Influenza viruses use the haemagglutinin (red) on their surfaces to bind to host cells.

Q&A Paul S. Keim for the NSABB

Reasons for proposed redaction of flu paper

The US National Science Advisory Board for Biosecurity (NSABB) recommends¹ (see page 153) that two papers reporting experimental adaptations of influenza viruses should be published in a form that withholds essential information. Yoshihiro Kawaoka of the University of Wisconsin-Madison and his colleagues show² that a mutated H5 haemagglutinin combined with genes from a pandemic human H1N1 virus is transmissible in respiratory droplets between ferrets. Ron Fouchier of the Erasmus Medical Center in Rotterdam, the Netherlands, and his colleagues report³ adaptations that make highly pathogenic avian H5N1 virus transmissible. To assist decision-making in response to the NSABB's challenging recommendation, Nature asked the board to explain the reasoning behind its conclusion for the Kawaoka paper. Acting NSABB chair Paul S. Keim coordinated the board's answers.

You have recommended that both papers be published in a redacted form even though the Kawaoka paper does not report transmissibility of fully avian H5N1. Why?

The Kawaoka and Fouchier manuscripts are indeed different, and the committee spent a considerable amount of time on each. The concern for the Kawaoka paper is that the authors provide a method for producing a transmissible H5N1 reassortant virus. They demonstrate the compatibility of segments of the 2009 pandemic influenza (A(H1N1)pdm09) backbone with H5 haemagglutinin (HA) to produce a virus that can be transmitted between ferrets.

Another concern is the high transmissibility

of this strain of H1N1 and the ability of influenza viruses to continually reassort in pigs. The detection of novel H3N2 reassortants in humans in 2011 raises additional worries about the use of reassortant H5 haemagglutinin on an H1N1 backbone.

Publication of the experimental details from either paper would, in our view, allow others to replicate the experiments and move closer to production capability of an avian flu virus for humans that is highly pathogenic and transmissible by respiratory aerosols.

Perhaps in time, the global community will decide that the availability of these data is not of concern. However, a decision to release these data now is not reversible,

whereas delayed publication of these details can easily be reversed on some future date.

The focus of your statement¹ is on the risks of high pathogenicity. As Kawaoka's H5 HA/H1N1 virus is not highly pathogenic, why consider it a public-health risk?

Although the reported pathogenicity² of the generated viruses is no greater than that of A(H1N1)pdm09, we believe that the techniques described could be used to generate other viruses with H5 HA that have potentially much greater pathogenicity.

The fact that humans have no previous immunological experience with H5 infections could lead to a more widespread pandemic than that of 2009, as part of the population had pre-existing immunity to A(H1N1)pdm09 because of exposure to other H1N1 strains before 1957.

Although the work performed by Kawaoka and his colleagues² is an important contribution, it crosses a line and raises the question of when the risks of widely disseminated experimental detail outweigh the benefits.

Once mammal-to-mammal respiratory transmission is accomplished, the virus is likely to adapt on its own to enhance the efficiency of respiratory transmission. If such viruses were misused or escaped from the lab, they would evolve in ways that cannot be predicted. H5N1 has been in birds since at least 1996, and despite the almost 600 human infections of which we are aware, this virus has not yet become efficiently transmissible between mammals. There might be good reasons why it hasn't achieved this capacity, including inherent biological limitations.

The artificial evolution of a new mammal-adapted H5N1 virus, as reported in these two papers, has removed the natural barriers that might have existed. Accomplishing this in the lab, however, doesn't mean that it can occur naturally.

We also need to consider the potential role of, and impact on, other species. Pigs are a well-known 'mixing vessel' for influenza viruses. This mixing could lead to the emergence of new antigenically shifted viruses.

Sialic acids in the respiratory tracts of pigs attach to sugars by both α 2,6-linkage (favoured as receptors by H1N1) and α 2,3-linkage (favoured by H5N1). This makes pigs susceptible to infection by the H5N1 virus and by the pandemic A(H1N1)pdm09 virus. However, like humans, pigs do not easily transmit the H5N1 virus and it is not very pathogenic in pigs. Adapting the H5 HA to bind to α 2,6-linked saccharides is likely to enhance transmission of H5 viruses between pigs.

Dogs and cats are also susceptible to H5N1 and A(H1N1)pdm09. Because humans have close contact with all three of these species, we need to be concerned about the possibility that the mutated H5 viruses may be

transmitted to and from humans and any of these species. This could greatly complicate disease control. There are an estimated 2 billion domestic pigs globally. An influenza virus with high morbidity and mortality in pigs that could be transmitted between them could have a devastating effect on the world's food supply; pigs would then serve as an intermediate host of virus adaptation to humans.

It is likely that the H5 HA/H1N1 mutations described in the Kawaoka paper are insufficient to provide a blueprint to construct a transmissible and highly pathogenic wholly avian H5N1 virus — additional mutations may be required. Why do you think publication is still risky?

The fact that Kawaoka's specific virus and mutations might not be the feared H5N1 pandemic strain is not the point. It is that this laboratory created a virus that has now bypassed apparent barriers to evolution in the wild. If this virus were to escape by error or by terror, we must ask whether it would cause a pandemic. The probability is unknown, but it is not zero.

Kawaoka's work establishes the feasibility and pinpoints those particular viruses as candidates for producing a transmissible virus. Advances in basic science are incremental and cumulative. This work significantly advances the ability to construct an H5 virus with catastrophic potential. This altered H5 HA gene could be combined with other influenza virus genes possibly leading to a pandemic. A major concern is that the human population does not have immunity to H5.

Do we want to take this gamble and thereby potentially jeopardize public health and safety as well as risk the resulting economic consequences, based simply on a belief that this probably won't occur?

Several of our independent advisers felt that the likelihood of H5 HA/H1N1-based influenza being used as an agent of bioterrorism is low, given that it cannot be targeted to a specific population, and vaccines and drugs exist to combat it, as Kawaoka reports. Why are you concerned?

No one should presume to know all the ways in which influenza virus could be misused, and the motivations for doing so, but the consequences could be catastrophic. There are many scenarios to consider, ranging from mad lone scientists, desperate despots and members of millennial doomsday cults to nation states wanting mutually assured destruction options, bioterrorists or a single person's random acts of craziness. These are low-probability events, but they could introduce a new evolutionary H5N1 seed into the environment that seems not to exist in nature. This might not cause

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a pandemic instantly, but it could start the virus on a new path for pandemic evolution.

H5N1 vaccines and a class of antivirals do exist, but not in sufficient quantities anywhere in the world — and in the event of an H5N1 influenza pandemic, they may have limited value. Neither the vaccine-generating capacity nor our pharmaceutical industry could cope with the rapidity of a pandemic that could potentially affect 7 billion people. The world population is immunologically naive to the H5 family of viruses. Work published in October 2011 indicates that current influenza virus vaccines are less effective than previously thought⁴. There is only one family of antiviral drugs available (the neuraminidase inhibitors) and resistance in A/H5N1 has already been documented⁵.

Several of our independent advisers also felt that the Kawaoka paper has important messages for surveillance and prevention preparedness. Do you disagree?

The major benefit of the work is to alert humanity to the potential threat posed by H5N1. It is important to convey how unprepared, on every level, the world is for an H5N1 pandemic. Initially, some NSABB members also advocated for communication to enhance surveillance. But further examination of the issue lessened our enthusiasm.

The practical benefits of this work may be limited, because there are many paths to the evolution of human-transmissible H5N1. Consequently, the utility of the specific mutations presented in this manuscript for surveillance and countermeasure development is unknown — and may even be misleading for surveillance. Furthermore, it is unlikely that the detection of these mutations in a single virus either in humans or in other animals will provide sufficient lead time so that effective public-health and safety action could be taken to pre-empt a pandemic.

In 2005, the highly pathogenic 1918 influenza virus was reconstructed and the information was published in full⁶. Why do you feel that the work on transmissible H5N1 is riskier?

Our unanimous decision in 2005 to recommend publication of the 1918 papers was a difficult one, reached after much debate. This judgement of the 1918 papers was made in the context of the time and with an awareness that this dual-use research — research that could be used for good or bad purposes — was very close to a line beyond which information would need to be restricted. There were two primary reasons that the NSABB did not consider the 1918 research paper to be of sufficient concern to warrant limited dissemination.

First, the 1918 H1N1 virus had already existed in nature as result of the 1918 pandemic. Given that this virus (and derivative strains) continued to circulate in the

population until 1957, and then returned in 1977, it was suggested that there may be a critical level of pre-existing population-level immunity from these exposures. In 2009, we learned that was not the case. However, exposure to A(H1N1)pdm09 does provide some cross protection against the 1918 virus, making transmission of the 1918 virus today much less likely.

Second, the eight mutations that resulted in the construction of the 1918 virus were obtained only from forensic investigation of pathology slides of lungs from fatal cases of 1918 influenza or from tissue from exhumed bodies of deceased patients who were buried in Alaskan permafrost. In 2005, it was considered highly unlikely that anyone with an intent for harm could reasonably assemble the required genes to make a 1918 virus. Now this argument holds little validity.

Are you only worried about research that specifically investigates H5N1 transmission?

We remain concerned about any type of research that enhances the virulence of influenza virus, facilitates trans-species or host-to-host infection or renders the virus resistant to all available drugs or vaccine-induced immunity. Consequently, we are concerned about the many variants of influenza virus that currently infect other animal species, because these studies^{2,3} show that some of these variants could also potentially be adapted for mammalian transmission or could provide raw materials for enhancing the virulence of mammalian-adapted viruses.

For avian and other highly pathogenic flu strains, experiments should be vetted carefully before being conducted. At this time, there is no formal, standardized mechanism for screening proposals and papers that contain dual-use research of concern, apart from assessments by authors, editors and reviewers. The NSABB has recommended a broad oversight mechanism for such research in the United States⁷.

We believe that a discussion ought to take place across the scientific, public-health and policy communities about those experiments that fall within the criteria of dual-use research of concern. ■

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