Session I: Results of the Risk-Benefit Assessment for Gain-of-Function Studies

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Comments

- Gryphon did a very good job summarizing the research landscape, the knowledge gaps and the approaches (GOF and alt-GOF).
- Important points to remember (these were mentioned in the RBA):
  - While presence of a known molecular marker of virulence or transmissibility often predicts these phenotypes, absence of known molecular markers does not mean that the virus will not be virulent or transmissible.
  - It is difficult to know how well transmissibility of influenza viruses in ferrets or guinea pigs translates to transmissibility in humans.
- A focus on highly pathogenic avian influenza viruses is understandable because of the ongoing H5 epizootic with associated sporadic severe illness in humans but we should not forget that the last 4 influenza pandemics were not derived from HPAI.

I do not have the expertise to assess the methods used for the RBA but here are a few items that I found surprising:

- All comparisons, including consequences of coronavirus GOF research were made to the 1918 pandemic.
- The section on pandemic viruses included 1918 and 2009 H1N1 viruses. Population immunity against both is high – this section should only focus on human H2N2 viruses.
- Table 6.7, p 118: Conducting CoV research at BSL2 instead of BSL3 only increased the probability of a laboratory acquired infection by 2-fold- the preceding paragraph states that for all except avian influenza, this is primarily caused by the addition of respiratory protection.
- Fig 6.23 p 122 vs. p 109 and 116: On p 109 and 116, the RBA states that although additional respiratory protection is worn in BSL3 labs working with coronaviruses, most infections are caused by aerosol exposure. However, on p 122 (Figure 6.23) the greatest increase in probability that a LAI would lead to an individual mingling in the community came from failure to wash hands (50-fold) and failure to double glove (4-fold), not respirator use/efficiency/reliability.

- Limitations:
  - Information risk doesn’t deal with new information
  - Need clarification: Page 133: …even dramatic increases in transmissibility do not relate to dramatic increases in chance that an outbreak will <u>extinguish</u>….is this correct as written?

GOF of concern?

- Nature and science are always evolving and scientists studying pathogens at the animal-human interface are generally addressing public health concerns posed by newly emerged pathogens. Technologies and biosafety practices in laboratories are also modified over time.
- Concerns about laboratory accidents and biosecurity threats must be balanced against public health needs.
- The fact that some experiments are of greater concern than others does not mean that they should not be studied in a laboratory or that they cannot be studied safely in a laboratory. A vast majority of experiments can be undertaken under greater oversight.

GOF of greater concern?

- Any highly virulent, highly transmissible virus associated with a high case fatality rate that is resistant to MCM.

Examples of GOF of less concern?

- Currently circulating seasonal influenza viruses
- Adaptation of CoV to mammals to develop animal models
- Improving the growth of a virus
- Mapping escape mutations against antibodies or drugs that are developed as MCM
- Reassortants or spike swaps on attenuated or host-range restricted backbones

- Overstated:
  - Laboratory manipulation of seasonal influenza viruses
  - Page 326: too much time spent on a rapid phenotypic assay for mammalian adaptation and transmissibility that doesn't yet exist.
  - Pages 353-354: the human population does not have widespread immunity to the 1918 virus. After the 2009 H1N1 pandemic, we do.
- Understated:
  - The risk of not conducting research that is needed to address public health concerns

What has not been addressed?

- The beneficial and detrimental effects the voluntary moratorium followed by the deliberative pause have had on influenza and coronavirus research in the US.
- Are influenza and coronaviruses stand-ins for all pathogens of high consequence? How and when will this debate extend to other aspects of microbiology? Antibiotic resistance?
- Can we balance the need for research on pathogens of high consequence that address important public health needs with biosafety and biosecurity concerns? Yes, we can minimize and mitigate risk and proceed with caution and oversight.