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Should we worry about “bird flu”?

A major human outbreak of H5N1 is plausible, and the risk is high

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Concerns are mounting over the threat to humans from a highly pathogenic avian influenza virus, a threat first recognised in the late 1990s when a new clade of the H5N1 virus was detected in domestic waterfowl in China. The first human cases, all linked with exposure to infected poultry, were reported from Hong Kong in 1997,[1] and the World Health Organization recorded a total of 463 deaths among 888 cases between January 2003 and March 2024.[2] Infections are under-reported, but the high ratio of deaths to cases (52%) suggests that H5N1 could cause a major public health emergency if human exposure and viral evolution lead to sustained person-to-person transmission.

We do not know if that will happen, but the likelihood seems to have risen over the past four years. One reason for this is the continuing spread of H5N1 clade 2.3.4.4b viruses in wild and farmed bird populations; thousands of outbreaks have now been recorded, from all continents. This reproductively successful clade of H5N1 is affecting poultry production and trade globally. It is also carried by migratory birds, whose trans-continental movements may have shifted with changes in climate and land use for agriculture.[3]

The threat is magnified by frequent spillovers of virus from birds to mammals, including sea mammals that have scavenged infected seabirds and foxes, mink, and raccoon dogs on fur farms in Finland and Spain.[4] **[correct?]** The recent surprising discovery of clade 2.3.4.4b viruses in US dairy cows adds to the evidence that H5N1 can be transmitted to and among mammals.[5] More than 40 farms are now affected in at least nine states. The virus has passed from the cows to cats and wild birds on farms, and into neighbouring poultry holdings. High

titres of infectious virus are present in milk, and although the virus can be inactivated by pasteurisation, human consumption of raw milk is not uncommon.[6]

Mutations in viral genes that enhance replication in mammalian cells have been detected in the sequences released from infected cows, and viruses are being closely monitored for further adaptive signatures.[7] At least three people **[Q to A mention third case with respiratory symptoms just announced?]** have been infected during the US outbreak: two livestock farm workers in Michigan and Texas developed conjunctivitis and recovered; more worryingly, a third in Michigan had a mild respiratory illness after unprotected exposure to an infected cow.[8]

So far, a full set of adaptations required for airborne transmission among people, including mutations that increase binding to receptors in the upper respiratory tract, have not been found together in H5N1.[4] But with the virus so prevalent in wild and farmed birds and mammals, people are exposed more than ever, providing a human land of opportunity for viral mutation and recombination.

The hazard and risk of a major outbreak of H5N1 are large, plausible, and imminent, so we need to put plans in place now for pandemic prevention, preparedness, and response. Decision makers must maximise available information about H5N1, manage uncertainty, fine tune tools for prevention and control, and align incentives for using them.[9]

Effective preparation

Information is required on the hazards posed by infection, such as infection fatality ratios; the risk of an outbreak, which depends on the source of infection, its transmissibility to and among people, and the potential for adaptive changes to the virus; and the likely timing of an outbreak, which hangs on the duration and frequency of animal-human contacts. These data are needed to evaluate threat levels and explain publicly the reasons for implementing restrictive control measures.

Some desirable facts are unknowable, no matter how much data are available. We cannot be sure whether the next outbreak of transmissible human influenza will be caused by H5N1 or by another avian flu subtype, for example. The next pandemic could be caused by an entirely different pathogen—perhaps a coronavirus (like MERS or SARS-CoV), a paramyxovirus (like Nipah), or a retrovirus (like HIV). Although the spotlight is now on H5N1, generic surveillance systems that track infections in animals (blood, milk, saliva), humans (clusters of unknown illness), and the environment (water, air, soil) can identify

outbreaks caused by many different pathogens and should be implemented as a priority worldwide.

On US dairy farms, use of personal protective equipment and restrictions on farm visits could limit human exposure to H5N1, while rigorous disinfection of farm equipment and facilities will help prevent spread among cows. The current PCR and lateral flow diagnostic tests for infection in both humans and animals should be evaluated for specificity and sensitivity to the current bovine virus, and modified accordingly. **[Do you mean that existing tests for H5N1 in both animals and humans could be evaluated for specificity and sensitivity to the current bovine clade? Are there any existing tests?]** Candidate vaccine viruses, generated from related H5 strains, are predicted to have antigenic overlap with the current bovine virus, **[ref?]** and these could be used to generate pre-pandemic vaccines. H5N1 remains susceptible to antiviral agents oseltamivir **[correct?]** and baloxivir marboxil **[correct? we don't use brand names] . [refs]**

Finally, plans for pandemic prevention must focus not only on what should be done but on how to encourage decision makers to do it. The current, tough negotiations over WHO's pandemic accord are a reminder that real conflicts of interest exist over access to pathogens for R&D **[meaning ok?],** benefit sharing, intellectual property, technology transfer, who provides and controls the money for pandemic control, and how signatories will be held to account.[10-12] Over the past decade, the Ebola, Zika, mpox, and covid-19 emergencies have underlined the value of a globally cooperative approach to pandemic prevention and control. A new accord will succeed only if it appeals to reason—aligning different perceptions of hazard, risk, and urgency to offer each stakeholder sufficient benefits for the costs incurred.

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