

Supplementary information to: Gain-of-function experiments on H7N9

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Risk mitigation. Many factors are included in the risk mitigation plans for working with potentially dangerous influenza viruses including 1918 virus and highly pathogenic avian H5N1 viruses. These same measures will be applied to pursue experiments with A(H7N9) viruses that may result in gain of function (GOF). Risk mitigation measures include:

1. Modifying the experimental design to reduce risks — Where possible, alternative approaches (for example, attenuated strains, *in vitro* methods, replication-incompetent viruses) will be taken to reduce the risk. Many times, this is not an option for an experiment to be biologically meaningful. However, combinations of functional gains will be avoided, so that studies on increased virulence, host range, or transmission will not be performed with viruses that – at the same time – are known to be resistant to antiviral drugs or have the capacity to evade host immunity.
2. Biocontainment — To mitigate potential risks, A(H7N9) virus research is performed under biosafety level 3-enhanced conditions (BSL-3+). The biosecurity and biosafety precautions included in the BSL-3+ criteria are specifically designed to prevent occupational virus exposure and ensure containment.
3. Personal protective equipment (PPE) — As for all studies involving highly pathogenic influenza viruses, staff follow recommendations in BMBL5 (<http://www.cdc.gov/biosafety/publications/bmbl5/index.htm>) and the “NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules” (available at http://oba.od.nih.gov/rdna/nih_guidelines_oba.html). Researchers conducting A(H7N9) virus experiments put on the appropriate PPE before transiting into the containment suites.
4. Operational precautions — Standard operating procedures (SOPs) for working with highly pathogenic influenza viruses will be followed. These include separation of viruses and response plans for various scenarios.
5. Personnel — Even though A(H7N9) viruses are not considered Select Agents*, only experienced personnel that have undergone relevant background checks and been approved by the CDC and APHIS will participate in the GOF experiments. Staff who work in BSL-3+ undergo regular training and assessment to ensure compliance with SOPs.
6. Occupational health plan — Staff engaged in A(H7N9) virus GOF experiments will adhere to plans outlined for work with highly pathogenic viruses including notification of authorized officials should they develop any respiratory symptoms associated with fever. Each institution has plans in place to communicate with Infectious Disease physicians and Public Health authorities.
7. Program oversight — Each research program involved in these studies will adhere to Federal and institutional oversight policies.
8. Evaluation of countermeasures — No vaccine is currently available for A(H7N9) viruses. Viruses will be tested to ensure they are oseltamivir-sensitive. If any changes are

introduced to alter resistance, investigators agree that these strains WILL NOT be used for any other GOF studies.

9. Communication of results — To advance A(H7N9) virus research, findings should be shared in refereed publications. Investigators agree to adhere to guidelines for responsible communication of results and every effort will be made to put the results in context and reduce sensationalism.

(*Note: a virus that acquires a cleavage site associated with high pathogenicity will meet the criteria to be listed as a Select Agent [SA] and be subject to all SA regulations.)

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