

## VIROLOGY

# Bird flu virus's promiscuity raises red flags

Novel variants of H7N9 and other strains are arising at alarming rate

By Dennis Normile

The most worrisome of the avian flu viruses to emerge in recent years is looking even more menacing. Since it first began killing people in eastern China 2 years ago, the H7N9 virus has infected poultry throughout the country and could be poised to spill into Central Asia. Worse, strains of H7N9 are promiscuously swapping DNA with other avian viruses in circulation, report virologist Yi Guan of the University of Hong Kong and colleagues this week in *Nature*. That could increase the chance that a pandemic strain will emerge.

Mindful of how predictions a decade ago of an imminent H5N1 pandemic proved shrill, public health officials are advising calm while heightening vigilance for any signs of H7N9 evolving into a form that could spread rapidly among people. In a document released last month, *Warning signals from the volatile world of influenza viruses*, the World Health Organization (WHO) notes that four new H5 avian flu viruses have emerged in the past 2 years. “The diversity and geographical distribution of influenza viruses currently circulating in wild and domestic birds are unprecedented,” WHO warns. “The world needs to be concerned.” As a first step, Guan and other experts are renewing calls to close China’s live poultry markets, where most victims catch H7N9—and where animals can contract multiple virus strains, allowing them to swap genetic material.

Based solely on case mortality rate—38%—the H7N9 virus is not as nasty as H5N1, a bird flu strain that has killed 55% of people known to have contracted it since 2003 (see table). But in just 2 years, H7N9 has infected 602 humans, running almost neck and neck

with H5N1. “Humans seem more susceptible” to H7N9 infection, Guan says. Two mysteries about H7N9 deepen the concerns. Researchers still don’t know where or if the virus circulates in nature, and infected poultry show no or very mild symptoms, confounding surveillance.

Still, H7N9 is clearly spreading (*Science*, 29 November 2013, p. 1031). The first human cases were in Anhui province and Shanghai,

genetic exchange.

Other bird flu viruses are reassorting like mad. The H and N in the nomenclature for flu viruses refer to two surface glycoproteins: hemagglutinin, for which 18 different genes are known, and neuraminidase, which is encoded by 11 different genes. Influenza viruses have shuffled these and six other viral genes into a dazzling array of combinations, and the reassortment “appears to be happening now at an accelerated pace,” WHO warns. Guan’s team amplifies the warning in their *Nature* paper. The “H5N1 and H9N2 viruses, along with the H7N9 virus, are now reassorting with other viruses in the influenza ecosystem in China,” the team writes.

The proliferation of strains over the past 2 years is a particular puzzle. “Something has changed, which made some of these more recent strains more readily able to produce reassortments,” says Les Sims, a Melbourne, Australia-based veterinary consultant. The WHO report concludes: “The emergence of so many novel viruses has created a diverse virus gene pool made especially volatile by the propensity of H5 and H9N2 viruses to

exchange genes with other viruses. The consequences for animal and human health are unpredictable yet potentially ominous.”

Attention focuses on China’s live poultry markets, where “we have a lot of different subtypes of avian viruses dynamically reassorting,” says George Gao, deputy director-general of the Chinese Center for Disease Control and Prevention. To forestall disaster, “we need to close the live poultry markets now and [halt] live poultry trading,” says Gao, who called for such steps last year in *Science* (18 April 2014, p. 235). As a start, authorities have banned markets from some urban centers. ■

## A tale of two bird flus

H7N9 may not be as lethal at present as H5N1, but virologists worry about its pandemic risk because of the number of cases and how fast the virus is mutating.

	H5N1	H7N9
Year identified	1997	2013
Human cases/deaths	777/428 (since 2003)	602/227 (since 2013)
Effect on domestic chickens	Highly pathogenic	No or mild symptoms
Natural host	Aquatic wildfowl	Unknown



China's live poultry markets are hotbeds of viral gene swapping.

along China’s east coast, in early 2013. By the following year, H7N9 had been reported in 11 provinces and municipalities. Last fall it popped up in Xinjiang, China’s westernmost region. From there, “this virus has the chance to get to other countries,” Guan says.

At the same time, it is rapidly diversifying. Guan’s team found that all H7N9 samples collected during the spring 2013 outbreak could be grouped in one clade, or phylogenetic branch. Samples collected a year later, from thousands of chickens in 15 cities across China, painted a different picture. Sequencing the viruses showed that H7N9 had split into three clades, as a result of rampant