OFFLU AVIAN INFLUENZA MATCHING (OFFLU AIM) INTRODUCTION AND BACKGROUND

Updated: June 2024

Scope: This document provides background information and recommendations on how to use OFFLU AIM

Introduction and background information

Currently, some countries using vaccines against avian influenza have mechanisms in place to monitor antigenic changes in field strains. However, this information is not always shared internationally or made publicly available. The goal of OFFLU Avian Influenza Matching (AIM) project (OFFLU AIM), which started in 2022, is to provide improved information on antigenic characteristics of avian influenza viruses (AIV) to support vaccination programs against avian influenza. It will also assist countries utilising vaccines to stay informed about potentially significant changes in the antigenic characteristics of circulating strains. This information is also of value to countries considering the introduction of vaccination as an additional preventive/control measure.

The OFFLU AIM project gives current epidemiological, genetic, and antigenic information on AI viruses circulating in different geographic regions. Data is analysed in a harmonised way and made freely accessible. Information comes from a range of sources including published information, data from countries monitoring for AIV including potential antigenic variants, vaccine challenge trials, specific antigenic cartography and other intelligence that warrants consideration by countries using or considering vaccination.

Several countries have been relying on vaccination against Gs/Gd lineage HPAI viruses to control recurrent outbreaks in poultry and reduce the number of zoonotic infections. Early adopters of vaccination include China, Egypt, Indonesia, Vietnam and Bangladesh – all places where these viruses were circulating in poultry before vaccination commenced. Recently, and especially due to the increased threat posed by clade 2.3.4.4b viruses, many countries in Latin and Central America have adopted vaccination and some countries in Asia are considering updating their vaccine strategies. Some countries (e.g., France and Hong Kong SAR), although free from HPAI, use preventive vaccination, because of the high risk of infection e.g. from spillover from wild birds, and the threat which it poses to the industry.Several other countries used vaccines briefly in poultry and unregistered vaccine is being applied in some other countries, a practice that OFFLU does not recommend.

Vaccination in poultry against avian influenza is commonly conducted using adjuvanted egg-based inactivated whole-virus vaccines, usually produced relying on viruses engineered by reverse genetics to increase virus yield and the safety of operators. Other vaccine technologies are also in use or under development, including viral vector vaccines such as those using the herpesvirus of turkeys (HVT) as the vector, subunit vaccines (used currently in France and Egypt), self-amplifying RNA vaccines, DNA vaccines, virus-like particles, and replicon particles. Some of these vaccines, especially those based on a live viral vector, can induce broader cross protection against heterologous strains of A(H5Nx) HPAI virus because they also stimulate cell mediated immunity (Palya et al., 2018). In some cases, the hemagglutinin gene insert of subunit and vector vaccines are computationally optimized to further expand the breadth of reactivity. This means that antigens used in these vaccines do not necessarily require updating as frequently as those contained in traditionally manufactured inactivated whole-virus vaccines. Nevertheless, irrespective of the vaccine technology, it is still critical to monitor vaccinated flocks to detect infection and to characterise viruses by undertaking a thorough assessment of their antigenic characteristics.

The focus of this first OFFLU AIM report is on HPAI viruses of the H5Nx subtype from the Gs/Gd lineage. These HPAI viruses emerged in China in 1996 and have been circulating as high pathogenicity viruses

since that time. They have evolved through genetic drift into multiple 5th order HA clades[1] and have reassorted to produce multiple subtypes and genotypes. These viruses have caused several episodes of intercontinental transmission since 2005 due mainly to dispersal by wild birds, presumably after spillback of infection from domestic poultry in places where wild birds and poultry mix freely. Of the initial 10 clades that emerged in the early 2000s, only derivatives of clade 2 viruses have persisted and continue to evolve. Viruses detected recently belong to clades 2.3.4.4b (widespread globally except Oceania), 2.3.2.1a (South Asia) and "2.3.2.1c[2]" (Southeast Asia). Vaccines targeting each of these clades have been developed, with each currently in use in at least one country.

This report should be read in conjunction with other reports such as EFSA Scientific Opinion on vaccination, WHO genetic and antigenic characteristics of influenza A viruses with zoonotic potential, and OFFLU avian influenza composition meeting reports. It is crucial to note that the focus of the VCM report is preparation of candidate vaccine antigens for use in humans for pandemic preparedness, but it provides important information on recently detected viruses. It also provides information on antigenic and genetic characteristics of viruses with the former obtained through the hemagglutination inhibition assays using ferret antisera immunised against human candidate vaccine reference antigens. Antigenic characterisation based on the use of ferret antisera may yield different results to one conducted with chicken antisera immunised against avian vaccine antigens.

OFFLU AIM is building network capacity to antigenically test viruses using antisera raised in chickens against poultry vaccine antigens, or surrogate (genetically similar) antigens when the vaccine strain is not available. The first report provided information on the antigenic characteristics of contemporary clade 2.3.4.4b viruses against clade 1, clade 2.2, clade 2.3.4, clade 2.3.2.1, clade 2.3.2.1a viruses and clade 2.3.4.4c vaccine antigens. In the second report, antigenic characteristics of clade 2.3.4.4b viruses from a broader geographical region are included as well as contemporary clade 2.3.2.1a strains. This work is continually expanding, and subsequent reports will include more currently used vaccine antigens or surrogates and update information as it becomes available covering a wider range of contemporary circulating clade viruses.

Two types of events are relevant when considering antigenic changes in circulating AIVs at a national/regional level. The first is the evolution of viruses where vaccines are being used within the country or region – also termed antigenic drift, leading to vaccine escape, meaning vaccines may no longer be efficacious against the viruses which continue to circulate. Examples include the antigenic variation that occurred in Egyptian clade 2.2 viruses and Indonesian clade 2.1 viruses, and their derivatives (Arafa et al., 2012, Swayne et al., 2015). In other instances, the same vaccine antigen has been used and remained appropriate over multiple years (e.g., vaccines used in Viet Nam against clade 1 viruses and their derivatives from 2005 onwards).

[1] Smith GJ, Donis RO, World Health Organization, World Organisation for Animal Health, Food Agriculture Organization, H5 Evolution Working Group. Nomenclature updates resulting from the evolution of avian influenza A(H5) virus clades 2.1.3.2a, 2.2.1, and 2.3.4 during 2013-2014. Influenza Other Respir Viruses 2015;9(5):271-6. Available at: http://onlinelibrary.wiley.com/doi/10.1111/irv.12324/epdf

[2] Clade 2.3.2.1c viruses have evolved into different sublineages since they were last formally classified in 2014. An updated, standardised clade nomenclature for viruses that previously fell within clade 2.3.2.1c is being developed but has not yet been accepted formally. Nevertheless, viruses from Indonesia that were previously referred to as 2.3.2.1c have been referred to as 2.3.2.1e in OFFLU and WHO documents for several years (see footnote 2), based on advice from molecular geneticists, given they differ from those found in mainland South East Asia. Further changes in classification are expected for viruses within clade 2.3.2.1c and OFFLU will advise once the new nomenclature has been accepted and adopted.

The second type of event is the introduction of a strain of virus that differs significantly from existing, dominantly circulating viruses such as the introduction of clade "2.3.2.1c[2]" viruses in Viet Nam leading to co circulating with the previously dominant clade 1.1.2 viruses. In such cases, antigenic changes in the novel strain emerged elsewhere, prior to the viruses' expansion into the new region (i.e. by wild bird movement or trade). This is exemplified by the recent introduction of A(H5N1) clade 2.3.4.4b to Indonesia where vaccines in use are designed to protect against A(H5N1) clade "2.3.2.1c[2]" viruses that still circulate there. In some countries the clade 2.3.4.4b has replaced the existing strain(s) but in other countries both pre-existing and new strains co-circulate, or the new strain is restricted to only part of the country.

The information in this document is generic in nature and depends on reports of information from individual countries on circulating viruses. It does not imply preference for specific vaccines or products. All countries considering vaccination should use the information in this document as a supplement to data collected locally on circulating strains and on available vaccines when determining the most appropriate vaccines and vaccination strategies to apply.

OFFLU scientists urge all countries to continue sharing information on novel strains of virus, especially those associated with clinical and virological vaccine failures suspected of being antigenic variants so that OFFLU can continue to provide up-to-date information on viruses in circulation. Where possible, and especially if there are suspicions of vaccine escape variants, viruses and gene sequences should be shared with OFFLU reference laboratories to allow full antigenic and genetic characterization.

Much of the information in this document is of relevance for inactivated whole virus vaccines which are the most used avian influenza vaccines globally), rather than other technology vaccines. We caution readers from drawing conclusions on the efficacy of vaccines solely based on antigenic distance. Although it's commonly accepted that the protective efficacy of inactivated whole virus vaccines is significantly affected by antigenic drift. There is a degree of tolerance that novel vaccine technologies have, in terms of changes in antigenic identity and highly immunogenic formulations might compensate for the narrow breadth of reactivity of conventional vaccines by inducing high antibody titers.

To that end, serological monitoring of vaccinated flocks for evidence of immunity to vaccines is strongly recommended especially for vaccines that generate a strong humoral response. Testing of vaccinated flocks is important to ensure that vaccines are stimulating a sufficient immune repose in birds to provide protection.

OFFLU scientists, FAO and WOAH are available to support countries with vaccination in poultry and provide technical advice and scientific information. Please contact secretariat@offlu.org

References

Arafa A, Suarez D, Kholosy SG, Hassan MK, Nasef S, Selim A, Dauphin G, Kim M, Yilma J, Swayne D, Aly MM. Evolution of highly pathogenic avian influenza H5N1 viruses in Egypt indicating progressive adaptation. Arch Virol. 2012 Oct;157(10):1931-47. doi: 10.1007/s00705-012-1385-9. Epub 2012 Jul 4. PMID: 22760662.

Palya V, Tatár-Kis T, Walkóné Kovács E, Kiss I, Homonnay Z, Gardin Y, Kertész K, Dán Á. Efficacy of a Recombinant Turkey Herpesvirus AI (H5) Vaccine in Preventing Transmission of Heterologous Highly Pathogenic H5N8 Clade 2.3.4.4b Challenge Virus in Commercial Broilers and Layer Pullets. J Immunol Res. 2018 Nov 21;2018:3143189. doi: 10.1155/2018/3143189. PMID: 30584541; PMCID: PMC6280313.

Swayne DE, Suarez DL, Spackman E, Jadhao S, Dauphin G, Kim-Torchetti M, McGrane J, Weaver J, Daniels P, Wong F, Selleck P, Wiyono A, Indriani R, Yupiana Y, Sawitri Siregar E, Prajitno T, Smith D, Fouchier R. Antibody titer has positive predictive value for vaccine protection against challenge with natural antigenic-drift variants of H5N1 high-pathogenicity avian influenza viruses from Indonesia. J Virol. 2015 Apr;89(7):3746-62. doi: 10.1128/JVI.00025-15. Epub 2015 Jan 21. PMID: 25609805; PMCID: PMC4403412.

Links to OFFLU AIM documents

OFFLU Avian influenza technical activity vaccination page

Concept note OFFLU AIM project - April 2022

OFFLU AIM presentation – February 2023

OFFLU AIM pilot report – October 2023