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## Highly pathogenic H5 avian influenza in 2016 and 2017 – observations and future perspectives

### Summary

During 2016–2017 novel strains of highly pathogenic H5 avian influenza virus within the Goose/Guangdong/96 (Gs/GD/96)-lineage (mainly H5N8) caused multiple outbreaks of disease in poultry and wild birds across much of Europe, parts of Asia, the Middle East and West Africa, and have extended for the first time to affect poultry in Eastern and Southern Africa. The virus was reported first in the Tyva Republic in late May 2016 before being detected elsewhere. This was the fourth intercontinental wave of transmission by an H5 virus within this lineage and was by far the most severe in terms of the number of countries affected.

Observations from earlier intercontinental outbreaks of Gs/GD/96-lineage H5 HPAI from 2005 onwards may help forecast the probable course of this current panzootic,<sup>1</sup> although it also demonstrates that the behaviour of H5 HPAI viruses in this and previous waves has varied. If the reasons for these differences can be determined, (viral, host and environmental factors), it may help improve forecasting and hence preparedness and early

detection of viral incursions. In particular, the detection of a novel virus in wild birds on the Tibetan plateau and surrounding areas largely devoid of commercial poultry production, (including northern Mongolia and southern Russian Federation), in May-June of any year is likely to be followed later that year by detection of a similar virus in other distant countries, extending into Europe, South Asia and Africa.

Evidence from earlier waves also suggests that the current virus could return to Europe in 2017–2018, although the number of outbreaks is expected to be lower than in 2016–2017.

In the current fourth intercontinental wave, the virus has been detected in a range of farm types, intensive and extensive, with a higher proportion in domestic ducks, geese and turkeys, but chickens have also been affected. Secondary spread between poultry farms appears to have occurred in at least six European countries: Hungary, France,

<sup>1</sup> Panzootic: an outbreak of an infectious disease in animals that spreads across a large geographic region or even worldwide

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Bulgaria, Germany, Poland and the United Kingdom, (APHA, 2017), but many appear to be primary cases not directly related to other cases on poultry farms.

At about same time as the H5N8 virus appeared in Europe an H5N6 subtype virus also within the Goose/Guangdong/96-lineage caused a massive outbreak of disease in layer chickens and ducks in the Republic of Korea. This virus has not been detected there since early April 2017.

Movement of both viruses has been associated with infection in wild birds and their role in the long distance transmission of these viruses during the autumn migration is now irrefutable. ●

## Background

In September 2016 FAO released an EMPRES Watch warning of the likely westward and southerly spread of H5N8 highly pathogenic avian influenza (HPAI) virus during the northern hemisphere autumn and winter of 2016–2017. This warning was based on detection of a novel H5N8 virus in wild birds at Lake Ubsu-Nur in the Republic of Tyva, southern Russian Federation, in late May 2016 (see Figure 1a, red oval).

By October 2016, closely related viruses were detected in India and Europe and continued to spread throughout the autumn, winter and spring of 2016–2017, eventually affecting 48 countries by the end of June 2017. In winter and spring of 2017 virus detection continued to occur across Europe and cases were also detected in Nepal, north-eastern China, the Republic of Korea and the Democratic Republic of the Congo. By May 2017 the number of new outbreaks in Europe had fallen dramatically but some new cases were still reported in June. New cases appeared in Turkey and extended eastwards to multiple areas in the Russian Federation including the Republic of Tatarstan and the Udmurt Republic. The virus spread to southern Africa with an outbreak in a breeder farm in northern Zimbabwe in late May, and multiple farms in South Africa in June 2017.

The 2016–2017 H5N8 viruses acquired genes from other low pathogenicity viruses circulating in wild birds, resulting in the emergence of multiple reassorted viruses including some that incorporated novel N5 or N6 genes and lost the N8 gene to produce H5N5

Figure 1a

H5N8 HPAI outbreaks officially reported in Asia, Middle East, Europe and Africa by onset date and bird type affected (domestic or wild), between 1 May and 31 December 2016



Note: The red oval denotes the first detection of the virus.

and H5N6 viruses (APHA, 2017). The common feature of all of these Gs/GD/96-lineage viruses is the H gene that can be linked back to the first occurrence detected in southern China in 1996, the initial virus in the lineage. Viruses in this lineage spread widely from 2003 onwards to more than 60 countries and remain endemic to a number of them.

This Focus On summarises observations from the current (fourth) intercontinental waves associated with Gs/GD/96-lineage viruses as well as information on other related H5 viruses spreading in 2016–2017. It provides information on the genetics of these viruses, some discussion on the likely progress of the current intercontinental wave and guidance for forecasting future waves. Socio-economic implications of the global spread of H5N8 HPAI, while acknowledged as highly important, are not covered in this report and will be reviewed separately. ●

## Clade 2.3.4.4 H5N8 HPAI virus – the fourth intercontinental wave

Since May 2016, considerable highly pathogenic avian influenza (HPAI) activity associated with Goose/Guangdong/96-lineage

(Gs/GD/96-lineage) H5 viruses belonging to clade<sup>2</sup> 2.3.4.4 has occurred. These events include the fourth intercontinental wave involving an H5N8 HPAI virus, likely associated with wild bird movements, as well as incursion of another clade 2.3.4.4 (H5N6) virus into the Republic of Korea, Japan; (Okamatsu *et al.*, 2017; Si *et al.*, 2017; Lee, Song *et al.*, 2017) and Taiwan Province of China, considered in more detail later in the document. A wide range of avian species, both captive and wild, have been affected by the H5N8 HPAI virus (APHA, 2017).

Early warning of the fourth intercontinental wave was provided by the detection and reporting in June 2016 of a clade 2.3.4.4 H5N8 virus in wild birds in the southern Russian Federation on the border with Mongolia - Lake Ubsu-Nur (FAO, 2016a; Lee, Sharsov *et al.*, 2017; Marchenko *et al.*, 2017). It is now recognised that a very closely related virus was associated with an earlier wild bird die-off at Qinghai Lake, China in May 2016 (Li *et al.*, 2017). Similar viruses have

<sup>2</sup> For Goose/Guangdong/96-lineage (Gs/GD/96-lineage) H5 clade nomenclature, please see Smith and Donis, 2015.

Figure 1b

H5N8 HPAI outbreaks officially reported in Asia, Middle East, Europe and Africa by onset date and bird type affected (domestic or wild), in January 2017

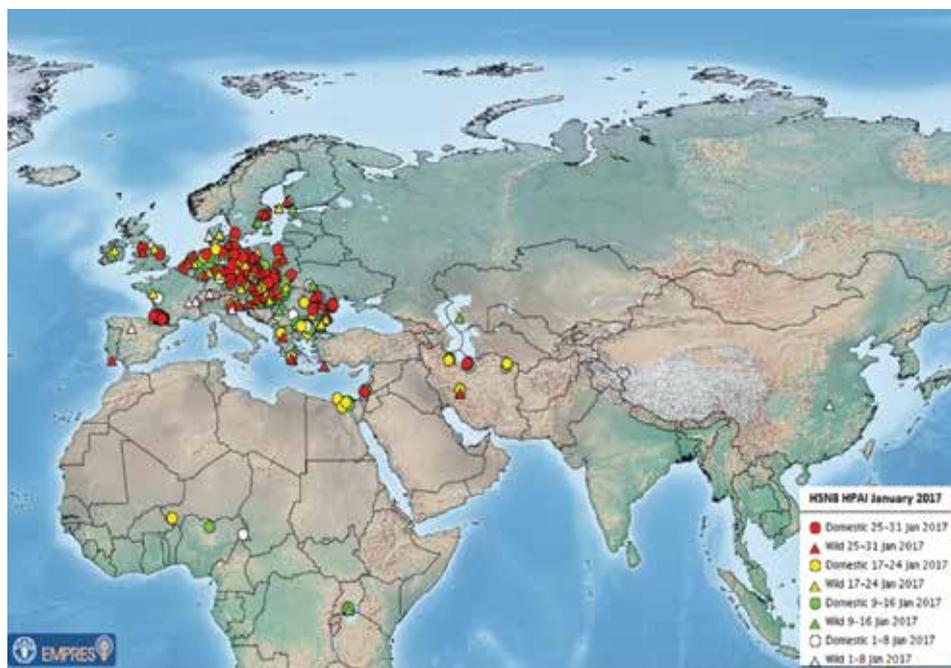
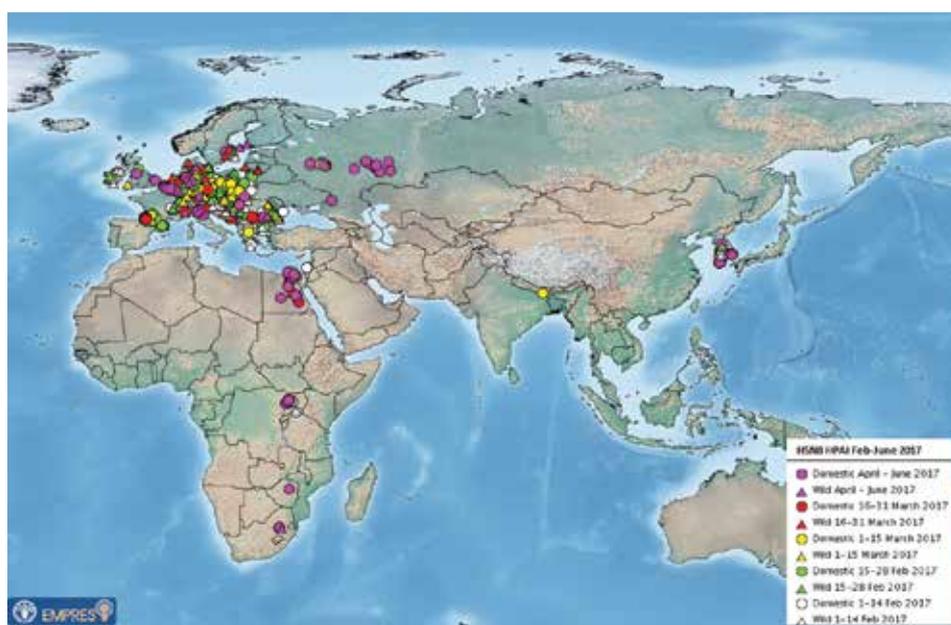


Figure 1c

H5N8 HPAI outbreaks officially reported in Asia, Middle East, Europe and Africa by onset date and bird type affected (domestic or wild), between 1 February and 30 June 2017



been detected in India (Nagarajan *et al.*, 2017), across much of the Middle East and Europe, and have spread into Africa where the extent of transmission is still being established. As of 30 June 2017 this virus has now been reported by 48 countries – 29 in Europe, plus the Russian Federation, Egypt, Israel, India, the Islamic Republic of Iran, other parts of China, the Republic of Korea, Tunisia, Kazakhstan, Kuwait, Nepal, Nigeria, Niger, Cameroon, Uganda, the Democratic Republic of Congo, Turkey, Zimbabwe and South Africa.

Locations of reported cases in poultry and wild birds in the fourth intercontinental wave as of 30 June 2017 in this wave are provided in Figure 1c.

Unlike the previous intercontinental wave in 2014–2015, a novel Gs/GD/96-lineage virus has not been detected in North America in this wave.

In the current fourth wave, the virus has been found in a range of intensive and extensive farm production systems and species with a higher proportion in domestic ducks, geese and turkeys than chickens (on a population basis). Hungary, France, Bulgaria, Germany and Poland have all reported clusters of cases, some considered to be the result of secondary spread in poultry. ●

### Earlier intercontinental HPAI waves – similarities and differences

The previous intercontinental waves of infection with Gs/GD/96-lineage H5 viruses provide some guidance on possible future events. The pattern and timing of H5N8 HPAI cases in this fourth transcontinental wave differ somewhat from those seen in the three previous intercontinental waves, (2005–2006, 2009–2010 and 2014–2015), described in the **EMPRES Watch** released in September (FAO, 2016a). For example, the current wave has been more severe than all previous waves, in terms of the number of wild birds affected as well as affected farms and zoological collections, especially in Europe. More cases have also been detected in the northern hemisphere during summer 2017 than in previous waves. Nevertheless, there are some aspects that provide insights into the possible course of the epizootic (see Table 1).

Table 1

Comparison of the four Gs/GD/96-lineage H5 HPAI intercontinental waves

	Wave 1 2005	Wave 2 2009	Wave 3a 2014	Wave 3b 2014	Wave 4 2016
<b>Clade of virus involved</b>	Clade 2.2 (H5N1) and derivatives	Clade 2.3.2.1c (H5N1)	Clade 2.3.4.4 (H5N8, H5N2, H5N1)	Clade 2.3.2.1 "c" (H5N1)	Clade 2.3.4.4 (H5N8, H5N5, (H5N2?))
<b>Origin of genes</b>	Other H5 viruses (related to clade 2.5.9).	Other H5 viruses	Other H5 viruses HA Buan-like ("A" sublineage)  Reassortment in North American isolates with viruses obtaining North American wild bird influenza viruses	Evolution of clade 2.3.2.1c strains	HA Gochang-like ("B" sublineage) initially detected in Eastern China. Considerable reassortment with novel genes from Eurasian wild bird influenza viruses
<b>Mammalian markers</b>	PB2 E627K				
<b>Human infections</b>	Yes	No	No	No	No
<b>Presence in Western China before intercontinental (I/C) spread</b>	Qinghai May 2005 (last detection 2007)	Qinghai May 2009 (last detection 2007)	Precursor viruses were detected in eastern China	No	Qinghai May 2016
<b>Presence in southern Russia reported before I/C spread</b>	Yes multiple locations	Yes	No	OIE report of virus in southern Russia	Yes Tyva Republic
<b>Presence in NE Russia reported before I/C spread</b>	No report	No report	No report	No report	No report
<b>Widespread in Rep. of Korea in spring, prior to I/C spread</b>	No	No	No	No	No (several isolates detected in early 2014 but disappeared)
<b>Areas affected</b>	China, Mongolia, Russia, Central Asia Europe (widespread), Transcaucasus, Middle East West Africa Japan Republic of Korea	China, Mongolia, Russia, Romania Bulgaria Nepal, Japan Republic of Korea	South Korea, Japan, Russia, Western Europe (Germany, England Netherlands Italy Hungary)	Russia, China, Middle East, West Africa, Cameroon, Romania, Bulgaria, Central Asia	China, Russian Federation, Central Asia, Middle East, Transcaucasus, Europe (widespread), South Asia, West Central, East, Southern Africa, Rep. of Korea

Briefly, the first intercontinental wave in 2005–2006 caused by a clade 2.2 H5N1 HPAI virus involved over 20 European countries, 11 of which experienced cases in poultry. In this wave, the virus first arrived in Europe in October 2005, with cases of infection in Romania and Croatia, after others were found across the southern parts of the Russian Federation and Central Asia. In 2006, there were cases in a range of countries in northern and southern Europe, the Middle East as well as North and West Africa. Movement of the virus across Europe in 2006 appeared to be correlated to the cold weather front, presumably as a result of wild bird movements (Sims and Brown, 2016).

The virus associated with this first wave appeared to be virulent for some wild bird species and lethal infection was reported at that time in a large number of wild birds from a range of species. Asymptomatic infection was produced in several wild duck species experimentally infected with clade 2.2 H5N1 virus demonstrating that healthy infected birds could play a role in the long distance spread of the virus (Gaidet *et al.*, 2010). The virus was detected in Europe until January 2009 with cases of disease in poultry occurring from 2005 to 2008, in West Africa until 2008 and became endemic to Egypt where it continues to evolve. The virus also persisted and evolved in south Asia until 2011. In all

places, few cases were detected during the northern hemisphere summer.

Compared to the fourth wave, in which no human cases have been reported to date, multiple human Influenza A(H5N1) cases were detected in South-east Asia, the Middle East, Transcaucasus and Africa during wave one.

More wild bird deaths and poultry cases were recorded during the fourth intercontinental wave in the fall and winter of 2016–2017 than for the same period during 2005–2006 in the first intercontinental wave, although a considerable number of cases occurred in smallholdings across southern Russia and in Turkey in 2005–2006.

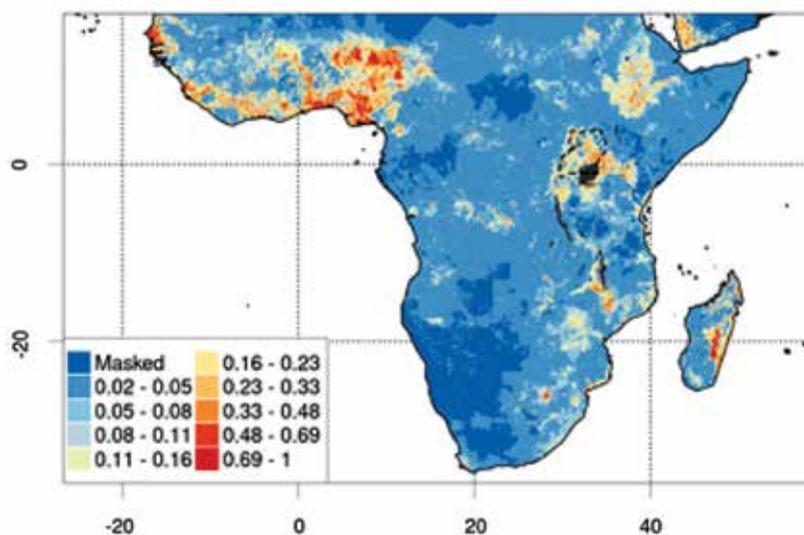
The **second intercontinental wave in 2009–2010** was mild in comparison to the other waves. The clade 2.3.2.1c H5N1 HPAI virus involved was found as far west as Romania and Bulgaria but not detected on the African continent. It was also found in Nepal in 2010. This particular strain of virus did not persist outside of Asia and no clinical human cases were detected.

The **third intercontinental wave in 2014–2015** involved two separate viral lineages and for convenience has been divided into waves 3a and 3b. **Intercontinental wave 3a** involved a clade 2.3.4.4 H5N8 HPAI virus, (related to, but clearly different from the 2016–2017 H5N8 HPAI virus), that was circulating in the Republic of Korea at the time of the 2014 spring migration. It was subsequently found in the far north-eastern part of the Russian Federation in September 2014. In the following winter season, (late 2014), it was detected in northern Europe in Germany, the Netherlands, England and Italy and subsequently in Hungary in February 2015. Events in this wave have been compared previously to those in the first intercontinental wave (Adlhoch *et al.*, 2014). It was concluded that efficient biosecurity, early detection, and stringent control measures were able to minimize the risks to poultry. The distribution of cases differed from that seen in the first wave, with cases first reported in northern Europe and subsequently in Eastern Europe. The Netherlands reported incursion of Gs/GD/96-lineage virus for the first time during this wave. This virus did not persist in Europe. An important feature was the apparent asymptomatic infection in wild birds with the virus rarely being detected in birds that were found dead.

At the same time, a similar H5N8 HPAI virus also travelled to North America and reassorted with North American wild bird influenza viruses to produce H5N1 and H5N2 HPAI viruses. The H5N2 virus caused an outbreak in western Canada before the massive epizootic in the upper Midwest of the United States of America in 2015, the last case was in July 2015. In this intercontinental wave the proportion of large-scale commercial farms affected appeared to be greater than in the other waves, although it is not yet clear whether this was due to particular characteristics of the virus.

Figure 2

Risk map demonstrating areas in sub-Saharan Africa suitable for sustained transmission of Gs/GD/96-lineage H5 HPAI once the virus is introduced to the area.



Source: Adapted from Dhingra *et al.*, 2016, suitability index ranging from 0: not suitable to 1: highly suitable.

In 2016–2017 only two clade 2.3.4.4 H5N2 HPAI viruses have been detected in North America, both in wild mallard ducks in Alaska in August 2016 (Lee, Torchetti *et al.*, 2017) and in December in Montana (OIE, 2017a). The detection in apparently healthy migratory ducks provided a timely warning to the poultry sector there to implement effective biosecurity measures. The findings indicate that the virus can persist in wild bird populations, or the environment frequented by wild birds, for several years even in the absence of further reports of poultry cases. The virus detected in a wild mallard in Alaska showed evidence of evolution (Lee, Torchetti *et al.*, 2017) indicating multiplication in avian hosts rather than just environmental persistence of an earlier strain. These findings suggest there was only one period of introduction of Gs/GD/96-lineage H5 virus into North America after considerable H5N8 replication in the Republic of Korea, the parent virus, at the time of the 2014 spring migration.

The possibility exists of invasion of North America in the future by different Gs/GD/96-lineage H5 virus strains via the Behring Strait,

especially if spring migration brings a novel H5 virus to the far north-eastern parts of the Russian Federation. Events in the Republic of Korea with the clade 2.3.4.4 H5N6 and H5N8 virus since December 2016 warrant close observation. If either virus travels with migratory birds further north to the eastern part of the Russian Federation, movement across the Bering Strait to North America remains a possibility.

Intercontinental wave 3b involved a H5N1 HPAI clade 2.3.2.1c virus that differed from the 2009 isolate. It was found in the southern part of the Russian Federation in the spring of 2014, thereafter being detected in the Middle East and next in West Africa before being found in Eastern Europe and India. This virus was still causing outbreaks of disease in the Middle East in 2016, (FAO, 2016b), and remains endemic to Nigeria with outbreaks reported in five West African countries, as occurred with the first wave. The virus also spread to Cameroon in Central Africa producing disease in poultry. ●



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In 2016/17, many dead aquatic birds tested positive for H5N8 HPAI virus

### Likely progress of the current H5 epizootic

By May 2017 case numbers in Europe were falling but some new cases were still being detected during the northern autumn and summer, e.g. eastern Sweden, a backyard flock in Norwich, England, Finland, Belgium, Luxembourg, Italy, parts of the Russian Federation and Turkey. Case numbers in poultry are expected to rise again in late 2017. Cases could recur on the Tibetan plateau, at Lake Ubsu-Nur and in Mongolia, although so far, there have been no reports of a return of the virus to these areas. Other African countries, in addition to Cameroon, Democratic Republic of the Congo, Egypt, Niger, Nigeria, Tunisia, Uganda, Zimbabwe and South Africa, could be affected. It is not yet clear how the outbreak in southern Africa will evolve. A feature of the European epidemic was a large number of cases in backyard or smallholdings of poultry, contrasting with previous epidemic waves. This might reflect the extent of environmental contamination, presumably mediated via wild birds. Areas of high poultry density with extensive production systems for domestic waterfowl or production of domestic turkeys appear to be at high risk, especially in late 2017 and early 2018 if the pattern seen in the first intercontinental wave recurs.

It is noteworthy that most H5 HPAI cases in poultry in this current fourth wave have occurred in areas predicted as high-risk by the large-scale suitability model of Dhingra *et al.*, (2016) and few in low-risk areas, including those with a large number of wild bird cases. The area around Lake Victoria in East Africa was also predicted as being a site with high suitability for transmission of H5 HPAI by the same model, extending into countries neighbouring Uganda (Figure 2).

The large number of wild bird cases in Europe, with known cases/deaths likely representing only a small proportion of the total, may alter the patterns of this disease compared to the past. The introduction of this virus to North America from Europe through overlapping Atlantic flyways remains a possibility since other avian influenza viruses have used that pathway, but the risk is regarded as low.<sup>3</sup> Gs/GD/96-lineage H5 HPAI viruses have not travelled to North America via this pathway in the past.

#### Clade 2.3.4.4 H5N8 HPAI in South Asia

The clade 2.3.4.4 H5N8 HPAI virus that appeared in October 2016 has not been detected recently in south Asia but may recur. This conclusion is based on experiences with other strains that have emerged there in the past, some of which have persisted for several

years; see, for example, Marinova-Petkova *et al.*, (2014) and the detection of a case in Nepal in March 2017, (OIE, 2017b). No new cases in poultry due to H5N8 HPAI virus have been identified in India since the last outbreak in Karnataka, detected on 24 November 2016, (OIE, 2017c). Cases in wild birds, including captive birds, were reported in December from Gujarat and Karnataka, zoological collection. Other, more recent HPAI cases appear to be due to viruses of the H5N1 subtype from clade 2.3.2.1a, (OIE, 2017d).

#### Clade 2.3.4.4 H5N8 virus in Egypt

Detection of the H5N8 virus in Egypt is of concern since it is very likely this will further complicate control of H5N1 HPAI there. H5N1 HPAI virus of clade 2.2.1.2 and its earlier relatives have been entrenched in Egypt since the first intercontinental wave in 2005–2006. The H5N8 strain is antigenically distant from vaccine strains currently used to assist in the control of this disease in Egypt's commercial sector and this may result in an increase in outbreaks and accelerated virus spread if it becomes established in poultry. In addition, the presence of two distinct strains will make laboratory detection more complex although options using clade-specific rapid diagnostic tools exist and have been used (Naguib *et al.*, 2017). As of June 2017 multiple cases have been reported in poultry in the Nile Delta (OIE, 2017e) and some have extended to Upper Egypt, suggesting the virus is likely to become widespread in poultry in this area with a potential spread to other parts of Egypt. Reassortment of genes between the H5N8 virus and the pre-existing H5N1 viruses and/or H9N2 viruses is possible.

#### Clade 2.3.4.4 H5N8 in West Africa

In two previous intercontinental waves, the first in 2005–2016 and third, 3b, in 2014–2015, initial cases in West Africa were detected in Nigeria during the northern winter. Available spatial, temporal and genetic evidence suggests wild birds as the source for each of these incursions, previously suggested by Cecchi *et al.*, (2008), although never proven. Some have theorized that H5N1 viruses in 2005–2006 were introduced via trade but the repeated pattern

<sup>3</sup> See Dusek *et al.*, 2014 for information on movement of other avian influenza viruses via these flyways.

of incursions by viruses detected elsewhere in wild birds suggests the wild bird route is more plausible. Nigeria has a large number of wintering Eurasian migratory ducks, African wild nomadic ducks, and a poultry industry in areas where direct or indirect contact between wild birds and poultry can occur. As of May 2017, the only known cases of H5N8 avian influenza in Nigeria were in Kano State (OIE, 2017f). Niger has also reported cases in the west of the country (OIE, 2017g). Other West African countries are also at risk of H5 virus incursion based on previous experiences. In addition, the H5N8 virus has been detected in Cameroon (FAO, 2017) in the area where Gs/GD/96-like H5N1 HPAI virus was first detected in the north of the country in 2006. Reassortment between H5N1 virus already circulating in West Africa and the H5N8 virus introduced in 2016–2017 could occur.

#### Clade 2.3.4.4 H5N8 in Uganda and southern Africa

The fourth intercontinental wave is the first to spread as far south as the equatorial region in Africa and beyond, other than a single case in southern Sudan in 2006. When the outbreak in Uganda occurred, the expectation was that the virus had the potential to be a major economic and social disaster for poultry owners. The vast majority of poultry in Uganda are in small household flocks, (FAO, 2008), and represent an important source of livelihoods and income.

As of May 2017, the virus had only been detected in one other district, Budaka, in Uganda other than those adjacent to Lake Victoria: Kalangala, Masaka and Wakiso Districts. Expansion to three other countries, Democratic Republic of the Congo (OIE, 2017h), South Africa (OIE, 2017i) and Zimbabwe (OIE, 2017j), has occurred. The future course of this outbreak in central, eastern and southern Africa remains uncertain.<sup>4</sup>

Timely reporting of poultry deaths in many African countries is weak and, as with other Gs/GD/96-lineage viruses, not all infected domestic ducks show signs of disease. These two factors can reduce the effectiveness of programmes aimed at detecting cases, controlling the spread of the virus and its elimination. It is possible that the virus may persist in Uganda and elsewhere in central, eastern and southern Africa for some time if new cases are not detected or detected late.

#### Clade 2.3.4.4 H5N8/H5N6/H5N5 in wild birds, including captive collections

For wild birds, the 2016–17 clade 2.3.4.4 H5Nx HPAI viruses were mostly detected in dead birds via passive monitoring. Initially the majority of infections were reported from diving duck species such as tufted duck (*Aythya fuligula*), greater scaups (*Aythya marila*) or common pochards (*Aythya farina*). Other Anseriform species, swans, geese, but rarely dabbling ducks and species from other waterbird families such as gulls, terns, coots, curlews, cormorants and grebes, were also infected. Some infected birds of prey, such as common buzzards (*Buteo buteo*) and white-tailed eagles (*Haliaeetus albicilla*), were found dead near water bodies at sites frequented by migratory birds and presumably exposed through feeding on infected prey. Raptor species affected in Europe are recorded in detail elsewhere (APHA, 2017; FAO, 2017). The main species affected in Uganda were white winged terns, *Chlidonias leucopterus*, a Eurasian migratory waterbird species that winter in sub-Saharan Africa.

Germany, Switzerland, the Netherlands and Denmark, in particular, detected the virus in numerous wild birds in multiple regions, initially mainly at sites frequented by migratory Anatidae. Cases occurred both in north (the Baltic Sea area) and central Europe (Lake Constance and Lake Geneva area), and new cases continue to occur. Cases have extended to places where Gs/GD/96-lineage H5 HPAI virus had not been seen previously, including Ireland, Portugal, Tunisia and Uganda. In the early stages of the outbreak in Europe, several large scale die offs in diving ducks occurred—whereas later in the outbreak only single cases were reported in other species and, in more recent outbreaks, also in diving ducks.

It is likely that certain avian species are more susceptible than others to these H5N8 viruses and their derivatives (H5N6/H5N5). Events in Europe indicate secondary spread amongst domestic Anseriformes with some affected populations of the same species showing variation in disease signs and overall mortality. The clinical spectrum in all species

of domestic birds associated with these particular viruses is not fully characterised, although to date, even in domestic ducks, the virus appears to be highly virulent and birds present with signs of disease. This may change as the virus becomes more adapted to domestic waterfowl in particular.

At Lake Ubsu-Nur a number of the positive cases were from potentially healthy hunter-killed birds – black-headed gull (*Chroicocephalus ridibundus*), great cormorant (*Phalacrocorax carbo*) – while others were from dead birds – grey heron (*Ardea cinerea*), common tern (*Sterna hirundo*), great crested grebe (*Podiceps cristatus*) and black-headed gull (*Chroicocephalus ridibundus*). Some of these species could be acting as sentinels. Rather than focusing on live birds, surveillance in Europe has been centered around dead ones, due to greater sensitivity, and almost certainly did not detect all infected wild birds. H5N5 HPAI virus was detected through active surveillance in an apparently healthy common teal in Montenegro (OIE, 2017k).

The virus in South Africa has been detected in resident and migratory wild birds including Egyptian Goose (*Alopochen aegyptiaca*), two dead passerine birds (Southern masked weaver – *Ploceus velatus*) and in a dead yellow billed duck (*Anas undulata*). Their specific roles in transmission remains to be determined (OIE, 2017l).

Spillover of the virus to captive bird collections and zoos has occurred in at least eight



Spillover of the virus to captive bird collections and zoos has occurred in several countries

<sup>4</sup> For updates see FAO EMPRES [http://www.fao.org/ag/againfo/programmes/en/empres/HPAI\\_Africa/situation\\_update.html](http://www.fao.org/ag/againfo/programmes/en/empres/HPAI_Africa/situation_update.html)

countries: Belgium, Luxembourg, Germany, India, the Russian Federation, Netherlands, Finland and Sweden, with one H5N8 case in a zoo in China also likely to be caused by a related virus. In several cases the infection occurred mainly in non-resident birds with spillover to captive birds. So far, in all but two cases in zoos, culling has been restricted to sick birds with other birds protected using a combination of measures including quarantine and enhanced hygiene.

It is important to stress that no benefit is gained by scaring off wild birds, hunting them indiscriminately, or destroying their habitat. Spraying disinfectant on birds or the environment is likewise counter-productive and harmful with potential long-term negative consequences to fauna, flora, agriculture and surface waterways. Furthermore, such actions are not recommended in good disease management practices. These activities will likely accelerate dispersal of potentially infected birds and hence, of the virus. There is also no justification for any pre-emptive culling of endangered species in zoological collections (see Globig *et al.*, 2016).

Further adaptation of the virus to poultry may develop when expanding secondary spread in domestic poultry occurs, as was seen in the North American H5N2 outbreaks in 2014–2015, (DeJesus *et al.*, 2016). ●

### What is the main source of the H5N8 virus?

Based on the temporal and recurrent spatial patterns of intercontinental outbreaks, it is now widely accepted that the dispersal of Gs/GD/96-lineage virus from East Asia, observed in most intercontinental waves, is associated with wild bird movements. Phylogenetic data, at this stage of analysis for the current H5N8 virus, essentially corroborates earlier observations (Global Consortium, 2016; Sims and Brown, 2016). It is reasonable to assume that the main birds involved were Anatidae given the current knowledge of the ecology of avian influenza in wild birds.

Satellite telemetry studies of migratory ducks, geese and swans have found that individual birds have the potential to disperse the virus as far as 1 500 km in only four days on average, assuming that infection does not reduce their movement capacities (Gaidet *et al.*, 2010).

A relay-like, stepping stone transmission pattern, between a series of migratory birds successively infected, probably allows these viruses to move considerable distances in a matter of weeks. Strains more likely to be transmitted over long distances are probably those best adapted to one or more host species and shed in relatively high quantities without producing severe disease in most infected birds. Once the virus arrives at stopover sites in a new wetland, other more vulnerable genera can be infected and bird die-offs can occur. This then provides opportunities for infection of carrion-eating birds scavenging on carcasses.

The detection of virus across a wide area in a very short time suggests high levels of infection at a congregation site just prior to movement of these birds into Europe. Weather conditions in late October 2016 in areas to the north-east of western Europe with sub-zero temperatures and snow, may have triggered movement of these birds. The time between September and November is a period of recurrent high infection rates of wild ducks with low pathogenic AI viruses in northern Europe (Latorre-Margalef *et al.*, 2014). Equivalent information on H5 HPAI viruses is not available but similar patterns could occur. Changes in weather patterns, especially the arrival of very cold weather across Europe, as in the first weeks of January 2017, may have resulted in further movement of birds and the virus to warmer areas. Furthermore, with such a heavy infection burden in wild birds, this will result in significant environmental contamination and, depending on climatic conditions, the virus may persist for many weeks in the environment in an infectious form, i.e. after wild bird populations have moved on.

In a number of earlier intercontinental waves, the virus has also returned to Asia, with cases detected in the southern part of the Russian Federation in the following spring and, on two occasions, in the Republic of Korea and Japan in the following winter. The 2005–2006 wave was the only one so far that resulted in recurrent cases in Europe over several years with the virus persisting intermittently until 2008–2009. In intercontinental wave 3b the virus was detected in Iraq for several years.

Other pathways for its introduction have been considered for each of the

intercontinental waves, including trade in poultry and poultry products. With the exception of isolated cases involving trade in captive birds, not associated with these four waves, the pattern of outbreaks and the molecular evidence are consistent with wild bird introductions for most countries. Initial observations suggest wild bird introduction of H5N8 highly pathogenic avian influenza virus to Zimbabwe and South Africa, and its subsequent spread. More details on movement of wild birds, in particular Anatidae, just prior to these outbreaks will help to determine their role, especially given the apparent timing of introduction to these two countries did not match the spatio-temporal pattern of long distance migrants. ●

### Genetic analysis of the 2016–17 H5Nx HPAI virus strains

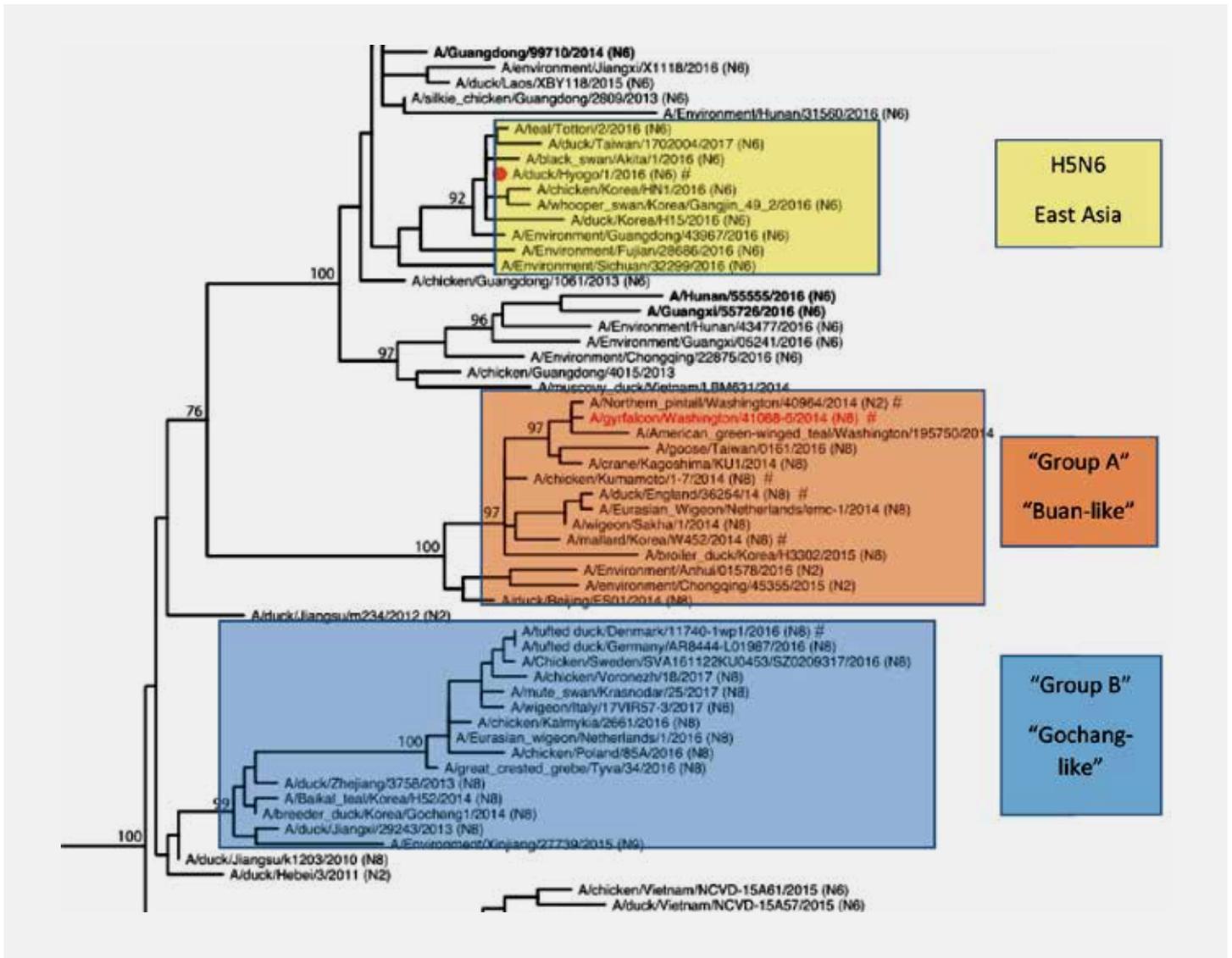
The viruses involved in the fourth intercontinental wave form part of a clearly distinguishable sublineage to the ones found in Europe in 2014. There is as yet no official nomenclature for this sublineage but some scientific papers refer to them as 2.3.4.4 "Group B" or "Gochang-like", (see for example Lee, Sharshov *et al.*, 2017; EFSA, 2016). This sublineage was first detected in birds in China in 2010: A/duck/Jiangsu1203/2010-like viruses. It reached the Korean peninsula in the winter of 2013–2014 but was not the dominant strain that year (Kim *et al.*, 2017); another sublineage of H5N8 virus, referred to as 2.3.4.4 "Group A" or "Buan-like", became established. This "Group A" virus was the sublineage detected in Europe and a number of Asian countries later in 2014 in intercontinental wave 3a.

Figure 3 shows that the Tyva Republic viruses along with those found subsequently in Europe in 2016–2017 are readily distinguishable from those H5N8 HPAI viruses ("Group A") detected in Europe and North America (light brown shading) during the previous wave in 2014–2015. Figure 3 also demonstrates that the H5N6 viruses from the Republic of Korea and Japan (yellow shading) in 2016–2017 fall into another sub-lineage within clade 2.3.4.4.

Detailed information on gene sequences for the H5N8 HPAI viruses from the Tyva Republic have been published (Lee, Sharshov *et al.*, 2017) confirming that the virus was a

Figure 3

Partial phylogenetic tree of clade 2.3.4.4 s/GD/96-lineage H5 viruses demonstrating the relationship between “Group A” (“Buan-like”) and “Group B” (“Gochang-like”) sublineages. The H5N6 viruses from East Asia in 2016–2017 are also highlighted.



Source: Adapted from WHO, 2017. Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness. March.

reassortant form possessing 3 genes (HA, NA, and NS) similar to earlier H5N8 viruses within clade 2.3.4.4 “Group B” (“Gochang-like” viruses). The other five genes identified derived from wild bird origin low pathogenic influenza viruses. Virus in this group had remained unreported since originally detected in China and the Republic of Korea during 2014 (Lee, Sharshov *et al.*, 2017) until it was reported again in Qinghai and the Tyva Republic in May–June 2016.

Other related H5N8 viruses (“Group B”) were found in wild birds in China in 2013 (Zhou *et al.*, 2016) and it is not yet clear why it has taken several years for this strain to undertake long distance intercontinental movement despite being detected in some birds in the Republic of Korea in 2014. The acquisition of internal genes from wild bird avian influenza viruses may be a factor.

Gene sequences from the isolates from Germany demonstrate that the 2016–2017

virus (“Group B”) there had acquired two new genome segments (PA and NP) from wild bird influenza viruses and had a truncated NS1 protein (Pohlmann *et al.*, 2017). The significance of these changes is yet to be determined.

Assessment of gene sequences from 2016–2017 “Group B” viruses in Europe indicates that they form a monophyletic group derived from a common ancestor (EFSA, 2016) but demonstrates some minor differences suggesting virus introductions by slightly



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H5N8 HPAI viruses are shed by wild birds into the environment

different pathways or flyways (APHA, 2017). Viruses from India are also closely related reassortant viruses (Nagarajan *et al.*, 2017) as are those from the Republic of Korea (Lee *et al.*, 2017c).

The possibility exists that these "Group B" viruses are shed by wild birds in high concentrations in faeces which may partly account for the apparently increased transmissibility of these wild bird isolates (EFSA, 2016). Many of the earlier Gs/GD/96-lineage H5 viruses are shed in larger quantities via the oropharynx. A 2014 "Group A" H5N8 virus from the Republic of Korea was shed in greater quantities in experimentally infected mandarin ducks than H5N1 viruses detected there earlier (Kang *et al.*, 2017). These "Group A" viruses appear to have a tropism for both respiratory and enteric tracts but do not seem to have preferential replication in one or other site compared to earlier Gs/GD/96-lineage H5 viruses. This work needs to be repeated for the "Group B" viruses.

#### Other reassortants

On 14 December 2016 the Netherlands reported an H5N5 virus from a dead wild bird. This virus presumably arose through reassortment between the "Group B" H5N8 virus and a wild bird HxN5 virus. Other very similar H5N5 viruses have subsequently been detected in 10 other countries and were associated with some outbreaks in poultry. An H5N6 reassortant virus has been detected in Greece. ●

#### Clade 2.3.4.4 H5N6 virus in the Republic of Korea and Japan

At about the time the H5N8 virus was detected in Europe, the Korean Peninsula and Japan once again reported the introduction of a Gs/GD/96-lineage H5 virus. This was a clade 2.3.4.4 virus of the H5N6 subtype (see Figure 3). This followed earlier incursions of Gs/GD/96-lineage H5 HPAI viruses in 2003–2004, 2006–2007, 2008 (spring), 2010–2011 and 2014–2015 – each time with a novel strain of virus that was, however, already circulating in the wider region. H5N6 HPAI virus has been the dominant strain circulating in mainland east and south-east Asia for the past four years (Bi *et al.*, 2016). It appears that, in line with past incursions, supported by documented wild duck movements and phylogenetic analyses, (Cappelle *et al.*, 2014; Hill *et al.*, 2015), wild birds introduced it to the Republic of Korea and Japan. This H5N6 HPAI virus is the seventh novel Gs/GD/96-lineage virus detected in these two countries.

The detection by Korean researchers of an H5N6 virus in faeces from wild birds gave a warning to poultry farmers there and in Japan to enhance biosecurity. However, this did not prevent widespread infection in the Republic of Korea where the outbreak has now exceeded that of 2014–2015 in terms of number of cases and total birds killed or destroyed. Information on the genetics of these viruses has been published (Si *et al.*, 2017; Lee, Song *et al.*, 2017). The HA and NA genes of this virus are similar to those from a dead great egret found on 2 January 2016 in Hong Kong SAR, China. The virus appears to be a reassortant, obtaining other genes from the wild bird influenza virus gene pool. Korean H5N6 viruses are similar to those detected in Guangdong province, China in early 2016. They could be divided into five genotypes based on their internal protein gene constellations. Several viruses acquired PA genes from the Eurasian wild bird influenza gene pool.

Japan detected over 170 virus positive cases among dead wild birds by mid-January 2017, but only eight farms had reported disease in poultry associated with this virus at that time. By early February this number had increased to 10 farms.

H5N6 HPAI virus is already widespread in poultry in China and Viet Nam and cases have

been detected in the Lao People's Democratic Republic and Myanmar. It was the predominant strain found in national surveillance programmes in poultry in the first half of 2016 in China (MoA China, 2016). This virus could travel to North America if migratory birds carry it to far eastern parts of the Russian Federation during spring migrations.

It is not clear why H5N6 viruses have not travelled previously to the Korean Peninsula and Japan given that they have been the dominant strain in Chinese poultry for a number of years. Perhaps this indicates strains that move via wild birds need to be well adapted to them while those in domestic chickens may not necessarily have this characteristic. We await experimental studies on these viruses in different hosts. The genetic reassortment that has occurred in these viruses may also be significant (Lee, Song *et al.*, 2017).

From February 2017 onwards outbreaks of H5N8 HPAI virus were also detected in poultry in the Republic of Korea. These were caused by "Group B" lineage viruses and represent new introductions of the virus (see above). ●

#### H5 HPAI threats elsewhere (clade 2.3.4.4 and other)

A number of countries are still infected endemically with Gs/GD-lineage H5 viruses that could spread from there to other countries. These include the clade 2.3.2.1c H5N1 HPAI strains from the fourth intercontinental wave that are still circulating in West Africa. Similar viruses were also detected in Iran (2015), Iraq and Lebanon (2016), (FAO, 2016b). Clade 2.3.2.1a viruses continue to circulate and cause disease in south Asia.

Egypt is still infected with derivatives of clade 2.2 (2.2.1.2) H5N1 HPAI virus from the first intercontinental wave in 2005–2006. Spillover of these viruses has occurred to other neighbouring countries in the past including Israel, Gaza and the West Bank and Libya although the pathways of transmission may include poultry or poultry products in some of these cases.

Various Gs/GD/96-lineage H5 viruses continue to circulate in mainland east and south-east Asia, including clade 2.3.4.4 viruses, mainly H5N6 HPAI, and clade 2.3.2.1c H5N1 HPAI viruses. Several isolates of an H5N9 HPAI virus have been reported. One of these

was a reassortant between an H5 HPAI and H7N9 virus in China and this development needs to be monitored closely given the high pathogenicity of both parent strains in humans (Yu *et al.*, 2015). Variant clade 2.3.2.1 viruses, with one referred to unofficially as clade 2.3.2.1e, have also been detected in wild birds in China in 2015 (Jiang *et al.*, 2017). These viruses are antigenic variants and so have the capacity to resist vaccine-derived immunity or naturally acquired immune responses from exposure to other H5 viruses in farmed and wild birds. Antigenic variation is likely to be an important factor in determining the extent of infection and viral shedding in infected wild birds. ●

## Conclusions and future perspectives

Broad patterns and observations have emerged that may be helpful in forecasting future intercontinental movement of Gs/GD/96-lineage H5 HPAI viruses and the course of epizootics. In particular, these are:

- i. The detection of a novel strain of Gs/GD/96-lineage H5 HPAI virus in the southern Russian Federation in the spring or early summer, which may be preceded or accompanied by reports of a similar virus on the Tibetan plateau or in Mongolia, preceded movement of the virus and infection of poultry in Europe, the Middle East and, in some cases, Africa
- ii. The presence of Gs/GD/96-lineage H5 virus during the spring migration in the Korean peninsula and/or Japan and later, detection of a virus in the far north-eastern part of the Russian Federation, preceded movement of H5 virus to Europe and North America in 2014. Although this pattern has only occurred once, it warrants close monitoring to see if it is repeated. There were new cases of H5N8 HPAI virus in early June 2017 in the Republic of Korea. We await information from the far eastern region of the Russian Federation to see if this, or the H5N6 virus, is detected there following the northern hemisphere spring migration in 2017.
- iii. Emergence of novel strains of Gs/GD/96-lineage H5 HPAI virus in eastern China, especially those detected in wild birds, could provide warning of possible spread

to the Korean peninsula, as occurred in 2014 and 2016. All novel strains need to be monitored closely, including full genome sequencing, to establish whether they have acquired genes from wild bird influenza viruses which may facilitate viral carriage by wild birds over long distances.

- iv. Apparently no strain of Gs/GD/96-lineage H5 HPAI virus has had continuous or semi-continuous infection cycles involving wild birds for longer than three years, although repeated spillover from poultry in places where certain strains become endemic is possible. It is noteworthy there is no record of northward long distance transmission of Gs/GD/96-lineage H5 virus from Egypt or West Africa by migratory birds despite the virus being either endemic or present there for a number of years.
- v. Based on the experience of the first intercontinental wave during which considerable infection in wild birds occurred, there is a possibility of a multi-year epizootic in Europe and Africa with the 2016–2017 H5N8 virus. The evidence available so far suggests considerable infection in the wild bird population for the current, fourth, intercontinental wave of infection.

We cannot predict the severity of intercontinental outbreaks or their exact patterns, both temporal and spatial, but as more information becomes available on the species of birds involved in long distance carriage and the characteristics of the viruses it may be possible to issue more precise forecasts. Greater integration of information on the ground from ornithological groups about movements of Anatidae in real time would be extremely helpful. For example, was there an increase in the number of migratory ducks in northern Germany just prior to the outbreaks in late 2016, or changes in the composition of the migratory duck community?

The role weather plays in such patterns needs further investigation. It has already been demonstrated in the first wave in Europe that there was some correlation with the zero degree isotherm and movement of the virus related to wild bird movements (Ottaviani *et al.*, 2010; Reperant *et al.*, 2010). Movement patterns of Anatidae could also be affected and even modified by atypical climatic conditions, such as the prolonged high Arctic

temperatures and freezing temperatures over the northern part of the Russian Federation in the winter of 2016–2017. Changes such as these may alter patterns of spread and transmission for Gs/GD/96-lineage H5 HPAI and other avian influenza viruses in the future.

So far all of the H5 HPAI viruses involved in intercontinental movement were first detected, and likely evolved, in east Asia. All belong to the so-called Gs/GD/96-lineage, or at least their HA gene does. Current farming systems, especially in southern and eastern China, in which domestic ducks and wild birds share ecosystems, provide ample opportunities for generation of novel strains of H5 virus within this lineage. This pattern of emergence of new strains and their spread to other countries every few years is expected to continue until such time as the virus is contained in domestic ducks. This production system is now also being used in north-east China.

There are many reasons why the control and prevention of H5 HPAI in these production systems have proved to be difficult (FAO, 2011). The measures applied for the past 19 years have not prevented emergence of new H5 HPAI viruses within the Gs/GD/96-lineage. Therefore, unless novel, alternative control and preventive strategies are devised and implemented, new strains will continue to emerge and spread globally. Elimination of Gs/GD/96-lineage H5 viruses is still regarded as highly unlikely. Too many factors prevent virus elimination (FAO, 2011), including, but not limited to, the nature of production and marketing systems.

There is little likelihood of significant changes to duck production systems in the short term. China is home to a standing population of some 800 million ducks with most reared outdoors on ponds and/or rice paddy fields. Some have made calls for a shift back to aggressive stamping out. But even if adopted, this approach is highly unlikely to be successful given the difficulties in detecting all infected duck flocks, especially when many show no signs of infection and the high risk of re-infection following such measures if production systems remain the same. There is a need to apply alternative control methods especially as the available evidence suggests that once the virus is eliminated from poultry it will likely also disappear from wild birds

within a few years, as occurred in the past following each intercontinental wave.

Since 2004, FAO has recommended assessment of all available measures for control and prevention of HPAI, including vaccination, by countries or regions at risk or those which have repeated virus incursions. Each country or region should make decisions on the strategic use of the suite of measures available based on consideration of local factors, including the frequency of outbreaks/incursions, public health, the nature of the poultry sector and a cost-benefit analysis of the various measures.

Alternative measures may also be necessary in places where extensive production systems with high population density favour introduction and transmission of the virus, especially where it is not possible to enhance biosecurity.

Finally, the capacity to make even modest predictions depends on information from surveillance systems in the places described above with early reporting of results to the global community, including genetic data on isolates. FAO commends those veterinary authorities that have shared information on cases and gene sequences of viruses in a rapid and timely manner. ●

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Notes



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