The FOUNDATION for VACCINE RESEARCH

WORKING TO SECURE OUR CHILDREN'S FUTURE

December 18, 2013

Mr. José Manuel Barroso
President of the European Commission
Berlaymont Building
200 Rue de la Loi, 13th Floor
1049 Brussels, Belgium

cc:
Mrs. Viviane Reding, Vice President of the European Commission
Mrs. Máire Geoghegan-Quinn, Commissioner for Research, Innovation and Science
Mr. Tonio Borg, Commissioner for Health and Consumer Policy
Mr. Neven Mimica, Commissioner for Consumer Protection

RESPONSE TO LETTER BY THE EUROPEAN SOCIETY FOR VIROLOGY
ON "GAIN-OF-FUNCTION" INFLUENZA RESEARCH
AND
PROPOSAL TO ORGANIZE A SCIENTIFIC BRIEFING
FOR THE EUROPEAN COMMISSION &
CONDUCT A COMPREHENSIVE RISK-BENEFIT ASSESSMENT

Dear President Barroso,

We are writing to you on behalf of the Foundation for Vaccine Research and the 56 undersigned scientists to express our concern about a recent letter sent to you by the European Society for Virology (ESV). Several members of our group and the undersigned are members of the ESV.

We would like to correct some of the scientific misstatements in that letter. We would also like to propose: (1) a scientific briefing for the European Commission on so-called "gain-of-function" research, more properly defined as research to increase the pathogenicity, transmissibility, or alter the host range of highly pathogenic microbes with pandemic potential, including, but not limited to, influenza A viruses such as H5N1 and H7N9, and (2) consideration of a comprehensive risk-benefit assessment of this type of research. It is overdue that the risks associated with gain-of-function research be rigorously assessed and quantified. Researchers stand poised to conduct gain-of-function experiments with the SARS coronavirus and a host of other microbes with pandemic potential.

Misstatements
We would like to rebut some of the misleading scientific statements contained in ESV's letter of October 16 about EU laws, rules, and regulations governing the submission of manuscripts to international scientific journals, especially the need for export licenses for papers describing the results of so-called "gain-of-function" transmission experiments with highly pathogenic avian influenza H5N1 viruses conducted by Dr. Ron Fouchier at the Erasmus Medical Center in Rotterdam (*1*).

We do not take a position on the issue of export licenses, although we do understand the Dutch government's concern.

Regarding the scientific misstatements in ESV's letter, we take particular exception to the following sentence:

"However, it has to be mentioned that, in this specific case, **the "gain of function" was used to reproduce what nature already selected** (as demonstrated by sequencing of field mutants) with the variation that the aim of the study was to predict/anticipate biological evolution and to provide us with critical information to specify preventive and therapeutic measures, e.g., the improved surveillance and proper evaluation of candidate vaccines and drugs."

First, the statement that gain-of-function was used "to reproduce what nature already selected" is incorrect. Nature has *not* already selected an H5N1 virus that is readily transmissible between mammals. Highly pathogenic avian influenza H5N1 viruses are primarily transmitted between birds, not between mammals, and are only inefficiently transmitted between humans, if at all.

Fouchier *et al.* created novel mutant strains of H5N1 viruses that are genetically different from *any* known H5N1 virus strain found in nature, and that, importantly, have a specific property that makes them more dangerous than *any* known natural H5N1 virus, i.e., they are efficiently transmitted between mammals via respiratory droplets. Using ferrets, the preferred animal model for research with influenza A viruses, Fouchier and colleagues employed laboratory techniques that do *not* exist in nature, notably laboratory-directed, so-called "forced evolution," to see "what it would take" for H5N1 viruses to become transmissible via the aerosol route. Naturally occurring H5N1 viruses are highly virulent for humans – killing as many as 60% of those with known infections – but are not readily transmissible between mammals, including between humans. The sole purpose of the experiments in question was to generate H5N1 viruses that could be transmitted between mammals as readily as seasonal flu via respiratory droplets, i.e., by coughing or sneezing.

Despite intensive field surveillance conducted by national health authorities, government agencies, local and regional disease surveillance networks in Southeast Asia and elsewhere over a period of 16 years, *there is no evidence that efficiently mammalian-transmissible H5N1 viruses have ever emerged naturally in the wild.* Whereas it is correct that some individual mutations and some subsets of mutations identified by Fouchier *et al.*, after repeated passage of H5N1 viruses between ferrets, have been found in nature, these mutations in different genetic backgrounds do *not suffice* to confer efficient binding to mammalian receptors. Additional mutations are necessary (*2*). The only unambiguous way to find out whether a field isolate is capable of aerosol transmission between ferrets is to perform a transmission experiment. Furthermore, whether the results of such experiments could extend to humans is unknown. Mapping mutations is *not* a surrogate marker for transmission. In summary, the statement that "gain-of-function" was used to reproduce "what nature already selected (as demonstrated by sequencing of field mutants)" is simply untrue.

Second, there is no compelling evidence or scientific basis for the assertion that gain-of-function research conducted by Fouchier *et al.* – or, indeed, by any other group (*3,4*) – can help us "predict or anticipate biological evolution and provide us with critical information to specify preventive and therapeutic measures, e.g., the improved surveillance and proper evaluation of candidate vaccines and drugs."

Given the highly unpredictable nature of influenza viruses, it is not possible to predict or anticipate biological evolution with any certainty and thereby to predict or anticipate the next influenza outbreak (*5-13*). Indeed, the track record in this domain is extremely poor. Evolutionary pressures result in multiple reassortment and mutational events that follow no clear pathway and are impossible to predict or associate with a specific outcome in any population (*11,14*). The experimental design of these influenza gain-of-function experiments is such that the outcome is strongly influenced by the experimenter. Hence, the probability of anticipating nature is very low indeed.

Third, there is no scientific basis for the claim that gain-of-function research may lead to the development of more effective vaccines, a major argument advanced by proponents of gain-of-function research, by providing "critical information for the proper evaluation of candidate vaccines."

Such a claim fails to appreciate the complexities of how influenza vaccines are developed (*14*). Gain-of-function studies on highly pathogenic avian influenza H5N1 viruses conducted to date in Europe, North America and Asia have contributed nothing so far to the development of new vaccines or prophylactic measures. The choice of H5N1 virus with which to make a vaccine is based on immunogenicity, not on virulence. Vaccine developers will need the actual H5N1 pandemic strain that is spreading in order to make that selection, rather than one obtained via gain-of-function experiments. Influenza vaccines have been manufactured for many decades based on the isolation of a virus with a specific pandemic potential or seasonal prevalence. It has so far been necessary to produce a new vaccine to protect against every influenza virus suspected of pandemic or seasonal threat, irrespective of the structure of the viral hemagglutinin or detected mutations in its amino acid sequence. Moreover, it is unlikely that any manufacturer would start epidemic vaccine production without knowing with certainty which strain to use. In this context, it is difficult to see how gain-of-function research can lead to more effective vaccines, at least in the near future.

Fourth, there is little evidence for the claim that gain-of-function research can provide "critical information for the proper evaluation of candidate drugs." Our 25 years of experience with HIV-1, another virus with a high propensity to mutate, has taught us that the only way to evaluate the efficacy of candidate antiviral drugs for RNA viruses is to conduct clinical trials. If ever H5N1 influenza went pandemic, we could only hope that the strain would be sensitive to some of the existing anti-influenza drugs. It would take several years to evaluate and get a new antiviral drug to market.

Taken together, these bold yet misleading claims made by the European Society for Virology are claims that have been repeatedly refuted (*14,15*). These misstatements weaken their case and should be corrected.

The power of synthetic biology has received considerable attention in recent years. Synthetic biologists do not deliberately try to increase the danger level of pathogens, toxins or the environment in which we live. It would be of the utmost concern if they did. By contrast, the influenza gain-of-function transmission experiments conducted by Fouchier *et al.* are notable for their *deliberate intent* to make a pathogen more dangerous for humanity. To justify such experiments, there must be extraordinary practical benefits that outweigh the risk of accidental release.

Despite significant improvements in safety conditions in research laboratories during the last decade, there is no such thing as "zero" risk. In this context, the potential for accidental release of a hazardous pathogen is real, not hypothetical, as demonstrated by an alarming increase in the number of potential and actual release events in laboratories working with high-threat pathogens (*16*). The number of potential and actual release events in Europe has not been recorded. However, between 2003 and 2009 the United States Centers for Disease Control and Prevention (CDC) recorded 395 domestic potential release events in laboratories working with high-threat pathogens (*17*). In Asia, three cases of laboratory-acquired SARS infections were reported in 2003, one in Singapore, one in Taiwan, and one in Beijing (*18-20*). These laboratory-acquired infections occurred after the WHO declared the end of the SARS outbreak. Moreover, the Beijing SARS infections spread beyond the laboratory into the community before the infections were detected and stopped.

Accidents do happen even in high-containment laboratories. The accidental release of even an attenuated virus strain can have global consequences. We need look no further than the re-emergence of the H1N1 influenza virus in 1977, after a 20-year hiatus. Most scientists who have investigated the 1977 outbreak concluded that the re-emergence was the result of an accidental release from a laboratory source (*21*), most likely from a laboratory in the former Soviet Union that was working on a live-attenuated H1N1 virus vaccine. Although the virus was an attenuated strain, it was nevertheless highly transmissible and went global, causing an epidemic, albeit a mild one.

For this reason, we are primarily concerned about the safety of gain-of-function research and the consequences of an accidental release. We are in a situation where the probabilities of a laboratory accident that leads to global spread of an escaped mutated virus are small but finite, while the impact of global spread could be catastrophic. Many other types of research on the biology of influenza viruses are possible that could provide crucial scientific information without creating a virus capable of transmission in mammals – that is, without the risk entailed by the experiments of Fouchier *et al.* In contrast to the substantial risks of gain-of-function research, the benefits of such research are hypothetical at best. There is little to no pre-existing immunity in the general population to the H5N1 virus, and none to the H7N9 virus discovered earlier this year in China. Moreover, there are only limited quantities of H5N1 vaccines readily available and stockpiled (vaccines which may not be a good match), and there is no licensed H7N9 vaccine. As a result, the accidental or deliberate release of an artificial, laboratory-generated, human-transmissible H5N1 or H7N9 virus into the community could be difficult or impossible to contain. There are few situations where a small but finite risk could, in the event of an accidental release, have such far-reaching consequences.

Proposals

1. A scientific briefing for the European Commission

Since the controversy surrounding H5N1 – and now H7N9 (*22*) – gain-of-function research is a complex scientific issue, and since the consequences of an accidental release affect the entire population of the European Union, we would like to propose that a scientific briefing be organized for the European Commission.

Such a briefing could be prepared at relatively short notice. The purpose of the briefing would be to inform Commissioners and their staff – and Members of the European Parliament, if desired – about gain-of-function research, presenting arguments in favour of and against the research. Given this information, Commissioners and MEPs would be in a better position to determine whether the risks are outweighed by the potential benefits, e.g., in predicting a pandemic or developing more effective vaccines. The National Academy of Sciences in Washington will shortly be debating these topics in a symposium. It is vitally important that European voices be heard and that Europeans participate in this debate. Indeed, there is an opportunity for Europe to take the lead on this issue.

The Foundation for Vaccine Research has the experience and the expertise to organize such a briefing, as one of the organizers and the moving force behind a 2-day international symposium, "H5N1 Research: Biosafety, Biosecurity and Bioethics," held at the Royal Society in London on April 3-4, 2012. The symposium was open to the public and webcast live. It was the first and remains the largest meeting organized to date on this topic. We would be happy to follow up with a detailed proposal regarding how such a scientific briefing could be organized for the European Commission.

2. A comprehensive risk-benefit assessment of gain-of-function research

Despite two years of controversy surrounding gain-of-function research and the lack of a scientific consensus, we still do not have a comprehensive risk-benefit analysis, as we would have hoped for on such an important topic. Many organizations, groups and individuals in Europe and the United States, including the journal *Nature*, have called for an independent risk-benefit assessment, but so far without success (*9,23*). A rigorous, comprehensive risk-benefit assessment could help determine whether the unique risks to human life posed by these sorts of experiments are balanced by unique public health benefits which could not be achieved by alternative, safe scientific approaches. Since scientists do not agree on the scientific merits of gain-of-function research, it will be hard to quantify the benefits. However, the risks *can* be quantified, as has been suggested in several preliminary studies (*24-28*). A comprehensive risk assessment would be able to quantify the risks of a release of a mutated virus into the community in terms of the loss of human life, the cost to health care systems, the financial and socio-economic costs, and the liability costs. These are man-made viruses and so liability becomes a novel issue, absent in the case of a naturally occurring epidemic.

Given your position as President of the European Commission, the combined experience and expertise of Commissioners and their staff, and the resources at your command, the Commission could make an important and immediate contribution by calling for a rigorous, comprehensive risk-benefit assessment of gain-of-function research to inform decision makers in Europe and worldwide. We have explored the feasibility of conducting such an assessment and would be happy to follow up with your staff with a detailed proposal regarding how an assessment could be undertaken.

Next steps

We would be honoured to follow up directly with Science Commissioner, Máire Geoghegan-Quinn, and her staff, on how a scientific briefing for the European Commission could be organized at short notice, as well as how a comprehensive risk-benefit analysis could be conducted.

We look forward to hearing from you,

Sincerely,

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FVR Board Chair