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Maternal antibody inhibition of recombinant Newcastle disease virus vectored vaccine in a primary or booster avian influenza vaccination program of broiler chickens

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ABSTRACT

Maternally-derived antibodies (MDA) provide early protection from disease, but may interfere with active immunity in young chicks. In highly pathogenic avian influenza virus (HPAIV)-enzootic countries, broiler chickens typically have MDA to Newcastle disease virus (NDV) and H5 HPAIV, and their impact on active immunity from recombinant vectored vaccines is unclear. We assessed the effectiveness of a spray-applied recombinant NDV vaccine with H5 AIV insert (rNDV-H5) and a recombinant turkey herpesvirus (HVT) vaccine with H5 AIV insert (rHVT-H5) in commercial broilers with MDA to NDV alone (MDA:AIV^{-}NDV^{+}) or to NDV plus AIV (MDA:AIV^{+}NDV^{+}) to provide protection against homologous HPAIV challenge. In Experiment 1, chicks were spray-vaccinated with rNDV-H5 at 3 weeks (3w) and challenged at 5 weeks (5w). All sham-vaccinated progeny lacked AIV antibodies and died following challenge. In rNDV-H5 vaccine groups, AIV and NDV MDA had completely declined to non-detectable levels by vaccination, enabling rNDV-H5 spray vaccine to elicit a protective AIV antibody response by 5w, with 70–78% survival and significant reduction of virus shedding compared to shams. In Experiment 2, progeny were vaccinated with rHVT-H5 and rNDV-H5 at 1 day (1d) or 3w and challenged at 5w. All sham-vaccinated progeny lacked AIV antibodies and died following challenge. In rHVT-H5(1d) vaccine groups, irrespective of rNDV-H5(3w) boost, AIV antibodies reached protective levels pre-challenge, as all progeny survived and virus shedding significantly decreased compared to shams. In contrast, rNDV-H5-vaccinated progeny had AIV and/or NDV MDA at the time of vaccination (1d and/or 3w) and failed to develop a protective immune response by 5w, resulting in 100% mortality after challenge. Our results demonstrate that MDA to AIV had minimal impact on the effectiveness of rHVT-H5, but MDA to AIV and/or NDV at the time of vaccination can prevent development of protective immunity from a primary or booster rNDV-H5 vaccine.

Abbreviations: APMV-1, avian paramyxovirus 1; BHI, brain heart infusion; d, day old; dpc, days post-challenge; dpv, days post-vaccination; EID_{50}, mean egg infectious doses; GMT, geometric mean titers; HA, hemagglutinin; HI, hemagglutination inhibition; HPAIV, highly pathogenic avian influenza virus; HVT, turkey herpesvirus; IBDV, infectious bursal disease virus; LPAIV, low pathogenicity avian influenza virus; MDA, maternally-derived antibodies; MDT, mean death time; MDV, Marek's disease virus; NDV, Newcastle disease virus; qRRT-PCR, quantitative real-time reverse transcriptase polymerase chain reaction; rgH5N1, reverse genetics H5N1 vaccine; rHVT-H5, recombinant HVT vaccine with H5 AIV insert; rNDV-H5, recombinant NDV vaccine with H5 AIV insert; SEPRL, Southeast Poultry Research Laboratory; SPF, specific pathogen free; Tk/MN/15, A/turkey/Minnesota/12582/2015 (H5N2) HPAIV; w, weeks old.

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1. Introduction

Outbreaks of highly pathogenic (HP) avian influenza (AI) virus (AIV) in poultry and wild birds have had a devastating economic and social impact worldwide [1,2]. The Eurasian H5N1 HPAIV that emerged in late 1990s in China [3] has expanded from Asia to Europe, Africa, and North America [4]. Also, H5 or H7 HPAIV have become enzootic in China, Indonesia, Vietnam, Bangladesh, Hong Kong, Egypt, and Mexico [5]. Newcastle disease (ND) is a significant worldwide disease of poultry caused by virulent strains of avian avulavirus 1 (former avian paramyxovirus 1 [APMV-1]), commonly known as Newcastle disease virus (NDV) [6–8]. The NDV is enzootic in multiple countries in Europe, Africa, the Middle East, Asia, Central America, and the northern part of South America, and has resulted in at least 4 panzootic outbreaks since it was first identified in the 1920s [9]. Oncogenic Marek's disease virus (MDV) is a worldwide, highly contagious, lymphoproliferative disease of chickens [10,11]. Therefore, vaccination programs have been developed to control all three pathogens. Routine vaccination against HPAIV has been used in control programs of enzootic countries, generally with inactivated whole-virus vaccines or recombinant vector vaccines expressing the hemagglutinin (HA) protein (i.e. the critical antigen to elicit neutralizing antibodies) with even more countries using targeted or risk-based strategies to reduce the costs and increase the efficiency of the HPAIV vaccination programs [5]. By contrast, routine vaccination against NDV is performed virtually worldwide [12,13], and immunization using MDV serotype 3 (MDV-3), also known as turkey herpesvirus (HVT), is used worldwide to protect chicken populations against MDV, but also HVT is used as a vaccine vector for other important viral poultry diseases including H5 AIV [11].

As a consequence of these routine vaccination campaigns, NDV and/or H5 HA maternally-derived antibodies (MDA) are found in the progeny of vaccinated meat chicken breeder flocks [14–17]. Noteworthy, cell-associated HVT vaccines, the most common type of HVT vaccine preparation, induce protection through cell-mediated immunity, which is not passed through the egg yolk to progeny [10,11]. For AIV, NDV, and other agents, the MDA are naturally passed from the hen to the chick through the egg yolk [18,19]. The type and amount of MDA transferred is representative of the circulating antibodies in the hen (produced from vaccination or by natural infection) at the time the egg was laid, and they have a characteristic half-life similar to host antibodies before they naturally degrade in the chick, usually between 2 and 3 weeks of age [19]. Although MDA can prevent or reduce clinical disease by passive immunization during the first weeks of the chick's life [20,21], they can also hinder the immune response to vaccination as seen with infectious bursal disease virus (IBDV) [22], NDV [16,23,24], and AIV [17,25–31] vaccines. Such MDA interference seems to be one of the reasons for the lack of virus eradication success in several HPAIV-enzootic countries using AIV vaccination, such as Egypt and Mexico [25,27,29,32]. This is particularly relevant for inactivated antigens (which comprise the most widely used field vaccines [33]), that are processed through the exogenous antigen presentation pathway [27,34] and therefore are susceptible to be bound by MDA, preventing proper antigen presentation to B cells and initiation of a primary humoral immune response [34]. Similarly, some recombinant vector vaccines, such as fowlpox or NDV, expressing the HA protein have shown to be impacted by MDA interference not only with the response to the HA protein, but also with the replication of the vector, diminishing the protective immune response to both [35,36].

The prime-boost approach is an effective vaccination strategy in HPAIV control; the viral vector vaccines work best as a primer *in ovo* or at 1 day old at the hatchery, and a different type of vaccine, often an inactivated adjuvanted vaccine, is given later as a boost on the farm at 3 weeks of age or older [36]. However, inactivated vaccines are negatively impacted by MDA, and their use requires handling and injection of individual chickens on the farm, creating a compromised biosecurity situation and high cost application scenario. As a consequence, there is growing interest for new vaccines and vaccination programs using recombinant vector vaccines that can fight off multiple diseases at the same time, overcome MDA interference, and be mass-applied in the hatchery or on the farm. The recombinant HVT vaccine with H5 AIV insert (rHVT-H5) is designed primarily for subcutaneous administration at 1 day of age in chicks and, because the virus spreads primarily cell to cell, it appears to lack or have minimal suppression when H5 MDA are present [36]. Studies using specific pathogen free (SPF) layers [37,38], commercial broilers [39,40], and commercial layers [41] suggested that rHVT-H5 vaccine is able to confer good protection against different H5N1 HPAIV isolates and clades, and that it is able to overcome the neutralizing effect of H5 MDA. In contrast, the recombinant NDV vaccines with H5 AIV insert (rNDV-H5) can be mass administered by drinking water or aerosol (spray) application. Because the cost of administration is such a large part of the cost of vaccination, a mass vaccination approach is greatly desired and is one of the primary benefits of rNDV-H5 [36]. The rNDV-H5 vaccines have shown to provide protection against LPAIV, HPAIV, and NDV velogenic challenges in SPF chickens without maternal immunity vaccinated by several different routes [36,42]. On the contrary, numerous studies indicate that high levels of NDV and/or H5 MDA can interfere with the protection of the rNDV-H5 vaccine against HPAIV challenge [28,31,36,43]. Yet, some studies using passively-transferred AIV antibody in young layer chicks show that the rNDV-H5 vaccine could provide an initial priming of the immune response [28,31]. Also, a high dose of rNDV-H5 vaccine given by eye drop to 8-day-old broilers seems to overcome AIV and NDV MDA [43].

Despite possible MDA interference to the vector, numerous advantages make rNDV-H5 vaccines ideal for AIV vaccine development [33]: (i) vaccination of chickens for NDV is routine worldwide; (ii) rNDV-H5 vector vaccines can be mass applied through spray in the hatchery or drinking water; (iii) NDV efficiently replicates in AIV-target tissues and organs, thus inducing strong local and systemic immune responses at the respiratory tract [44]; and (iv) NDV replicates in both chickens and turkeys. Overall, these benefits underscore the need for continued evaluation and optimization of rNDV-H5 vaccines and vaccination programs that can overcome passive immunity and be mass-applied in the field. Therefore, the goal of the present study was not to assess the efficacy of rNDV-H5 and rHVT-H5 vaccines for licensing, as both vaccines are registered in multiple countries including China and Mexico [45], but to determine their effectiveness under conditions experienced in a field vaccination program. This study assessed the effectiveness of a spray-applied rNDV-H5 vector vaccine (Experiment 1) and prime-boost protocols using rHVT-H5 and rNDV-H5 vaccines (Experiment 2) in vaccination programs utilizing commercial broiler chickens with MDA for protection against a homologous HPAIV challenge.

2. Materials and methods

2.1. Vaccines

Four vaccines were utilized in this study. First, a commercial tetravalent inactivated vaccine (hereafter LaSota) (Bursa Guard N-B-R, Boehringer Ingelheim, Gainesville, GA) included LaSota NDV strain, IBDV (standard and variant E strains), infectious bronchitis virus (Massachusetts and Arkansas serotypes), and reovirus (1133, 2408, and MSB strains). The inactivated LaSota vaccine

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