



H7N9 is a virus worth worrying about

Warnings about the emergence of another influenza virus may elicit scepticism, but we should not be complacent, cautions Peter Horby.

Once again an animal influenza A virus has crossed the species barrier to cause an appreciable number of human cases. Now, two months after the first known human infections with the H7N9 virus, the question is: which of the paths set by previous emerging influenza viruses will it follow?

One predecessor, H5N1, generated alarm owing to its high pathogenicity in humans. It has proved to be a tenacious adversary, remaining endemic in poultry across large parts of Asia, but thankfully it has not adapted to humans and person-to-person transmission remains rare. A second, H7N7, caused a number of mostly mild human infections in the Netherlands in 2003, with some evidence of limited person-to-person spread, but extensive poultry culling controlled it. A third, the H1N1 swine influenza virus that emerged in 2009, successfully adapted to humans and caused a pandemic.

So will H7N9 prove to be controllable? Will it remain entrenched in animals? Or will it, like the H1N1 virus, stably adapt to humans and cause a pandemic? The fine line between foresight and alarmism can only be drawn in retrospect. Nevertheless, my colleagues and I consider that H7N9 has many of the traits that make a new flu virus worrisome.

The H7N9 haemagglutinin protein — which binds to target cells — resembles those of other avian flu viruses that cause only mild disease in birds. This means that the virus is likely to spread silently in domestic and probably wild birds. Human infections are therefore the sentinel events, and the numbers and geographic extent of human cases — all of them so far in China — suggest that a hidden epidemic in other animals is well under way.

The small number of poultry in which H7N9 has so far been detected is rather puzzling, as are the 20% of people infected with the virus who have not reported exposure to poultry. Nevertheless, domestic birds are likely to be the main source of human infections. And the animal epidemic is likely to spread farther, with large suppliers distributing poultry across China. Flying wild birds are another possible mode of spread. Given that the virus probably does not cause severe disease in birds, and the uncertainty surrounding the animal source, containing the animal epidemic poses an enormous challenge.

So far, extensive monitoring of contacts has not found evidence that the virus has spread efficiently between people. Limited human-to-human transmission may have occurred but, as we saw with H5N1 and H7N7, this does not necessarily represent the early stages of a trajectory towards full human adaptation. However, H7N9 viruses isolated from patients possess some genetic signatures that are associated with effective replication and transmission, and with high virulence in mammals. The regions of China

where H7N9 seems to be circulating have large populations of pigs as well as humans, providing opportunities for further adaptation to mammals and for re-assortment with human- or pig-adapted viruses.

The clinical epidemiology of H7N9 cases has some similarities to human seasonal influenza. Unlike the H7N7 cases in 2003, which usually took the form of conjunctivitis, the H7N9 infections so far detected have caused respiratory illness, with cases in all ages but being most severe in the elderly and people with underlying illnesses. However, the fact that the average age of people infected is high — around 60 years — and that most reported infections have been severe suggests that the virus is not yet well adapted to humans. Only further clinical and epidemiological data will reveal the full spectrum of infection and severity.

Standardized collection and sharing of clinical data would aid risk assessment and treatment. A clinical protocol and case-record and informed-consent forms developed by the International Severe Acute Respiratory and Emerging Infection Consortium and the World Health Organization are available online (see go.nature.com/fpsioj).

If H7N9 were to stably adapt to humans, it would probably meet with little or no human immunity. Detecting and tracking a partially human-adapted H7N9 virus in a city as vast as Shanghai or Beijing would be difficult; tracking a fully adapted virus would be impossible. And it could easily spread nationally and internationally. Eastern China is now one of the most 'connected' population centres in the world. Seventy per cent of the global popula-

tion outside China lives within two hours of an airport linked to the outbreak regions by a direct flight or a single connection (see go.nature.com/tvfev8). Travel restrictions or border screening will not contain pandemic influenza for long.

If there was an overreaction to H1N1, we should not compound the error by under-reacting to H7N9. Hopefully H7N9 will remain an animal virus, and maybe the fact that it has circulated for at least two months without stably adapting to humans indicates that the species barrier is too great for it; but maybe not. The first human case of H7N9 outside mainland China is perhaps only a matter of time. Then the public-health and clinical community will need to assess, carefully and quickly, whether it represents a single imported case of animal-to-human transmission, an animal epidemic that has spread abroad, or the international spread of a partially or fully human-adapted virus. ■

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