Issues in dual-use biology publishing

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Content/summary

- H5N1 gain-of-function reprise:
  -NSABB recommendation to redact, WHO role, Nature's risk-benefit advice, decision to publish
- More recent experience: no rejections based on dual-use risk, some redaction of scientifically inessential but potentially harmful details in two cases
- Trends in science practice and journal scale

Nature-journals' DURC process

- All DURC submissions seen by internal DURC review committee: Editor-in-Chief of Nature and Nature publications, Editorial Director, Chief Biology Editor of Nature, Executive Editor (life sciences), Head of Policy of Nature publications;
- If assessed positive for risk, sent to external technical assessors associated with biosecurity
- Risk-benefit assessment reviewed by DURC committee, who advise relevant Chief Editor, and have the power to impose a veto on publication.

NSABB concerns about the Nature and Science submissions about flu GOF experiments

I am here highlighting aspects of the handling of the Nature paper and discussions stimulated by the biosecurity concerns, and by the NSABB proposal that papers be partially redacted.

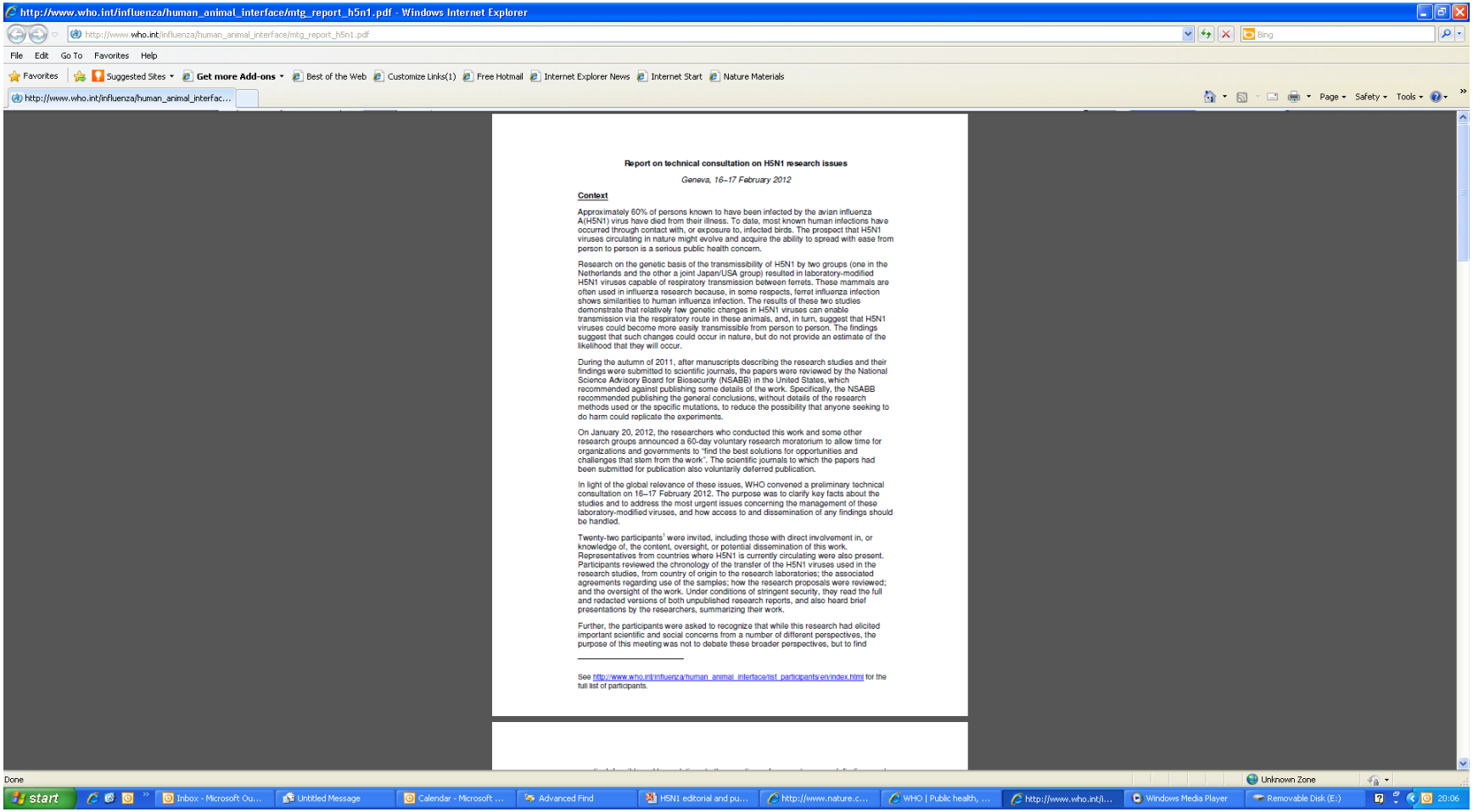
NIH press release Dec 2011

- Following its review, the NSABB decided to recommend that HHS ask the authors of the reports and the editors of the journals that were considering publishing the reports to make changes in the manuscripts. Due to the importance of the findings to the public health and research communities, the NSABB recommended that the general conclusions highlighting the novel outcome be published, but that the manuscripts not include the methodological and other details that could enable replication of the experiments by those who would seek to do harm.

- The NSABB also recommended that language be added to the manuscripts to explain better the goals and potential public health benefits of the research, and to detail the extensive safety and security measures taken to protect laboratory workers and the public.

- HHS agreed with this assessment and provided these non-binding recommendations to the authors and journal editors.

WHO meeting in February 2012 helped clarify the confused messages and claims…



WHO meeting in February 2012 helped clarify …..

…that no ferrets died in the aerosol transmissibility experiments conducted by Ron Fouchier.

…and the problems with restricted publication and dissemination

There is a preference, from a public health perspective, for full disclosure of the information in these papers. However, there are significant social concerns surrounding this research. Two critical issues that must be addressed before publication of the papers are: (1) a focused communications plan to increase public awareness and understanding of the significance of these studies and the rationale for their publication, and (2) a review of the essential biosafety and biosecurity aspects of the newly developed knowledge.

Participants discussed the concept of publication of redacted manuscripts with a mechanism for providing the restricted information to legitimate recipients. The group recognized the difficulty of rapidly creating and regulating such a mechanism in light of the complexity of international and national legislation. A consensus was reached that the redaction option is not viable to deal with the two papers under discussion in view of the urgency of the above mentioned public health needs. The participants noted there may be a need for such a mechanism in the future.

Independent biosecurity assessment of paper submitted to *Nature*

What information is provided and to what extent is it novel?

This paper shows that Influenza A virus H5 N1 ("Avian influenza") can be adapted by a combination of classical virology and molecular biology to become transmission-competent in mammals. The novelty of this discovery lies in the fact that mammal to mammal (and by implication human to human) transmission of this virus has previously been unknown.

Independent biosecurity assessment of paper submitted to *Nature* (cont.)

Are there potential risks to public health from application or utilization of this information? If so, please describe.

There is no doubt that this information could be used immediately by an exceptionally competent laboratory to provide the foundation for a programme to develop a pandemic strain of this virus. There is no evidence that this reassortant virus would be fully pathogenic in humans. This paper does not provide sufficient information to produce fully competent dangerous pathogen.

Independent biosecurity assessment of paper submitted to *Nature* (cont.)

Are there potential benefits to public health from application or utilization of this information? If so, please describe.

It is vital that science gains an understanding of the potential for emergent influenza viruses to cause pandemics – this information is an essential part of building such an understanding.

Independent biosecurity assessment of paper submitted to *Nature* (cont.)

Are there potential benefits of the information for national security? If so, please describe.

There are real national security benefits – the work will enable those of us in the CB security community to understand the limitations and possibilities of the risks posed by the deliberate manipulation of the causative agents of emergent disease.

Independent biosecurity assessment of paper submitted to *Nature* (cont.)

Will this information be useful to the scientific community? If so, how?

It represents a building block in the construction of an effective vaccine, in anticipation of the emergence of a fully competent natural variant.

Independent biosecurity assessment of paper submitted to *Nature* (cont.)

Based on the risks and benefits identified, and considering the time frame in which these might be realized: Do the benefits of communicating the information outweigh the risks? Do the risks outweigh the benefits?

Independent biosecurity assessment of paper submitted to *Nature* (cont.)

The risk benefit calculation is complex. This information could be used by an aggressor, and shows one of the building blocks for the development of a potential BW weapon. The aggressor, however, would need to be in possession of an advanced molecular biology capability and the ability to passage, and evaluate, pathogenic material in animals. This latter is a demanding capability, probably beyond the capacity of the majority of those groupings of concern.

On the other hand, not publishing this information would slow, or even block, the development of a vaccine against a virus that still has the potential to mutate **naturally** to a pandemic form, which could cause huge numbers of fatalities world-wide.

Independent biosecurity assessment of paper submitted to *Nature* (cont.)

The greater risk of non-disclosure, in my opinion, however, lies in the potential of such an act to discourage scientists from working in this field. Many studies, within defence and more generally, have revealed that the majority of life scientists fear the emergence of diseases for which we have no medical countermeasures, and pushing the best scientists towards blander areas in which they can more easily publish must increase our vulnerability to such entities.

On the balance of probabilities, the risks of publication do not outweigh the benefits.

NSABB meeting March 2012

(where redaction recommendation was reversed)……

… was confidential, but I do want to celebrate the clarity of Yoshi Kawaoka's presentation and the great emphasis he placed on the bio-safety aspects of his methods and set-up.

I believe that **such clarity and additional explanation by researchers is absolutely essential in creating trust** in the public, in political and regulatory circles and with biosecurity advisers. And accordingly, we journal **editors need to be permissive in space constraints,** and we at *Nature* are anyway very flexible.

In the face of eg congressional attention, scientists need to accept that they are accountable and have no inherent right to be left to their own individual and community devices. They need to communicate in that spirit. They also need to be aware that these discussions will sometimes be highly subjective and emotive. Confidence building is key.

May 2012

LETTER

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Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets

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REPORT

Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets

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viruses caused lung lesions (Supplementary Information and Supplementary Figs 10 and 11).

To assess whether current control measures may be effective against the H5 transmissible reassortant mutant virus, we examined the reactivity of sera from individuals vaccinated with an H5N1 prototype vaccine[28] against a virus possessing the N158D/N224K/Q226L/T318I mutations in HA. We found that pooled human sera from individuals immunized with this vaccine reacted with the virus possessing the mutant H5 HA (N158D/N224K/Q226L/T318I) at a higher titre than with a wild-type H5 HA virus (VN1203/PR8; Supplementary Table 6), indicating that current H5N1 vaccines would be efficacious against the H5 transmissible reassortant mutant virus. In addition, the H5 transmissible reassortant mutant virus (HA(N158D/N224K/Q226L/T318I)/CA04) was highly susceptible to a licensed NA inhibitor, oseltamivir (Supplementary Table 7). These experiments show that appropriate control measures would be available to combat the transmissible virus described in this study.

Currently, we do not know whether the mutations that we identified in this study that allowed the HA(N158D/N224K/Q226L/T318I)/CA04 virus to be transmissible in ferrets would also support sustained human-to-human transmission. In particular, we wish to emphasize that the transmissible HA(N158D/N224K/Q226L/T318I)/CA04 virus possesses seven segments (all but the HA segment) from a human pandemic 2009 H1N1 virus. Human-virus-characteristic amino acids in these seven segments may have critically contributed to the respiratory droplet transmission of the HA(N158D/N224K/Q226L/T318I)/CA04 virus in ferrets. Examples include amino acids in the PB2 polymerase protein that confer efficient replication in mammalian, but not avian, cells[29–31]. As the PB2 gene of the HA(N158D/N224K/Q226L/T318I)/CA04 virus is of human virus origin, the virus possesses high replicative ability in mammalian cells. In contrast, most avian virus PB2 proteins lack these human-type amino acids, although one of these changes (a glutamic-acid-to-lysine mutation at position 627) is found in highly pathogenic avian H5N1 viruses circulating in the Middle East[14]. As a second example, the viral NA gene may contribute to viral transmissibility. The NA protein cleaves α-ketosidic linkages between a terminal sialic acid and an adjacent sugar residue, an activity that balances the sialic-acid-binding activity of HA. A recent study found that a human virus NA gene was critical to confer limited transmissibility to a mutant H5 avian-human reassortant virus[14]. In general, a human-type receptor recognizing H5 HA alone may not be sufficient to confer transmissibility in mammals, but may have to act together with other human-virus-characteristic traits (in PB2, NA, and/or other viral proteins). Therefore, at this point we cannot predict whether the four mutations in the H5 HA identified here would render a wholly avian H5N1 virus transmissible.

Three of the residues identified here (N224, Q226 and T318) have been strictly conserved among H5 HA proteins isolated since 2003. However, as H5N1 viruses continue to evolve and infect people, receptor-binding variants of H5N1 viruses, including avian–human reassortant viruses as tested here, may emerge. One of the four mutations we identified in our transmissible virus, the N158D mutation, results in loss of a glycosylation site. Many H5N1 viruses isolated in the Middle East, Africa, Asia and Europe do not have this glycosylation site. Therefore, only three nucleotide changes are needed for the HA of these viruses to support efficient transmission in ferrets. In addition, the H5N1 viruses circulating in these geographic areas also possess a glutamic-acid-to-lysine mutation at position 627 in the PB2 protein, which promotes viral replication in certain mammals, including humans[29,30]. Therefore, these viruses may be several steps closer to those capable of efficient transmission in humans and are of concern.

Our study highlights the pandemic potential of viruses possessing an H5 HA. Although current vaccines may protect against a virus similar to that tested here, the continued evolution of H5N1 viruses reinforces the need to prepare and update candidate vaccines to H5 viruses. The amino acid changes identified here will help individuals conducting surveillance in regions with circulating H5N1 viruses (for example, Egypt, Indonesia, Vietnam) to recognize key residues that predict the pandemic potential of isolates. Rapid responses in a potential pandemic situation are essential in order to generate appropriate vaccines and initiate other public health measures to control infection. Furthermore, our findings are of critical importance to those making public health and policy decisions.

Our research answers a fundamental question in influenza research: can H5-HA-possessing viruses support transmission in mammals? Moreover, our findings have suggested that different mechanisms (that is, receptor-binding specificity and HA stability) may act in concert for efficient transmissibility in mammals. This knowledge will facilitate the identification of additional mutations that affect viral transmissibility; the monitoring of this expanded set of changes in natural isolates may improve our ability to assess the pandemic potential of H5N1 viruses. Thus, although a pandemic H5N1 virus may not possess the amino acid changes identified in our study, the findings described here will advance our understanding of the mechanisms and evolutionary pathways that contribute to avian influenza virus transmission in mammals.

METHODS SUMMARY

Viruses. All recombinant viruses were generated by using reverse genetics essentially as described previously[28]. All experiments with the viruses possessing the wild-type HA cleavage site were performed in an enhanced biosafety level 3 (BSL3+) containment laboratory approved for such use by the CDC and the USDA.

Infection and transmission in ferrets. Six- to ten-month-old female ferrets (Triple F Farms) were intranasally anaesthetized and intranasally inoculated with 10^6 p.f.u. (500 μl) of virus. On days 3 and 6 after infection, ferrets were killed for virological and pathological examinations. The virus titres in various organs were determined by use of plaque assays in MDCK cells.

For transmission studies in ferrets, animals were housed in adjacent transmission cages that prevented direct and indirect contact between animals but allowed spread of influenza virus through the air (Shows Science; Supplementary Fig. 7). Ferrets were intranasally inoculated with 10^6 p.f.u. (500 μl) of virus (inoculated ferrets). Twenty-four hours after infection, naive ferrets were each placed in a cage adjacent to an inoculated ferret (contact ferrets). To assess viral replication in the nasal turbinates, we determined viral titres in nasal washes collected from virus-inoculated and contact ferrets on day 1 after inoculation or co-housing, respectively, and then every other day. Animal studies were performed in accordance with Animal Care and Use Committee guidelines of the University of Wisconsin–Madison.

Biosafety and biosecurity. All recombinant DNA protocols were approved by the University of Wisconsin–Madison's Institutional Biosafety Committee after risk assessments were conducted by the Office of Biological Safety, and by the University of Tokyo's Subcommittee on Living Modified Organisms, and, when required, by the competent minister of Japan. In addition, the University of Wisconsin–Madison Biosecurity Task Force regularly reviews the research program and ongoing activities of the laboratory. The task force has a diverse skill set and provides support in the areas of biosafety, facilities, compliance, security and health. Members of the Biosecurity Task Force are in frequent contact with the principal investigator and laboratory personnel to provide oversight and assure biosecurity. Experiments with viruses possessing the wild-type HA cleavage site were performed in enhanced BSL3 containment laboratories approved for such use by the CDC and the USDA. Ferret transmission studies were conducted by three scientists with both DVM and PhD degrees who each had more than a minimum of 6 years of experience with highly pathogenic influenza viruses and animal studies with highly pathogenic viruses. Our staff wear powered air-purifying respirators that filter the air, and disposable coveralls; they shower out on exit from the facility. The containment facilities at University of Wisconsin–Madison were designed to exceed standards outlined in Biosafety in Microbiological and Biomedical Laboratories (5th edition; http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf). Features of the BSL3-enhanced suites include entry/exit through a shower change room, effluent decontamination, negative air-pressure laboratories, double-door autoclaves, double HEPA-filtered exhaust air, and gas decontamination ports. The BSL3-Agriculture suite features include all those listed for BSL3-enhanced plus HEPA-filtered supply and double-HEPA-filtered exhaust air, double-gasketed watertight and airtight seals, airtight dampers on all ductwork, and the structure was pressure-decay tested during commissioning. The University of Wisconsin–Madison facility has a dedicated alarm system that monitors all building controls and sends alarms (~500 possible alerts). Redundancies and emergency resources are built-in to the facility including two air handlers, two compressors, two filters each place filters are needed, two effluent sterilization tanks, two power feeds to the building, an emergency generator in case of a power failure and other physical containment measures in the facility that operate without power. Biosecurity monitoring of the facility is ongoing. All personnel undergo Select Agent security risk assessment by the United States Criminal Justice Information Services Division and complete rigorous biosafety, BSL3 and Select Agent training before participating in BSL3-level experiments. Refresher training is scheduled on a regular basis. The principal investigator participates in training sessions and emphasizes compliance to maintain safe operations and a responsible research environment. The laboratory occupational health plan is in compliance with the University of Wisconsin–Madison Occupational Health Program. Select agent virus inventory is checked monthly and submitted to the University of Wisconsin–Madison Research Compliance Specialist. Virus inventory is submitted 1–2 times per year to the file holder in the Select Agent branch of the CDC. The research program, procedures, occupational health plan, documentation, security and facilities are reviewed annually by the University of Wisconsin–Madison Responsible Official and a regular intervals by the CDC and the Animal and Plant Health Inspection Service (APHIS) as part of the University of Wisconsin–Madison Select Agent Program.

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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NB - cooperation

- NSABB, funders, authors and editors all co-operated.
- Nothing was compulsory other than export regulations.

Redaction is not the solution

- Redacting key data or methods disables subsequent research and peer review.

- Distributing the redacted information to a select group of people on a need-to-know basis is practically unfeasible:
  - who holds the data?
  - which criteria are used to determine who is allowed to see the redacted information?
  - who decides?
  - by which mechanisms is the information then made accessible?
  - how can information distributed to university or public health laboratory remain confidential?

“Having now considered these matters in depth, the editors of this journal have decided that we will not consider either alternative [redacting the key findings or distributing to selected recipients only] for papers in *Nature* in the foreseeable future.”

Nature, 3 May 2012

Further consequences

- Integrity of a field of research
  - biosecurity constraints on publication risk to erode the robustness of the field if reproducibility is not championed.
- Attractiveness to young scientists
  - delays and uncertainty about ability to publish and get credit may discourage young scientists from entering the field.

More recent experience

- Nature, Nature research journals, Nature Communications, Scientific Reports
- Disease pathogens/agents: Flu, meliodosis, Middle East Respiratory Syndrome Coronavirus, Botulinum neurotoxin, sarin
- Six examples in 2015-16

Outcomes

- No paper rejected on the basis of risk
- Details of safety added
- Scientifically inessential details of protocols omitted on two occasions:

  -in a paper relating to sarin, details of sarin synthesis

  -in a paper relating to Burkholderia pseudomallei, details of construction of an antibiotic-resistant strain

Thank you