

# An update of H5N1 viruses: Are they still a threat to Australia?



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**Highly pathogenic avian influenza (HPAI) H5N1 viruses are now endemic in poultry over much of Asia and in areas of Africa. The continued presence of the virus has led to repeated outbreaks in poultry, with associated economic losses, and also to increased cases of human infection. In this article we summarise the continuing evolution and activity of these H5N1 viruses.**

The Asian HPAI H5N1 virus lineage was first described from an outbreak in geese in 1996 in Guangdong, China<sup>1</sup>. The viruses in this lineage have shown remarkable ecological success, demonstrating an unusually broad host range, persisting in diverse avian species with frequent introduction to multiple mammalian species including domestic cats<sup>2</sup>. Previous analysis has suggested that this broad host range may have resulted from the transmission of H5N1 viruses through the mixed poultry populations in farms and markets in China, the centre of origin of the lineage, which has selected HPAI H5N1 viruses that are well adapted to multiple hosts and reduced the barrier for interspecies transmission of these viruses<sup>3</sup>.

During the 15 years of their evolution, the HPAI H5N1 lineage has diverged rapidly and the WHO/OIE/FAO working group responsible for tracking the genetic evolution of this virus lineage currently recognises 19 major H5N1 sub-lineages (or clades)<sup>4,5</sup>. However, only six of the 19 major clades of HPAI H5N1 virus continue to circulate in various part of the world (Figure 1). The reasons for the success or failure of these different lineages are difficult to ascertain with available data and could be due to a myriad of virological, immunological and ecological factors. However, available data suggests that the spread of the virus to distant geographic regions are usually associated with migratory bird infections<sup>6,7</sup>, while their persistence may be due to the poultry population structure<sup>3</sup>. These factors may explain the observed diversity of H5N1 viruses.

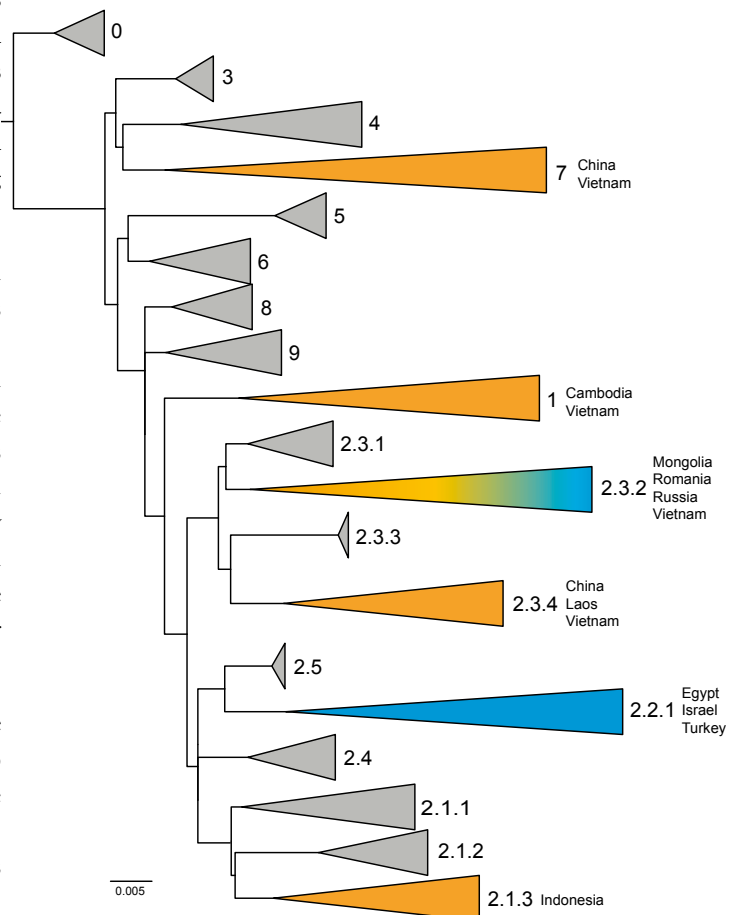


Figure 1. Stylised phylogenetic tree of H5N1 virus haemagglutinin illustrating evolutionary relationships of major virus lineages (clades). Coloured triangles indicate actively circulating virus lineages in Asia (orange), North Africa and the Middle East (blue), Asia and Europe (orange/blue gradient). Country names indicate areas that corresponding virus lineages have been detected in poultry or humans in the past two years. Grey triangles indicate virus lineages that have not been detected in over two years.

Available data also suggests that much of the genomic diversity of H5N1 viruses were generated within southern China<sup>8</sup>, with more than 40 genotypes generated in the region<sup>9</sup>; however, no subsequent reassortment has been detected upon transmission to other geographical regions. Evolutionary analyses showed that this genotypic diversity was generated through the regional poultry system, which contains a diverse group of aquatic and terrestrial birds that harbour endemic populations of H9N2 and H6N1 viruses, along with the frequent introduction of the genes from the wild gene pool<sup>9</sup>. While surveillance for the H5N1 virus worldwide has intensified, prevalence of other subtypes, particularly H9N2 and H6N1 viruses that are thought to be endemic in several countries, remains sparse.

The virus that caused the resurgence on H5N1 in South-east Asia (clades 1, 2.1, 2.2 and 2.3), denoted genotype Z, contained gene segments that were prevalent in poultry since 1992<sup>3</sup>. Genotype Z viruses were also responsible for the infection of migratory birds in Qinghai in 2005, followed by their spread towards West Asia, Europe and Africa<sup>7</sup>. Subsequently, in 2005, a new genotype (V)<sup>10</sup> that had acquired the PA gene from the wild aquatic gene pool emerged in China. These viruses, which belong to H5N1 HA clade 2.3.2 have been dominant in southern China since 2005<sup>11</sup> and have subsequently been detected in South-East Asian countries<sup>4,5</sup>.

In 2010, 17 countries reported either outbreaks of H5N1 in poultry or detected H5N1 in wild birds. The majority of countries reporting poultry outbreaks were in Asia (n=12) with the greatest outbreak activity seen in Indonesia and Vietnam<sup>12</sup>. In Africa, reported poultry outbreaks were restricted to Egypt, where the virus is apparently endemic with H5N1 detected in poultry throughout 2010, and in the Middle East only Israel reported poultry outbreaks. Wild bird infections were recorded in all three European countries (Bulgaria, Romania and Russia) that reported H5N1 activity in 2010, while only Romania and Russia reported poultry outbreaks<sup>12</sup>.

In addition, the frequent introduction to humans, often with fatal outcome<sup>13</sup>, suggests this virus presents a continuing pandemic threat. Since the resurgence of H5N1 viruses in 2003 there have been 516 cases of human infection confirmed by the WHO with 306 fatalities (59%) (Table 1). However, there is a wide range in case fatality rate, from 33% in Egypt and 82% in Indonesia. Many factors may contribute to this variation, such as time to hospitalisation as appears to be the case in Egypt<sup>14</sup>; animal experiments have also suggested variation in pathogenicity of viruses from different clades<sup>15</sup>.

The detection of H5N1 viruses in pigs in China and Indonesia<sup>16,17</sup> compounds this issue, raising the possibility of reassortment of H5N1 with circulating swine or human influenza A viruses, thereby increasing the pathogenicity or transmission potential of these viruses; however, at present there is no evidence for persistent transmission of H5N1 viruses between any mammals.

Table 1. Cases of human H5N1 infection and associated mortalities<sup>13</sup>.

Country	Cases	Deaths
Azerbaijan	8	5
Bangladesh	1	0
Cambodia	10	8
China	40	26
Djibouti	1	0
Egypt	120	40
Indonesia	171	141
Iraq	3	2
Laos	2	2
Myanmar	1	0
Nigeria	1	1
Pakistan	3	1
Thailand	25	17
Turkey	12	4
Vietnam	119	59
<b>Total</b>	<b>517</b>	<b>306</b>

Despite intensive efforts to control this virus, either through vaccination or culling, H5N1 continues to infect poultry populations through large sectors of the world. The continuing evolution of H5N1 viruses, and the development of endemicity in Indonesia and Egypt present a continuing threat. Of particular concern for Australia is the situation in Indonesia. Due to the geography of Indonesia – a fragmented archipelago that allows isolated populations of the virus to persist – this has been a major area of diversification of H5N1 viruses and allowed the emergence of lineages with little antigenic cross-reactivity<sup>4,5</sup>. This situation greatly complicates control measures and, in the absence of effective universal vaccination in poultry populations, it is therefore unlikely that H5N1 virus can be effectively controlled any time in the near future. Yet the fact remains that HPAI H5N1 virus has not been detected in Australia, despite circulating in Indonesia for over seven years. Given that the mechanisms for transfer of this virus over large distances – particularly the role of migratory and other wild birds – are still debated, the reason for this is difficult to ascertain. However, it has been suggested that the prolonged geographic separation between virus gene pools in Eurasia and North America has resulted in fundamental differences in the viral fitness between the two lineages, and that this may be a factor in long-distance influenza transmission<sup>17</sup>. As Australian influenza viruses appear to form genetically separate lineages from the Eurasian and North American lineages<sup>18</sup>, this proposed mechanism could help explain the failure of H5N1 viruses to reach Australia.

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## Biographies

**Gavin & Vijay** are Principal Investigators of the Laboratory of Virus Evolution (LoVE) at Duke-NUS Graduate Medical School Singapore. LoVE's major research focus is on the ecology, evolution and interspecies transmission of emerging infectious diseases, particularly influenza. Our research is directed at efforts to better understand virus ecosystems in Asia, specifically at the animal-human interface, to inform and enhance disease control.

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