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IDSA
Infectious Diseases Society of America

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Robbin Weyant, PhD
Director, Division of Select Agents and Toxins
Centers for Disease Control and Prevention
1600 Clifton Road, NE; Mailstop A–46
Atlanta, Georgia 30329

Re: CDC-2015-0050: Possession, Use, and Transfer of Select Agents and Toxins; Addition of Certain Influenza Virus Strains to the List of Select Agents and Toxins

Dear Dr. Weyant:

The Infectious Diseases Society of America (IDSA) is pleased to have this opportunity to comment on the addition of influenza viruses containing the hemagglutinin (HA) from the Goose/Guangdong/1/96 lineage (A/Gs/Gd/1/96) to the select agent and toxins list (SATL). In our 2012 response to the Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC)'s request for information, our Society recommended that high pathogenicity avian influenza (HPAI) H5N1 viruses that contain the A/Gs/Gd/1/96 lineage HA be regulated as select agents, while strains engineered for increased pathogenicity or mammalian transmissibility be regulated as Tier 1 select agents. IDSA applauds HHS/CDC's efforts to implement this level of oversight to ensure that research using these influenza strains is conducted appropriately.

However IDSA also advocates balancing the public health risk of impeding the conduct of H5N1 research against the public health risk of an accidental laboratory accident or act of bioterrorism. In particular, it is critical that vaccine manufacturing is not unnecessarily impeded by adding influenza viruses with A/Gs/Gd/1/96 lineage HA to the SATL. Without appropriate consideration for vaccine candidates, any attenuated vaccine strain would require verification that it is no longer a select agent, possibly causing weeks to months of delay in vaccine availability should HPAI containing A/Gs/Gd/1/96 HA develop human to human transmissibility. If manufacturers move forward with vaccine production while the strain remains on the SATL, they would be forced to harden manufacturing facilities normally used to make seasonal influenza vaccines, a cost-prohibitive measure with no commensurate benefit for public safety. IDSA is pleased to see that HHS/CDC is considering this key issue. Below we offer specific comments to the solicitation's questions.

1) **Are there any vaccine candidates that include the HA from the A/Gs/Gd/1/96 lineage that should be considered for an exclusion from the regulation?**

growing attenuated versions of circulating influenza strains, killing the viruses, and extracting the HA for formulation into vaccines. To create these attenuated strains, a key pathogenicity determinant, the polybasic cleavage site of the HA, is removed through genetic engineering or gene synthesis. The HA and neuraminidase (NA) genes are then incorporated into a new virus in the context of other genes from low-pathogenicity strains to create the attenuated virus, which can then be handled safely with biosafety level 2 (BSL2), non-select agent procedures. The attenuation of high pathogenicity avian influenza strains to make vaccine viruses for manufacturing is very reliable, and as of December, 2014, the World Health Organization has made available 27 H5N1 vaccine strains, each attenuated in this manner. IDSA recommends that vaccine candidates of the lineage in which the polybasic cleavage site of HA has been removed and the HA and NA genes of the strain are expressed in the context of other genes from non-high-pathogenicity strains should be excluded from the SATL.

2) **What are the criteria that could be used for exclusion of attenuated strains which could include vaccine candidates?**

As stated above, the IDSA believes the deletion of the polybasic cleavage site of HA and incorporation of the HA and NA genes into viruses in which the other genes are from non-high-pathogenicity strains, as well as the absence of NA sequence motifs associated with oseltamivir resistance are appropriate criteria for exclusion. IDSA recommends HHS/CDC consider a short-term exclusion for these candidates of several months, with longer-term exclusions contingent on phenotypic confirmation of attenuation. Additionally, because the absence of trypsin independent growth in culture correlates so well with lack of pathogenicity in testing in poultry, we recommend CDC/HHS consider dropping the requirement for poultry testing of attenuated viruses that do not grow in the absence of trypsin.

3) **What criteria or experimental conditions should be considered in defining transmissibility among mammals via respiratory droplets?**
4) **What criteria or experimental conditions should be used to define an appropriate mammalian model of influenza transmission?**

It is not known whether “transmissibility among mammals by respiratory droplets” is a well-defined phenotype, where transmitted infection via respiratory droplets in one mammalian species translates to some or all mammalian species. For example, while respiratory droplet transmissibility can be correlated between ferrets and humans (as measured by the existence of sustained transmission in populations or by evidence of household transmission), there are influenza strains that transmit effectively (likely via respiratory droplets) in swine, seals, and horses that are not easily transmissible among humans. While no experiment short of deliberate person-to-person transmission can perfectly assess the transmissibility of a virus strain in humans, respiratory droplet transmission in guinea pigs, ferrets, or other mammals chosen for similarity to human infection and transmission should be presumptive evidence that the virus strain in question may be reasonably expected to transmit efficiently in humans. This is the phenotype of concern and would be, in an ideal world, the definition used to characterize the Tier 1 select agent.

5) **What is the impact of designating as a Tier 1 select agent any influenza virus that contains the HA from the A/Gs/Gd/1/96 lineage that was made transmissible among mammals by respiratory droplets in the laboratory?**

IDSA supports the addition of mammalian transmissible influenza with HA from the A/Gs/Gd/1/96 lineage as a Tier 1 select agent. However we are extremely concerned if a product of an experiment with this lineage gains mammalian transmissibility, whether by intent or not, it could be automatically classified as a Tier 1 select agent, and thus place the investigator in violation of the law by possessing a select agent without permission. This possibility creates a tremendous disincentive for researchers to pursue any experiment where there is a chance, no matter how remote, that the resulting product may cross into the realm of illegality. This could severely hamper future research to develop medical countermeasures and improved surveillance capabilities for emerging avian influenza strains. IDSA strongly recommends that the SATL designation for a mammalian transmissible influenza with the A/Gs/Gd/1/96 lineage HA should not be defined by an experimental result of mammalian transmission alone, or that a grace provision is included for newly, inadvertently generated influenza with the A/Gs/Gd/1/96 lineage HA that exhibit mammalian transmission.

6) **Is the potential for influenza A H5 viruses that contain the HA from the A/Gs/Gd/1/96 lineage to be a low pathogenic avian influenza (LPAI) (by design or nature) but still pose a severe threat to public health and safety significant enough to regulate as a select agent?**

In addition to pathogenicity and transmissibility, antigenic novelty and antiviral resistance are characteristics of influenza viruses that have higher potential risk for human populations. However, absent high pathogenicity, IDSA believes biosafety level 3 handing of samples should provide sufficient protection without the additional biosecurity measures of select agent status. Today, novel antigenic variants of influenza viruses that are not highly pathogenic, and some of which exhibit antiviral resistance, are routinely propagated with appropriate biocontainment without being designated as select agents, and we do not foresee any factors that would require changing these activities.

IDSA thanks HHS/CDC for this opportunity to ensure that oversight of influenza viruses containing A/Gs/Gd/1/96 lineage HA ensures appropriate research is conducted without impeding efforts to prepare for, and respond to, pandemic avian influenza outbreaks. Should you have any questions or concerns about these comments, please contact Greg Frank, PhD, IDSA Program Officer for Science and Research Policy, at gfrank@idsociety.org or 703-299-1216.

Sincerely,

Stephen B. Calderwood, MD, FIDSA
IDSA President

About IDSA

IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii, Klebsiella pneumoni*ae, and *Pseudomonas aeruginosa*, and, finally, emerging infectious syndromes such as Ebola virus fever, enterovirus D68 infection, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and infections caused by bacteria containing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.