

The Pause on Avian H5N1 Influenza Virus Transmission Research Should Be Ended

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ABSTRACT A voluntary 60-day pause on avian H5N1 influenza virus transmission research was announced in January 2012 by the international community of influenza scientists engaged in this work to provide time to explain the benefits of such work and the risk mitigation measures in place. Subsequently, the pause was extended to allow for time for review of the biosafety and biosecurity conditions. After almost 8 months, these conditions have been met in some countries and are close to being met in others. Because H5N1 virus transmission studies are essential for pandemic preparedness, researchers who have approval from their governments and institutions to conduct this research safely under appropriate biosecurity conditions should resume this important work.

On 20 January 2012, 39 influenza virus experts from around the globe announced a voluntary 60-day pause on research that would potentially lead to the generation of highly pathogenic avian influenza (HPAI) H5N1 viruses with increased respiratory transmission in mammals (1, 2). This pause was triggered by an intense debate about two scientific publications that showed that viruses possessing a hemagglutinin protein from HPAI H5N1 viruses can become transmissible in ferrets. Concerns were raised about safety, security, and dual-use aspects of the work, and the influenza experts recognized the need to better explain the benefits of this research and the measures that were taken to minimize possible risks. In addition, the pause provided time for organizations and governments around the world to find the best solutions for opportunities and challenges that stemmed from the work.

On 16 and 17 February 2012, the World Health Organization (WHO) convened a technical consultation with the purpose to clarify key facts about these studies and to address the most urgent issues concerning the management of the laboratory-modified viruses and how access to and dissemination of research findings should be handled. One of the consensus points reached at this meeting was to recommend continuation of the voluntary moratorium until the biosafety and biosecurity conditions under which further research would be conducted on the laboratory-modified H5N1 viruses were fully clarified by the relevant authorities. This was considered a matter of urgency, to be achieved as quickly as possible (3). Influenza investigators agreed to comply with this extension.

Since the pause began, the two studies that raised concerns have been published (4, 5). These in-depth publications described the purpose of the research, the conditions under which the work was conducted, the study conclusions, and the implications for public and animal health. A third paper, published in conjunction with the Herfst et al. paper, expanded on the risk assessment of such transmissible viruses emerging in nature (6). The publications were accompanied by numerous editorials and commentaries in the journals *Nature* and *Science*, and an extensive communication strategy was deployed to inform people of the press from around the world. Well before these publications, the WHO launched its own comprehensive communication plan that fo-

cused on Indonesia and Vietnam, the countries from which the research teams gratefully obtained H5N1 viruses for research (7).

These communications helped many people understand the experimental approach, the stringent biosafety conditions, the strict regulations under which these laboratories operate, and the public health benefits this research provides. Data-driven risk assessments by biosecurity experts concluded that this research was completed under appropriate biosafety and biosecurity conditions. These pivotal papers showed that viruses possessing the avian H5N1 hemagglutinin protein have the capacity to adapt to mammals, that circulating H5N1 viruses have some of these mutations, and that now more than ever, this research must resume if we are to fully assess the pandemic potential of H5 viruses.

Since the pause on H5N1 virus transmission studies began, international organizations and governments have been reviewing oversight and the biosafety and biosecurity required for this type of research. Some governments have implemented new policies or regulations (e.g., the U.S. Government Policy for Oversight of Life Sciences dual-use research of concern), while others have decided not to. Careful analyses of biosafety and biosecurity by experienced professionals have been conducted. The Netherlands Commission on Genetic Modification (COGEM) has informed the Dutch government that the enhanced animal biosafety level 3 (ABSL3+) conditions outlined in the original permit of Erasmus MC (as detailed in the supplement accompanying Herfst et al. [5]) are still deemed appropriate (8). The Public Health Agency of Canada concluded in January 2012 that H5N1 viruses capable of efficient human-to-human transmission, including via aerosols or the airborne route, are considered risk group 4 human pathogens and require containment level 4 physical containment

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and operational practices (9). In the United States, the Intergovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC) has reviewed conditions for future research on mammalian-transmissible H5N1 viruses and is expected to make their advice public in the *Federal Register* any day. We concur with the WHO that researchers should never conduct this type of research without the appropriate facilities and oversight (10). Scientists should not restart their work in countries where, as yet, no decision has been reached on the conditions for H5N1 virus transmission research. However, it is unreasonable to extend the pause on H5N1 transmission research until every country has made a final decision.

By lifting the moratorium on avian H5N1 influenza virus transmission research, influenza experts by no means ignore their responsibility to participate in the global debate on overarching issues, including oversight and transparency, ethical aspects of infectious disease research, and potential misuse of research reagents and data. It is important to note, however, that these issues are generic and not limited to research leading to the generation of HPAI H5N1 viruses with increased respiratory transmission in mammals. These will be complex discussions that will have limited value in the absence of broader global agreement relating to infectious disease research with direct relevance to animal and public health.

The published studies identified changes in viruses possessing an H5 hemagglutinin protein that enabled them to transmit in a ferret model and suggested that both receptor-binding and hemagglutinin stability play roles in host adaptation. Now we know it is possible that these viruses could adapt to mammals, but without more data, we cannot fully assess the risk or implement appropriate containment measures. To contribute meaningfully to pandemic preparedness, we need to conduct more experiments to better understand transmission of H5N1 viruses in mammals, in a timely manner. This commentary is not the place to outline in detail every experiment that will be conducted. However, examples of the experiments we propose and some of the benefits we anticipate include the following:

- (i) Identify additional mutations that enable H5N1 viruses to adapt to mammals. This is important for understanding the scientific basis for adaptation to mammals in addition to providing comprehensive data for focused surveillance and to identify appropriate vaccine candidates.
- (ii) Determine how readily adaptation occurs from different mutant H5N1 virus starting points. Evaluating this risk experimentally will provide critical data for risk assessment.
- (iii) Define the molecular mechanisms responsible for H5N1 virus transmission and pathogenicity. This knowledge will

help to determine whether adaptation to mammals will lead to an attenuation of pathogenicity—this is critical information to guide risk assessment evaluations.

- (iv) Evaluate transmission in other mammalian species (e.g., guinea pigs) to determine whether the mutations identified are predictive in general for adaptation to mammals. This will help us to assess the actual risk these viruses pose to humans.

The benefits of H5N1 virus transmission research may or may not result in immediate applications—accumulating knowledge in basic research is an incremental process. However, we believe that our best way to limit the impact of pandemics is to be better prepared than we are now by knowing more about the pathogen and how it may evolve. Since the requirements to resume this research have been met in some countries, we believe it is imperative that investigators that have approval from their governments to conduct these experiments resume their research, which is of direct importance to public health.

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