PUBLIC HEALTH

Public Health Risk from the Avian H5N1 Influenza Epidemic

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The ongoing H5N1 influenza epidemic in Asian bird populations poses risks to public as well as animal health (*1*), due to the potential for cross-species transmission to humans and subsequent reassortment of avian and human influenza viruses in coinfected individuals (*2*). Reassortment could link the high transmissibility associated with human-adapted viruses with the high rates of mortality observed in the current human cases and thus trigger a potentially devastating pandemic.

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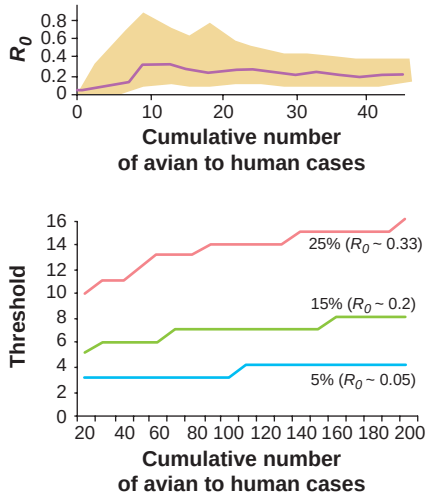
Good pandemic planning (*3*) and worldwide surveillance is central in mounting an effective global response to combat such threats. However, surveillance must be linked to appropriate analysis for the stuttering beginnings of a threatening epidemic to be detected rapidly and reliably. Currently the World Health Organization (WHO) tracks the number of avian-to-human and possible human-to-human transmission events reported. Detection of even a single case of human-to-human transmission of an avian virus can cause an increase in pandemic alert levels—at potentially high cost to affected countries (particularly if travel advisories are issued). Here, we argue that observation of low-level human-to-human transmission is not a key threshold, but rather the primary focus should be on detecting increases in viral transmissibility at a stage where containment might be feasible. To help ongoing consultation (*4*), we present a method to detect increases in viral transmissibility based on examination of clusters of human cases.

The WHO Global Influenza Network (*5*) was established in 1948, and today comprises 4 collaborating centers and 112 institutions recognized as WHO national influenza centers in 83 countries. The major focus of the network is on compiling information for influenza vaccine formulation, based on the analysis of viral isolates collected in the participating countries. It also serves as a mechanism for alerting countries to the emergence of strains with pandemic potential or unusual pathogenicity. A survey of the network in 2002 resulted in the development of a WHO action plan for the next 5 years to improve on current surveillance weaknesses (*6*). Issues highlighted were the current wide variability in the number of viral isolates submitted by different countries, and the limited fraction of isolates that undergo detailed analysis and sequencing.



Analyzing avian influenza surveillance data. (Top) Illustration of the reliability of R_0 estimation methods. R_0 estimates (the shading delineates the 95% confidence intervals) are shown derived from data on the number of avian-to-human cases seen, the number of human-human clusters, and the size of the largest cluster. The surveillance data used was generated by simulating an avian influenza epidemic with R_0 = 0.2 in humans. **(Bottom)** Threshold size of the largest cluster expected by chance for a range of levels of human-to-human transmission, as quantified by the proportion of avian-to-human cases generating secondary cases (approximate R_0 values are also shown). Anomalous behavior might be suspected if a cluster exceeds this threshold size. Note how the expected maximum cluster size increases cases accumulate. See supporting online material for methods.

Surveillance of avian and livestock (particularly porcine) influenza is less satisfactory. Government veterinary services are responsible for surveillance, with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) collating data from those countries submitting information on disease outbreaks. There is no systematic surveillance for influenza in livestock or wild birds based on random sampling or other well-defined sampling schemes. Most data are collated from outbreaks causing high morbidity and mortality. Furthermore, outside of the developed world, few countries have the veterinary services infrastructure to undertake effective surveillance. As the current H5N1 avian epidemic highlights, the zoonotic origin of pandemic influenza strains means that improved surveillance and control of animal (particularly avian) influenza needs to be a priority—as much to safeguard public health as to promote animal welfare.

The demands of annual vaccine preparation inevitably mean that greatest emphasis is placed on monitoring antigenic variation and understanding its molecular basis. However, improving pandemic surveillance additionally requires more research (in secure laboratory settings) to measure the frequency of viral reassortment in hosts exposed to multiple different viral strains and to define the detailed genetic basis of host specificity, pathogenicity, and transmissibility (*7*).

How do we quantify the possible risks of a pandemic strain's emerging, and how can we rapidly but reliably detect the emergence of such a strain? Simple mathematical analysis can provide some insights. At any time point, the risk of a reassortment event is proportional to the number of people coinfected with human and avian strains. Making the reasonable assumptions that 10% of the population are infected with human influenza over the 12 weeks of a typical influenza season (*8*), and that there is a 1-day window in early infection where coinfection with an avian strain is possible, then 0.12% of the population are susceptible to coinfection with an avian strain at any one time. Hence, even if reassortment is certain following coinfection, the probability of a reassortment event having occurred after n cases of avian influenza in humans is $1 - (1 - 0.0012)^n$; so 600 human infections would be required for a 50% chance of reassortment, and around 45 for a 5% chance. If reassortment is a rare out-

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come of coinfection or other processes reduce the chance of coinfection (*9*), then the number of infections required for reassortment to become likely increases substantially. The risk of a pandemic is therefore currently small but not negligible. As the risk increases directly with the number of human H5N1 infections, it is critical that the avian epidemic is contained as rapidly as possible and that the risk of human-avian contact is minimized in affected areas.

In designing a surveillance strategy to detect the start of a pandemic—namely, sustained human-to-human transmission of an H5N1-like virus—it is important to note that a small number of human-to-human transmission events is not necessarily an indication that reassortment has occurred. Even if the avian virus has not adapted to humans, some infected individuals might be expected to have low-level infectiousness (*10*, *11*). However, human-to-human transmission occurring below self-sustaining levels does not intrinsically pose any greater risk of reassortment than avian-to-human transmission (*12*). Self-sustaining transmission occurs when the number of secondary cases caused by a primary case [termed the basic reproduction number, R_0 (*13*)] is greater than 1, as this allows amplification of case numbers from one round of infection to the next. If $R_0 < 1$, then chains of human-to-human transmission will inevitably die out

We believe that a valuable added dimension to surveillance could be provided by systematically quantifying transmissibility (as measured by R_0) of avian influenza viruses threatening human populations. This would provide estimates of the baseline rate of human-to-human transmission events expected in the absence of a reassortment event. Only then is it possible to provide robust early warning of levels of human-to-human transmission which fall outside this expected range.

The first priority of surveillance is clearly to identify all cases of avian influenza in humans. Quantifying human-to-human transmission then requires detailed case investigation and contact tracing to allow avian-to-human and human-to-human transmitted cases to be separately enumerated. Data on both types of case incidence and application of simple mathematical models of disease transmission (*14*–*16*) (see supplementary information) then allows R_0 to be estimated as $p_C/(1 - p_C)$, where p_C is the proportion of avian-to-human cases generating secondary cases.

In the absence of reassortment, all human cases would be expected to be infected with viruses of similar (low) intrinsic infectiousness. Any reassortment event leading to a new virus of significantly higher transmissibility (and thus heightened public health risk) will result in an anomalously large cluster (a cluster being defined as a set of human cases all linked back to a single avian-to-human index case) with increased R_0. Mathematical analyses can be used to test whether the size of the largest cluster observed is consistent with the overall numbers of avian-to-human and human-to-human cases recorded. Simulation studies (see supporting online material) show that this is a sensitive and specific test for early detection of anomalous clusters.

It is therefore also important for surveillance systems to monitor how human-to-human cases are distributed into clusters, with the size of the largest cluster being the most critical statistic to be recorded. Availability of data on clusters as well as overall case numbers also improves the reliability with which R_0 can be estimated as the avian epidemic unfolds. High precision does not require large case numbers. Simulation shows that reliable estimates can be obtained (see figure on page 968) with as few as 30 cases (as were recorded in 6 weeks during the current H5N1 epidemic).

The same model used to estimate R_0 can also be used to calculate the threshold size of the largest human cluster above which reassortment (or another anomalous occurrence—such as a "super-spreading event" of the original avian virus) is likely to have occurred (see bottom of figure). Taking a hypothetical example of a future H7 avian epidemic, let us suppose secondary transmission was seen in 25% of 100 avian to human cases recorded. Looking at the upper curve, occurrence of a cluster of more than 14 cases would suggest that reassortment (or other anomalous event) had occurred. Such thresholds could act as a trigger for heightening alert levels or containment measures—but only if great care is taken to ensure the consistency of case reporting and detailed epidemiological investigation of all potential clusters.

In the current avian epidemic, by April 2004, a total of 33 H5N1 cases in humans resulting from the avian epidemic had been reported (*17*). Of these, 31 have been conclusively attributed to avian-to-human transmission, with only 2 cases (in sisters) being possible (though unproven) candidates for human-to-human transmission (from their brother) (*18*). Making the conservative assumption that those two cases and their brother make up a single transmission cluster gives an estimated R_0 of 0.06 (95% confidence interval: 0.01,0.2)—well below the $R_0 = 1$ threshold for self-sustaining transmission.

However, the uncertainty in this estimate is greater than just the quantifiable statistical uncertainty, and it also includes the unquantifiable uncertainty in surveillance data. Given the understandable clinical focus on severe clinical cases, there is considerable scope for underascertainment of total case numbers. Where multiple possible exposure pathways are identified within clusters (for example, individuals potentially exposed to both avian and human sources of infection), there is also clearly a risk of case misclassification. These issues affect the reliability of epidemiological estimates (*15*) (see supporting online material), but their impact might be reduced if even qualitative assessments of the area of coverage and reliability of national surveillance programs were reported alongside raw case reports in WHO situation updates.

What we are suggesting is not a complete overhaul of surveillance systems, but more a reappraisal of how surveillance data are reported, analyzed, and interpreted by public health agencies. Focusing on the case cluster size distribution is a better method for detecting the stochastic beginnings of a pandemic, rather than decision-making being based on case numbers exceeding particular thresholds. Detailed case investigation (including contact tracing and virologic testing to look for genetic evidence of reassortment) is essential to provide the reliable data required. Good data capture is therefore critical, and it is to this that the greatest international attention should be devoted.

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Supporting Online Material

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