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Efficacy of Hemagglutinin Gene of Highly Pathogenic Avian Influenza as a Vaccine Candidate in Poultry: A Review

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ABSTRACT

The most prevalent fatal disease in poultry that can result in high morbidity and mortality is highly pathogenic avian influenza (HPAI), subtype H5N1. A vaccination program is the most frequent way to prevent HPAI cases in poultry, especially against the H5 subtype of HPAI. There are currently a number of avian influenza vaccines available, including recombinant and inactivated whole virus vaccines. The foundation of a recombinant vaccine is possible by the expression of an avian influenza gene of interest following insertion into a carrier vector (no pathogenic virus). A recombinant HPAI vaccine is required to further challenge avian influenza cases in poultry. As a recombinant vaccine inserted into a carrier vector, the hemagglutinin (HA) gene has proven effective. The recombinant Herpes Virus Turkey (rHVT) vector vaccine for avian influenza has been discovered and is commercially available. The rHVT vaccine was developed using a hemagglutinin insert from the HPAI virus clade 2.2. Overall, studies in this review aimed to determine the efficacy of any developed recombinant avian influenza vaccine that uses the HA gene from different clades challenged with any avian influenza virus (AIV) isolate. It was found that the efficacy of hemagglutinin as a recombinant vaccine could be promising for future HPAI vaccine development. In addition, it is possible to design a recombinant vaccine using local isolates to protect poultry farms, particularly in endemic regions.

Keywords: Avian influenza, Efficacy, Hemagglutinin, Poultry, Recombinant vaccine

INTRODUCTION

Due to the high mortality rate from highly pathogenic strains in poultry and the possibility of zoonotic transmission made by the spread of domestic poultry species, avian influenza (AI) poses a significant threat to the entire world, especially in the poultry industry (Suttie et al., 2019; El-Shall et al., 2021). Numerous highly pathogenic avian influenza (HPAI) outbreaks have occurred since 1996, resulting in significant losses in Southeast Asia, the Middle East, Europe, and Africa (Balzli et al., 2018). The majority of HPAI viruses of subtypes H5 and H7 evolved from low pathogenic H5 and H7, resulting in significant mortality and economic losses in poultry (OIE, 2021). One of the most significant HPAI outbreaks is a subtype of H5N1. These H5N1 viruses have spread to several nations and become endemic, including China, Indonesia, Vietnam, and Egypt (FAO, 2011). Mass culling is no longer acceptable in developing countries, according to the World Organization for Animal Health (OIE) and the United Nations Food and Agricultural Organization (FAO), for ethical, ecological, and economic reasons (Peyre et al., 2008). Restricting bird migration, enhancing biosecurity, and starting a vaccination campaign are all necessary for controlling AI in endemic countries (Nassif et al., 2020).

Vaccination has been recommended as an AI eradication or control program strategy in endemic countries (Hsu et al., 2014). It is a powerful combination when combined with good biosecurity and monitoring programs (Kapczynski et al., 2015). The antigens in vaccines should be sufficient to produce a protective level of antibody titer (vaccine potency). The vaccine must protect the bird against virus infection (Vaccine efficacy) and be properly administered to a large proportion of the susceptible population (Swayne and Kapczynski, 2008). In different countries, inactivated vaccinations have been used to limit the spread of highly dangerous H5 and H7 avian influenza viruses (Qiao et al., 2009). In fact, the parental route is the only way to administer inactivated vaccines individually, which is laborious, time-consuming, and puts the vaccination crews at risk of spreading the field virus (Rauw et al., 2011).

In order to make sure that inactivated vaccines are still effective against field virus strains that are currently circulating, their efficacy should be routinely evaluated. The effectiveness of inactivated vaccines is primarily determined by the vaccine properties, passive immunity's presence or absence, and the targeted host's age (Rauw et al.,

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2011; Kapczynski et al., 2016). However, due to inadequate protection and weak flock immunity, AI vaccination had only a limited impact on domestic poultry (Peyre et al., 2009). In addition, there have been numerous reports of HPAI vaccination failures in the commercial broiler, layer, and breeder flocks (Swayne et al., 2015). This happened because the immune systems of the immunized poultry population were compromised, favoring viral mutation and antigenic drift field viruses from the vaccine strain (Kilany et al., 2015). The ideal AI vaccine should be effective, safe, only require one dose, be affordable, and make it possible to distinguish between infected and vaccinated animals (Bertran et al., 2015).

AIV vaccines can be classified into two broad technological groups in field usage; there are inactivated whole AIV vaccine and recombinant vectored AI vaccine expressed HA protein (Capua and Alexander, 2008; Swayne, 2009). To combat current threats of H5N1 infection in the poultry industry, a recombinant Herpes Virus of Turkey (rHVT) vaccine was recently created. This vaccine expresses the HA gene of an HPAI H5N1 strain (Soejoedono et al., 2012). The rHVT could be a good candidate for a recombinant vaccine-based viral vector that meets most of the criteria for an ideal AI vaccine (Reemers et al., 2021). Furthermore, the studies in this review were aimed to determine the efficacy of developed recombinant avian influenza vaccine that uses the HA gene from clade 2.2 challenged with any AIV isolate. Therefore, the present review article focused on the efficacy of the hemagglutinin gene as a vaccine candidate in a poultry clinical trial.

Role of hemagglutinin

Avian influenza virus is made up of eight single-stranded negative-sense RNA segments, each of which codes for one or more viral proteins. The antigenic characteristics of the hemagglutinin (HA) and neuraminidase (NA) glycoproteins determine the specificity of the AI subtype (Wibowo et al., 2015). It is currently known that there are eleven NA and 18 HA subtypes in the AI virus (N1-N11). Subtypes H1-H16 and N1-N9 are mainly found in avian species. The only viruses known to cause HPAI are viruses of the H5 and H7 subtypes although not all of these subtypes possess these characteristics (Alexander, 2000). As a prerequisite for host restriction and pathogenicity, the HA protein binds to sialic acid receptors on the surface of host cells to begin viral infection (Suttie et al., 2019). The HA is a major envelope glycoprotein with the potential for vaccine development. A subunit vaccine against H5N1 infection has been developed using recombinant HA (rHA) proteins. The rHA vaccine approach is an appealing vaccine manufacturing option. It eliminates the need for H5N1 influenza virus vaccine production based on eggs or cells (Lin et al., 2011). Protection is primarily due to a humoral immune response against HA and secondarily against NA. However, such protective responses are only subtype-specific (Swayne, 2009).

By binding to the cellular receptor sialic acid and assisting in the fusion of the viral and host membranes, the surface glycoprotein HA is in charge of identifying the target cell and facilitating viral genome entry into the target cell. A homotrimeric precursor known as HA is produced by the viral genome's fourth segment (HA0, Schrauwen et al., 2012). During the viral life cycle, the cleavage of HA0 into HA1 and HA2 subunits by host cell protease is essential for viral infection. The HA2 subunit promotes membrane fusion, while the HA1 subunit binds to the cellular receptor sialic acid (Wang et al., 2019). The nucleocapsid can be released into the cytoplasm to begin viral replication with the viral envelope and endosomal membrane fused at low pH. This is made possible by the significant conformational changes that HA experiences inside the endosome (Wu et al., 2012). The HA1 subunit can be identified by its membrane-distal globular head domain, which contains the receptor-binding site (RBS), while the HA2 subunit can be identified by its membrane-proximal stem region (Yamada et al., 2006). The majority of highly potent neutralizing antibodies induced by viral infection and vaccine immunization target the globular head domain of HA1 (Wang et al., 2019). These antibodies are generally strain or clade-specific because of the high variability of their HA1 epitope residues. Therefore, the antibodies formed against the HA protein are potent neutralizing antibodies that slow disease progression and prevent viral infection (Chiu et al., 2015).

Efficacy of rHA from clade 2.2 challenged against different isolate

During the HPAI challenge, effective AIV vaccinations have been shown to reduce virus shedding from birds' respiratory and gastrointestinal tracts and protect against morbidity and mortality (Criado et al., 2019). The Herpes Virus of Turkey (HVT) might be a good candidate for an AI vector vaccine since it meets the most optimal AI vaccine criteria. HVT may be used in the hatchery either *in ovo* or subcutaneously, and it has previously been commercially used as a vector vaccine worldwide (Reemers et al., 2021). The rHVT vaccine was created using a genetic insert derived from the HA gene of the clade 2.2 HPAI virus A/swan/Hungary/4999/2006, which is expressed for a protracted amount of time by HVT (Balzli et al., 2018). Using a live viral system that can remain in the host while expressing the targeted insert for immune modulation triggers a cellular and humoral immune response, which are the advantages of the rHVT vaccine technology over inactivated whole vaccines (Kapczynski et al., 2015). The higher homology between the H5 present in the rHVT-H5 and the inactivated H5N1 vaccines may cause the better effect seen in rHVT with the H5 insert gene (Rauw et al., 2012).

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However, some challenge studies must be conducted to determine the vaccine efficacy. It will be beneficial to conduct a clinical trial with challenges against various isolates to determine the vaccine's level of protection (Swayne et al., 2015). Considering the current review studies, the rHA vaccine uses HVT as a viral vector and has different protectivity with challenge strains from different clades described in Table 1. On specific pathogen free (SPF) Chicken, rHVT show different protectivity indicated by survival rate result. The survival rate was fully protected, explaining that no dead chickens were in the trial group vaccinated against rHVT on the first day of age and challenged with different isolates. Meanwhile, rHVT is fully effective in protecting SPF chickens from a challenged pathogenic isolate from America, Mongolia, Bangladesh, Egypt, Turkey, and Germany (Table 1). Another trial from the studies indicated that rHVT is not fully protected in SPF Chicken against challenge pathogenic isolate (Soejoedono et al., 2012; Nassif et al., 2020). As a result, many chickens died after exposure to pathogenic isolates from Asia. A few were from Egypt and Indonesia (West Java-Subang, Purwakarta-Cilingga). It demonstrates that when tested against isolates from Asian strains, the isolates used in rHVT are not entirely protective. This refers to the homology characteristics of the hemagglutinin gene of the clade 2.2 strain with isolates of other pathogenic strains and different clades. Further genomic analysis is needed regarding the gene alignment of the various isolates and whether they have significant differences.

In addition to offering excellent clinical protection against antigenically drifted H5Nx HPAI strains, the rHVT-H5 vaccine can potentially pose a significant challenge to the suppression of virus shedding (Nassif et al., 2020). Vaccine efficacy failure in the field is typically attributed to the antigenic distances between the vaccine and the circulating field strains (Swayne et al., 2015; Peeters et al., 2017). It is well known that maternal derived antibodies (MDA) prevent the development of protective immunity after vaccination (Vriese et al., 2010). The cell-associated rHVT-H5 vaccine creates a pathway inside lymphocytes that may promote cell-mediated immunity. Along with the humoral response, this cell-associated immune response is thought to be insensitive to MDA interference with the HVT virus. After using inactivated vaccines, MDA has been observed to interfere with eliciting an immune response against various antigens. On the other hand, commercial day-old chickens (DOC) have MDA against HVT. If given a sufficient dose, these antibodies do not revoke protection but may reduce the efficacy of cell-associated HVT vaccines (King et al., 1981; Poetri et al., 2011; Kilany et al., 2015). Additionally, rHVT vaccination induces long-lasting immunity because the antigen is continuously expressed (Reddy et al., 1996).

Table 1. Summary of efficacy Hemagglutinin HPAI H5N1 Clade 2.2 strain A/swan/ Hungary/4999/2006 challenged with different HPAI isolates and vaccinated using vector rHVT on the first day of chick

References	Challenge strain	Animal Test	Virus given	Virus (EID/50)	Survival rate (%)	Control (%)
(Balzli et al., 2018)	A/turkey/Minnesota/12582/2015	SPF	4 wpv	1 x $10^{7.5}$	100	0
(Kwon et al., 2021)	A/chicken/Bangladesh/NRL-AI-3237/2017	SPF	4 wpv	1 X 10^{6}	100	0
(Rauw et al., 2011)	A/Chicken/Egypt/1709-6/2008	SPF	3 wpv	1 X 10^{6}	100	0
(Reemers et al., 2021)	A/turkey/Turkey/01/2005	SPF	3 wpv	1 x 10^{6}	100	0
(Steensels et al., 2016)	A/turkey/Germany- MV/R2472/2014	SPF	4 wpv	1 x 10^{6}	100	0
(Kapczynski et al., 2015)	A/Whooper Swan/Mongolia/3/2005 A/chicken/West Java Sbg/29/2007	SPF Com	6 wpv 4 wpv	1 X 10^{6}	100 80	0
(Soejoedono et al., 2012)	A/CK/WJava-Subang/029/ 2007 A/CK/Purwakarta-Cilingga/142/2010	SPF	4 wpv	1 X 10^{6}	80 95	0
(Nassif et al., 2020)	A/chicken/Egypt/173CAL/2017 A/duck/Egypt/VG1099/2018 A/chicken/Egypt/FL6/2018	SPF	4 wpv	1 X 10^{6}	90 90 80	0
(El-Shall et al., 2021)	A/chicken/Egypt/Alex-2/2017	Com	3 wpv	1 x $10^{6.3}$	50	0
(Kilany et al., 2015)	A/Chicken/Egypt/128S/2012	Com	3 wpv	1 X 10^{6}	80	nr

*SPF: Specific pathogen-free, Com: Commercial broiler, wpv: Weeks post vaccination, EID: Egg infective dose, nr: Not reported

Serology test result and viral shedding of rHA vaccine

Measuring the humoral response to hemagglutinin, the main surface glycoprotein of the influenza virus, is the primary method for assessing the efficacy of AI vaccines. The strain-specific hemagglutination inhibition (HI) test is the gold standard for determining AI immunity response (Swayne et al., 2015). The HI antibody level thought to be the cut-off for susceptibility for the whole-virus inactivated vaccine is 4 log 2 (Qiao et al., 2009). To combat infection with particular AI strains, specific antibody titers are required. Although many vaccinated survivors also have low levels of HI antibodies, the bird that died from infection had low HI antibody titers on pre-challenged chickens. This suggests that

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the HI antibody titer to the required viral challenge is greater than 4 log 2. It might provide protection for antigenic variants and be a reliable indicator of survival (Ross et al., 2019).

The discrepancy between the achieved high protection level and the lower serologic response than a predicted protective level of HI titers observed in many studies can be explained by the rHVT-H5 vaccine's inability to induce strong specific cell-mediated immunity in the immunized chickens (Rauw et al., 2011; Criado et al., 2019; Nassif et al., 2020). According to studies, the rHVT-H5 vaccine induces a humoral and cell-mediated immune response (Kilany et al., 2014; Kapczynski et al., 2015). When antibody titers to the challenge virus strains are lower than to the vaccine virus strain, this indirectly indicates the antigenic distances between the vaccine and challenge strain (Palya et al., 2016). The summary of HI titers results from experimental vaccination with recombinant hemagglutinin (rHA) vaccine is shown in Table 2.

One-day-old chicken that had received the rHVT-H5 vaccine had significantly less viral excretion during the initial stages of infection via the oropharyngeal and cloacal routes. As a result, there was significantly less viral shedding in vaccinated chickens that were producing specific antibodies than in negative controls. Vaccinated chicks were seen to shed early after infection with high-challenge doses, especially by the respiratory tract. This was observed in both vaccinated and unvaccinated chicks. In addition to this, the effect of the dose became clear (Steensels et al., 2016). In addition, the continued development of a vaccine based on hemagglutinin has the potential to lessen the amount of virus that is shed following exposure to the virus. Vaccinated chicks were found to have significantly less viral shedding than unvaccinated chicks when exposed to high-challenge doses (Kwon et al., 2021).

Table 2. Summary of serology tests and viral shedding from rHA-based vaccine in specific pathogen-free and commercial chickens

References	HI ANTIGEN	GMT HI Pre (Log_2)	GMT HI Post (Log_2)	Swab Collected	Oral swab	Cloacal swab
(Soejoedono et al., 2012)	Vaccine	7.14	nr	2, 4, 7 dpc	7 dpc (+)	7 dpc (+)
(Nassif et al., 2020)	Vaccine	5.1	6	3, 7, 10 dpc	10 dpc (+)	10 dpc (+)
(Balzli et al., 2018)	Vaccine	6	9	2, 4 dpc	4 dpc (+)	4 dpc (+)
(Kwon et al., 2021)	Challenge	6	10	2, 4 dpc	4 dpc (+)	4 dpc (+)
(Rauw et al., 2011)	Vaccine	4	9	3, 7 dpc	7 dpc (+)	nr
(Reemers et al., 2021)	Challenge	4.6	8.6	4, 7, 14 dpc	14 dpc (+)	14 dpc (-)
(Steensels et al., 2016)	Vaccine	4.5	8.5	2, 5, 9, 14 dpc	14 dpc (+)	14 dpc (-)
(Kapczynski et al., 2015)	Challenge	5.1 5.5	6.4 8	2, 4 dpc	4 dpc (-) 4 dpc (+)	4 dpc (-) 4 dpc (+)
(El-Shall et al., 2021)	Vaccine	3	6	3, 5, 7 dpc	7 dpc (+)	7 dpc (+)
(Kilany et al., 2015)	Vaccine	Nr	4.4	3, 6, 9, 14 dpc	14 dpc (-)	14 dpc (-)

*HI: Hemagglutination inhibition, GMT: Geometric mean titer, dpc: Days post challenge, (+): Positive, (-): Negative, nr: Not reported

CONCLUSION

It has been demonstrated that the effectiveness of hemagglutinin in avian influenza as a vaccine candidate against various isolates has a high level of protective efficacy. The survival rate, the antibody titer level, and the amount of viral shedding can measure this level of efficacy. The method for developing a recombinant vaccine is a commonly used viral vector with HVT. The conclusion that can be drawn from this is that the development of an avian influenza recombinant vaccine could use any homologous isolate with the virus challenge strain in an area and give cross-protection among the various types of AIV. The vaccine will have good protectivity and inhibit viral shedding if the clade or isolate for recombinant vaccine is homologous. The developing recombinant vaccine used the HA strain identically as a vaccine and produced in vector expression to provide poultry with constant protection against virus mutation in the field. Further studies about universal clade based on ethnicity are needed to find acceptable prevention against different types of avian influenza.

DECLARATIONS

Data availability and material

All information pertaining to the review study is presented in the article.

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Authors' contribution

Armanda Dwi Prayugo initiated the manuscript drafting and production of the final draft. Both authors (Toto Subroto and Wyanda Arnafia) contributed to conceptualizing the idea, editing, and production of the final draft. All authors checked the last draft of the manuscript and confirmed it before submission to the journal.

Competing interests

No conflicts of interest are disclosed by the authors of this review.

Ethical consideration

Plagiarism, lack of consent to publish, misconduct, fabrication and/or falsification of data, duplicate publication and/or submission, and redundant information were all investigated by the authors.

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