

The Future of Research and Publication on Altered H5N1 Viruses

Sander Herfst, Albert D. M. E. Osterhaus, and Ron A. M. Fouchier

Department of Virology, Erasmus Medical Center, Rotterdam, Netherlands

(See the perspectives by Bouveir, on pages 1632–5 and Osterholm and Relman, on pages 1636–8, and the editorial commentary by Hirsch, on pages 1621.)

Recently, we and others obtained experimental evidence that highly pathogenic avian influenza virus subtype H5 can acquire the ability to transmit via aerosols between ferrets. Upon submission of manuscripts describing the results of these studies, the US National Science Advisory Board for Biosecurity was consulted and recommended that the main conclusions of the work be published but without the experimental details and mutation data that would enable replication of the experiments. Over the past few months, these events have led to intense discussions. Should this type of experiment be conducted? If so, under what conditions? Do the scientific and public health benefits of the work and its publication outweigh the potential risks? In February 2012, public health and influenza experts discussed these issues during a World Health Organization–organized technical consultation. This perspective article reviews the current state of the field and the recommendations made during the meeting.

Influenza A virus is a fascinating pathogen from a scientist's perspective, with a potentially high impact on animal and human health. The virus is enzootic in wild migratory birds of aquatic habitats around the world [1]. Influenza A viruses occasionally spill over from this avian "virus reservoir" into other animal hosts, including domestic poultry, pigs, horses, a variety of carnivores, and marine mammals. Most spillover events involve limited numbers of animals, but on occasion, when more sustained transmission within the new species takes place, they may result in large outbreaks. Sporadically, the viruses adapt to their

new animal hosts, leading to enzootic virus circulation for years or decades [2].

Zoonotic influenza A virus infections also occur relatively frequently, often without serious consequences for public health [3]. However, the introduction of "novel" influenza viruses from animals into the human population can result in pandemics. One of the most devastating examples was the 1918 H1N1 "Spanish influenza" pandemic, which is estimated to have caused approximately 50 million deaths over a short period [4]. The later pandemics in 1957, 1968, and 2009 were mild compared with that of 1918, but they still caused excess morbidity and mortality involving up to several million human cases. After the pandemic period, the pandemic viruses become epidemic viruses and continue to cause substantial morbidity during seasonal epidemics, with, on average, 500 000 deaths globally each year [5].

Two major requirements determine the ability of a "new" influenza A virus strain to establish itself in the human population and cause a pandemic: (1)

virus adaptation that enables efficient replication in the human respiratory tract and transmission between humans and (2) the absence of preexisting immunity in the human population. What exactly determines transmission of influenza viruses in humans has remained largely unknown, but all pandemic viruses studied to date have had the ability to be transmitted efficiently via aerosols or respiratory droplets (ie, airborne transmission) [6]. Only when we fully understand the viral and host factors that drive airborne transmission can we start to estimate the risk that influenza viruses in the animal world may pose for future influenza pandemics. Important information and insights can come from studies of pandemic and zoonotic viruses in the laboratory, using animal model systems and reverse genetics. One candidate virus for such studies is the highly pathogenic avian influenza (HPAI) A/H5N1 virus.

Since its first detection, in 1997, HPAI A/H5N1 virus has devastated the poultry industry of numerous countries

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Correspondence: Sander Herfst, PhD, Department of Virology, Erasmus Medical Center, Dr. Molewaterplein 50, 3015GE Rotterdam, Netherlands (s.herfst@erasmusmc.nl).

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of the Eastern Hemisphere. The continued circulation of A/H5N1 viruses in poultry for over a decade and their occasional spill over to wild birds and mammals, including humans, have led to ongoing virus evolution. More than 10 distinct “clades” of H5N1 viruses have been described since 1997, from which new sub-lineages or clades emerge periodically [7]. Whether such ongoing evolution could eventually lead to the emergence of A/H5N1 virus with pandemic potential has remained a key question since the first documented infections in humans, in Hong Kong. Many experts have judged this risk to be very low because of existing dogmas in the influenza field that stem from historical data on influenza pandemics: since all known previous pandemics were caused by influenza virus subtypes H1, H2, and H3 and since at least the last 2 emerged as a consequence of reassortment (ie, the mixing of genes of animal and human influenza viruses), it has often been argued that fully avian viruses of the H5 subtype could not gain pandemic potential [6]. Our research program aimed to test whether A/H5N1 virus could acquire the ability to spread via aerosols in mammals after undergoing genetic changes similar to those identified in previous pandemic viruses. The results of such work would help to better assess the risks of the current A/H5N1 epizootics for human health and would increase our understanding of the contribution of particular mutations or reassortments and their associated biological traits to transmission of the virus. In other words, this work may have major prognostic value for prediction, prevention, and treatment of the next pandemic.

OVERSIGHT AND CONSULTATION

The work of Yoshihiro Kawaoka’s team and our team followed the normal route in which research in the life sciences is performed. The research agenda within

the influenza field was discussed with a broad range of experts at meetings coordinated by agencies such as the World Health Organization (WHO), the United Nations Food and Agriculture Organization (FAO), and the National Institute of Allergy and Infectious Diseases (NIAID) in the recent past. The need for more information on viral factors that affect transmission and contribute to the emergence of pandemic viruses was highlighted in the “Report of the Blue Ribbon Panel on Influenza Research, September 11–12, 2006” [8], the conclusions of the FAO–World Organization for Animal Health–WHO Joint Technical Consultation on avian influenza at the human-animal interface, held in Verona, Italy, during 7–9 October 2008 [9], and the “WHO Public Health Research Agenda for Influenza, 2009” [10]. Subsequently, funding agencies published requests for proposals to specifically address these issues [11, 12] or considered funding such work through open competitive grant programs. Proposals were then peer reviewed, and the most competitive proposals were funded. At that stage, the need to perform this particular line of research was clearly agreed upon by the research field as a whole, the scientists proposing the work, the funding agencies, and the external reviewers. From the conception phase of the research onward, biosafety and biosecurity experts were consulted to provide assurance that facilities and working conditions were such that the safety and security could be ensured at all times [13].

BIOSAFETY

Work on HPAI A/H5N1 viruses has been carried out in many laboratories throughout the world since 1997. In most countries, such work is performed in enhanced biosafety level 3 (BSL3) facilities. A/H5N1 and other influenza viruses have not escaped from the laboratories in which such research has been performed. Although individual (unreported)

laboratory-acquired infections may have occurred, this is in sharp contrast to the scenario discussed by Klotz and Sylvester [14], who concluded that 1% is the estimated probability of an escape from a single lab in a single year. This percentage was calculated on the basis of documented escapes of SARS coronavirus from laboratories that did not adhere to the BSL3 standards that are used in most countries. Research on class 3 pathogens, including transmissible HPAI A/H5N1 virus, can be done safely under enhanced BSL3 conditions by well-trained laboratory professionals, using strictly defined biosecurity and biosafety regulations to protect the researchers, the environment, and the public.

It is important to emphasize that even if individual occupational exposure to HPAI A/H5N1 virus occurred on rare occasion, primarily because of human error by personnel working under BSL3 and BSL4 conditions, several options are available to prevent subsequent exposure of the public at large and the environment. All of these options are in place at our facilities. First, H5 vaccines are offered to personnel handling the virus. Second, antiviral drugs are available for use as effective postexposure prophylaxis. Third, personnel can be quarantined upon exposure. Thus, despite the minute risk of occupational exposure, which is inherent to this type of work and perhaps unavoidable because of human error, the risks for the public and the environment can be reduced to nearly zero.

HOW DANGEROUS WOULD AN AEROSOL-TRANSMISSIBLE H5N1 VIRUS BE FOR HUMANS?

Human cases of A/H5N1 virus infection are sporadic and occur predominantly upon direct exposure to infected birds and their products or to contaminated environments in areas where the virus is circulating in poultry. As of February 2012, 584 laboratory-confirmed cases of HPAI A/H5N1 virus infections in

humans have been reported to the WHO, often with a clinically severe outcome and a high case-fatality rate of approximately 60%. Sustained human-to-human transmission of HPAI A/H5N1 virus has not yet been reported [15–17].

The case-fatality rate of 60% does not take into account potential mild or asymptomatic infections in people who are not seen by physicians or at hospitals. Serological studies in humans demonstrated that the incidence of H5N1 infection in exposed human populations is 1%–2% [18]. As a consequence, the case-fatality rate of A/H5N1 virus infection among humans may be significantly lower than the 60% deduced from laboratory-confirmed cases reported to the WHO.

Extrapolating from animal studies involving both macaques and ferrets, the virulence of the 1918 H1N1 virus, which had an estimated case-fatality rate of 2.5% in humans, was found to be within the same range as that for A/H5N1 virus [19]. Serious limitations of these animal studies are that virulence in animals and humans may be different, that virulence may vary with the route and dose of virus inoculation, and that virulence may be strain dependent. Overall, it is our opinion that data from human cases, serological analyses, and animal studies indicate that the case-fatality rate of 60% is a vast overestimate. Additional work to provide better estimates is urgently needed.

SHOULD RESULTS OF THIS WORK BE PUBLISHED?

The likelihood of the airborne A/H5N1 virus being used by individuals or organizations with bad intentions is low. The possibility to do harm with this virus is probably low in terms of its transmission and virulence in humans, because it is unlikely that the virus would spread like a seasonal influenza virus in humans and because the case-fatality rate is likely much lower than currently estimated. The techniques that

we used to create airborne A/H5N1 virus are not new and can be found in many virology textbooks. Individuals with bad intentions do not need to read the details in our manuscript because the methods for creating similar viruses have already been published widely. Moreover, the generation of such a virus requires well-trained experts and high-tech research techniques and facilities. In addition, there are many easier and cheaper ways for people with bad intentions to create a climate of fear by using infectious agents collected directly from nature.

Censoring the manuscripts on A/H5N1 virus transmission will, therefore, only create a false sense of security. Research aiming to unravel the genetic fingerprints associated with virus virulence, fitness, host range, and transmission needs to be done to enhance preparation for newly emerging infectious diseases. We agree with Peter Palese [20] that the more danger a pathogen poses, the more important it is to study it. As a consequence of our work, strong advice may be given to A/H5N1-affected countries about how to eradicate the virus from its animal reservoirs. Surveillance programs in countries where A/H5N1 is enzootic can now specifically target particular mutations that render A/H5N1 transmissible. In addition, we now have a relevant virus that can be used to test the efficacy of existing antivirals and to evaluate pre-pandemic vaccines. For the longer term, research of this and similar viruses will help us increase our fundamental understanding of why and how influenza viruses acquire the ability of aerosol transmission.

THE WAY FORWARD

The fear that the transmissible A/H5N1 may escape from laboratories or may be intentionally released by people with bad intentions has resulted in a global public debate on the benefits and potential harm of this research. To provide time to better explain the benefits of this

essential research and to explain the measures taken to minimize its possible risks, the influenza research community agreed to a voluntary pause of 60 days on any research resulting in A/H5N1 viruses that are more transmissible in mammals [21]. During the WHO-coordinated technical consultation in mid-February 2012 on H5N1 virus transmission research, unanimous support was given for this type of research, in the interest of science and public health. It was advised that the competent authorities should re-review biosafety and biosecurity conditions required to perform this work. At the same time, there should be focused communications to reduce anxiety among the public, increase awareness of the significance of this work, reassure that this type of work can be done safely and securely, and explain why the details of the work need to be published. It was further concluded that hiding key details from publications does not serve science or public health and that the confidential sharing of data classified as “dual use of concern” is impossible within a relevant time frame. As a consequence, the consensus view of the participants of this meeting was that full details of the studies should be published, in the interest of science and public health. After the expert judgments by the US National Science Advisory Board for Biosecurity and the WHO-assembled technical group, there is clearly also a need for broader consultation. We trust that in the interest of public health, the outcomes will be positive and constructive; that is, that the work will continue and that the manuscripts will be published responsibly, in the very near future.

Notes

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possible conflict of interests, Erasmus MC policy dictates that the shares as such are held by the Stichting Administratiekantoor Erasmus Personeelsparticipaties. The board of this foundation is appointed by the Board of Governors of the Erasmus MC and exercises all voting rights with regard to these shares.

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