Conversation with Marc Lipsitch about biosecurity, January 29, 2014

Participants

- Marc Lipsitch – Professor of Epidemiology, Harvard University School of Public Health
- Alexander Berger – Senior Research Analyst, GiveWell

Note: This set of notes was compiled by GiveWell and gives an overview of the major points made by Marc Lipsitch.

Summary

GiveWell spoke with Professor Marc Lipsitch as part of its investigation of the cause of biosecurity. Topics included: risks and benefits of dual use research, the need for a comprehensive assessment of risks and benefits to guide future research, the emergence of pandemics, and issues with disease surveillance. The conversation also covered the role of philanthropic funding in biosecurity research and opportunities for further investment.

About Professor Lipsitch

Marc Lipsitch is a Professor of Epidemiology at Harvard University's School of Public Health and the Director of the Center for Communicable Disease Dynamics, which is funded by the Modeling of Infectious Disease Agent Study (MIDAS) program of the National Institutes of Health/National Institute of General Medical Sciences.

Dual use research

Risks and benefits of dual use research

"Dual use" research refers to research in the life sciences that produces information or technologies that could threaten public health if misused. The type of dual use research Professor Lipsitch is most concerned about is research that attempts to make virulent pathogens more transmissible between humans (by making them more transmissible in animal models like ferrets). This is often referred to as "gain of function" research, though the particular functions being gained in this case are extremely dangerous, and Professor Lipsitch prefers to refer to it as research on "potential pandemic pathogens." The creation of such transmissible, virulent pathogens increases the risk of a disastrous accident, and there is very limited evidence of the benefits of this research.

What is needed is a comprehensive assessment of the risks and benefits of this research. Ideally, this would be carried out very soon, as the research is already ongoing. A comprehensive assessment should be conducted by a credible and disinterested third party with appropriate expertise, rather than the scientists who get funded to do these experiments. Academic input would be helpful for such a project, especially in estimating the benefits of the research, which are generally "knowledge benefits." It would also be useful to involve vaccine manufacturers, experts in flu surveillance, and ethicists to provide guidance on how to make decisions regarding the risks and benefits.

The U.S. Department of Health and Human Services is currently committed to funding "gain of function" research and, although it says in its guidance document that a risk assessment should be performed before funding is extended, no such risk assessment has been made public. Numerous groups, including the Foundation for Vaccine Research, have taken a look at the feasibility of commissioning a privately-funded, comprehensive risk-benefit assessment of GOF, and several groups have undertaken preliminary studies. Still, a comprehensive assessment is missing. This issue has been framed, inaccurately in Professor Lipsitch's opinion, as a matter of freedom of scientific inquiry. All funding decisions for scientific research consider risks and benefits, and sometimes the risks are determined to be too high and the research will not be funded. It is very likely that such an assessment will clarify whether this research should be done, and would be used to govern the decisions of major funders, including both governments and foundations (ideally not just in the U.S.).

Risks of synthetic biology research

Laurie Garrett's recent article in *Foreign Affairs* gives important context on synthetic biology and concerns that could arise in the coming decades. However, it's not clear that anything can be done to address these concerns before they become actual threats.

There is a risk that publicizing the potential risks of synthetic biology research could do harm by increasing the chances that malevolent agents learn about synthetic biology, but it could also be beneficial by drawing attention to the need to mitigate risks. Lawrence Wein published an article in the *New York Times* a few years ago about how easy it would be to poison large numbers of Americans, especially children, by contaminating the milk supply with botulism toxin. Wein's point of view of was that this is an obvious choice if you're a bioterrorist, but others felt it was irresponsible to write about it so publicly, because it could increase the likelihood that such an attack would be carried out.

Pandemics from naturally evolving pathogens

There have been four flu pandemics in the last hundred years, and one (the 1918 pandemic) had a very high case fatality rate, though not as high as H5N1 in its pre-pandemic state. Other than the most recent one, all of these pandemic strains have been more deadly on a case fatality level than a typical seasonal flu.

The most recent flu pandemic risk is the A(H7N9) virus, which has had a few human-to-human transmissions, but not yet enough to emerge as a global pandemic. H7N9 is as concerning as any other strain has been at this stage, even compared to H5N1, but there have not been comprehensive steps taken to keep it from emerging. There have been some warnings issued, but most bird markets remain open because there are economic ramifications of shutting down live bird markets and changing the agricultural system in China.

Virulence and transmissibility

There is debate on the question of whether viruses become less virulent as they become more transmissible. One theory on this question was that transmission requires keeping the host alive, and therefore the deadliest strains would not be highly transmissible. However, this theory is no longer widely held by experts. If a virus kills its host after two weeks, that may still be enough time for the host to transmit the virus, and if a virus achieves high levels of replication within its host, that could increase transmissibility *and* lead to the death of the host. Evolutionary biologists tend not to believe that transmissibility and virulence are inversely related, though some in the infectious disease community do still believe this. Professor Lipsitch believes it is overly optimistic to suggest that high pre-pandemic virulence will limit transmissibility or that virulence will necessarily be reduced as transmissibility increases.

Control measures for pandemics

Vaccination is the only control measure that can create permanent immunity once a pandemic has emerged. Other than that, measures can be taken to mitigate consequences of the pandemic, such as modifying social mixing by closing schools, businesses, and airports, and treating people with prophylaxis and anti-viral drugs. These measures must be done consistently to be effective, which means they are not a permanent solution, but can help limit infection and fatalities until everyone has been vaccinated.

The Biomedical Advanced Research and Development Authority (BARDA) has been very effective at finding ways to speed up the process of manufacturing vaccines, especially the production of a first set of vaccines for trials, which then enables the scale up of vaccines that work. The best solution to the threat of flu pandemics, if it's possible, would be a

universal flu vaccine (one that doesn't need to be changed every time there is a new strain). Professor Lipsitch's understanding is that such a vaccine is conceptually possible, but that significant research and development remains to be done. Such research is currently receiving significant attention from research funders.

Surveillance

The current system for sampling birds for flu is slow and incomplete. It typically takes about one year from the time a strain is isolated until its sequence is made public, though the time and cost of sequencing are decreasing due to technological advancements. The disease surveillance community currently has a very limited understanding of how to interpret sequences, so this is a bottleneck to improving surveillance. It would be great to increase the speed and volume of sampling, but even if surveillance was a hundred times better than it currently is, it's unlikely to be especially helpful in identifying potentially bad strains in time to take effective control measures.

Once a disease emerges in humans, it's easier to identify candidates for potential pandemics and prioritize among them based on expected transmissibility and virulence. The surveillance of human diseases has a higher likelihood of success than just sampling birds, but there is still significant room for improvement. For example, insurance companies, hospitals and health practices already collect data on diseases, but it is not aggregated in a meaningful way. If this data were aggregated, it could be used for surveillance. Another opportunity for improvement is increasing investments in surveillance of respiratory infections in China.

Funding for biosecurity research and preparedness efforts

The funding for biosecurity research is fairly concentrated among a few entities. This is an issue for gain of function research, because the people who fund this research (mainly at the U.S. Department of Health and Human Services) are the same people who might fund a study rigorously assessing its costs and benefits.

There is a degree of groupthink, especially around the idea that social media and big data are the answer to problems of disease detection and surveillance. This idea may be useful, but it is still at an early stage, and the attention it receives may prevent other ideas from gaining support.

Philanthropy should consider the magnitude of public health problems in determining what to fund. One issue that has received outsized support relative to the magnitude of the problem is the use of antimicrobial drugs in farmed animals. This has become a hot topic

for debate and attracted attention from major scientific and consumer advocacy groups. However, the use of antimicrobial drugs in farmed animals has caused measurable, yet relatively small negative impacts on human health -- probably contributing to much less than 1000 deaths per year in the United States. Solving this problem is worthwhile but pales in comparison to other infectious disease risks, such as pandemic influenza and other aspects of antimicrobial resistance. Efforts to deal with antimicrobial resistance should more productively focus on diseases for which treatment is an important aspect of the control strategy, for which antimicrobial resistance rendering the treatment of individual cases ineffective would also have significant negative effects on public health. These diseases include sexually transmitted diseases, HIV, and tuberculosis.

Opportunities for investment

One area where greater investment could be beneficial is in using pathogen genome sequencing to understand transmission. For outbreaks that have occurred since 1900, each case is recorded with information about the place and time of the infection. In the future, it will be possible to add the genomes of the infecting pathogens to the set of information that is recorded. Genomic data provides biological information about the characteristics of the infection, and also enables inferences to be made about how transmission occurred and how fast the virus is spreading, based on the relationships of sequences. The main barrier to expanding this work right now is securing funding to extract genomic material for sequencing. Professor Lipsitch's group at the Harvard School of Public Health receives funding from MIDAS to analyze genome sequence data of pathogens, but does not have a consistent source of funding for obtaining this data. Most of the costs involved in this process are decreasing, but soon obtaining the genetic material will be the most expensive part of the process. In order to fund DNA extraction, funders normally have to be interested in the particular biological problem, which is difficult and especially problematic in the case of an outbreak where there would be time constraints.

In the longer term, there will be a need to fund the development of better methods to analyze sequence data. There is currently very limited capacity in public health departments to understand these data. It's at the cutting edge of academic research, so there is an education and a tool gap for those in public health departments. Academics need to develop tools that are more usable by public health professionals. This is happening at a small scale, but it is still very early stage.

A third area where investment is needed is in impact-based public and policy advocacy work. Policies to reduce pandemic risks have the potential to protect millions of lives, particularly those that either prevent a pandemic from emerging or lead to timely immunization of a large number of people globally when the next one does emerge. The

issue of agricultural antibiotic use, described above, is one example of a cause that gets much more attention from advocacy groups yet has a much smaller impact on human life and well-being, Dr. Lipsitch argues.

Other people for GiveWell to talk to

- Simon Wain-Hobson, Scientific Director, and Peter Hale, Executive Director, Foundation for Vaccine Research, who are working to stimulate assessment of the risks and benefits of experiments on potential pandemic pathogens.
- Don Burke, Dean, University of Pittsburgh School of Public Health, and Director, University of Pittsburgh's Center for Vaccine Research.

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