Ferret-Transmissible Influenza A(H5N1) Virus: Let Us Err on the Side of Caution

The recent experiments with highly pathogenic avian influenza A(H5N1) virus conducted in the laboratories of Fouchier and Kawaoka have set off a debate about whether it is appropriate to publish all of the details of these experiments publicly and about how the viruses generated in these labs should now be handled. A wide range of opinions has been expressed, both for and against restrictions on publishing this work and on working with these viruses. I would like to discuss some ideas put forth as arguments against such restrictions.

First, it has been suggested that H5N1 is probably not a particularly dangerous virus and that the official WHO case fatality rate (CFR) of approximately 60% is almost certainly a vast overestimate (1–3) ("likely orders of magnitude too high" [1, 3]). This claim is based on the findings of several human seroprevalence studies conducted in several East and Southeast Asian countries since the emergence of H5N1 as a zoonotic pathogen, reporting up to 9.1% prevalence of H5N1 antibodies (1, 2). The rationale would be that if up to 9% of the population in enzootic regions—many millions of people—has been infected with H5N1 and survived, whereas there have been only a few hundred fatal cases, as tallied by the WHO, then the true CFR could be vanishingly small. However, there are methodological concerns about some H5N1 seroprevalence studies; it has elsewhere been estimated from seroprevalence studies that meet WHO H5N1 serology criteria that fewer than 0.5% of the study subjects (26 out of 5,333 participants) are positive for H5N1 antibodies (4). More seroprevalence studies are clearly needed. But if the true seroprevalence is approximately 0.5%, on average, in enzootic regions, then WHO CFR estimates would be a substantially incorrect measure of the actual lethality of this virus. To complicate matters, however, one must also consider the flip side of this problem with official WHO estimates, which is that in areas rife with infectious disease morbidity and mortality, and with deaths due to pneumonia and acute respiratory distress syndrome in particular, a significant number of fatal H5N1 infections are probably never identified as such. It is thus currently extremely difficult to arrive at an accurate CFR, where a case is defined as any infection with the H5N1 virus. What is clear, however, is that this virus is amply capable of causing severe disease and death. Even if official WHO estimates were 2 orders of magnitude too high, which is quite possible, an H5N1 pandemic would be worse than the 1918–1919 pandemic, which had a CFR of >2.5% (5). But since we do not know the true lethality of the H5N1 virus and since it is capable of rapid evolution, it would be beneficial to err on the side of caution.

An additional problem with the idea that H5N1 should not be considered a highly lethal virus in humans is that this idea emerges from cumulative data from a large number of studies of different populations in multiple countries. In reality, different H5N1 strains of different evolutionary lineages have been circulating in different areas at different times, and different human CFRs have been observed across different geographical regions as well (6). While multiple factors, including the timing and quality of medical interventions, most likely contribute to variability in these CFRs, it is also conceivable that different strains inherently vary in lethality. Indonesia, in particular, has seen the highest official CFRs, and the only two Indonesian seroprevalence studies published to date have found no one seropositive for H5N1, out of a combined total of 1,336 study participants (7, 8). It is possible that the true Indonesian CFR is 80 to 90%. Thus, it may be more meaningful to consider CFRs specific to individual geographic regions or evolutionary lineages.

Second, it has been claimed that the fact that the Fouchier lab and Kawaoka lab viruses are transmitted well between ferrets is of little or no predictive value for assessing the likelihood of their efficient transmission between humans (1–3). The ferret is generally regarded as a good, but not perfect, model for studying influenza virus transmissibility (9, 10). Ferret-transmissible viruses are not necessarily transmitted well between humans (9, 10), and thus, it is true that we cannot know whether these viruses would be transmissible between humans. However, in addition to discussing the likelihood of efficient transmissibility as an all-or-none quality, it would also be useful to ask how close the new viruses are likely to be to being transmissible between humans, in terms of the number of additional genetic changes that would be required. The Fouchier and Kawaoka studies suggest that only a few mutations are likely to be required for H5N1 to adapt to humans but also that efficient transmission would not occur until all of the required mutations are accumulated. While ferrets are not humans, an avian virus that has recently been made ferret transmissible is probably quite close to being transmissible among humans, in terms of the numbers of additional mutations required, if it does not already have all of the required mutations. A comparison with the emergence of oseltamivir resistance in pre-2009 pandemic, seasonal H1N1 is instructive; in that case, it seems likely that once a permissive genetic background evolved, only one additional mutation generated within one or more human hosts, independently, was required to unleash fit, oseltamivir-resistant strains that then spread rapidly, at least within one region of the globe (11). It also appears that avian influenza virus strains can infect a wide range of mammalian species naturally and that H5N1 has infected an especially broad range of hosts, even among birds (12, 13). The Fouchier lab and Kawaoka lab viruses are not highly ferret-adapted strains that have been passaged a very large number of times through ferrets alone; the Fouchier lab viruses were passaged 10 times through ferrets, and the Kawaoka lab viruses may even have been passaged a smaller number of times (14, 15). These strains are most likely poised to spread through a variety of mammals, including humans, with a minimal number of additional changes required.

Thus, at a minimum, it seems prudent to handle the Fouchier

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lab viruses at biosafety level 4 (BSL-4). Because the Kawaoka lab viruses contain only the hemagglutinin gene of avian H5N1 and did not cause any deaths among the ferrets studied (15), perhaps the Kawaoka lab viruses need not be handled at BSL-4. But since lab accidents happen with regularity, even at BSL-4 (16, 17), and since the consequences of escape of the Fouchier lab's ferret-transmissible H5N1 viruses could potentially be so catastrophic, let us choose the path of caution with the Fouchier lab viruses. The consequences of underestimating these viruses' pathogenicity or propensity for transmission among humans are simply too great.

Redacting the details of the experimental methods and results of the Fouchier and Kawaoka studies would also be an important step in the right direction. We cannot assume that potential bioterrorists or hobbyists would have specific, logical goals or that they would be competent in achieving those goals. We cannot assume that they would have a command of all prior literature or, indeed, that they could put together methods for a project from multiple sources. Let us erect as many barriers as possible between the results of these studies and anyone who may try to produce a highly pathogenic H5N1 virus that is transmitted well between humans, in the hope that one of these barriers would be sufficient.

Fundamentally, the way biological research is done needs to change; new threats are emerging where there were fewer before. As others have noted, biological research is now facing situations similar to that faced by physics research in the 1940s (18, 19). At many institutions, it is an understood and accepted reality that there are things one cannot talk about in public. It is also understood that the decisions about what one can talk about in public are not up to the individual scientist but rather are decided by security experts and policies that attempt to balance academic freedom and national security concerns. It is time for such controls to be considered more broadly for biological research, so that we may more readily avoid situations such as the present one. And if increased security hampers scientific research and progress in influenza virus or other pathogen research, so be it. Significantly worse things could happen.

It will be very useful to have a uniform set of guidelines to govern future work in dual-use areas of biological research. It would be most beneficial for such guidelines to emerge from international discussion and agreement. Our international community needs to decide which kinds of experiments we wish to allow, what safety and security protocols should be followed when conducting such experiments, and what may be published and discussed publicly. These are large decisions with potentially large consequences for the world as a whole, and they should not be left to individuals to decide. Let us hope that with such guidelines in place, we will not soon be engaging in more after-the-fact discussions akin to those we are having today.

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