

A conversation with Dr. Wendy Barclay on October 2, 2014

Participants

- Dr. Wendy Barclay – Professor, Chair in Influenza Virology, Imperial College London
- Nick Beckstead – Research Analyst, the Open Philanthropy Project

Note: These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Professor Barclay.

Summary

The Open Philanthropy Project spoke with Professor Barclay about the benefits and risks of gain-of-function (GOF) research on the H5N1 avian flu virus, roles for philanthropy in GOF research, and how GOF research can be improved.

Benefits of gain-of-function research on influenza viruses

In GOF research, scientists investigate how a pathogen currently not transmissible between humans, like H5N1 (avian flu), could mutate and gain transmissibility. Researchers genetically alter strains of pathogens in a laboratory setting and then test their transmissibility using animals. In addition to pure gains to scientific knowledge, GOF research may also lead to better vaccines and a better understanding of the severity of the risk that specific pathogens pose.

Gains to scientific knowledge

It is not appropriate to only value GOF research on influenza viruses in terms of immediate impacts on preventing and controlling diseases. Instead, it is wiser to think of the advancement of scientific knowledge as inherently beneficial, since knowledge gained may make future research and breakthroughs possible in ways we cannot anticipate.

Development of live attenuated H5N1 vaccines

Live attenuated vaccines use a live version of a virus instead of an inactivated one, and are usually administered through a nasal spray. Live attenuated vaccines are currently used in the UK and US, especially for children, and are much cheaper and quicker to manufacture than traditional inactivated vaccines. While inactivated vaccines are only functional when using the exact strain causing an outbreak, live attenuated vaccines also have the advantage of being less “strain-specific,” meaning that they can provide protection against a broader range of strains of a virus.

Attempts to make a live attenuated vaccine for H5N1 have not been successful so far since the virus cannot grow in human nasal passages. Recent GOF research on H5N1 found that a lack of pH stability was possibly the key factor preventing H5N1 from growing in human

nasal passages. Further research could now use this knowledge and lead to a strain of the virus pH stable enough to survive in human noses long enough to cause an immune response, which would be the key to developing a live attenuated H5N1 vaccine.

In the event of a major H5N1 pandemic, inactivated vaccines would be of limited use. Taking the specific strain of virus causing the outbreak and creating an inactivated vaccine would take around 6 months, during which time millions of people could have died. If we had a live attenuated vaccine for H5N1, we could quickly manufacture many more vaccine doses than would be possible if we only used inactivated vaccines. Inactivated vaccines alone could not be manufactured quickly enough to vaccinate everyone in an H5N1 pandemic, which would likely mean that most citizens of developing countries would not have access to vaccines.

GOF research that improves our knowledge of H5N1 virus stability could also improve other live attenuated vaccines that currently break down in hot conditions.

Surveillance benefits and more robust predictions on the severity of a H5N1 pandemic

When people contract H5N1 from direct contact with birds, around 60% of them die. However, if a strain of H5N1 mutated and became transmissible between humans, we do not know if this level of virulence would remain. Some scientists hypothesize that as a virus becomes more transmissible, it loses some of its virulence.

We do not know the likelihood of a scenario in which H5N1 mutates and becomes transmissible between humans, yet remains highly virulent. More information about the likelihood of different levels of virulence in a H5N1 pandemic would be very valuable, and might be gained through further GOF research. Plans for dealing with a H5N1 pandemic would be very different if researchers found that it was most likely that only 1% of people who contracted H5N1 died, as opposed to 60%.

If the theory that pH stability is the key factor preventing transmissibility in humans is correct, then further research may also have some surveillance benefits. Since pH stability is easy to test, it might be possible to use tests of pH stability of H5N1 as an early warning of an outbreak.

Risks of gain-of-function research on influenza viruses

There is a risk that pathogens from GOF research could be accidentally released or purposefully misused. GOF research could be purposefully misused by someone physically breaking into a lab and releasing a pathogen, or by someone using knowledge gained from GOF research to manufacture pathogens independently.

When considering risks of GOF research, it is important to realize that research with live viruses in laboratory settings must be a part of our approach for understanding influenza viruses and pandemics. After acknowledging that the work must be done, the question is how to minimize the risks.

Methods for minimizing risk

- **Using less dangerous viruses for research:** Some conclusions about H5N1 transmissibility reached by Yoshihiro Kawaoka and Ron Fouchier in their research could have been reached by using less dangerous viruses. Daniel Perez had earlier reached similar conclusions about transmissibility using less dangerous H9 viruses. However, researchers have an incentive for working with dangerous viruses, since research on dangerous viruses is more likely to be published in a high-impact journal. Working with dangerous viruses cannot be completely avoided since certain research questions, like whether or not H5N1 loses pathogenicity as it gains transmissibility, could not be answered satisfactorily by using less dangerous viruses.
- **Molecular biocontainment:** Researchers have engineered extra pieces of genetic information which can be added to viruses to prevent them from growing in certain species. “MicroRNA targeting” biocontainment strategies have very significantly reduced the risks of infection from some viruses in laboratory settings. More research needs to be done to show that molecular biocontainment strategies do not skew experimental results before this method is widely accepted in the scientific community.
- **Sharing best practices:** Researching dangerous pathogens has become much safer over the past 25 years. However, more open best practices sharing in the research community would reduce the risk of accidents.

Costs seem to outweigh benefits for other suggested methods for minimizing risk:

- **BSL-4 requirements for research on H5N1:** Some have suggested that researchers use the US Center for Disease Control and Prevention’s most stringent biosafety precautions, BSL-4, when working with H5N1. BSL-4 work is done in cumbersome spacesuits, is very expensive, and is usually used for untreatable pathogens. We do have drugs with which to treat influenza infected people. It does not seem that using BSL-4 would provide significant advantages over BSL-3 for working with H5N1.
- **Requiring formal cost-benefit analysis:** Researchers already frame their projects in terms of qualitative costs and benefits when writing grants. However, formal cost-benefit analysis would require quantifying very uncertain risks and benefits. Quantification of risks used to be a more significant aspect of a risk assessment of research with genetically altered microbes at least in the UK, but the practice was

abandoned since the quantifications seemed arbitrary, and arguments about which numbers to use could continue indefinitely.

- **Requiring insurance for GOF research:** Since scientists themselves know the most about the risks of a project, insurers would likely ask the scientists for risk estimates, defeating the purpose of hiring a neutral third party. Requiring insurance would drive up the costs of research, but not provide clear risk reduction.

Roles for philanthropy

- **Funding research:** A philanthropist may want to directly fund certain experiments, especially those that would not likely be funded through other grants. Research grants are most often awarded to projects that aim to have immediate impacts controlling or preventing specific diseases. A philanthropist may be more interested in understanding if microRNA targeting skews research results, or other specific topics. These types of research studies usually cost between 200,000 and 1,000,000 GBP.
- **Convening meetings:** Recent presentation-style meetings between researchers have not resolved fundamental disagreements about the risks and benefits of GOF research. A philanthropist may want to fund a roundtable discussion meeting so that some consensus can be reached on the best way to approach GOF research and pandemic risk reduction. Meetings on best-practices for risk assessment could also be useful.

Improving GOF research

Some GOF research has not been rigorous enough to provide useful information. Previous research on the transmissibility of H5N1 tested if the virus was transmissible from one animal to another, but did not test if the virus could be transmitted from the second animal to a third animal. Further research needs to be more rigorous for us to gain a better understanding of the likelihood of a H5N1 pandemic.

Who else to talk to

Attempts to change procedure for GOF research would go beyond the influenza field, so it is important to talk to experts in other pathogens, including a bacteriologist.

It would be useful to talk to Michael Imperiale for more information about how genetic engineering changes the characteristics of viruses, and to Vincent Racaniello of This Week in Virology.

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