Reply to "Comments on Fouchier's Calculation of Risk and Elapsed Time for Escape of a Laboratory-Acquired Infection from His Laboratory"

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In a letter to the editor (1), Dr. Lynn C. Klotz challenges my conclusion (2) that laboratory-acquired infections (LAIs) are expected to occur at an extremely low frequency in facilities such as those used at Erasmus MC for studies on airborne transmission of influenza viruses between ferrets and that these studies pose negligible risks to humans and the environment. Unfortunately, Dr. Klotz does not provide a scientific justification of how the numbers should be adjusted based on the biosafety measures that are in place in these facilities, which is the key challenge in this debate. Dr. Klotz suggests that incidents at the U.S. CDC laboratories and the long history of escape of LAI agents and other escapes from laboratories show that my estimates of the likelihood of LAIs occurring at the Erasmus MC facility are too low. However, it is unclear to me how the incidents at the U.S. CDC—which did not lead to LAIs—would affect my calculations. In addition, I have pointed out previously that historical data on LAIs do not take into account the specific pathogen types or the numerous biosafety measures that are in place to mitigate the risks in laboratories where transmission research is conducted (2).

Dr. Klotz proposes to multiply the low likelihood of LAIs by 300, based on an estimated 30 laboratories involved in the "whole research enterprise" for 10 years, and assumes that part of this research enterprise may lack the rigorous safety practices in place at Erasmus MC. Both assumptions are wrong, to the best of my knowledge; just over a handful of laboratories have worked on airborne transmission of avian influenza viruses, each of which has rigorous safety practices in place (3-7).

Another key aspect is that Dr. Klotz estimates the likelihood of onward transmission from a case of LAI as 0.1 (10%), in contrast to my justification for an adjusted likelihood of $<1 \times 10^{-5}$, based on the specific conditions under which the research is performed, without providing a rationale for that important deviation (2).

Finally, Dr. Klotz describes the (apocalyptic) scenario of an influenza pandemic with 140 million fatalities based on a 10% case-fatality rate in 20% of the world's population. These numbers not only ignore the scientifically justifiable counterarguments raised before (2) but also are at odds with the documented influenza pandemics of the past. In my view, the "gain-of-function" debate has suffered from the apocalyptic scenarios that are provided as factual whereas they provide estimates that are far beyond the observed worst cases (8). In calculations of the probability of a community LAI ("*E*"), Dr. Klotz further assumes that transmission studies in the Erasmus MC facility will be performed for a period ("*y*") of 1 million years. I am hopeful that our research enterprise will have reached solid conclusions on determinants of airborne transmission a bit sooner.

With the caveats listed above, I agree with Dr. Klotz in reference to another *mBio* publication (9) that provides some arguments as to why my calculations of the probability of LAIs may be too low. Taking into account the conditions of work at Erasmus MC (2), there are three arguments that are valid in that publication. First, I assumed that the enhanced biosafety measures at Erasmus MC would yield a decrease in the probability of LAIs by at least a factor of 10 compared to "ordinary" BSL3 laboratories through the physical separation of personnel from the viruses with which they work, the use of class 3 isolator units and class 3 biosafety cabinets, the use of personal protective equipment, the extensive training program, the use of experienced personnel only, and the application of a two-person rule to reduce human error during animal experiments. This is an explicit assumption, and the factor of 10 requires further analysis, as others and I have pointed out (2, 9, 10). Second, Dr. Lipsitch and Dr. Inglesby are correct in stating that vaccines are not readily available for transmission studies with some avian influenza viruses (e.g., subtype H7), thus increasing the risks of potential LAIs and onward transmission in such cases, albeit modestly. Third, biosafety measures cannot prevent malicious removal of viruses from the lab and intentional release into the environment. On this latter point it is important to note that numerous security measures are also in place in facilities like ours, but those cannot be disclosed in detail for obvious reasons. However, our facility has been secured by procedures recognized as appropriate through in-depth audits by the institutional biosafety officers and facility management at Erasmus MC as well as national and international (U.S.) government inspectors. It is also important to note that these and many of the other biosafety and biosecurity arguments that continue to be raised against so-called "gain-of-function" research apply equally to natural pathogens, and—in my opinion—are not valid arguments to shut down or restrict a specific line of virus research.

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Published 14 April 2015

Citation Fouchier RAM. 2015. Reply to "Comments on Fouchier's calculation of risk and elapsed time for escape of a laboratory-acquired infection from his laboratory." mBio 6(2):e00407-15. doi:10.1128/mBio.00407-15.

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