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Review

Vaccines against influenza A viruses in poultry and swine: Status and future developments

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ABSTRACT

Influenza A viruses are important pathogens with a very broad host spectrum including domestic poultry and swine. For preventing clinical disease and controlling the spread, vaccination is one of the most efficient tools. Classical influenza vaccines for domestic poultry and swine are conventional inactivated preparations. However, a very broad range of novel vaccine types ranging from (i) nucleic acid-based vaccines, (ii) replicon particles, (iii) subunits and virus-like particles, (iv) vectored vaccines, or (v) live-attenuated vaccines has been described, and some of them are now also used in the field. The different novel approaches for vaccines against avian and swine influenza virus infections are reviewed, and additional features like universal vaccines, novel application approaches and the "differentiating infected from vaccinated animals" (DIVA)-strategy are summarized.

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1. Introduction

Avian influenza (AI) in poultry and swine influenza (SI) in pigs are economically important diseases, which are caused by influenza A viruses (IAV) [1–3]. Certain phenotypes of IAV subtypes H5 and H7, termed highly pathogenic (HP) AI viruses, cause devastating mortality in gallinaceous poultry, as well as affect water fowl in a more strain dependent manner [4]. Furthermore, AI viruses (AIV) of low pathogenicity (LP) may cause economically tangible losses in gallinaceous poultry due to a drop in egg production in layer flocks and reduced daily weight gains in fattening poultry. In addition, substantial mortality in galliforme poultry may be noticed also in association with LP AIV infection in concert with bacterial or viral co-infections [5]. Influenza virus infections of swine are characterized by an acute febrile respiratory disease of usually short duration that often is complicated by opportunistic bacterial infections and then may lead to reduction in daily weight gains of fattening pigs; also, fertility disorders such as fever-induced abortion in sows have been associated with SI virus infections (reviewed by [6]). Influenza virus infected poultry and swine are also of pivotal importance for public health as they may play a role as sources of parental influenza virus from which, by reassortment and adaptation processes, yield virus strains with zoonotic and even pandemic potential that by spill-over transmission, may spread to human populations [7–9].

Education of stakeholders, strict biosecurity regimes combined with rapid diagnosis and surveillance programs and rigorous eradication measures ("stamping out") comprise the recommended primary line of defense against AI in especially poultry industrial holdings [10–13]. Such regimes, however, require comprehensive investments in stable facilities and farm management, veterinary administration and laboratory capacities, and are out of scope for production units in developing countries, smallholders and backyard rearing communities [14–16]. Preventive vaccination against AI in poultry is generally considered as a secondary line of defense and its pro's and con's should be weighted with respect to the specific epidemiologic situation including, in particular, (i) extent and impact of AI related disease, (ii) incursions into areas with a high density of poultry populations, (iii) establishment of endemic infections, and (iv) increased risks of spill-over infections of zoonotic IAV to humans [17–21]. In case of outbreaks of notifiable AI, i.e., caused by subtype H5 or H7 viruses, further caution is recommended and the use of vaccination might require explicit legal permissions by the competent authorities [22]. Protection against clinical disease caused by SI and its economical impact are of primary interest in case of vaccination against SI; SI viruses, some of them with zoonotic potential, are endemic to the worlds swine population and there are no mandatory eradication programs (at least in Europe).

Vaccination against AI in poultry and SI in pigs follows two primary intentions: (i) Successful vaccination reduces clinical signs of disease upon infection and, hence, prevents economic losses, (ii) vaccinated animals excrete significantly less virus following infection with field virus whereby reducing risks of further spread of

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field virus. A reduction of the amount of circulating virus is of particular interest if outbreaks are caused by zoonotic influenza viruses that may cause spill-over infection in humans, e.g., in the course of the on-going hemiglobal epizootic of Asian origin H5N1 HPAI virus or the emerging H7N9 virus in China [18].

1.1. Classical vaccines: inactivated influenza virus

Historically, influenza vaccination is based on culture-grown IAVs. Usually, embryonated chicken eggs from specific pathogen free (SPF) flocks are used for vaccine virus propagation, mainly because of their unsurpassed yield of virus compared to cell culture systems. For use in pigs or poultry, culture-derived virions in crude allantoic fluids are chemically inactivated and then formulated into mineral oil emulsion vaccines whereby avoiding, in contrast to vaccine formulations for human use, sophisticated and costly purification steps for the enrichment of the immunodominant envelope glycoproteins hemagglutinin (HA) and neuraminidase (NA) [22]. Depending on the host species, primary and booster vaccinations by the subcutaneous or intramuscular routes are required to induce protective levels of systemic hemagglutination-inhibiting (HI) antibodies, and at least annual re-vaccinations are required to ensure that such antibody levels are maintained [23]. Success in prevention largely depends on a maximized antigenic match between the virus strain used for vaccine preparation and the virus(es) circulating in the field [13]. Epidemiological data supported by model calculations indicated that achieving and maintaining a broad and resilient herd immunity is another prerequisite for successful influenza vaccination in pigs and poultry [24]. Vaccine-induced immunity that imprecisely fits the antigenic make-up of the circulating viruses and patchy herd immunity are major drivers of antigenic drift and silent virus spread [25]. Viral antigenic drift by continuing accidental point mutations in the hemagglutinin gene and consecutive selection of mutants that escape vaccine-induced immunity will lead to the emergence of virus escape mutants that gradually replace older circulating virus strains (*see* e.g., [26,27] *and references therein*). In such case, spread of circulating field viruses under the cover of a vaccination campaign, i.e., "silent spread", ensues: clinically the animals may still be protected to an extent that incursions of virulent virus into these flocks would easily be missed by syndrome surveillance [28]. This situation prompts an update of the vaccine to re-attain efficacy by using the escape mutant strain for production [29]. Escape mutants have repeatedly emerged at different geographic localizations (China, Indonesia, Vietnam, Egypt) in the course of the HPAI H5N1 epizootic [26,27] and there is evidence for antigenic drift also in SIV [2,30,31]. By the use of reverse genetics the antigenic makeup of vaccine virus strains is adjustable to circulating viruses within a relative short time period: recombinant viruses with the HA and NA antigenic determinants specifically replaced have been successfully applied against HPAI H5N1 [13]. Furthermore the use of inactivated influenza vaccines and serology techniques based on detection of antibodies directed against NS1 protein permits the establishment of the "differentiating infected from vaccinated animals" concept (DIVA) (see Section 2.8) and are therefore an option for eradication programs [32].

The ideal vaccine, in an infectological sense, should induce sterilizing immunity that blocks infection with circulating field viruses completely after a single immunization. Protection should be generated against changing field strains, i.e., a broader cross protection, at best even across different subtypes, is needed. Maternally derived immunity should be circumvented to enable protection as early as possible in life. High numbers of animals in industrial settings, sequestration of backyard poultry in difficult-to-reach locations and rapid turnover rates of swine and poultry populations are mounting further practical problems of vaccine delivery [13]. Reaching every individual animal by needle and syringe for prime-and-boost vaccination rounds becomes practically near impossible [13]. The available licensed vaccines and approved vaccine strategies provide no universal solution to these problems and intensive research, as reviewed here, is required to provide new solutions to vaccination against IAV infections in pigs and poultry.

2. Novel approaches in influenza virus vaccination in swine and chickens

2.1. Nucleic acid based vaccines

Nucleic acid-based vaccines combine the advantages of (i) a molecularly defined antigen, (ii) the induction of both humoral and cellular immune response associated with MHC class I and class II molecules, (iii) a fast and cheap development without the need for embryonated eggs and even without handling the potentially hazardous pathogen when synthetic nucleic acids are used, as well as (iv) the reduced need of an adjuvant, as the nuclide acid in it itself represents a potent target for the immune system.

2.1.1. Messenger RNA-based vaccines

The proof-of-principle of mRNA vaccines has first been described in the mouse model 20 years ago with an mRNA of the influenza virus nucleoprotein (NP) [33], and due to its simple and safe production and its tailored immunogenicity, this strategy has been further improved in the recent years. These vaccines typically comprise of a simple vector carrying the information for the antigen of interest, as well as 5′ and 3′ untranslated regions (UTR), the CAP structure, and the poly-A-tail for an efficient translation and the stability of the vector within the eukaryotic cell [34]. Optimizing these *cis*-acting structures is one goal of the recent improvements of the mRNA vectors [35–39]. The mRNA vaccines are produced by an enzymatic *in vitro* transcription from the tailored DNA template downstream of a suitable promoter, followed by purification steps. Thus, only sequence information of the nucleic acid of the antigen of interest is needed [34]. This process can be easily adapted to new antigens in emergency scenarios, allowing cost-effective manufacturing processes in classical clean-room settings. Recent improvements have been made regarding the enzymatic reactions [40–42], purification [43], delivering [37,44] and complexing with stabilizing proteins such as protamine [45]. In contrast to DNA, exogenous RNA only has to cross the cell membrane to facilitate protein expression in the cytoplasm and several cell types tend to take up mRNAs by receptor-mediated endocytosis [46–49]. The physical delivery, improved uptake, increased protein expression and induction of the immune system are also under development [45,50–53]. In the host, the RNA is recognized by pattern recognition receptors (PRRs) like toll-like receptors (TLRs), retinoic acid inducible gene I (RIG-I), or protein kinase R (PKR) [54–56], leading to the activation of CD8+ T cells (by delivering the antigen to the MHC-I processing pathway) and B cells directly or via the induction of interferon expression [49,57,58]. Dendritic cells (DCs) represent the best target as mRNA-mediated antigen expression in these cells or in secondary lymphoid tissue induces cellular immunity [36,59], but it was suggested that also other cell types, that take up the mRNA after intramuscular or intradermal application, are able to transfer it to DCs and other immune cells and induce the immunity via cross-priming [48,60–62]. In addition, antigen expression activates the signaling pathway for B cells [63]. As most of the studies are done in the mouse model, further studies are needed to adapt these principles to pigs and/or poultry species. Recently, Petsch et al. showed that vaccination with the mRNAs of HA, NA, and NP of H1N1, H3N2, and H5N1 viruses, which have previously been optimized regarding GC content and the UTR sequence composition,

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