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Review

Vaccine efficacy against Indonesian Highly Pathogenic Avian Influenza H5N1: systematic review and meta-analysis

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ABSTRACT

Indonesia has implemented multiple strategies to control Highly Pathogenic Avian Influenza H5N1 (HPAI/H5N1), including the licensure and use of multiple vaccine formulations. The continuous drift of Indonesian HPAI/H5N1 viruses and emergence of a new clade in 2012 that became dominant in 2016, demands the assessment of commercial vaccine formulations against Indonesian field viruses.

Seven databases were explored to identify relevant literature reporting performance of commercial vaccines against Indonesian HPAI/H5N1 viruses. After methodological assessment, data were collated and analyzed to report immunogenicity and vaccine efficacy (VE) to prevent respiratory and cloacal viral shedding 2-day post challenge, and death at the end of the follow-up period. Meta-analyses were performed to assess VE consistency of alternative formulations and to explore sources of heterogeneity in VE.

In total, 65 studies and 46 vaccine formulations from 13 articles were grouped per OIE's VE protocols (group 1) and variations of it (groups 2,3,4). We found that concurrence of vaccine-seed and challenge-viruses in a clade designation might be a better proxy of VE than current estimates based on vaccine-homologous HI antibody titers, particularly against current fourth order clade viruses (groups 1&2). Prime-boosting was efficacious across different chicken breeds (group 3), and early vaccination may increase the risk of death (group 4). One Indonesian vaccine was tested against the new dominant clade, conferring consistent protection in chickens but not in ducks. Meta-analyses revealed high inconsistency ($I^2 \geq 75\%$) and inefficacy of LPAI formulations against current field viruses, while potential sources of inconsistent VE were formulation of seed-homologous vaccines and the species vaccinated.

We conclude that the VE of commercial vaccines in Indonesia changes as Indonesian HPAI/H5N1 evolve into new clades, which should warrant continuous matching between vaccine-seeds and emerging HPAI/H5N1. Furthermore, given the characteristics of the new Indonesian dominant HPAI/H5N1 clade, further studies to confirm VE across species are warranted.

Abbreviations: A/turkey/Wisconsin/1968, Wis68; A/turkey/England/N28/1973, Eng73; A/duck/Potsdam/1402/1986, Potsdam86; A/chicken/Mexico/232/1994, Mex94; A/chicken/Legok/2003, Legok03; A/chicken/West Java/Pwt-Wij/2006, Pwt06; A/chicken/Indonesia/7/2003, Indo03; A/chicken/West Java/Smi-Hamd/2006, Smi-Hamd06; A/chicken/West Java/Smi-Mae/2008, Smi-Mae08; A/chicken/Purwakarta-Cilingga/142/2010, Cillingga10; A/chicken/Papua/TA5/2006, Papua06; A/chicken/West Java/Smi-Pat/2006, Smi-Pat06; A/chicken/West Java-Subang/029/2007, Subang07; A/duck/Sukoharjo/Bbvw-1428-9/2012, Suko12; Haemaglutinin antigen expressed in a recombinant fowlpox virus (FPV)-vectored vaccine (Trovac™ – AI H5, Merial): A/swan/Hungary/499/2006, HVTvect06; Haemaglutinin antigen expressed in a recombinant herpesvirus of turkeys (HVT)-vectored vaccine (Vectormune® HVT AI, Ceva-Biomune) A/turkey/Ireland/1378/1983, FPvect83; Reverse genetics-generated vaccines: A/goose/Guangdong/1/1996, RG-Guang96; A/duck/Vietnam/C57/2004, RG-Viet04; A/chicken/Legok/2003, RG-Legok03.

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Contents

1. Introduction

Highly Pathogenic Avian Influenza H5N1 (HPAI/H5N1) is a transmissible disease that causes substantial morbidity and mortality in chickens [1]. Although zoonotic spillover remains a rare event, the ongoing reporting of human cases [2] makes the virus of public health importance.

Initial efforts to control HPAI/H5N1 in Indonesia were based on *stamping out* [3]; but these were unsuccessful. In 2004, the Government of Indonesia adopted a vaccination program to control the spread of HPAI/H5N1 among production systems with limited biosecurity, including most free-range, backyard, and semi-commercial systems [4]. The high cost and logistic difficulties of vaccinating these poultry, led to a program reformulation in 2006–2007 shifting the emphasis to semi-commercial flocks, designated by the Food and Agriculture Organization (FAO) of the United Nations FAO as sector 3, in areas of high infection risk [5,6]. The Indonesian vaccine program was implemented by licensing multiple vaccine formulations produced overseas and by promoting the production of vaccines by local companies [6]. It has been suggested that unlicensed vaccine might have been used in Indonesia [6,7] favoring the emergence of new antigenically distinct HPAI/H5N1 clades [7].

Accurate assessment of efficacy of commercial vaccines against Indonesian circulating strains is essential, because the antigenicity of virus lineages that become enzootic tend to drift away from the original virus [8]. Per the World Organization of Animal Health (OIE) manual of Diagnostic Tests and Vaccines for Terrestrial Animals (OIE's manual) [1], the hemagglutination inhibition test (HI) is the standard for assessing immunogenicity and potential efficacy of vaccines against this agent. The OIE's manual suggests that vaccine-induced seroprotective levels equivalent to geometric mean titers (GMT) $\geq$ 32 might prevent mortality after viral infection, while antibody levels equivalent to GMT $\geq$ 128 might reduce viral replication and shedding [1]. It is relevant to note though, that vaccine immunogenicity is generally estimated using the vaccine homologous antigen [7], which may be antigenically distant to the circulating viral strain.

While HI seroprotective titer is our best proxy measure of likely vaccine efficacy (VE) [1], bridging studies demonstrating the relationship between threshold titers and clinical outcomes of importance (reduced viral shedding and mortality) are fundamental. Such studies inform strategies to reduce the economic losses caused by HPAI/H5N1 but most importantly, to reduce the threat that this agent poses for both animal and public health. Thus, following the guidelines for reporting systematic reviews in veterinary medicine [9], the objective of this work is to answer the question: *'what is the efficacy of commercial monovalent vaccine formulations administered to healthy domestic poultry against Indonesian HPAI/H5N1 in terms of immunogenicity, reduction in the number of birds shedding virus through the respiratory or cloacal routes, and protection against mortality, when compared to unvaccinated or sham vaccinated healthy domestic poultry, measured in randomized control trials, controlled trials or challenge studies?*

2. Methods

We produced a research protocol following the guidelines for reviews of interventions in animals, agriculture and veterinary medicine [10], to evaluate vaccine efficacy following the efficacy requirements in the OIE's manual [1], defined as the *'minimum HI serological titers that would protect from mortality and viral shedding'* and '*the statistically significant reduction in the number of birds shedding virus from the oropharynx or cloaca'*. Once the research question was defined, we developed the eligibility criteria. A publication was eligible for this review if: (1) it was peer-reviewed; (2) it described a primary research study; (3) it described an intervention using a commercial vaccine; (4) vaccination was applied to healthy domestic poultry; (5) VE was evaluated against an Indonesian HPAI/H5N1 virus; (6) it included a control group, and (7) it reported a study design and outcome that allowed estimation of VE, i.e. articles had to report a randomized controlled trial, controlled trial, or challenge study [11] and report either seroprotective levels after vaccination, viral shedding, or mortality after challenge [1].

Seven key databases for veterinary science, Medline (Web of Science), Medline (Ovidsp), CABI, BIOSIS, Web of Science (Core Collection), Scopus, and Embase were explored to identify relevant scientific literature published since the oldest database's record up to March, 17th, 2016 (date of last search). Search terms were divided into strings addressing population, disease, intervention, evidence of infection, and location (Table S1). Articles returned by each search string were combined to produce a list of publications for each database. Lists were imported to Endnote [12] for consolidation, de-duplication, and storage.

JVC and MC conducted independent unblinded screening of titles and abstracts without restriction of language to identify eligible articles. If title and abstract were insufficient to judge relevance, articles were retained for full text assessment. Likewise, publications with English title and abstract but written in a different language were retained and the corresponding author consulted for an English version; if this was not available, the article

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