostatic properties, thereby effectively disrupting the life cycle of the parasite and mitigating its transmission. In the context of commercial chicken production, the management of avian coccidiosis principally relies on routine chemoprophylaxis. Nonetheless, the emergence of drug-resistant strains has engendered considerable apprehension regarding the effectiveness of these control strategies.

Eimeria sporozoites are characterized by a high degree of immunogenicity, rendering them significant targets for the elicitation of protective immune responses which results in their constrained development within immune chicken as outlined by Murray [21]. As a result, vaccination has emerged as a pivotal strategy for disease control [22]. The use of live vaccines for avian immunization, a concept initially proposed by Johnson [23], has since emerged as a standard methodology. The first commercial live coccidiosis vaccine, CocciVac®, was launched in 1952, containing a mixture of oocysts administered to birds at around ten days old [24]. Since then, extensive developments have resulted in various types of vaccines [25]. In the endeavor to mitigate coccidiosis, vaccination is acknowledged as a viable and sustainable approach; however, the implementation of live vaccines encompasses significant challenges, particularly the potential reactivation of pathogenic strains [26]. Eimeria parasites exhibit both host and site specificity within the host's intestine and the immune response to coccidial infections is highly species-specific,

necessitating the inclusion of multiple strains in effective vaccine development. The aforementioned considerations, coupled with the inherent complexities associated with the utilization of live vaccines, have engendered valid concerns regarding the overall efficacy of vaccination strategies aimed at combating coccidiosis. Consequently, there is an emerging focus on the development of vaccines predicated on protective recombinant proteins as a progressive and innovative control strategy [27,28]. Since the initial documentation of recombinant vaccine development in the 1980s, substantial variety of potential antigens has been specified [29]. The concept of recombinant subunit vaccine development was derived from the acknowledgment that distinct developmental stages within the life cycle of parasites possess immunogenic attributes that confer protective immunity [30,31]. The motile stages of Eimeria parasites, namely sporozoites and merozoites, are characterized by the presence of microneme proteins on the surface of apical organelles, a distinctive feature of apicomplexan parasites. These proteins are integral to the mechanisms of host cell adhesion and invasion, facilitating the efficient internalization of sporozoites into the intestinal epithelial cells of the host [32,33]. In the pursuit of developing a prophylactic vaccine, leveraging active immunity to neutralize invasion proteins in advance is a logical approach aimed at preventing parasite internalization. Recent advancements in recombinant DNA technology have facilitated the development of sophisticated methodologies for the production of subunit vaccines. These vaccines incorporate recombinant proteins or antigenic determinants derived from various developmental stages of the Eimeria parasite. The antigens derived from sporozoites or merozoites have garnered significant interest as potential vaccine candidates, owing to the conserved characteristics of their epitopes across various species [34,35]. The identification of antigen-encoding genes that invoke specific immune responses is of considerable importance. Numerous DNA sequences encoding proteins that stimulate immunity have been discovered across various developmental stages of Eimeria species [36,37].

The cloning and expression of the Eimeria Tenella Microneme-1 gene (EtMIC1), derived from an outbreak sample, have been documented in research evaluating its viability as a subunit vaccine for poultry [38]. The study indicates that recombinant EtMIC1 can enhance protective immunity against coccidiosis by increasing antibody levels and activating both humoral and cell-mediated immune responses. Furthermore, E. tenella microneme-2 (EtMIC2) EtMIC4 has also emerged as a promising vaccine candidate, capable of providing protective immunity in immunized birds [39]. The sporozoite cell-membrane protein known as Immune mapped protein 1 (IMP1) has emerged as a potential vaccine candidate, demonstrating the capability to provide protective immunity [40]. A substantial variety of proteins have been recognized for their capacity to confer protection against challenges posed by coccidiosis including apical membrane antigen 1 (AMA1), antigens with molecular weights of 14 kDa, 30 kDa, and 230 kDa, along with additional antigens of 56 kDa and 82 kDa, surface protein TA4 rhomboid-like protease, SO7, and lactate dehydrogenase [41]. To augment the efficacy of vaccination initiatives necessitates the incorporation of adjuvants, specifically non-antibiotic immunomodulators such as cytokines and antimicrobial peptides [5]. Research has indicated that the administration of chicken cytokine or chemokine genes in conjunction with the EtMIC2 protein vaccine results in a statistically significant enhancement of protective efficacy when compared to the administration of the EtMIC2 protein in isolation [39]. Furthermore, the strategic combination of EtMIC1 and EtMIC2 with interleukins, specifically IL-8 and IL-16, as well as transforming growth factor-β4 and lymphotactin, has been demonstrated to effectively induce both humoral and cell-mediated immune responses during coccidiosis infection [38-42].

A multitude of parasitic antigens have been identified as prospective candidates for the development of recombinant vaccines. Nevertheless, the intricate genomic nature of Eimeria species poses significant challenges in the assessment of these antigens. Subunit vaccines, designed to elicit a protective immune response, utilize only select components of the infectious agent. As a result, the attainment of a substantial immunological response typically necessitates multiple doses in conjunction with the administration of adjuvants. The incorporation of adjuvants as immunostimulatory agents has become an established standard for enhancing the immunogenicity of recombinant vaccines. Furthermore, within commercial contexts, the efficacy of recombinant anticoccidial vaccines remains inadequately explored. Thus, there exists an imperative to investigate additional strategies that may augment the effectiveness of these vaccines [42,43].

AUTHORSHIP CONTRIBUTION

Shagufta Iqbal: Writing – original draft; Data curation; Software; Conceptualization.

Syed Tanveer: Writing – review and editing; Supervision.

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