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# Interview Guides for Risk and Benefit Analysis of Gain-of-Function Research

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# Introduction to the Interview Guides

## How the Interview Guides Were Used

The following sets of interview questions are grouped by stakeholder (e.g. researcher versus industry stakeholder) and/or by interview goals (e.g. questions related to the benefit assessment versus questions related to the biosafety risk assessment). Not all questions were asked of all participants. Rather, each interviewed stakeholder was asked the set or sets of questions that were appropriate given his or her expertise. These questions served as a basis for discussion, and interviews followed the flow of conversation. Each interviewee was provided with the following background information about the scope and purpose of Gryphon's Risk and Benefit Assessment as well as their set of relevant interview questions prior to the interview.

## Background

Gryphon Scientific has been asked on behalf of the NIH Office of Science Policy to conduct formal risk and benefit assessments (RBA) of "gain of function" (GoF) research involving pathogens with pandemic potential. The results of the RBA will inform the NSABB in their development of recommendations to the USG regarding the appropriate level of Federal oversight of GoF research. The assessment has been divided into four components – benefits assessment, biosafety risk assessment, biosecurity risk assessment, and biosecurity risk assessment of information. The purpose of this assessment is to provide NSABB with an assessment grounded in science.

As guided by the NSABB's "Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research," our assessment will focus on evaluation of research involving influenza viruses, SARS-CoV, and MERS-CoV and will include experimental approaches that are reasonably anticipated to confer one or more of the following phenotypic changes to wildtype pathogens:

- Enhanced transmission in mammals, including altered routes of transmission and increased host or tissue tropism;

- Enhanced morbidity and mortality in appropriate animal models;

- Enhanced pathogen production as a result of changes in the replication cycle or growth;

- Resistance to anti-virals or evasion of vaccines and other medical countermeasures (MCMs);

- Evasion of existing natural or induced immunity.

We'll be evaluating all experimental approaches that could produce any of the phenotypic changes listed above, including serial passaging of virus in animals or cells, reverse genetics and reassortment studies, various types of selection, and other approaches.

Although our assessments focus on influenza viruses, SARS, and MERS (hereafter referred to collectively as "PPPs"), we welcome relevant examples featuring other pathogens during the course of our discussion, recognizing that many types of basic research applications are not pathogen-specific.

# 1. Interview goals related to the Benefit Assessment (BA)

Background:
Our first set of interview questions related to the BA will focus on elucidating gaps in scientific knowledge about PPPs and gaps in public health and medical capabilities related to the prevention and control of PPP outbreaks in humans and animals. This information will provide critical context for our evaluation of the potential benefits of GoF research. Questions will address:

1. What are the critical gaps in knowledge about influenza viruses (including seasonal and pandemic influenza), SARS, and MERS?

2. What are the critical gaps in existing medical countermeasures for influenza viruses, SARS, and MERS (including vaccines, therapeutics, and diagnostics)?
   a. What are the limitations in existing vaccines, with respect to vaccine efficacy, vaccine production, vaccine longevity, and other factors?

   b. What are the limitation in existing anti-virals, with respect to efficacy and other factors?

Importantly, our BA will be comparative – that is, we will assess the potential benefits of GoF research *relative* to alternative approaches. Thus, our second set of questions related to the BA will focus on elucidating the potential benefits of GoF research, as well as any barriers that impact the likelihood and timing of the realization of the benefits.

Questions will address:

1. How does GoF research address gaps in basic science knowledge?

2. Are there alternative approaches that may produce the same or similar knowledge? Please elaborate on the type of basic science information that can be gleaned from GoF studies versus alternative approaches.
   a. For example, do GoF studies have the potential to produce more conclusive information? To produce unique information? To produce valuable information more quickly than alternative approaches?

   b. Do studies using alternative approaches mentioned above need to be repeated in high virulence strains for causality? And because of the issues of epistasis in influenza biology for example?

3. What are the potential benefits of GoF research to public health and medicine? (How might knowledge or products gleaned from GoF research be applied to challenges in public health and medicine?)
   a. How are molecular determinants of phenotypic properties of concern used in surveillance? How does use of GoF information in the interpretation of surveillance data change downstream public health responses (e.g. development of CVVs, production/stockpiling of vaccines, etc.)?

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b. How do antigenic escape studies and emergence of resistance studies contribute to the development of new vaccines and drugs? How do studies that lead to evasion of immunity lead to the development of better vaccines? Or how can these studies improve public health or medical responses during an outbreak?

c. How do other types of GoF studies contribute to advancements in public health and medicine?

4. Are there alternative approaches that may yield the same or similar benefits to public health and medicine? Please elaborate on how information gleaned from alternative approaches can be applied to gaps in public health or medicine, and how the applications of alternative research outputs differ from the applications of GoF research outputs.
   a. Are there types of GoF research that have potential to provide benefits to public health and medicine more readily than alternative approaches, i.e. within a shorter timeframe or with fewer investments in research and other resources?

5. As translating basic science into advancements in public health and medical practice can be a challenging and lengthy process, please describe any concerns related to the likelihood that benefits will be achieved, as well as the timescale for realization of the benefits.
   a. How readily can the research be applied to gaps in public health and medicine? Does application of the research depend on other factors, including other scientific or technological advancements as well as non-scientific factors? How might these factors impact the likelihood and timing of the realization of the benefits?

   b. Are there other factors that may limit the ultimate impact of the research applications on the health of human and animal populations? How might these factors impact the likelihood and timing of the realization of the benefits?

# 2. Interview goals related to the Biosafety Risk Assessment (RA)

Background:
In the context of research involving PPPs, our biosafety risk assessment will consider:

- The probability that laboratory accidents lead to loss-of-containment;

- The probability that loss-of-containment leads to human infections and subsequent secondary transmission in the community;

- The consequences of the outbreak should it spread beyond local control.

To inform the laboratory accident and initial outbreak modeling components of the RA, we are interested in collecting the following data about the types of experiments you conduct involving influenza viruses, SARS, and MERS. These questions are highly detailed. However, we are not conducting an audit or compliance inspection of your facility. Instead, these questions are detailed so that we may model research in containment labs using real, accurate information instead of estimations.

We realize that some of this information may be sensitive, such as information relating to the number of animals used in your experiments and housed in your facilities. To alleviate your potential concerns, we want to let you know that in our final report, we have no need (and no plans) to show data on a lab by lab basis. Instead, we will use the data from all facilities to provide a range of parameter values related to laboratory activities (e.g. experiments with infected animals occur from 1.4-3.8x a month with of a mode of 2.3; these experiments last from 4-12 days--mode 6--before the last animal is sacrificed, etc.). Of course, we would collect these data on a lab-by-lab basis and the raw data would exist in some form somewhere (but would not be in the final report).

Finally, the RA will also be comparative, in that we will be assessing the net risk posed by research involving GoF pathogens relative to research involving wild-type pathogens.

Questions:

1. What types of experiments involving influenza/SARS/MERS do you conduct in your lab, including both GoF and alternative approaches?

2. Please describe the logistical aspects of conducting each type of experiment:
   a. Please walk through the basic protocol, including the containment level in which each step is conducted.

   b. What type of PPE are you wearing during each step?
      i. What type of respirator or PAPR do you wear? [e.g., PAPR with hood, PAPR with just face shield, etc.]

   c. How much pathogen do you have on hand during the experiment? Please describe volumes and pathogen concentrations. What types of containers are you using (e.g. what type of microcentrifuge tubes, what type of caps, etc.)? [Want units in PFU or TCID50s]

   d. How often do you conduct this experiment?

      i. Note – recognize that experimental activity waxes and wanes throughout the lifetime of a research project. If experiment is performed regularly, then elicit average experiment frequency. If not, then elicit experiment frequently when experiment is being actively performed, and length of time period during which experiment is regularly performed.

    e. If the experiment involves animals, which type, and how many are used at one time, and over the course of a particular experimental series? How long are the animals infected during the course of an experiment, and at what point are the animals euthanized?

    f. What types of waste does this experiment generate? How is liquid waste disposed of? How is solid waste disposed of? How are animal carcasses handled—are they autoclaved or also incinerated?

    g. What is the exit procedure for your containment lab? Do you shower out?

    h. Does liquid waste from your containment lab collect in an effluent decontamination system (EDS) as some BSL3 and all BSL-3ag facilities use, or is it decontaminated at the point of use as most BSL3 labs do?

3. Please describe logistical aspects of preparing and storing stocks of virus for experiments.
    a. Please walk through the protocol, including the containment level in which each step is conducted.

    b. What type of PPE are you wearing during each step?

    c. What volume and at what concentration of virus do you typically produce?

    d. What amount of virus is typically in each aliquot?

    e. How often do you prepare virus stocks?

4. Please describe logistical aspects related to animal facilities.
    a. In what type of cages are animals housed? [HEPA filtered or isolator cages, etc.]

    b. Are infected and uninfected animals caged in the same area or in different areas? Can asymptomatic infected and uninfected animals be distinguished in some way? How?

    c. Given the typical flux of experiments in your facility, how many infected animals are typically caged in the facility at a given point in time?

    d. How are animals inventoried and traced over the course of an experiment?

5. Consider a lab-created avian-origin influenza strain that is transmissible between ferrets (i.e. an H5N1 strain that was lab-evolved to become airborne transmissible between ferrets through serial passaging with selection for airborne transmission).
    a. This may be outside your area of expertise, but relative to the original strain, what is the likely transmissibility of this strain:
      i. Between wild birds?
      ii. Between wild birds and poultry?
      iii. Between wild birds and swine?
      iv. Between poultry and humans?

v. Between swine and humans?

6. Please describe any training programs, informal or formal, that researchers in your lab undergo before beginning unsupervised work in the containment lab.
    a. Are the training sessions repeated or are follow-up verifications done? How often do these occur?

    b. Does the lab do any scenario drills? If so, what situations are drilled and how often do they occur?

    c. Are there stages of training, e.g., do workers have to demonstrate competence in BL2 before working in BL3?

    d. Are there any procedures where you cannot work alone? How did you determine which, if any, procedures, require a buddy?

    e. Please describe any efforts, formal or informal, that focus on identifying and preventing common types of human errors that may occur during the course of routine laboratory work.
        i. Are there standardized protocols that are followed for typical laboratory experiments?

7. Please describe how samples and virus stocks in your lab are inventoried.
    a. What percentage of tubes/vials are inventoried? How often are they inventoried?

    b. Are there any formal or informal lab requirements on storage, labeling, or other aspects of inventory?

    c. Is there a "check out" procedure when personnel leave the laboratory with respect to inventory?

8. Please describe how samples may move from a higher level of containment to a lower one, e.g., from BL3 to BL2.
    a. What types of experiments or studies result in inactivation and movement of samples (e.g., RNA purification for sequencing)

    b. How are viruses or other infectious materials inactivated prior to leaving containment? Is the inactivation verified, and, if so, what percentage of inactivated samples are verified?

    c. How are samples transported between containment rooms?

9. Please describe how packages containing potentially infectious materials are received by the lab
    a. Are they delivered to a campus-wide shipping/receiving center first?

    b. If not, do FedEx/UPS sometimes/usually/always deliver packages to the lab directly, or do they sometimes get delivered to an intermediate, such as an administrative assistant?

    c. How many times per year do you receive select agent materials?

    d. Excluding select agents, how many times per year do you receive materials that must be opened in containment?

10. Please describe the standard monitoring procedures in place to detect potential loss of containment events prior to illness, if any are in place. (For example, swabbing and testing of laboratory surfaces.

a. If a surface comes back contaminated with a potential pathogen, what would be the standard response to such an incident?
   i. Would workers be isolated and/or quarantined prior to symptoms appearing?
   ii. Would the laboratory be shut down for a period of time?

b. What procedures are in place for monitoring workers?
   i. Are laboratory personnel routinely vaccinated?

   ii. Do personnel monitor their health routinely (e.g. through regular temperature monitoring)?

   iii. Are laboratory personnel's interactions with swine or poultry restricted?

11. Imagine that a potential laboratory exposure has occurred to a pathogen of pandemic potential, for example, highly pathogenic influenza. Please elaborate on the steps that are taken following that exposure.
    a. Do people that have been potentially exposed have any restrictions placed on their movements/are they taken directly to a clinic or isolated?

    b. Would the laboratory be shut down for a period of time as a precaution?

    c. If the number of people exposed was not immediately clear (e.g. an accident created a splash on several workers), how would you determine which individuals to monitor and/or treat?

    d. If multiple people were potentially exposed is the response different in a significant way from exposure by a single individual?
       i. Are people potentially exposed treated differently from those certainly exposed (e.g. those who have suffered a needle stick)?

       ii. Are potentially exposed individuals treated with countermeasures preventatively?

    e. Are there standard procedures for contacting local public health officials?
       i. What conditions initiate those procedures?
       ii. What information is shared with local public health officials?

    f. Does the research facility have any procedures to encourage reporting or discourage non-reporting, for example, a work-in-pairs requirement?

12. Now, imagine that laboratory workers are falling ill without a known route of exposure, with a pathogen suspected to be of laboratory origin. Please elaborate on the steps that would be taken following this type of discovery.
    a. Are people that have been potentially exposed immediately isolated or taken to a clinic?
    b. How would the institution attempt to find the source of the infection?
    c. Would the laboratory be shut down for a period of time as a precaution?
    d. What types of information would be communicated to local public health officials, and when?

13. How many full-time equivalent research employees do you have in your laboratory typically, and what percentage of their time is spent within the containment suite, on average, per year?

# 3. Interview Goals Related to Research Proliferation

Background:
An additional component of our RA will be evaluation of the risks posed by proliferation of the research in additional US laboratories. Our questions will address the current size of the GoF research community in the US, as well as how the debate surrounding GoF research has influenced your interest in doing this work in the future.

Questions:

1. Approximately, how many groups represent the GOF research community in the US?

2. Approximately, how many BSL-3 and 4 facilities are currently available to do GOF research in the US?

3. Have the moratorium and the dialogue surrounding GOF research influenced your interest in doing this work in the future? If yes, in what direction? What about your students' interests and plans?

4. One of the variables in the risk-benefit analysis is the extent of potential future expansion of GOF research if it continues. To try to estimate this, we are looking for a discovery/scientific advance made approximately 10 years ago, so that we can trace its uptake. Can you suggest a discovery that would make a meaningful case study?

# 4. Questions for Laboratory Biosafety Officials, for Biosafety RA

Background:
Understanding the SOPs for responding to laboratory exposures and LAIs is essential to parameterize a model of outbreak spread following a laboratory release. Biosafety officers may have insights into these SOPs. They can also provide information on institutional connections to local public health resources. Information here feeds into the parameterization of the probability of detection of an outbreak or loss of containment event.

Questions:

1. Please describe any training programs that researchers in containment labs at your institution undergo before beginning work.
   a. Are the training sessions repeated or are follow-up verifications done? How often do these occur?

   b. Are there stages of training, e.g., do workers have to demonstrate competence in BL2 before working in BL3?

   c. Are there any procedures where researchers cannot work alone? How did you determine which, if any procedures, require a buddy?

   d. Does the lab do any scenario drills? If so, what situations are drilled and how often do they occur?

2. Please describe how packages containing potential infectious materials are received by labs
   a. Are they delivered to a campus-wide shipping/receiving center first?

   b. If not, do FedEx/UPS sometimes/usually/always deliver packages to the lab directly, or do they get delivered to an intermediate, such as an administrative assistant?

   c. How many times per year do you receive select agent materials?

   d. Excluding select agents, how many times per year do you receive materials that must be opened in containment?

3. Please describe the standard monitoring procedures in place to detect potential loss of containment events prior to illness, if any are in place. For example, swabbing and testing of laboratory surfaces.
   a. If a surface comes back contaminated with a potential pathogen, what would be the standard response to such an incident?
      i. Would workers be isolated and/or quarantined prior to symptoms appearing?
      ii. Would the laboratory be shut down for a period of time?

   b. What procedures are in place for monitoring workers?
      i. Are laboratory personnel routinely vaccinated?
      ii. Do personnel monitor their health routinely?
      iii. Are laboratory personnel's interactions with swine or poultry restricted?

4. Imagine that a potential laboratory exposure has occurred for a pathogen of pandemic potential, for example, highly pathogenic influenza. Please elaborate on the steps that are taken following that exposure.
   a. Do people that have been potentially exposed have any restrictions placed on their movements/are they taken directly to a clinic or isolated?

   b. Would the laboratory be shut down for a period of time as a precaution?

   c. If multiple people were potentially exposed, are the same steps taken, or is the response different in a significant way?

   d. Are there standard procedures for contacting local public health officials?
      i.  What conditions initiate those procedures?
      ii. What information is shared with local public health officials?

5. Now, imagine that laboratory workers are falling ill without a known route of exposure, with a pathogen suspected to be of laboratory origin. Please elaborate on the steps that would be taken following this type of discovery.
   a. Are people that have been potentially exposed immediately isolated or taken to a clinic?
   b. How would the institution attempt to find the source of the infection?
   c. Would the laboratory be shut down for a period of time as a precaution?
   d. What types of information would be communicated to local public health officials, and when?

6. Now, please imagine that an infection is occurring in the community and evidence suggests it is of a laboratory origin, potentially from a lab at your institution. Please describe the response to such a discovery.
   a. Are you in regular contact with local public health officials? At what point would you expect local public health officials to reach out to you if they suspected a case or outbreak caused by a laboratory acquired infection?

   b. Would all workers using this pathogen be monitored, isolated and/or subjected to diagnostic testing?

   c. How would the investigation into the potential sources of the infection be carried out?

   d. What resources would your institution add for epidemiological investigation and contact tracing, or would your efforts be focused on identifying the source?

# 5. Questions for Local Hospital or Clinic Personnel

Background:
Modeling the stochastic phase of a lab-caused infectious disease outbreak will require information about disease surveillance and reporting measures, in order to determine how fast lab-acquired and secondary infections are likely to be detected, as well as the type and level of local public health responses, in order to understand how control measures will influence outbreak spread. The two overarching questions we are trying to understand in this section are: (1) What is the likelihood of diagnosing an infection with a loss-of-containment strain and (2) How quickly does that happen?

Questions:

1. Imagine that an individual in the community arrives at a clinic with a respiratory illness with flu-like symptoms. Please elaborate on the treatment and diagnostics that a typical individual may receive.
   a. What infection control measures are typically used for patients with ILI prior to a definitive diagnosis?
      i. At an outpatient clinic? At a hospital ER?
      ii. How many other people (including healthcare workers and other patients) would you expect the sick patient to interact with in either setting prior to isolation?

   b. Would an individual be tested, and if so, what diagnostic test or tests would be performed?
      i. At an outpatient clinic? At a hospital ER?
      ii. How quickly would results be delivered back to the clinic?
      iii. Are patients that have been diagnosed with pneumonia or bronchitis typically tested for influenza as well, to account for the possibility of misdiagnosis (including the possibility that the diagnosed agent is opportunistically causing disease in the context of an influenza infection)?

   c. If diagnostic testing came back negative, what would be the next steps?

   d. Would the control measures and diagnostic tests you just described vary between cases appearing during the flu season versus those outside of it?

2. Imagine now that an infection with an atypical disease is suspected, for example SARS or highly pathogenic avian influenza H5N1, either because of the patient's symptoms and/or negative results on a previous diagnostic test. Please describe what steps would be taken next.
   a. What infection controls measures would be put into place? Would any special procedures be put into place or measures be taken?

   b. Where would samples be sent, and what diagnostic tests would be performed? How quickly would results be delivered back to the clinic?

3. How would the possibility that a nearby laboratory was creating novel strains of pathogens affect the tests, control measures, or treatment protocols, if at all?

# 6. Questions for Local Public Health Officials

Background:
Modeling the stochastic phase of a lab-caused infectious disease outbreak will require information about disease surveillance and reporting measures, in order to determine how fast lab-acquired and secondary infections are likely to be detected, as well as the type and level of local public health responses, in order to understand how control measures will influence outbreak spread. The two overarching questions we are trying to understand in this section are: (1) What is the likelihood of diagnosing an infection with a loss-of-containment strain and (2) How quickly does that happen?

Questions:

1.  Imagine that a local clinic or hospital has alerted you of a potential case of disease caused by an atypical transmissible respiratory pathogen, such as highly pathogenic avian influenza, SARS, or MERS.
    a.  Would contact tracing, quarantine, or other special measures be implemented?
        i.  If so, what are the trigger points for those actions to be taken?
        ii. How many personnel would immediately be available for this effort? How quickly would additional personnel arrive (federal or through MOUs), and how much manpower would you expect?

2.  Now imagine that a confirmed outbreak with an atypical, communicable, respiratory pathogen such as SARS or novel influenza has started in your community. Please describe the local capacity to respond to such an outbreak, and what steps would be taken to combat it.
    a.  If contact tracing were necessary, how many personnel would be immediately available for this effort? How quickly would additional personnel arrive (federal or through MOUs) and how much manpower would you expect? Given this level of manpower, approximately how many contacts could be traced and isolated?

    b.  Would special measures be taken, such as the closing of schools or workplaces, or at-home isolation or quarantine?
        i.  What are the thresholds for implementing these measures?
            1.  How large would an outbreak be before these steps would be taken?
            2.  Do the thresholds changed based on the disease?
            3.  How fast could these measures be implemented?

    c.  Would you seek assistance from the Federal government?
        i.   What type of assistance would you seek, and from what agency?
        ii.  What would be the thresholds for seeking Federal support?
        iii. How quickly would additional federal personnel arrive, and how many?

3.  Now imagine a similar outbreak, but this time with a novel pathogen engineered in a laboratory, such as a new flu strain, with unknown effects on the community. Please explain whether any of the above measures would change if the disease were novel.
    a.  Does the source of the infection matter it and of itself, or only the pathogen itself?

    b.  How would you approach decisions for implementing community-level interventions for a pathogen with unknown properties? Would measures be put into place earlier and/or would more

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aggressive measures be implemented? Or would you wait until epidemiological investigations had been conducted to have a stronger evidence base for your interventions, given that such interventions are disruptive?

4. Do you maintain regular contact with your local colleges and/or universities about the strains they are working with?
   a. What types of information are exchanged?

   b. If a potential lab exposure occurred, what information about the incident would you expect to receive?

   c. To where is this information distributed? For example, would local clinics be notified?

   d. Does your community have a cache of influenza MCM, and if so, what?

# 7. Wildlife and animal agriculture researchers

1. Do you conduct research on influenza viruses that may lead to enhancement of the pathogenic properties of the virus? Please describe any past or ongoing research efforts that have led to:
   a. Enhanced transmissibility?
   b. Enhanced viral replication in eggs, cell culture, or animal models?
   c. Enhanced virulence?
   d. Evasion of vaccines, or natural or existing immunity?

2. What were the goals of these experiments?

3. How do GoF approaches help you answer key scientific questions about influenza biology?

4. How do you apply knowledge gleaned from GoF research to challenges in animal health (such as animal influenza surveillance and vaccine development)?

5. Please describe any alternative approaches you use to address similar questions.
   a. What are the benefits and drawbacks of these approaches relative to GoF approaches?

6. Please discuss the risks of GoF research to human and animal health, relative to research on wild-type pathogens with pandemic potential. (Please comment on GoF research conducted within the wildlife and animal agriculture community as well as GoF research conducted within the public health community.)
   a. Influenza viruses, including swine and avian influenza viruses?
   b. SARS and MERS coronaviruses?

7. Please discuss potential benefits of GoF research to public health and medicine? Do you have any concerns related to whether and when these benefits can be realized, and why?

8. We are planning to model the spread of influenza viruses in human populations following loss of containment from a lab, including loss-of-containment events that lead to environmental release of virus and potentially expose wildlife and domestic poultry populations. We would like to consider the role of wildlife in disease spread during the initial stages of the outbreak, i.e. the possibility that infected wild birds will infect poultry, which will then infect humans, at which point we assume that human-to-human transmission will drive spread within human populations.
   a. Please discuss the extent to which wildlife has or could play a direct role in initiating human outbreaks of zoonotic influenza viruses (i.e. absent the intermediate role of animal husbandry).

   b. Please discuss any data or case studies that speak to the role of wildlife in initiating outbreaks of zoonotic influenza viruses in domesticated poultry or swine populations.
      i. Please discuss the relative roles of infected wildlife versus human movement of fomites and infected animals in the spread of poultry and swine-infectious influenza between flocks or herds in the US.

      ii. If avian-influenza infected wild birds are in the same local area as poultry flocks, what is the probability that poultry flocks become infected, and what are the primary factors that determine that probability?

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9.  Consider a lab-created avian-origin influenza strain that is transmissible between ferrets (i.e. an H5N1 strain that was lab-evolved to become airborne transmissible between ferrets through serial passaging with selection for airborne transmission).
    a.  Relative to the original strain, what is the likely transmissibility of this strain:
        i.    Between wild birds?
        ii.   Between wild birds and poultry?
        iii.  Between wild birds and swine?
        iv.   Between poultry and humans?
        v.    Between swine and humans?

# 8. Surveillance stakeholders – state of pandemic risk assessment

Background:
A common application of research, including information derived from GoF research, to disease surveillance is using knowledge about molecular determinants of various phenotypic properties of concern (pathogenicity, anti-viral resistance, mammalian transmission, etc.) to predict the pandemic potential of circulating viruses and focus prevention and control resources accordingly. This set of interviews aims to understand the strengths and limitations of current pandemic risk assessment strategies and tools

Questions:

1.  What are the goals of pandemic risk assessments?
    a.  How do pandemic risk assessments inform prevention and preparedness initiatives?

2.  What types of data are considered for pandemic risk assessments?
    a.  Specifically, how is information about molecular signatures associated with the following phenotypic properties used?
        i.   Anti-viral resistance?

        ii.  Antigenic escape?

        iii. Enhanced transmission in mammals (including airborne transmissibility and sialic acid receptor binding specificity)?

        iv.  Enhanced virulence?

    b.  Please specifically address the role of molecular signature data relative to other types of data under consideration.

3.  Consider data showing that a particular mutation or set of mutations is *associated* with a phenotypic property of concern, such as anti-viral resistance, versus data showing that particular mutations *cause* anti-viral resistance. Would you consider those types of data differently in the context of a pandemic risk assessment? How?

4.  Please discuss the strategy of inferring functional information from genetic sequence data rather than directly testing the phenotypic properties of the virus strain in question.
    a.  What are the barriers to the latter strategy (sample sharing issues, timeliness, etc.)?

5.  How does the quality and quantity of surveillance data influence the quality of pandemic risk assessments?
    a.  What additional surveillance data are needed to improve the quality of pandemic risk assessments (e.g. from particular areas, particular species, etc.)?

6.  Please describe any concerns related to the use of molecular signatures of phenotypic properties of concern in pandemic risk assessments.
    a.  Given the limitations in our ability to predict phenotype from genotype, does molecular signature data play a valuable role in pandemic risk assessments? Why or why not?

b. What additional data are needed to validate the use of molecular signature data in pandemic risk assessments? (Examples about other viruses may be relevant.)

7. We are interested in your opinion about scientists' potential to predict phenotype from genotype for influenza viruses in the future –
   a. Do you think this will be possible at some point in the future? Is this a worthwhile goal for improving pandemic preparedness? Why or why not?

   b. What additional data are needed? Can these data be generated through alternative approaches (such as comparative analysis of field strains), or do GoF studies provide unique information that drives this field forward?

# 9. Public Health Policy Stakeholders

<u>Background:</u>
GoF information that informs pandemic risk assessments of circulating animal-origin influenza viruses and coronaviruses may inform pandemic preparedness activities undertaken by the USG. The goals of this set of interviews are to understand:

- How the government prepares for pandemics caused by highly transmissible, respiratory viruses, including relevant policies and available resources for pandemic preparedness activities;

- What factors influence the extent to which pandemic preparedness activities are implemented, in particular what types of scientific information are considered;

- What scientific information drives public health decision-making during outbreaks abroad and in the US.

<u>Questions:</u>

1. Please describe the actions that have been taken or could be taken to prevent and prepare for a pandemic caused by an animal-origin, highly transmissible disease, such as pandemic influenza or SARS (e.g. pre-pandemic vaccine development, pre-pandemic vaccine stockpiling, development and deployment of diagnostics, issuance of travel guidelines or restrictions, etc.).

2. Please describe the factors that influence the timing and scale of each preparedness activity –
   a. What information drives decisions about when to develop pre-pandemic vaccines and whether and how much to stockpile in advance of a potential outbreak?
      i. What types of epidemiological data are considered (e.g. number and location of human cases)? How do you consider information about human cases versus animal cases of disease?

      ii. What types of scientific information are considered (e.g. laboratory data about the transmission or virulence characteristics of strains isolated from human or animal cases of disease)?

      iii. What are the challenges in determining when and to what degree resources for pre-pandemic vaccine development/stockpiling should be activated? Are existing data (epidemiological or scientific) timely enough to influence decision-making?

      iv. What additional data are needed to inform decision-making about pre-pandemic vaccine development/stockpiling?

      v. What are the challenges in collecting these additional data?

   b. What information drives decisions about other pre-pandemic preparedness activities?

3. Recent influenza pandemics (1958, X, 2009) have been caused by strains that emerged through reassortment between human, avian, and/or swine influenza strains, not by avian influenza strains that directly evolved to become readily transmissible between humans. Did the 2012 demonstration by the

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Kawaoka and Fouchier labs that highly pathogenic avian influenza H5N1 could evolve the capacity for airborne transmission between ferrets in the lab, through a small number of mutations influence influenza pandemic preparedness activities?

    a. Did any pandemic preparedness policies change, and if so, how?

    b. Did any pandemic preparedness activities, such as pre-pandemic H5N1 vaccine development or stockpiling investments, change, and if so, how?

    c. Would laboratory demonstration that additional strains of avian influenza could evolve the capacity for airborne transmission between mammals impact pandemic preparedness planning, and if so, how?

    d. Please consider laboratory demonstrations of pathways for pathogen evolution that could happen in nature (e.g. evolution of altered routes of transmission, increased virulence, etc.). How do you consider that information in public health policy decision-making?

4. Please describe how the following types of scientific data about PPPs influence pandemic preparedness decision-making:

    a. Identification of particular genetic mutations or sets of mutations that confer a phenotype of concern, such as anti-viral resistance, to PPPs in laboratory experiments –
        i. Do you consider this information when evaluating the risk posed by animal-origin flu viruses or coronaviruses in general, or when evaluating the risk posed by specific strains of these viruses?

        ii. Do you act on this information, and if so, how?

    b. Identification or particular genetic mutations or sets of mutations that are associated with phenotypes of concern in PPPs, such as the ability to transmit between people –
        i. Do you consider this information differently from the causative mutations described previously? If so, how?

5. What information guides public health policy decision-making during an outbreak abroad?

    a. Are previous scientific data about the transmissibility or pathogenicity of the pathogen considered, and if so, how? Or is the information about the epidemiology of the particular outbreak sufficient to guide decisions?

    b. Do you consider this kind of information differently during a nascent outbreak versus in the midst of an outbreak? For example, during a nascent outbreak, before field data has been collected, can this type of information guide treatment or response decisions?

6. What information guides public health policy decision-making during an outbreak in the US?

    a. Are previous scientific data about the transmissibility or pathogenicity of the pathogen considered, and if so, how? Or is epidemiological information sufficient?

    b. Do you consider this kind of information differently during a nascent outbreak versus in the midst of an outbreak? For example, during a nascent outbreak, before field data has been collected, can this type of information guide treatment or response decisions?

# 10. GoF interview questions related to vaccine development and production

Background:
- Understand how use of viruses with wildtype *in vitro* growth properties instead of high-growth reassortants would impact the timeliness of vaccine production and the quantity of vaccine that could be produced, for seasonal flu vaccines and pandemic flu vaccines;

- Understand major gaps in vaccine development and production, with respect to vaccine efficacy as well as production efficiency at each step;

- Understand how information from GoF studies guides pre-pandemic vaccine development relative to other types of epidemiological and scientific information about risk of animal influenza viruses;

- Understand how other types of GoF information (such as antigenic escape studies) may influence vaccine development.

Questions:

1. Please walk through the process of producing a monovalent vaccine for a new strain of pandemic influenza, starting from emergence of the new strain and assuming that no "pre-pandemic" reagents have been prepared. Please describe the approximate time length of each step, as well as any limitations or gaps in existing processes.
   a. Development of candidate vaccine viruses (CVVs)?
      i. How long does the reassortment step take? Is PR8 typically used, or are other attenuated, high-growth virus backbones also used?

      ii. How long does the CVV characterization step take?
         1. Would any of the testing steps (sequence analysis, viability testing in eggs, pathogenicity testing in ferrets, genetic stability upon passaging, and antigenic characterization) be skipped during a pandemic? Which steps, and how much time would that save?

      iii. What fold increase in virus production is typically achieved using the CVV versus the field virus?

      iv. What factors limit the timeliness and/or efficacy of CVV development?

   b. Development of vaccine seed strain?
      i. Please describe the process of developing high-growth vaccine seed strains. Does this involve serial passaging in eggs (or cell culture) and/or reverse genetics to introduce mutations associated with high yield?

      ii. How long does this process take?

      iii. What fold increase in virus production is typically achieved using the seed strain versus the CVV? (Or what range is observed?)

      iv. What factors limit the timeliness and/or efficacy of vaccine seed strain development?

    c. Production of vaccine?
        i. How long does it take to produce each lot of vaccine?
            1. Production of virus in eggs?

            2. Collection and preparation of viral antigen?
                a. For LAIV versus inactivated vaccine?

            3. Testing of antigen?

            4. Preparation of vaccine?

        ii. Please describe how production of vaccine lots is staggered – what is the overlap between production cycles?

        iii. How many doses of vaccine are typically produced per lot? How many lots would you expect to produce during a pandemic?

        iv. What factors limit the efficacy of vaccine production?

    d. Preparation of reagents for testing of the vaccine (e.g. antibodies for SRID assay, standard HA antigen)?
        i. How long does this take?
        ii. Please describe the timing of reagent preparation relative to other steps in the vaccine production process – when is reagent preparation initiated and completed? Are reagents typically ready before or after the first clinical lot of vaccine has been produced?

    e. Clinical trials?
        i. Would clinical trials be undertaken during the development of a vaccine for a novel strain of pandemic influenza? Which stages, and how long would it take?

        ii. Please discuss the timing of clinical trials relative to other steps in the vaccine production process.

2. One type of GoF research of potential concern that we are evaluating is the set of experimental approaches that enhance viral production, which includes reassortment procedures to produce CVVs and serial passaging to produce high-yield vaccine seed strains. We plan to evaluate the benefit of using high-growth reassortant strains in vaccine development by exploring how use of viruses with growth properties similar to those of field viruses would impact the quality of vaccines and the timeliness and scale of vaccine production. Using epidemiological outbreak models, we will then quantify how these consequences would impact human morbidity and mortality during an influenza pandemic.
    a. Please describe how the use of viruses with growth properties similar to those of field viruses would impact vaccine production.
        i. Which stages of vaccine production would this impact?
            1. Note – expect that CVV and vaccine seed strain development would be skipped, and that vaccine production would be slowed due to lower yields of vaccine antigen per egg.

        ii. Would you adapt by:
            1. Injecting more eggs per lot?

2. Producing more lots? Given that production is staggered, how much extra time would each additional lot add to the production timeline?

3. How would limitations in the number of available eggs affect either strategy?

4. Would lower yields per egg change your vaccine preparation procedures, and if so, how would that affect the production timeline?

iii. How might lower yields impact the cost of vaccines?

iv. Please discuss how lower yields would impact vaccine delivery. Would limited amounts of vaccine be released on the usual timescale (i.e. as soon as the first large lot was ready)? Or would release of the vaccine be delayed until larger quantities had been produced?
1. How frequently would new lots of vaccine be released?

v. What other aspects of vaccine production would be affected, and how?

b. Do you think vaccine production by other manufacturers would be similarly affected?

3. Please walk through the process of producing trivalent/quadrivalent seasonal influenza vaccines (will focus on steps that differ from pandemic flu vaccine production).
   a. What are the differences in development of CVVs and vaccine seed strains for seasonal versus pandemic influenza vaccines?
      i. How often are the influenza B components of the vaccine changed?
      ii. Do influenza B viruses also undergo passaging in eggs/cells to create high-growth vaccine seed strains?

   b. Production of seasonal flu vaccines –
      i. Are the different antigenic components of vaccines produced simultaneously or consecutively?

      ii. Currently, do you prepare all needed doses of vaccine in advance of flu season or do you continue production during flu season?

      iii. How would use of viruses with growth properties similar to field viruses affect the vaccine production process?
         1. If antigenic components are produced consecutively – would your time delay and yield decrease estimates for each component be similar to the estimates for production of monovalent pandemic vaccines?

         2. Would you start production farther in advance of flu season or would you release smaller quantities of vaccine at the start of flu season and continue production during flu season?

         3. How would starting production farther in advance of flu season impact the efficacy of the vaccines?

   c. Over the next few influenza seasons, what percentage of total flu vaccines used in the US do you expected to be inactivated versus LAIV versus recombinant?

   d. What are the major gaps in the current process for development and production of seasonal influenza vaccines?

4. Factors that influence the extent of development of pre-pandemic vaccines –
   a. Please describe the pre-pandemic vaccine development pipeline – i.e. how far into the vaccine production process might pre-pandemic vaccines be taken?
      i. Verify timing of each stage, i.e. how much time would be saved by carrying out pre-pandemic vaccine development to that stage?

      ii. Who is responsible for carrying out each stage (practically and financially)?

   b. Please describe the factors that are considered in decisions about whether and how far to develop pre-pandemic vaccines.
      i. Who makes decisions about each stage of pre-pandemic vaccine development?

      ii. How is information gleaned from GoF studies considered?
         1. Specifically, information gleaned from –
            a. Studies about adaptation to mammals (e.g. sialic acid receptor specificity) or transmissibility between mammals?

            b. Antigenic escape studies?

            c. Pathogenicity studies?

            d. Other types of GoF studies?

         2. How is causative information from GoF studies considered relative to correlative information from alternative approaches?

      iii. What other types of information are considered?
         1. How is GoF information considered relative to other types of information? For example, consider the observation that the number of human cases caused by a particular strain of H5N1 has risen. What pre-pandemic vaccine development decisions would be made based on this information alone? Consider now that this strain is shown to contain genetic signatures associated with mammalian transmissibility, pathogenicity, anti-viral resistance, or vaccine resistance. How would vaccine development decisions change?

         2. How would decisions about whether and how far to develop pre-pandemic vaccines change if GoF information were not considered? Does GoF information simply help prioritize which CVVs are developed, or are additional CVVs developed, and farther, than if GoF information were not considered?

         3. What limits the number of pre-pandemic CVVs that are developed?

5. Development of CVVs for highly-pathogenic avian influenza viruses involves mutation or deletion of the poly-basic cleavage site, to increase the safety of the vaccine virus and its viability in eggs. Please describe whether and how information about other sequences that are associated with pathogenicity is used during CVV and/or vaccine seed strain development.
   a. Does (or could) any of this information arise through GoF studies?
   b. Would this affect the production, safety, or efficacy of influenza vaccines?

6. Please describe any additional applications of GoF research to the development or production of influenza vaccines.

a. How do antigenic escape studies influence vaccine development?

b. How do experiments that lead to evasion of natural or existing immunity influence vaccine development?

c. Are there other applications of GoF research to vaccine development and production that we haven't yet discussed?

# 11. Questions related to influenza therapeutics

1. What are the limitations of existing influenza anti-viral drugs? (For example, limitations in efficacy for treatment certain age groups or special populations; limitations in when, during the course of illness, treatment is effective; limitations in efficacy against certain strains of influenza, due to emergence of resistance or other factors; etc.)

2. What are the major challenges for development of next-gen anti-virals against influenza viruses?
   a. Are the challenges different for development of anti-virals targeting seasonal influenza viruses versus animal influenza viruses?

3. How do the following types of studies inform development of anti-virals or other therapeutics (such as therapeutics that modulate the immune response)?
   a. Experiments that lead to emergence of anti-viral resistance?
      i. Against existing anti-virals? Against next-gen anti-virals that are in development?

   b. Experiments that lead to evasion of existing or natural immunity?

   c. Experiments that identify molecular determinants of virulence (e.g. identification of mutations that confer enhanced morbidity or mortality in animal models)?

# 12. Influenza and epidemic modelers

Background:
This set of interviews establishes the state-of-the-science for influenza and epidemic modeling, and ensures that the methods and models Gryphon has chosen to use are applicable and have not been eclipsed by more accuracy or more advanced models. We are also hoping to solicit feedback on our approach to ensure that it's reasonable.

Our current approach is comprised of three parts:

1. Individual agent based model to model the stochastic initiation phase of the outbreak in a local community, including effects of control measures (Vespignani group, Northeastern U in Boston)

2. Turn to a deterministic SEIR compartmental model once the outbreak is seeded and has escaped local control. (NIH ASPR model used for H1N1)

3. We are only measuring the impacts on human health, but do want to model the disease dynamics in domestic and wild birds for flu, to examine the affect it may have on human health. We are planning on using a separate spatial metapopulation model to incorporate this feature. (Rao group, Miami University of Ohio)
    a. This models populations as circles on the surface of the earth. Wild bird circles may move to simulate migration, while human and poultry circles do not. Wild birds start infections with a probability dependent on the extent of spatial overlap between circles. Wild birds infect poultry, and then poultry can infect human populations.

Questions:

1. What are your thoughts on our approach?
    a. Are there any obvious challenges or shortcomings we may face?
    b. Are there models already available we may be able to use that you are aware of?
    c. Are there alternate approaches you might consider?

2. What is your strategy for determining parameters for which there is little to no data available?
    a. (for interspecies modelers) How did you arrive at your interspecies transmissibility parameters?
    b. (for interspecies modelers) How did you arrive at your interspecies contact rates?
    c. (for modelers considering human decision making) How did you determine rates of choices for individuals?

3. How have you handled modeling epidemics that span many orders of scale?
    a. Does splitting into multiple models, each operating at different scales a viable strategy?
    b. Are there any accurate, computationally tractable models that could handle the entire scale?
    c. Are there more computationally tractable models that may be able to handle the initiation phase of the outbreak

4. (If they have a model we may want) Is the code for your model(s) available, and would you be comfortable sharing it with us?

5. Is there anything else you'd like to mention that we haven't covered?

# 13. Interview Goals for Biosecurity Risk Assessment - Background

The security component is grounded in knowledge about biosecurity procedures at U.S. research institutions, biosecurity governance in the United States, and biological threats.

The security component involves three steps: 1) identification of likely threats, including the type of actor, the type of deliberate security breech, and the possible consequences; 2) identification of how different security measures are implemented at U.S. research institutions and any challenges associated with implementation; and 3) assessment of security risks using realistic scenarios that are based on the information collected from steps 1 and 2.

This interview is designed to gather information about how security is implemented at different institutions and with different agents – specifically H5N1 influenza, SARS, and MERS – and whether and to what extent implementation challenges exist. The information we collect will be anonymized, aggregated, and generalized to inform the biosecurity risk assessment. <u>The interviews are not an audit or regulatory review; Gryphon Scientific will not make information about individual institutions available to the public.</u>

# 14. Biosecurity RA - Environmental Health & Safety, Biosafety and Institutional Security Officials

**Biosecurity policies, plans and implementation**

1. Overarching Question: What is the probability of an incident arising from shortcomings or exploitation of vulnerabilities in the security of pathogens?

2. Do the current biolab security policy/regulatory environment and the implementation of the security requirements mandated therein adequately address the various types of potential malicious actor threats?

3. In your opinion, are there specific gaps in policy or regulation (including staff awareness and training programs) or in the implementation thereof that represent an exploitable vulnerability? (please address the areas listed below)
   a. personnel reliability/security
   b. physical/electronic access control
   c. inventory/accountability processes
   d. pathogen storage protocols
   e. transfer, shipment, and chain-of-custody protocols
   f. surveillance and monitoring
   g. malicious actor detection
   h. incident reporting
   i. emergency response protocols

4. What challenges do you face in implementing current federal regulations? How might these challenges affect facility vulnerability (increase, decrease, or no change)?

5. Are there state and local laws that increase the vulnerability related to unauthorized individuals gaining access to information, counter federal regulations, or impose barriers to implementation of federal regulations?

6. What state and local laws decrease biolab facility vulnerability or otherwise support federal regulations?

7. Have you ever experienced a malicious actor threat to or act against your facility?

8. Are representative security plans and training/awareness programs for high containment facilities in alignment with governing policies/regulations and best practices, and, if so, do they adequately address the threat? Are there specific gaps or concerns?

9. In your opinion, if gaps exist in terms of policy or regulation or in the implementation thereof, what are your recommendations to remedy them?

10. In addition to policy and/or regulatory requirements, are there any best-practices for biolab security (in use domestically or internationally) that you would recommend?

11. To what degree does your institution interact with the local FBI WMD Coordinator to stay ahead of potential threats and to inform them of potential problems?

12. Can you recommend any additional studies, reports, analyses, real world case studies etc. that would be important for us to consider?

13. Can you recommend anyone else who would be important for us to interview?

# 15. Biosecurity RA – Researchers

1. Overarching Question: What is the probability of misuse or theft arising from authorized laboratory staff?

2. What processes/protocols exist in the laboratory and within the institution to prevent misuse of research, theft of agent, or malicious use of an agent? Are there specific gaps or concerns?

3. What types of biological security training do laboratory staff receive? Are there specific gaps or concerns?

4. What processes exist for researchers to report suspicious or unusual events or actions? Are there specific gaps or concerns?

5. What processes exist to interact with relevant institutional officials to identify and reduce security risks associated with your research? Are there specific gaps or concerns?

6. Do laboratory staff consider security (i.e., misuse of research or theft) a high priority concern?

7. Can you recommend any additional studies, reports, analyses, real world case studies etc. that would be important for us to consider?

8. Can you recommend anyone else who would be important for us to interview?

# 16. Biosecurity RA – Intelligence and Law Enforcement Officials

1. Overarching Question: What is the risk that may ensue based on the successful targeting of a biolab facility in the U.S. on the part of a malicious actor (i.e. target attractiveness)?

2. What are the various types of malicious actors that have posed or may pose a specific threat in this area and what is their demonstrated or postulated motivation for targeting a biolab facility?
   a. What types of actors are known to have targeted laboratories or may find laboratories an attractive target to:
      i. cause an intentional on-site release of an agent;
      ii. cause facility disruption or destruction;
      iii. acquire information, agent, or expertise for malicious purposes?
      iv. Can you provide specific examples of the above?

   b. What types of actors have joined or would be most likely to join laboratories to build their own skills?

   c. Are any types of actors likely to acquire a strain from a laboratory but NOT use them (use them in their own R&D programs or defensive programs).

   d. Is the distribution of these actors equal throughout the world or more concentrated in one or more specific region(s), or one or more category(ies) of malicious actor?

3. Are certain types of malicious actor threats and malicious act modalities more prevalent, more likely and/or more concerning than others? Why or why not?

4. Would a successful hostile act against a biolab facility achieve the stated or postulated objectives of a given threat actor (see threat matrix)? More so than a hostile action against another type of target?

5. Would you recommend any adjustments to our draft threat matrix (provided in advance) based on your knowledge and understanding of potential malicious actor threats to laboratory facilities? If so, what are specific things we should improve or change?

6. How might malicious actors target and take action against a laboratory to gain access to materials or expertise relating to GOF research (i.e. tactics, techniques and procedures)?

7. What specific capabilities are required to permit malicious actor access to or launch an attack against a facility?
   a. Physical
   b. Cyber
   c. Documentation

8. In what ways have actors tried to gain access to facilities, materials and expertise relating to advanced genetic engineering or, more specifically, GOF research?

9. Can you recommend any additional studies, reports, analyses, real world case studies, etc. that would be important for us to consider in better understanding actor capability, access and motivation?

10. Can you recommend anyone else who would be important for us to interview?

*Information Risk Questions:*

11. Which actors, if any, are interested in the use of contagious agents in an attack? Does the possibility that the US has a relatively robust public health system to mitigate an outbreak and therefore many/most deaths may occur elsewhere figure into the calculus of these actors?

12. Is influenza virus or MERS or SARS particularly of interest to any actor (compared to other deadly, contagious agents)?

13. Has any substate actor shown any interest in manipulating a biological agent to make it more dangerous?

14. Does any substate actor have the capability to manipulate a viral agent?

15. How long is a substate actor willing/capable to work on developing an agent to execute an attack?

16. Have any actors (state or substate) been known to insert operatives into a laboratory to gain knowledge or skills in particular techniques in the life sciences for the purposes of developing a weapon?

17. Are any actors interested in agents that are countermeasure resistant?

18. Does the publication in the scientific literature of *various* methods to modify a dangerous pathogen increase state/substate actor interest in attaining a biological agent or modifying a pathogen to make it more dangerous compared to the publication of just one route to modify a pathogen? Or is a terrorist who is interested in modifying an agent going to seek out means to do so from the literature, regardless of how many dual-use articles are published?