

Avian flu research controversy



**ASSIGN
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Introduction

Avian influenza (AI), also known as Bird Flu, is an infectious disease caused by various strains of AI virus. It majorly affects wild water fowl for example geese and ducks, however it can cause large-scale outbreak among domestic poultry resulting into significant economic loss ¹. Majority of AI viruses do not cross the species barrier and infect humans, nonetheless, two strains – namely A (H5N1) and A (H7N9) – have exhibited zoonotic potential, causing serious illness and even deaths in people. Moreover, human infections caused by these two strains of virus have been linked with high mortality rates. WHO has received 650 case-reports of A (H5N1) infections since 2003 from 15 different countries, 60% of which proved fatal ². A(H7N9) strain of AI virus have infected 130 humans in China since March 2013, causing 43 deaths ³. Most human cases of AI infections to date are believed to be caused by exposure to infected birds, either dead or live. The virus is not known to transmit from person to person so far. However, natural mutations in the virus may enable it to cross over and spread among humans ⁴. With its high mortality potential, increased transmissibility will render it sever threat to public health ¹. Moreover, wide-spread outbreaks in poultry severely debilitate local as well as international trade.

Two groups, one based in US led by Dr. Yoshiharo Kawaoka at University of Wisconsin Madison and another based in Netherland led by Dr. Ron A. M. Fouchier at Erasmus Medical Center, have been specialized in avian influenza research. Their recent experiments aimed to create novel strain of

AI virus with enhanced transmissibility in ferrets triggered intense controversy ^{5, 6}. Both scientific and general community expressed their concerns regarding utility and handling of super-mutant viruses.

‘ Gain-of-Function’ (GOF) Experiments

Research groups engaged in creating mutant AI virus strains argues that in order to assess the pandemic potential of natural virus completely, further investigation is required which may involve ‘ gain-of-function’ experiments ³. These experiments are aimed to identify mutations which can enhance immunogenicity, host adaptation ability, drug resistance, transmissibility, and pathogenicity of the natural virus. Due to its close resemblance with human infection, ferret infection model is commonly used among influenza research community. Studies on these mammals have shown that relatively small set of mutations in H5N1 virus enables its respiratory transmission. Such genetic changes, if acquired by naturally circulating virus could result in worst outcome for human population. The proponents of these experiments propose that knowledge gained from genetically engineered virus research can help identifying set of the mutations to look for during the epidemic, and designing vaccines and pharmaceuticals in advance which can counteract the viral resistance. They also claim that controversy surrounding these experiments has increased dialogue on the matters of biosafety and biosecurity, and raised public awareness in this field ³.

Concerns

Experiments involving genetically modified viruses have stirred up numerous concerns not just among the general public but also among the research community. Genetically engineered viruses resulting from GOF experiments often regarded as ‘ Potential Pandemic Pathogens’ (PPPs) due to its potential for enhanced transmission and substantial virulence. Because of its novel characteristics, current human population is likely to have limited immunity against them ⁷ . Some public health experts have expressed their fear that accidental or deliberate release of these PPPs can lead to man-made epidemic. They also remains skeptical regarding benefits of GOF experiments. Suitability of ferret infection model have been questioned by some scientists who argues that the strategy disregards the phenomena called epistasis, which states that phenotype resulting from any mutation largely depends on its interaction with genetic background of different species ^{8, 9} . Regarding the vaccine claims, the opponents of these studies offers that in-depth molecular mechanism of transmission is not necessary for vaccine development. They further suggests that efforts on improving and stockpiling existing universal influenza vaccines alongside efficient large-scale production would be more worthwhile than mass-producing assorted vaccines which targets limited number of antigens with genetic variations ¹⁰ .

Ethical considerations

Due to its potential for being misused, experiments involving PPPs are usually regarded in context of ‘ dual use research of concern’ (DURC) ¹⁰ . Because of its pandemic potency, access to this knowledge and/or

pathogens into wrong hands poses significant danger to public health.

According to sixth point of Nuremberg Code, “ The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.” ¹¹ Seventy four national academies of science have also expressed that “ Scientists have an obligation to do no harm. They should always take into a consideration the reasonable consequences of their own activities” ¹² . Both the guidelines emphasize consideration and evaluation of long-term risk to general population. Moreover, second point of Nuremberg Code states, “ The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.” ¹¹ The opponents of GOF experiments have put forward several strategies to investigate nature of influenza infections which do not require creation of mutant viruses. Going forward without thorough consideration of these experimental strategies would disregard basic concern of biosafety.

Regulatory guidelines and policies

Soon after confronted by the controversy, research groups working on mutant AI viruses voluntarily declared 60-day moratorium on their experiments to allow government and other regulatory agencies to form required framework. Meanwhile, WHO gathered a panel of experts in the field of avian influenza research and public health for technical consultation, and issued several seminal suggestions for moving forward ⁴ . US Department of Health and Human Services (HHS) have delineated the

framework for new review procedure for research proposals involving highly pathogenic avian influenza (HPAI) viruses. Scope of this framework includes but not limited to reviewing research proposals for making funding decisions, evaluating potential for significant scientific and public health benefit, and assessing biosafety and biosecurity risks involved ¹³ . Centers for Disease Control and Prevention (CDC) also carried out review of required biosafety measures for such experiments and issued recommendations for risk-assessment ¹⁴ .

Restricted Access:

Another important aspect of this issue is access to the knowledge on how to create PPPs by selective mutations of already deadly virus. Experts feared that despite high security storage of mutant viruses, published methodology will be sufficient to generate PPPs for those who have intent to harm.

National Science Advisory Board for Biosecurity (NSABB) intervened in this situation and recommended that detailed methodology be excluded from the original manuscripts. While some scientists welcomed the move, the other group was disappointed for depriving responsible avian influenza research community from the useful knowledge. In its technical recommendations, WHO notes that there is no practical mechanism available that allows release of such information to limited audience. Moreover, it would not be too difficult for the expert scientists in the field to figure out the omitted information since there was no novel methodology was utilized ⁴ .

Personal verdict

Taking quantifiable risk associated with these experiments into consideration, I would suggest that meticulous and objective risk-benefit assessment should be executed before planning and conducting such experiments. Alternative experimental strategies such as studying infectious nature and genetic variability of field-isolates, and focusing on biophysical interaction resulting from interaction of multiple sites among viral proteins, rather than single amino acid substitutions should be pursued to the maximum possible extent to avoid unnecessary risk. If working out through these considerations needs more time, I would definitely sign on the moratorium.

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