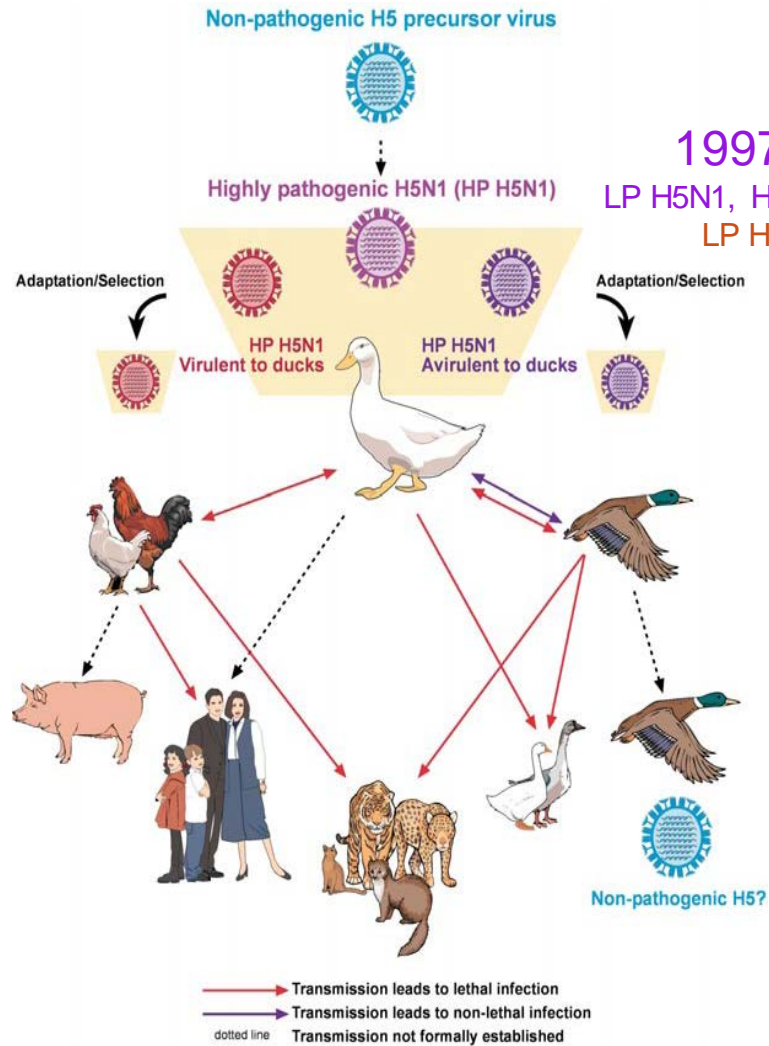


# OVERZICHT VAN HET ZONOTISCH PROFIEL VAN DE AZIATISCHE HP H5NX STAMMEN SINDS 2004

# REVUE DU PROFIL ZONOTIQUE ÉVOLUTIF DES SOUCHES ASIATIQUES DE HP-H5NX DEPUIS 2004

# HP H5 family introduction

## Back in time

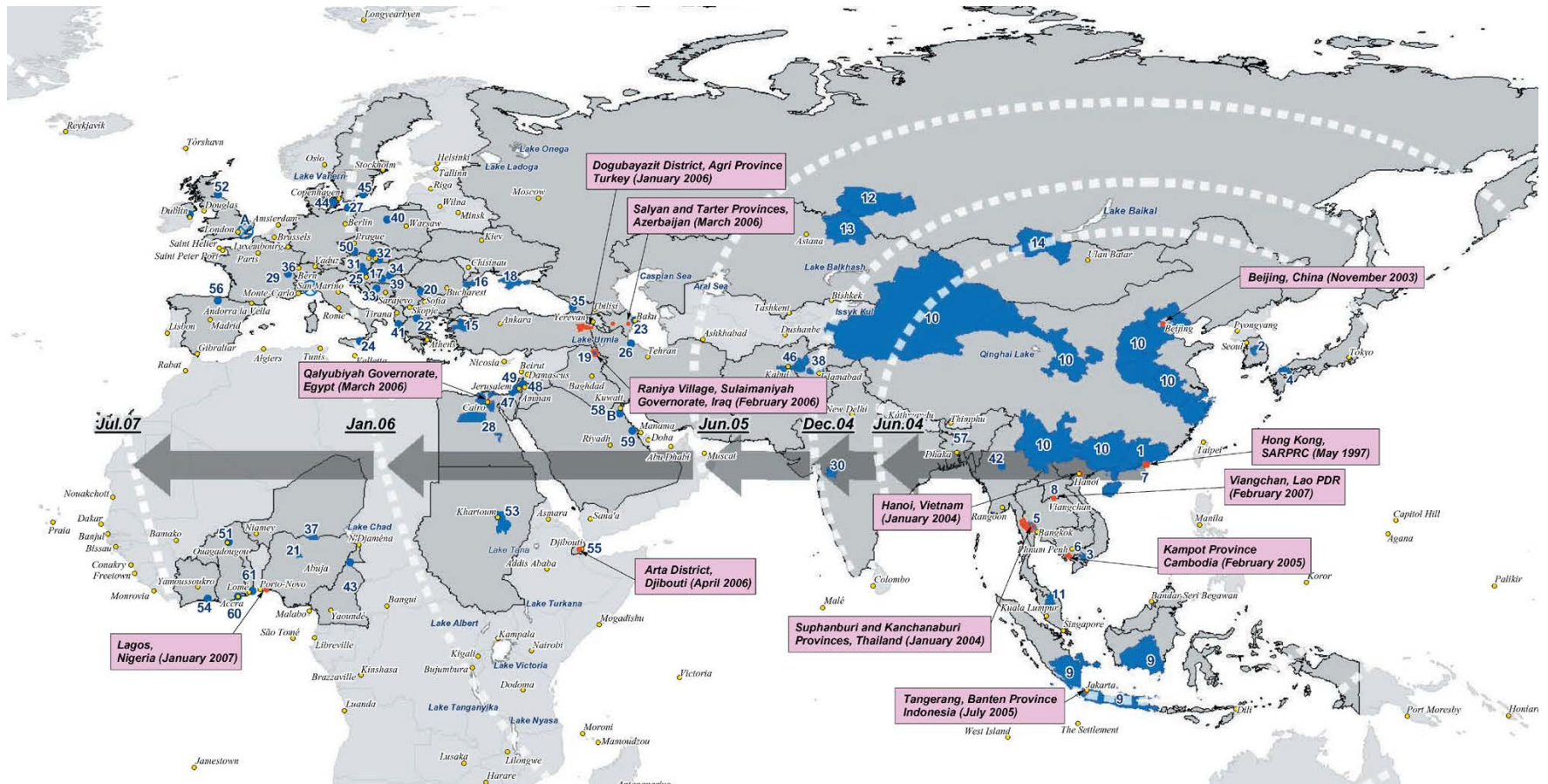


1996 GsGd precursor

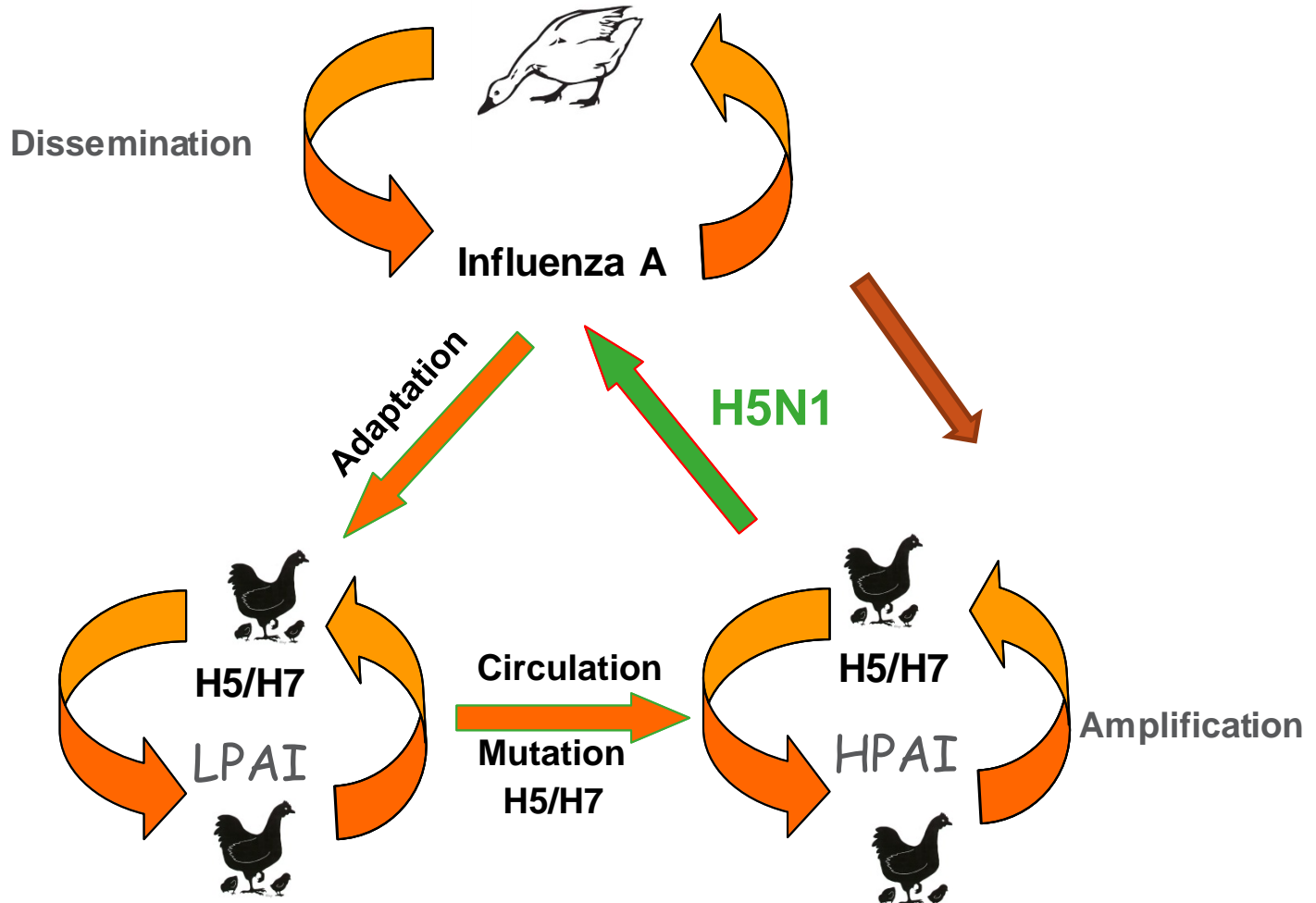
1997 and 2001 °HP H5N1  
 LP H5N1, H6N1 and H9N2-G1 reassortment  
 LP H5N1, H9N2 Y280, other LP avian viruses

⇒ ° New genotypes  
 A-E, Y, W, Z and Z+

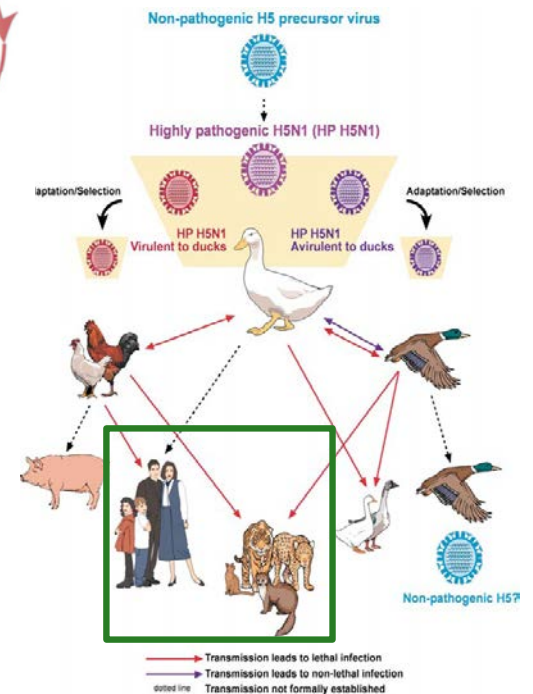
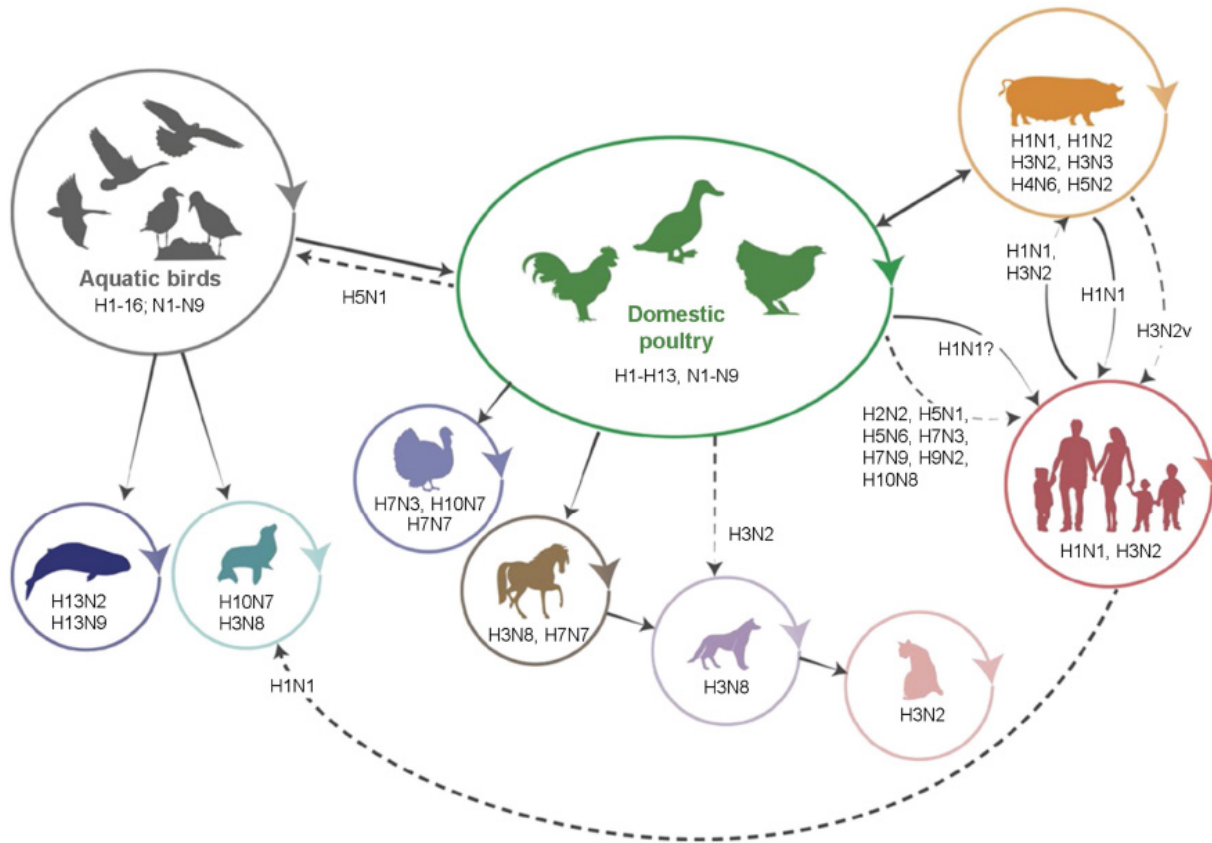
# HP H5-GsGd family



# AI paradigm 1



# HP H5 sporadic 'spill-over'

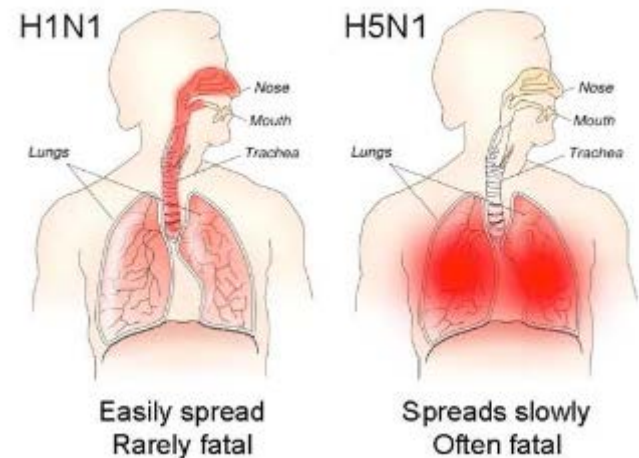
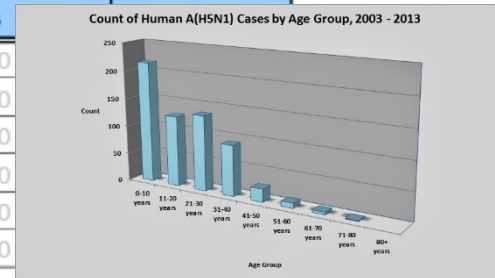




# HP H5N1 'spill-over'

## Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2021

| Country                          | 2003-2009* |            | 2010-2014* |            | 2015-2019* |           | 2020  |        | 2021  | Total |         |
|----------------------------------|------------|------------|------------|------------|------------|-----------|-------|--------|-------|-------|---------|
|                                  | cases      | deaths     | cases      | deaths     | cases      | deaths    | cases | deaths | cases | cases | deaths  |
| Azerbaijan                       | 8          | 5          | 0          | 0          | 0          | 0         | 0     | 0      | 0     | 0     | 0       |
| Bangladesh                       | 1          | 0          | 6          | 1          | 1          | 0         | 0     | 0      | 0     | 0     | 0       |
| Cambodia                         | 9          | 7          | 47         | 30         | 0          | 0         | 0     | 0      | 0     | 0     | 0       |
| Canada                           | 0          | 0          | 1          | 1          | 0          | 0         | 0     | 0      | 0     | 0     | 0       |
| China                            | 38         | 25         | 9          | 5          | 6          | 1         | 0     | 0      | 0     | 0     | 0       |
| Djibouti                         | 1          | 0          | 0          | 0          | 0          | 0         | 0     | 0      | 0     | 0     | 0       |
| Egypt                            | 90         | 27         | 120        | 50         | 149        | 43        | 0     | 0      | 0     | 0     | 359 120 |
| Indonesia                        | 162        | 134        | 35         | 31         | 3          | 3         | 0     | 0      | 0     | 0     | 200 168 |
| Iraq                             | 3          | 2          | 0          | 0          | 0          | 0         | 0     | 0      | 0     | 0     | 3 2     |
| Lao People's Democratic Republic | 2          | 2          | 0          | 0          | 0          | 0         | -     | -      | -     | -     | -       |
| Myanmar                          | 1          | 0          | 0          | 0          | 0          | 0         | -     | -      | -     | -     | -       |
| Nepal                            | 0          | 0          | 0          | 0          | 1          | 1         | -     | -      | -     | -     | -       |
| Nigeria                          | 1          | 1          | 0          | 0          | 0          | 0         | -     | -      | -     | -     | -       |
| Pakistan                         | 3          | 1          | 0          | 0          | 0          | 0         | -     | -      | -     | -     | -       |
| Thailand                         | 25         | 17         | 0          | 0          | 0          | 0         | -     | -      | -     | -     | -       |
| Turkey                           | 12         | 4          | 0          | 0          | 0          | 0         | -     | -      | -     | -     | -       |
| Viet Nam                         | 112        | 57         | 15         | 7          | 0          | 0         | -     | -      | -     | -     | -       |
| <b>Total</b>                     | <b>468</b> | <b>282</b> | <b>233</b> | <b>125</b> | <b>160</b> | <b>48</b> |       |        |       |       |         |



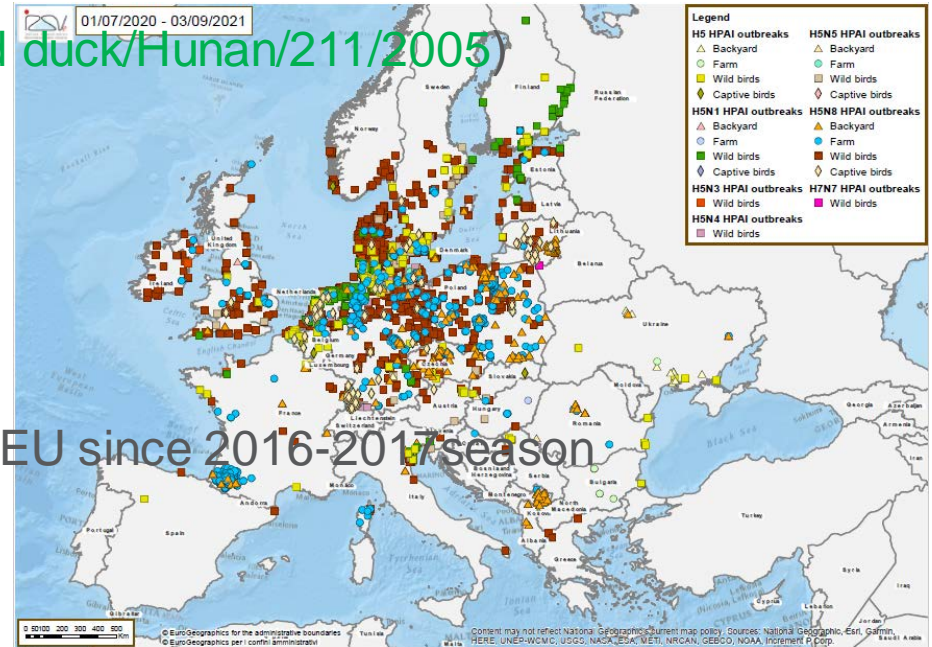
\* 2003-2009, 2010-2014 and 2015-2019 total figures. Breakdowns by year available on subsequent tab  
 Total number of cases includes number of deaths.  
 WHO reports only laboratory-confirmed cases.  
 All dates refer to onset of illness  
 Source: WHO/GIP, data in HQ as of 22 June 2021

# Zoonotic potential of the CLADE 2.3.4.4.B circulating in Europe?

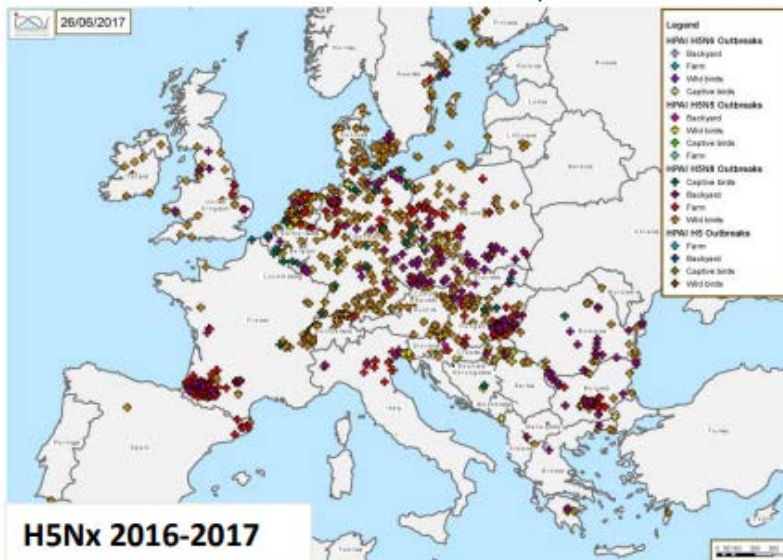
°2008 From clade 2.3.4 H5N1 (A/wild duck/Hunan/211/2005)

Gs/Gd reassortments

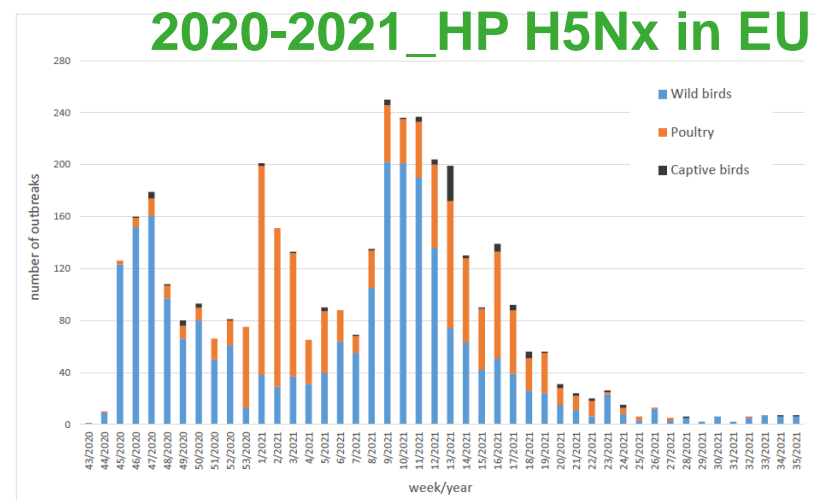
→ groups A-H



B. H5N8 China 2013+14, Korea 2014, EU since 2016-2017 season



## 2020-2021\_HP H5Nx in EU



# CLADE 2.3.4.4.B Europe Species affected

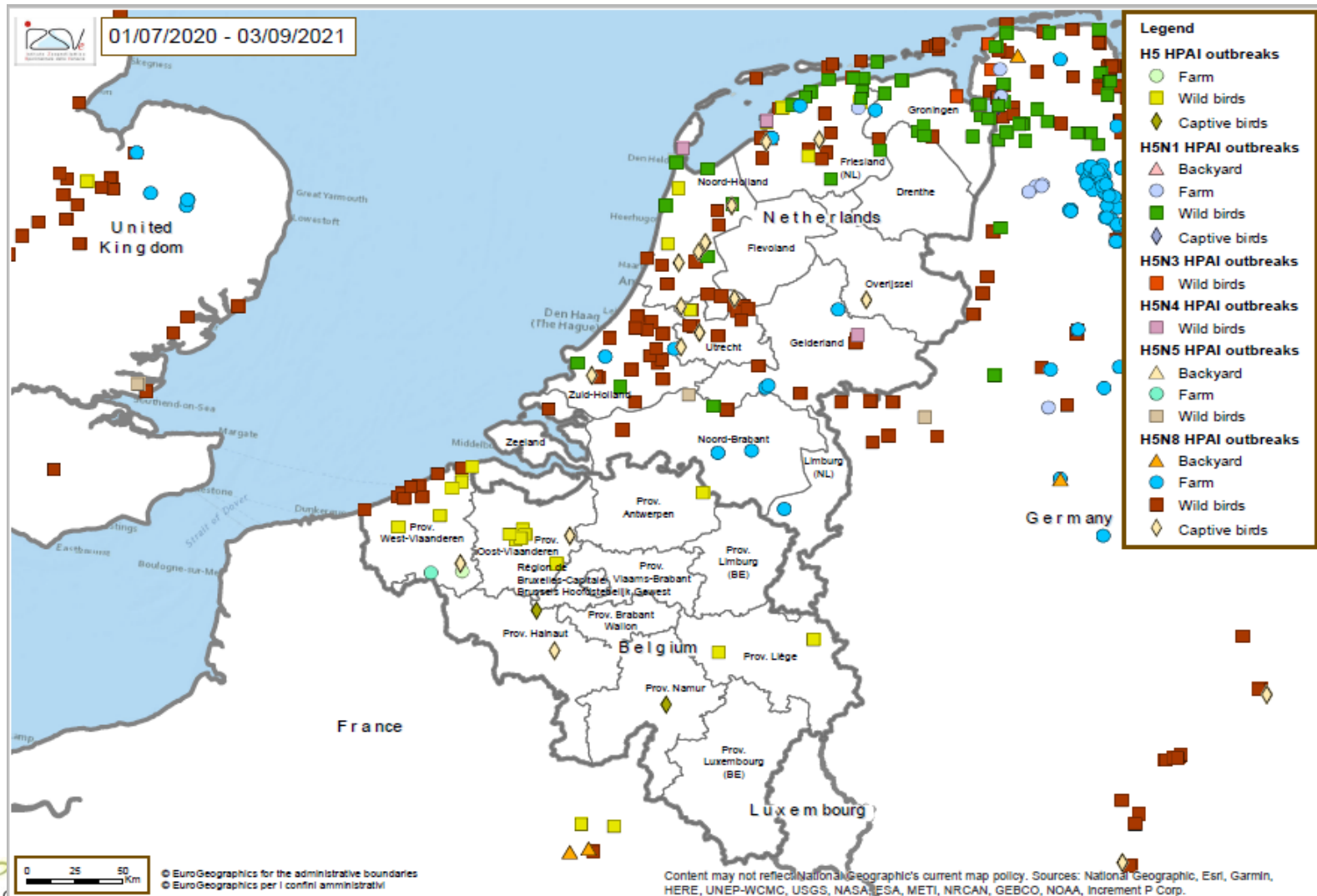
- > 80 species affected
- Wild waterfowl families, Swans and Geese, remain
- Prolonged circulation      Unnoticed circulation  
Need for active monitoring?
- Shift in species: 2005 – 2016 – 2020
  - ⇒ Swans and Raptors: “early warning/sentinels”
  - ⇒ Dabbling ducks as carrier?
  - ⇒ Rethink species lists
- Link to initial population affected?  
Flexibility to allow understanding of changing epidemiology

Table 1. Wild birds species involved in the HPAI epidemic, by order and number of cases

| Species   | Order            | number of cases |
|---|------------------|-----------------|
| Barnacle goose ( <i>Branta leucopsis</i> )              | Anseriformes     | 196             |
| Greylag goose ( <i>Anser anser</i> )                    | Anseriformes     | 93              |
| Eurasian wigeon ( <i>Mareca penelope</i> )              | Anseriformes     | 66              |
| Mute swan ( <i>Cygnus alor</i> )                        | Anseriformes     | 58              |
| Common buzzard ( <i>Buteo buteo</i> )                   | Accipitriformes  | 30              |
| Mallard duck ( <i>Anas platyrhynchos</i> )              | Anseriformes     | 28              |
| European herring gull ( <i>Larus argentatus</i> )       | Charadriiformes  | 16              |
| Gull ( <i>Laridae</i> )                                 | Charadriiformes  | 14              |
| Curlew ( <i>Numenius arquata</i> )                      | Charadriiformes  | 13              |
| Peregrine falcon ( <i>Falco peregrinus</i> )            | Falconiformes    | 10              |
| Taiga bean goose ( <i>Anser fabalis</i> )               | Anseriformes     | 8               |
| Eurasian teal ( <i>Anas crecca</i> )                    | Anseriformes     | 8               |
| Brent goose ( <i>Branta bernicla</i> )                  | Anseriformes     | 8               |
| Black-headed gull ( <i>Chroicocephalus ridibundus</i> ) | Charadriiformes  | 7               |
| Canada goose ( <i>Branta canadensis</i> )               | Anseriformes     | 7               |
| Eurasian eagle-owl ( <i>Bubo bubo</i> )                 | Strigiformes     | 6               |
| Greater white-fronted goose ( <i>Anser albifrons</i> )  | Anseriformes     | 5               |
| Wild black swan ( <i>Cygnus atratus</i> )               | Anseriformes     | 5               |
| Unspecified wild bird                                   |                  | 5               |
| Common kestrel ( <i>Falco tinnunculus</i> )             | Falconiformes    | 4               |
| Common eider ( <i>Somateria mollissima</i> )            | Anseriformes     | 3               |
| Great black-backed gull ( <i>Larus marinus</i> )        | Charadriiformes  | 3               |
| Accipitriformes ( <i>Accipitriformes</i> )              | Accipitriformes  | 3               |
| Pink-footed goose ( <i>Anser brachyrhynchus</i> )       | Anseriformes     | 3               |
| Eurasian sparrowhawk ( <i>Accipiter nisus</i> )         | Accipitriformes  | 2               |
| Northern shoveler ( <i>Spatula clypeata</i> )           | Anseriformes     | 2               |
| White-tailed eagle ( <i>Haliaeetus albicilla</i> )      | Accipitriformes  | 2               |
| Common shelduck ( <i>Tadorna tadorna</i> )              | Anseriformes     | 1               |
| Northern pintail ( <i>Anas acuta</i> )                  | Anseriformes     | 1               |
| Egyptian goose ( <i>Alopochen aegyptiaca</i> )          | Anseriformes     | 1               |
| Whooper swan ( <i>Cygnus cygnus</i> )                   | Anseriformes     | 1               |
| Gadwall ( <i>Mareca strepera</i> )                      | Anseriformes     | 1               |
| Shelduck ( <i>Anatidae</i> )                            | Anseriformes     | 1               |
| Eurasian oystercatcher ( <i>Haematopus ostralegus</i> ) | Charadriiformes  | 1               |
| Curlew sandpiper ( <i>Calidris ferruginea</i> )         | Charadriiformes  | 1               |
| Falcon ( <i>Falconidae</i> )                            | Falconiformes    | 1               |
| Strigiformes ( <i>Strigiformes</i> )                    | Strigiformes     | 1               |
| Short-eared owl ( <i>Asio flammeus</i> )                | Strigiformes     | 1               |
| Tawny owl ( <i>Strix aluco</i> )                        | Strigiformes     | 1               |
| Gruidae ( <i>Gruiformes</i> )                           | Gruiformes       | 1               |
| Common crane ( <i>Grus grus</i> )                       | Gruiformes       | 1               |
| Common moorhen ( <i>Gallinula chloropus</i> )           | Gruiformes       | 1               |
| Common coot ( <i>Fulica atra</i> )                      | Gruiformes       | 1               |
| Great cormorant ( <i>Phalacrocorax carbo</i> )          | Suliformes       | 1               |
| Northern gannet ( <i>Morus bassanus</i> )               | Suliformes       | 1               |
| Eurasian magpie ( <i>Pica pica</i> )                    | Passeriformes    | 1               |
| Common pheasant ( <i>Phasianus colchicus</i> )          | Galliformes      | 1               |
| Unspecified Charadriidae                                | Charadriiformes  | 1               |
| Great crested grebe ( <i>Podiceps cristatus</i> )       | Podicipediformes | 1               |
| Common wood pigeon ( <i>Columba palumbus</i> )          | Columbiformes    | 1               |



# 2020-2021\_clade 2.3.4.4.B HP H5Nx in Belgium



# 2020-2021 season CLADE 2.3.4.4.B Mammalian cases

## Bird flu: Russia detects first case of H5N8 bird flu in humans

© 2 days ago



December 2020



100% identical to local HP H5N8 wb strains

PA MEDIA

Russia has reported the first case of a bird flu strain, H5N8, being passed from poultry to humans.

## UK: Avian influenza H5N8 strain detected in seals and fox

18 March, 2021



[99.9%] identical to avian-origin H5N8  
mute swans



wildlife rescue centre  
33 AA's

November 2020

## Sweden, H5N8 in a grey seal March 2021



Home > News > WBVR tests foxes positive for bird flu (H5N1) >



100% identical to local HP H5N1 wb strains

News

BRAIN

WBVR tests foxes positive for bird  
flu (H5N1)

May, 2021

# Human molecular markers

Table 1 | Major viral determinants of host range for influenza A virus pandemics

| Amino acid                         | Avian | Human | Refs   |
|------------------------------------|-------|-------|--------|
| <b>Gene segment PB2</b>            |       |       |        |
| 271                                | T     | A     | 60135  |
| 590                                | G     | S     | 96-100 |
| 591                                | Q     | R     | 96-100 |
| 627                                | E     | K     | 46,67  |
| 701                                | D     | N     | 63-66  |
| <b>Gene segment HA (H1)</b>        |       |       |        |
| 190                                | E     | D     | 63,64  |
| 225                                | G     | D     | 63,64  |
| <b>Gene segment HA (H2 and H3)</b> |       |       |        |
| 226                                | G     | S     | 63,64  |
| 228                                | Q     | L     | 63,64  |
| 192                                | R     | G     | 63,64  |
| 226                                | Q     | L     | 63,64  |

HA, haemagglutinin; PB2, polymerase basic protein 2.

Taken from Long et al, Nature reviews, 2019



## Clade 2.3.4.4. EU 2020-2021

PB2 D701N

UK mammals H5N8, Dec 2020

Po duck and geese H5N8, May 2021

↑ replication in upper resp tract mammalian cells, and increased virulence in mice

PB2 E627K

Sw Grey Seal, H5N8, Mar 2021

Ro chickens H5N5, Febr 2021

↑ replication in upper resp tract and virulence mammals



# RISK ASSESSMENT: Zoonotic potential of the CLADE 2.3.4.4.B circulating in Europe?

- ❖ Intense circulation
  - Genetic variability: Reassortment + Mutation
  - Shared habitat wild/domestic birds and mammals
- ❖ Clinical healthy infected wild birds!! (EU season 2020-2021 / Russia 2021-2022)  
Persistence in wild birds and environment! ▶ Continued outbreaks/Herd Immunity/disappearance?
- ❖ Avian type receptor preference maintained  
°'13: >2800 close contacts 31 countries, eg culling activities: NO transmission to humans
- ❖ Sporadic
  - transmission to mammals
  - detection of mammalian molecular markers



**SURVEILLANCE in wild and domestic birds passive and active**

**Remain alert for zoonotic potential**

**Monitor viral evolution (genotypes, mutations, new virus introductions, ...)**

**Investigate dispersion**

# HP\_H5 clade 2.3.4.4.B human health risk

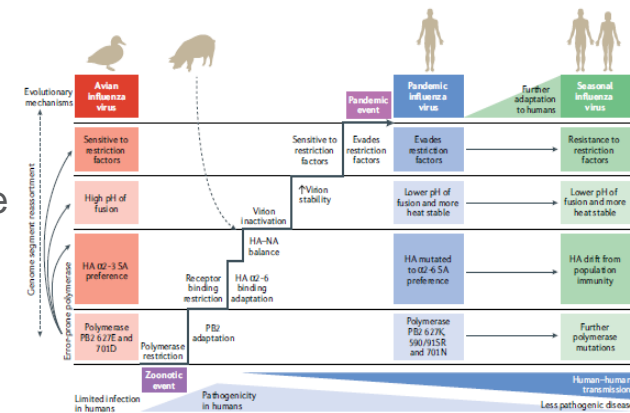
WHO

- Sporadic spillover and small clusters are possible



Pandemic pre-requisites

- spillover
- efficient replication\*: change receptor/pH/Temp-preference
- no pre-existing immunity
- efficient human-human transmission\*



Taken from Long et al, Nature reviews, 2019

- \*Studied in ferrets (guinea pigs) – contact+airborn ferret-ferret trm?
- **Risk human-to-human transmission low** (general public very low, occupational: low)
- Important to remain vigilant: Circulation = Evolution = Risk

**Surveillance** of viral evolution

**Awareness in human health sector**

(farmers and associates, veterinarians, ...)



# Avian Influenza Spill-over to humans

|   |       |
|---|-------|
| 1996 : UK (1 conjonctivitis)                | H7N7  |
| 1997 : Hong Kong SAR (18 cases/6 deaths)    | H5N1  |
| 1998 : China (5 cases)                      | H9N2  |
| 1999 : Hong Kong SAR (2 cases)              | H9N2  |
| 2002: Virginia (1 case)                     | H7N2  |
| 2003 : Hong Kong SAR (1 case)               | H9N2  |
| 2003 : Hong Kong SAR (2 cases, 1 death)     | H5N1  |
| 2003 : NI-Be : > 100 sero+-cases, 1 death   | H7N7  |
| 2003: NewYork (1case)                       | H7N2  |
| 2003-2014 : Eurasia : 650 cases, 386 deaths | H5N1  |
| 2004: Canada (2 cases: LP/HP)               | H7N3  |
| 2007: UK, Wales (4 cases: conj+ILI)         | H7N2  |
| 2007: HK (1 case)                           | H9N2  |
| 2013: Asia/China                            | H7N9  |
| 2013: Asia/China                            | H10N8 |
| 2013: HK (1case)                            | H9N2  |

↑ trend

# OTHER HUMAN INFECTIONS

**HP H5N6 (°2014)** 42 lab confirmed cases (12 August 2021) (Clade 2.3.4.4.a,b,d,g,h)  
 22 deaths, 52%  
 >50% contains PB2E627K or D701 substitution

**H7N4**

1 lab confirmed case (14 Feb )

**H7N9 (early 2013)**

| Clade    | Year(s)                | Number of human sequences | Country       |
|----------|------------------------|---------------------------|---------------|
| 2.3.4.4  | 2014-2015              | 6                         | China         |
| 2.3.4.4a | 2014                   | 1                         | China         |
| 2.3.4.4b | 2017 and 2020          | 2                         | China, Russia |
| 2.3.4.4d | 2015, 2016             | 9                         | China         |
| 2.3.4.4e | 2014, 2015             | 3                         | China         |
| 2.3.4.4g | 2016                   | 2                         | China         |
| 2.3.4.4h | 2017, 2018, 2020, 2021 | 10                        | China         |

33 HPAI's (14 Feb 2017)

no increase in transmissibility to and between humans

**H9N2 (12/2015)** 57 cases lab confirmed cases (23 August 2021), mild

**H10N3** 1 lab confirmed case (June 2021)

Most sporadic human cases ~ close contact with poultry  
 Likelihood Human-Human spread **LOW**

VIGILANCE FOR  
 VIRAL/EPIDEMIOLOGICAL/CLINAL  
 EVOLUTION

CLOSE MONITORING OF HUMAN  
 CASES AND  
 STUDY OF HUMAN ISOLATS

# H9N2, the devil in disguise?

Circulating in Asia since 1994

Enzootic in poultry populations in parts of Africa,  
Asia  
the Middle East

Widespread circulation in poultry, with wild bird ancestor

Poultry pathology      Respiratory problems  
Drop in egg-production  
Can affect shell quality  
Diarrhoea

**Delivered the 6 internal genes for**

**the H7N9 LP**

**Human**

**the H5N1 HP**

**Human/Poultry**

**the H10N8 LP**

**Human**

# CONCLUSION

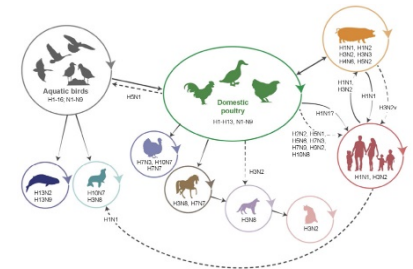
## Influenza as a zoonosis

There is a **huge reservoir** of antigenically variable influenza A viruses in wild birds

**Humans** may become **infected** either directly or indirectly (intermediate hosts/environment)

Human infections result mostly in minor **clinical symptoms** and limited **human to human transmission**

Severe clinical symptoms are mostly linked to underlying infections/diseases



**The potential  
to result in the emergence of a pandemic virus  
is present**