Avian Influenza
Summary

Introduction

1. This note provides a brief summary of an analysis undertaken by a DISCONTOOLS group of experts on Avian Influenza (AI). They reviewed the current knowledge on the disease, considered the existing disease control tools, identified current gaps in the availability and quality of the control tools and finally determined the research necessary to develop new or improved tools. Full details of the analysis can be downloaded from the website at http://www.discontools.eu/

Disease profile

2. Sporadic outbreaks of Highly Pathogenic Avian Influenza Virus (HPAIV) have been eradicated from domesticated poultry in most developed countries but eradication of HPAIV H5N1 on a global scale is not expected in the short term as pockets of endemic infection, especially in domestic waterfowl, continue to exist in several countries. Low Pathogenic Avian Influenza Virus (LPAIV) strains are found worldwide as a sequelae of sporadic spill over infection from wild bird populations to domestic bird flocks but also as entrenched endemic infections of poultry.
3. AI infections are widely distributed in aquatic wild bird populations. The majority of infections are acute, short-lived, and asymptomatic. Faecal-oral transmission chains dominate. The environment (surface water, sediments) probably acts as an important factor of virus perpetuation. Incidence of infection is cyclic in the natural hosts and peak values of up to 30% correlate with autumn migration of aquatic wild birds in the Northern hemisphere.
4. In poultry, infections by LPAIV may go undetected and usually cause only mild clinical signs. However, HPAIV may cause disease with extensively high mortality rates within 48 hours.

Risk

5. Avian Influenza viruses (AIV) in general have considerable genetic flexibility through point mutations which accumulate due to an intrinsically high mutation rate of these viruses (genetic drift) and through exchange of gene segments during co-infection of a single host cell with AIV of different sub- and genotypes (genetic shift or reassortment). Therefore, HPAIV can arise by mutation *de novo*, especially in gallinaceous poultry, from LPAIV precursor viruses maintained in the natural host reservoir. To date, all naturally occurring HPAIV come from subtypes H5 and H7 but with varying N subtypes (i.e., H5N1, H5N2, H5N5, H5N6, H5N8, H7N2, H7N9, etc.). However, the majority of H5/H7 in circulation is of the LPAIV phenotype.
6. Influenza viruses circulating in animals pose threats to human health. The primary risk factor for human infection appears to be direct or indirect exposure to infected live or dead animals or contaminated environments. Efficient or sustainable human-to-human transmission of AIV has not yet been reported; yet exposure to high doses of virus leads to infection of humans at occupational risk, especially humans with compromised immune systems or co-morbidities.
7. Eradication of LPAIV in domestic animals is extremely difficult due to the ongoing infection in the reservoir hosts of the vast aquatic wild bird populations. Of great concern are the numerous deaths due to HPAIV H5N1 that have been reported in migratory wild birds including extremely endangered species since these migratory wild birds were previously thought to carry AIV asymptomatically. Furthermore, the spill over of HPAIV into numerous wild and domestic mammalian hosts with whom humans have close contact (house and barn cats) or are raising for food (dairy cows, sheep and goats) and fiber (alpaca and sheep) has resulted in a virus-laden shared ecosystem where humans and animals coexist under constant threat of infection.

Diagnostics

8. Diagnostics are available worldwide but variations in their timely deployment and use exist. Technology for characterisation of strains is quite advanced, but sophisticated genotyping efforts are lagging behind in developing countries. The number of commercially produced and distributed test kits is growing and includes antibody and antigen detection ELISAs, PCR (including real time-PCR, viability PCR, and quantitative PCR), rapid antigen detection assays (lateral flow) and available antigens are distributed for serological purposes.
9. Cheap, stable and sensitive tests fit for purpose are needed which will allow high-throughput generic and subtype-specific multiplex serological and antigen-detection tools. The development of pen side antibody tests in order to detect the optimal age at vaccination (birds could be vaccinated at an age when maternally derived immunity is still present and might have a negative impact on the uptake of the vaccine). In addition, rapid and sensitive methods of assessing infectious status of flocks such as testing of routine mortalities needs to be developed.

Vaccines

10. H5, H7, H9 vaccines are available. While vaccination of wild birds is often considered not feasible, vaccination research trials have been conducted on black vultures and endangered California condors. There are two types of vaccines commercially available at present. Inactivated (whole virus and subunit) and recombinant vaccines (e.g., fowl pox, NDV, HVT). Recombinant vaccines have been licensed and used in a number of countries. In response to the 2021 epizootic of H5 globally, additional vaccine developments have been made, making more vaccine types available, such as reverse-genetics-derived inactivated vaccines and mRNA vaccines, among others.
11. There is a need for easy to apply, single dose, cheap, marker vaccines that induce clinical broad protection and bring virus shedding to a minimum. Information from field studies on the most effective method of application is required with the long term aim of using mass application routes (e.g., spraying or drinking water application) if possible in combination with other vaccines (e.g., NDV).
12. Further development of heterologous vaccines (i.e., those that have a different N subtype than the field strain but with the same H subtype) and recombinant vaccines is required. These include but are not limited to the following: a) using backbones which favour induction of protection in ducks (e.g. duck herpes viruses etc.); b) investigating whether such vaccines are capable of circumventing the potentially negative effect on immune response in birds still having maternally derived antibodies; c) undertaking field studies to evaluate the DIVA principle using new recombinant vaccines in practise and with larger flocks.
13. There are approaches to **d**ifferentiate **i**nfected from **v**accinated **a**nimals (DIVA). The validity of DIVA tests for HPAI, however, remains to be assessed under field conditions.

Pharmaceuticals

14. The H5NX viruses causing outbreaks globally since 2022 have retained their susceptibility to antivirals (e.g., the neuraminidase inhibitors oseltamivir phosphate (Tamiflu ®) and zanamivir (Relenza ®)). However, their use in animals is prohibited due to the risk of antimicrobial resistance and hazard thereof for humans.

Knowledge

15. Avian influenza has been studied for many years, but despite this there are still significant areas of uncertainty in the understanding and knowledge about the disease especially in relation to **pathogenesis, immunology, vaccinology, epidemiology, ecology and control**. Research is needed to fill these gaps in knowledge as many of these are closely linked to the research requirements to develop more effective tools for the control of the disease. Full details of the gaps are shown in the Disease and Product Analysis for Avian Influenza on the DISCONTOOLS website.

Conclusions

16. Losses to the poultry, reductions in milk production in dairy cattle, and the downstream negative effects on allied industries and the economy at large in an outbreak of HPAI can be severe. Eradication of the disease in poultry relies on early detection and on rapid and strict response to any outbreak.
17. The rapid implementation of strict controls including stand still, culling and safe disposal of infected or in contact birds and cleaning and disinfection has historically been deemed essential to prevent spread within and between domestic poultry populations. However, with widespread dissemination of the H5N1 clade 2.3.4.4b virus, in particular, to myriad wild and domestic avian and mammalian species, there is scientific, regulatory, and political support for the implementation of a strategic vaccination program along with more targeted culling of infected or contact birds instead of the “stamping out” approach of yore.
18. In countries where national veterinary services are unable to detect and respond rapidly to outbreaks and notifiable AIV has gained endemic status, systematic vaccination should be used as an intermediate control measure.
19. Vaccination is an important method for controlling AI but can pose some risks. Without proper marker systems it will be difficult to differentiate infected from vaccinated animals.. Failure of all available vaccines to induce sterile immunity implies risks of silent spread of virus by apparently healthy but infected vaccinated poultry.