Avian influenza: past, present and future

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Summary

Avian influenza is not a new disease, but the emergence of high pathogenicity avian influenza (HPAI) viruses of the A/Goose/Guangdong/1/96 lineage (GsGD) has necessitated fundamental changes to prevention and control of this disease. It is no longer just an avian disease but capable of causing severe disease in humans and is considered a potential human pandemic threat requiring One Health approaches. GsGD HPAI viruses also developed the capacity to be carried across and between continents by migratory birds. With persistence of the current A(H5N1) clade 2.3.4.4b viruses in wild birds, enhanced measures to prevent and control infection will be needed. In most countries infection in poultry can be eliminated, although questions will continue about sustainability of repeated stamping out. Systematic preventive vaccination should be seriously considered as a method for reducing outbreaks. HPAI will not be eliminated from countries where GsGD viruses remain enzootic until major changes are made to the way poultry are reared and sold, vaccination is improved and other factors that inhibit reporting and response are overcome. While current attention is mainly focused on GsGD HPAI, control of other low pathogenicity avian influenza viruses also requires attention, including properly matched vaccines.

Keywords

Clade 2.3.4.4b – Control – Enzootic – High pathogenicity avian influenza – HPAI – One Health – Vaccination – Wild birds – Zoonosis.

Introduction

Avian influenza remains a major threat to poultry and wild animal health, can lead to severe zoonotic disease and is regarded as a potential human pandemic threat. The world is currently focused on the panzootic caused by clade 2.3.4.4b high pathogenicity avian influenza (HPAI) viruses that causes devastating losses in poultry and wild animals across all but Oceania [1]. However, HPAI viruses are not the only concern. Multiple low pathogenicity avian influenza (LPAI) viruses, in particular those of the A(H9N2) subtype, are enzootic in poultry and required increased efforts to prevent and control them [2].

In this issue, Swayne *et al.* [1] provide detailed information on avian influenza and the changes that have occurred especially since the emergence of A/Goose/Guangdong/1/96 lineage (GsGD) HPAI H5N1 subtype viruses. This paper highlights key historical aspects of avian influenza that will determine the future course of the current panzootic and methods that should be considered to reduce the threat that avian influenza viruses pose, with a particular focus on countries where these viruses remain enzootic in poultry.

The past

HPAI is not a new disease. It was first recognised as a specific avian disease (and referred to as fowl plague, among other names), when large- scale outbreaks in poultry occurred, commencing in Europe in the late 19th century. These outbreaks were associated with viruses of the A(H7) subtype [3,4]. Another extensive outbreak occurred in North America in 1924–1925. Measures based around quarantine, movement controls and stamping out were successful in controlling these outbreaks, despite limited knowledge about their cause. This contrasts with the situation today. Previously, only few large flocks of poultry existed, which facilitated control. Nevertheless, there was considerable national and transboundary trade in live poultry, and virus spread occurred predominantly by movement of live birds. This included an outbreak associated with a poultry exhibition in Brunswick, Germany, in 1901. Vaccines to control this disease were developed and used experimentally but were not applied for disease prevention and control [4].

HPAI H5 subtype viruses were first identified during a localised outbreak in a farm in Scotland in 1959. This was followed in 1961 by the first epizootic of, HPAI in wild birds (common terns) in South Africa [5] giving the first indication of the capacity of wild birds to carry and spread HPAI viruses, although, in this case, no associated poultry outbreaks were reported. The source of this HPAI virus was never determined and it did not persist in wild birds.

Until the emergence of GsGD viruses, HPAI outbreaks resulted from LPAI viruses carried by wild birds spilling over to flocks of domestic chickens and converting to HPAI viruses by genetic mutation [1]. This occurred in places where direct or indirect contact (e.g.

through drinking water) between wild birds and poultry could occur. After HPAI virus emerged it spread via movement of poultry and contaminated fomites. These outbreaks of HPAI were usually extinguished using methods similar to those applied 100 years ago based on stamping out and movement control.

Spillover of low pathogenicity viruses from wild birds to poultry and subsequent transformation to HPAI virus still occurs sporadically but another dominant pattern appeared with the emergence of GsGD HPAI viruses in 1996 and their subsequent adaptation to domestic ducks [6,7] persisting as HPAI viruses since then. Wild birds are now recognised as hosts of GsGD HPAI viruses and this has resulted in trans- and inter-continental spread by migratory wild birds on multiple occasions, including the current panzootic in which A(H5N1) HPAI viruses belonging to clade 2.3.4.4b have spread globally, except Oceania [1]. Trade in poultry is no longer the most important mode of spread between countries and this shift has seen a change in the way the disease is managed, including greater acceptance of the role of preventive systematic vaccination [1].

Human health risks associated with avian influenza viruses

Human infections with avian influenza viruses from poultry were reported only rarely until 1997; they were non-fatal and associated with viruses of the A(H7) subtype (both LPAI and HPAI). This changed in 1997 when 18 human cases of influenza A(H5N1) with six fatalities occurred in Hong Kong, Special Administrative Region (SAR) of the People's Republic of China (PR China), associated with infections in poultry, especially in live poultry markets [8]. This raised concerns about the potential for a severe human influenza pandemic and was the catalyst for depopulation of virtually all farmed poultry and all poultry in live bird markets in Hong Kong SAR.

This particular strain of virus, which was shown to be a reassortant containing genes from A(H9N2) viruses, was eradicated but GsGD HPAI A(H5N1) viruses persisted and evolved in mainland China [6,7]. Subsequent human infections occurred in mainland China and other countries from 2003 onwards as these A(H5N1) viruses spread to other parts of Asia and the Middle East, resulting in high case fatality rates. Sporadic cases of human infections with A(H5) GsGD HPAI viruses still occur where these viruses are circulating.

Other avian influenza viruses have also been associated with human infections, including A(H7N9), both LPAI and HPAI, in PR China from 2013 to 2017, which caused over 600 fatalities. Human influenza A(H7N9) cases essentially ceased after a compulsory vaccination programme for poultry was introduced.

One Health approaches to avian influenza

Avian influenza is exemplary for One Health/EcoHealth approaches to disease control and prevention. It has human health, animal health and environmental components and relies on contributions from multiple stakeholders (farmers, traders, government officials, consumers, human health practitioners, ecologists, social scientists, etc.). Work involving One Health aspects has been a feature of avian influenza prevention and control for many years. All human and mammalian influenza viruses were initially derived from avian influenza viruses providing further justification for a One Health approach.

Recognition of this linkage is long standing. Early work that resulted in detection of LPAI viruses in wild birds in the late 1960s and their role as carriers of influenza viruses was funded by the World Health Organization (WHO) acknowledging that the H3 gene of the 1968 human influenza pandemic virus was likely derived from an avian virus [9]. Considerable work was done in southern China including Hong Kong SAR from 1977 onwards testing domestic animals for influenza viruses to understand their behaviour in animals and the emergence of human influenza pandemics [10].

A One Health approach to avian influenza prevention and control was adopted in Hong Kong SAR from 1997 onwards [10] and was formally adopted for emerging infectious diseases including avian influenza by the international animal and human health organisations (Food and Agriculture Organization of the United Nations, WHO and World Organisation for Animal Health) following the International Ministerial Conference on Avian and Pandemic Influenza (IMCAPI), New Delhi in 2008 [11].

The future

The following issues and areas will be important when developing prevention, control and eradication efforts for avian influenza complementing Swayne *et al.* [1]. The focus here is mainly on countries where these viruses remain enzootic in poultry.

Clade 2.3.4.4b GsGD HPAI viruses could persist in wild birds

Previous intercontinental and transcontinental waves of infection with GsGD viruses were self-limiting in wild birds [1]. So far this has not happened with clade 2.3.4.4b viruses. If they continue to circulate widely in wild birds, enhanced biosecurity will be needed to keep these viruses out of farms. Measures will also be needed to stop the virus from multiplying in poultry including greater uptake of vaccination as an added layer of prevention, and continued use of stamping out when these measures fail. Infections in dairy cattle in the United States of America in early 2024 demonstrate that other domestic animals are also threatened by these viruses.

Other GsGD HPAI A(H5NX) viruses could spill over to wild birds causing new transcontinental waves of infection

At present, opportunities still exist for other GsGD HPAI A(H5Nx) viruses to spread from poultry to wild birds especially in countries where these viruses remain enzootic in poultry with close associations to wild birds. This could result in new rounds of spread, as have occurred since 2005. Different clades of GsGD HPAI viruses are still circulating in South Asia (clade 2.3.2.1a), Indonesia and Southeast Asia (clade 2.3.2.1c/e) and new GsGD strains could emerge as in the past. Infected domestic ducks reared outdoors on ponds, lakes, water courses and paddy fields are a particular concern since they share habitats with wild birds. At present, infection with GsGD virus in domestic ducks remains poorly controlled and is often not recognised because infection can be subclinical. There is also scope for transmission of avian influenza viruses in the reverse direction from wild birds to poultry and to become established in poultry. One recent example is the emergence of A(H3N8) viruses that have caused zoonotic infections and have acquired genes from influenza A(H9N2) viruses [12].

Approaches to control enzootic GsGD-lineage virus infection in poultry

Unlike the HPAI cases 100 years ago, some countries have seen GsGD HPAI viruses persist in poultry since they first emerged or arrived. This is due to the nature of the poultry production and selling systems that allow HPAI viruses to multiply and transmit [13]. This is compounded by the relative weakness of veterinary systems (both public and private) especially when dealing with large, highly fragmented poultry production and selling systems with variable biosecurity and no or very limited access to affordable animal health services that deal with poultry [14]. Control is also affected if there are no incentives for reporting disease outbreaks, worsened by limited trust in veterinary services and alternative avenues for sale of sick or even dead poultry. Stamping out in these situations results in ‘case harvesting’, not virus elimination, as most infected flocks will not be detected or will be sold without being reported [15,16].

These factors have persisted for the past 15 years and there is little evidence to suggest sufficient change will occur to alter the situation in the near- to mid-term. Changes are being made in countries with enzootic infection, including formation of infection-free compartments [1], but the virus will likely persist outside these compartments.

Improvements can be made but change to long-standing practices can be difficult to introduce

Vaccination will remain a cornerstone of prevention and control in most countries with enzootic influenza virus infection in poultry. However, there is room for considerable improvement to ensure high level immunisation, including adoption of measures referred to as Avian Influenza Vaccine Stewardship [17].

However, vaccination alone will not solve the problem. Changes will be needed to the way poultry are reared and how they are handled after leaving the farm via traders, middlemen, and live bird markets. Enhancements are needed to farm biosecurity, although, in some countries, gains will be limited due to the high density of farms and moderate scope for improvements to farms. Some production systems are especially susceptible, such as free grazing ducks or ducks on ponds or channels.

Appropriate changes will also be required to existing selling practices in particular when vaccination cannot prevent infections in certain production sectors, which usually occurs if insufficient birds can be immunised. Among the modifications that have been applied or considered for enhanced control and prevention of avian influenza viruses is compulsory vaccination so that only well immunised birds are sold in live bird markets. Stopping sales of certain species in live bird markets by centralised slaughter e.g. domestic ducks [10] or white feather broilers has also been used. For example, when white feathered broilers are sold at a very young age, they often only receive an insufficient single dose of killed antigen vaccine [18]. Field experiences with mass vaccination of domestic ducks in countries with enzootic infection in poultry suggest uptake of existing killed antigen vaccines is low and does not produce appropriate population immunity [19]. Multiple doses of vaccine are required for domestic ducks and there may be few incentives to do so.

Other measures that have been applied include reducing the time that poultry are kept in markets to prevent cycles of infection from occurring, including no overnight keeping [10]; straightening of value chains should also be considered so that birds move more quickly from farm to sale or processing, especially if this involves holding of birds before sale for several days.

All these measures can help to reduce rates of infection but the many barriers to their implementation need to be recognised [20,21]. Where possible, One Health approaches should be applied to these problems involving all affected stakeholders to develop appropriate systems for growing and selling birds but even this may not be enough to drive change. For example, immunisation of small-scale household level poultry can be difficult to achieve for a range of reasons [14]. Every effort must made to protect livelihoods of small-scale producers when making changes to production and selling systems.

Other enzootic avian influenza viruses need to be addressed

GsGD HPAI viruses are not the only ones that remain enzootic in poultry. Several are also known to be zoonotic and potential donors of genes to other avian influenza viruses that can alter the biological characteristics of the virus. A good example is A(H9N2) LPAI which has been a donor of genes for zoonotic A(H5N1) and A(H7N9) viruses. Some of these viruses show changes that suggest they may be becoming better adapted to mammalian hosts or even have pandemic potential [22]. Most affected countries do not have formal programmes in place to contain these LPAI viruses and the vaccines available are frequently out of date and offer insufficient protection so that virus shedding and transmission can still occur despite vaccination.

Better vaccines would help to prevent, control and eliminate avian influenza viruses

Appropriate vaccines are able to induce a strong immune response when applied adequately, but most require injection of several doses of vaccine. An effective vaccine, suitable for mass application by spray or drinking water, would be extremely valuable given the costs associated with individual injection of birds. It might also be suitable for remote delivery to colonial wild birds or wild mammals at risk of infection. Better vaccines for ducks would also be of value and there are hopes that duck virus enteritis virus vector vaccines might help to improve immunity in ducks reared outdoors [23]. Improved vaccines against A(H9N2) viruses that produce greater mucosal immunity may also enhance control and prevention. As a minimum, the antigens in existing H9N2 vaccines need to be updated more frequently to match circulating strains.

Conclusions

Avian influenza prevention and control is ideally suited to One Health approaches. Much can be done to control and even eliminate HPAI viruses but systems of poultry production and sale provide sites where these viruses persist, resulting in enzootic infection. Control and prevention measures of HPAI in high income countries are not necessarily universally applicable and alternative approaches have been adopted. Nevertheless, it is evident that more can be done including better usage of vaccines and appropriate changes to the way birds are managed and sold. Greater attention also needs to be placed on LPAI viruses capable of causing zoonotic infection. It is not expected that GsGD HPAI viruses will be eliminated from poultry in all countries but reductions in the likelihood of infection in poultry and spillover to wild birds and humans can be achieved.

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