Report on technical consultation on H5N1 research issues

Geneva, 16–17 February 2012

Context

Approximately 60% of persons known to have been infected by the avian influenza A(H5N1) virus have died from their illness. To date, most known human infections have occurred through contact with, or exposure to, infected birds. The prospect that H5N1 viruses circulating in nature might evolve and acquire the ability to spread with ease from person to person is a serious public health concern.

Research on the genetic basis of the transmissibility of H5N1 by two groups (one in the Netherlands and the other a joint Japan/USA group) resulted in laboratory-modified H5N1 viruses capable of respiratory transmission between ferrets. These mammals are often used in influenza research because, in some respects, ferret influenza infection shows similarities to human influenza infection. The results of these two studies demonstrate that relatively few genetic changes in H5N1 viruses can enable transmission via the respiratory route in these animals, and, in turn, suggest that H5N1 viruses could become more easily transmissible from person to person. The findings suggest that such changes could occur in nature, but do not provide an estimate of the likelihood that they will occur.

During the autumn of 2011, after manuscripts describing the research studies and their findings were submitted to scientific journals, the papers were reviewed by the National Science Advisory Board for Biosecurity (NSABB) in the United States, which recommended against publishing some details of the work. Specifically, the NSABB recommended publishing the general conclusions, without details of the research methods used or the specific mutations, to reduce the possibility that anyone seeking to do harm could replicate the experiments.

On January 20, 2012, the researchers who conducted this work and some other research groups announced a 60-day voluntary research moratorium to allow time for organizations and governments to "find the best solutions for opportunities and challenges that stem from the work". The scientific journals to which the papers had been submitted for publication also voluntarily deferred publication.

In light of the global relevance of these issues, WHO convened a preliminary technical consultation on 16–17 February 2012. The purpose was to clarify key facts about the studies and to address the most urgent issues concerning the management of these laboratory-modified viruses, and how access to and dissemination of any findings should be handled.

Twenty-two participants[1] were invited, including those with direct involvement in, or knowledge of, the content, oversight, or potential dissemination of this work. Representatives from countries where H5N1 is currently circulating were also present. Participants reviewed the chronology of the transfer of the H5N1 viruses used in the research studies, from country of origin to the research laboratories; the associated agreements regarding use of the samples; how the research proposals were reviewed; and the oversight of the work. Under conditions of stringent security, they read the full and redacted versions of both unpublished research reports, and also heard brief presentations by the researchers, summarizing their work.

Further, the participants were asked to recognize that while this research had elicited important scientific and social concerns from a number of different perspectives, the purpose of this meeting was not to debate these broader perspectives, but to find

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[1] See http://www.who.int/influenza/human_animal_interface/list_participants/en/index.html for the full list of participants.

practical, feasible, *ad hoc* solutions to the questions of access to research findings and management of the laboratory-modifed viruses.

Overview of the research findings

The studies indicated that different experimental methods can generate viable H5N1 or other influenza viruses with certain H5 characteristics, which demonstrate increased transmissibility in ferrets. In each study, the increase in capacity for transmission by the respiratory route was associated with a group of specific mutations, although these differed between the two studies. Both studies were essentially proof-of-principle experiments, and thus were not designed to elucidate the pathogenicity or degree of transmissibility of the laboratory-modified viruses. It was noted that the research methods used in these studies are not novel and are widely used in biomedical research.

Participants agreed on the public health value of the data on genetic modifications for improving the existing surveillance performed by both the human public health and animal health sectors, so as to monitor for variants that may be indicative of important changes among circulating H5N1 viruses. The findings of these studies provide a valuable complement to the accumulating data on virus evolution occurring in nature, and to ongoing analyses of in-host pathogen evolutionary dynamics.

Participants noted that the research findings had to be considered within a social context. The studies had raised concerns about the potential misuse of the viruses and the research findings. The participants also noted that, if disseminated to the public health and scientific community, the results would offer significant benefits to global health. Specifically, the findings could be used to improve the sensitivity of public health surveillance, facilitate the early detection of potentially pandemic H5N1 strains, and might aid the development of vaccines and the assessment of the potential value of other countermeasures.

Overview of options discussed

Several issues relating to publication were considered:

- If the research were to be published in redacted form, would genetic sequence data and/or the research methods remain completely restricted, or should the information be made available to a limited audience, after a public health justification for use of the information?
- If the latter, what workable mechanism would allow selective access to this information by laboratories involved in public health surveillance and legitimate research?
- What criteria would be required for access, and which organization would exercise governance over access?
- How could dissemination to those permitted access be performed securely?
- Could the confidentiality of the information be maintained?

On the question of limiting access to the results through publication of redacted versions, some participants observed that there was no current practical mechanism to limit access. Further, it would not be difficult for knowledgeable scientists to determine the information that had been removed, as novel methods had not been used. Limiting access to those with a need for the information would pose insurmountable practical problems. Chief among these problems are the development and implementation of a mechanism to disseminate the information to diverse and geographically distributed groups while maintaining the confidentiality of the detail. Therefore, such a mechanism would not realistically resolve concerns about dual-use research. There may be benefit in creating such a mechanism to deal with other dual-use research information in the future. However, this will require thorough consideration of and international agreement on practical issues such as security, access requirements, governance, and liability.

Establishing such a mechanism and implementing it effectively in the very short term was not considered to be feasible based on the information known to this group.

Six questions were explored with regard to the two laboratory-modified viruses:

- After the current moratorium on this research expires, should the viruses be destroyed?
- Should the samples be kept at their current locations?
- Is it necessary to transfer them to locations of increased laboratory biosecurity?
- What biosafety and laboratory biosecurity considerations and standards should be required for any subsequent work?
- If the viruses are not to be destroyed, how could the findings of research be applied towards the development of vaccine-candidate viruses or other countermeasures?
- What further research would be acceptable or desirable, especially in light of the PIP Framework?

It was not believed that any purpose would be served by destroying these laboratory-modified viruses, given their utility for future research and public health surveillance. Although the viruses are currently in facilities that met or exceeded the required biosafety and biosecurity standards, the participants were in agreement that an urgent review is needed to define the conditions under which future research on laboratory-modified H5N1 viruses might take place. The participants noted the need, after the moratorium, for clear guidance on the biosafety and biosecurity standards necessary in other research sites, and for a comprehensive system of monitoring.

Next steps

The next steps will be:

1) to convene a qualified group to define the essential biosafety and laboratory biosecurity standards and practices to be observed in future work with these laboratory-modified viruses;

2) to increase awareness of the nature and objectives of this research and to place the results in the context of the current assessment of the threat posed by wild-type H5N1 viruses and our rapidly increasing understanding of their biology. This situation has also highlighted the continuing need for better communication across all cultural settings about the intrinsic value of research for the protection of global public health and for conveying a sober assessment of the threat posed by H5N1 to human health;

3) to hold a further discussion on the scientific and societal issues raised by this kind of research. Specific topics to be addressed include how to strengthen public safety and security while ensuring that critical scientific research continues, as well as mechanisms to assess and manage sensitive research.

Consensus points[2]

- Recent work discussed at this meeting underscores that influenza A(H5N1) viruses remain an important risk for causing a future pandemic. Therefore, research on these viruses, including on transmissibility and pathogenicity, remains critical to close important gaps in knowledge in order to reduce the danger posed; such research should continue. The PIP Framework,[3] which was

[3] These consensus points were initially posted on the WHO web site immediately following the meeting.

[3] See http://www.who.int/influenza/pip/en/ for details.

adopted by all WHO Member States in 2011, now provides a global framework for the sharing of influenza viruses with human pandemic potential and the sharing of benefits arising from such sharing. Implementation of this Framework is integral to global pandemic preparedness and response. Future research projects should involve countries from which source material were obtained.

- The two studies that were conducted to better understand the transmissibility of H5N1 influenza viruses have shown that these viruses have the potential to become more transmissible among mammals. In light of the continuing evolution of H5N1 viruses, the results of these studies provide an important contribution to public health surveillance of H5N1 viruses and to a better understanding of the properties of these viruses.

- At the same time, these studies have raised important and valid concerns about whether they increase risks to the safety of humans. Concerns which have been raised include the potential misuse of the results or methods as well as potential breaches in biosafety and biosecurity related to pathogens. These concerns highlight how important it is that researchers are aware of such issues, exercise judgment about the conduct of their research, dissemination of the results, and for institutional bodies reviewing such studies to identify and address potential concerns about "dual use". Such safeguards already exist, but continued emphasis should be placed on assuring and reinforcing safety and security.

- The laboratory-modified H5N1 viruses are currently stored in well-established research facilities with high security and high safety (BSL3+).[4] There have been no safety breaches related to the storage of the laboratory-modified H5N1 viruses at these facilities. At the same time, the biosafety and biosecurity conditions under which further research is conducted on the laboratory-modified H5N1 viruses should be fully addressed by relevant authorities. This is a matter of urgency and should be achieved as quickly as possible. In the interim, the laboratory-modified H5N1 viruses should remain in their present locations. In addition, the current moratorium on research to enhance the transmissibility of H5N1 influenza viruses and the further research on the laboratory-modified viruses should continue until the conditions have been determined. Other research on H5N1 viruses should not stop.

- There is a preference, from a public health perspective, for full disclosure of the information in these papers. However, there are significant social concerns surrounding this research. Two critical issues that must be addressed before publication of the papers are: (1) a focused communications plan to increase public awareness and understanding of the significance of these studies and the rationale for their publication, and (2) a review of the essential biosafety and biosecurity aspects of the newly developed knowledge.

- Participants discussed the concept of publication of redacted manuscripts with a mechanism for providing the restricted information to legitimate recipients. The group recognized the difficulty of rapidly creating and regulating such a mechanism in light of the complexity of international and national legislation. A consensus was reached that the redaction option is not viable to deal with the two papers under discussion in view of the urgency of the above mentioned public health needs. The participants noted there may be a need for such a mechanism in the future.

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[4] Biosafety level 3(enhanced) containment laboratory.

- Apart from consideration of these two manuscripts, participants acknowledged the existence of broader issues requiring more detailed exploration and advised that these be considered in subsequent consultations involving other stakeholders.