Questions and Answers About the Influenza A (H2N2) Panels: Background Information

Distribution of influenza A (H2N2) samples: How did samples of influenza A (H2N2) get distributed to labs as part of proficiency testing (PT) panels?

What is proficiency testing under Clinical Laboratory Improvement Amendments of 1988 (CLIA) and why is it important?

Proficiency testing PT is a process which is mandated under CLIA to evaluate the accuracy of non-waived medical laboratory testing. This is accomplished by distributing samples designed to mimic the patient samples a laboratory might receive; having the laboratories test them; and then having the results scored by the PT provider. Microbiology samples test the laboratory's ability to identify organisms that would commonly be included in patient specimens or determine the presence or absence of particular organisms.

Why and how did these proficiency testing samples come to contain influenza A (H2N2) virus, and where did the samples originate?

Apparently, Meridian Bioscience, Inc., acting contractually on behalf of four PT providers, selected the H2N2 strain of influenza A virus. It is our understanding that Meridian obtained the H2N2 sample from a supplier of biological specimens and kept the sample under storage since approximately 2000.

In most circumstances, contractors who provide PT samples select samples that have a low risk of potential harm to laboratory workers or the public. We don't know why this strain was selected or if Meridian was aware that it was the H2N2 strain. Although we have no proof in this case, experience with viruses indicates that under circumstances of multiple passages (i.e., growing the virus through a series of cultures) in a laboratory, viruses often lose some of their potential infectivity. Therefore, although the infectiousness for humans of this particular strain has not been studied, it is possible that the threat of human infection and transmission has been reduced due to extensive laboratory passage. It is encouraging that there have been no reported cases of influenza A (H2N2) this flu season.

Who sent out the proficiency testing specimens that contained H2N2 virus?

The PT samples were distributed by four PT programs: the College of American Pathologists (CAP), Medical Laboratory Evaluation (a program of the American College of Physicians), the American Academy of Family Physicians (AAFP), and the American Association of Bioanalysts. According to the CAP, for their samples, Meridian Biosciences, Inc. shipped bulk samples to Seracon Diagnostics, a Texas firm, which then shipped the samples in individual packets to enrolled laboratories.

Approximately 4,400 samples containing influenza A (H2N2) were sent to clinical laboratories in the United States and internationally. Meridian also sent out an additional 188 samples to a variety of clients that use PT material for evaluation or manufacture of in vitro diagnostic devices. Thus, approximately 4,600 samples containing the H2N2 strain were sent out, the vast majority being to U.S. sites.

What is the statutory line of authority governing transportation of specimens?

Different regulatory agencies regulate different aspects of transportation of specimens. For example, the Centers for Disease Control and Prevention (CDC) regulates the interstate shipment of etiologic agents, Part 72 of Title 42 of the Code of Federal Regulations. The U.S. Department of Health and Human Services (HHS) regulates the transfer of select agents, including clinical specimens and proficiency test samples

that are identified as containing select agents. The U.S. Department of Agriculture (USDA) has the responsibility for the importation and interstate movement of animal and plant pathogens. The Department of Transportation (DOT) regulates the movement of hazardous materials, including hazardous biological materials. International air shipment is regulated by the International Civil Aviation Organization (ICAO).

What is the statutory line of authority governing selection of specimens for testing?
PT materials are provided by HHS-approved programs, such as the CAP, and these programs identify what bacteria and/or viruses are included in PT samples. The CLIA regulations specify general examples of the bacteria or viruses that should be included in the PT surveys over time, but all PT programs offered under CLIA must be reviewed and approved on an annual basis by HHS. The review of the programs is conducted by the Centers for Medicare and Medicaid Services (CMS), with technical consultation provided by CDC. An approved program must meet all of the criteria spelled out in Title 42, Chapter IV, Part 493, Subpart I of the Code of Federal Regulations.

What responsibility does CDC have, given the agency's role as an accreditor of laboratories?
CDC does not accredit laboratories for CLIA; CMS is responsible for certification of laboratories that test human specimens for clinical and patient management via CLIA. Laboratories may voluntarily choose to be accredited by organizations such as the CAP to meet the federal requirement for CLIA certification.

The only approval of laboratories where CDC has any regulatory role is in laboratories that use select agents.
NOTE: Human influenza strains are generally not select agents. However, influenza A (H5N1) strains isolated from humans are regulated as select agents, because they are considered by USDA to be highly pathogenic avian influenza viruses (HPAI).

Are proficiency tests being done using other non-contemporary influenza strains?
None that we are aware of.

How can similar incidents be prevented in the future?

Proficiency Testing Issues

Are proficiency testing program providers regulated?
All PT programs offered under CLIA must be reviewed and approved on an annual basis by HHS. The review of the programs is conducted by CMS, with technical consultation provided by CDC. An approved program must meet all of the criteria spelled out in Title 42, Chapter IV, Part 493, Subpart I of the Code of Federal Regulations.

Briefly, the criteria a proficiency testing program must meet to receive HHS approval include:

1) The program must be offered by a private nonprofit organization or a Federal or State agency or entity acting as a designated agent for the State.
2) The program must provide technical assistance to laboratories and must assure the quality of test samples, appropriately evaluate test results, and identify performance problems in a timely manner.
3) The program must demonstrate to HHS that it has the technical ability required to prepare or purchase samples in conformance with the appropriate good manufacturing practices required in 21 CFR parts 606, 640, and 820; to distribute homogeneous samples, which will be stable within the time frame for analysis by proficiency testing participants; and to assure that samples mimic actual patient specimens, when possible.

4) The program must provide a scientifically defensible process for determining the correct result for each challenge offered by the program and offer a sufficient annual challenge to establish that a laboratory has met minimum performance requirements.
5) The program must have the resources needed to provide statewide or nationwide reports to regulatory agencies on individual laboratory performance on testing events, cumulative reports and scores for each laboratory or individual, and reports of specific laboratory failures using grading criteria acceptable to HHS.
6) The program must include a laboratory attestation statement that proficiency testing samples were tested in the same manner as patient specimens.
7) The program must provide a mechanism to notify participants of the PT shipping schedule and for participants to notify the proficiency testing program within three days of the expected date of receipt of the shipment that samples have not arrived or are unacceptable for testing. The program must have provisions for replacement of samples that are lost in transit or are received in a condition that is unacceptable for testing; and
8) The program must have a process to resolve technical, administrative, and scientific problems about program operations and comply with all applicable packaging, shipment, and notification requirements of 42 CFR part 72.

Should more specific guidelines for proficiency testing programs be developed?
Current regulatory language may provide sufficient authority to enable government agencies (e.g., CMS, CDC) to implement additional steps that might reduce the likelihood of repetition of this incident. However, investigation of this event may provide evidence that more specific guidance for PT is needed.

How are decisions made about inclusion of specific components in a proficiency testing program?
The PT program makes the basic decisions about what to include in the annual program's content. However, the decisions must follow CLIA requirements. For example, an HHS-approved program for virology must provide a minimum of five samples per testing event and include at least three testing events per year. A program must include viral species that are the more commonly identified viruses. The annual program must include samples for viral antigen detection and viral isolation and identification. A program must furnish HHS with a description of samples that it plans to include in its annual program no later than six months before each calendar year. The program must include other important emerging viruses (as determined by HHS) and viruses commonly occurring in patient specimens. Occasionally, during the course of the PT year, the samples which the program had intended to include are substituted with alternate samples containing other viruses that meet the CLIA specifications.

Did this testing take place under CLIA?
The PT testing of the samples containing the H2N2 strain of influenza A virus took place under CLIA. CMS regulates all clinical laboratory testing (except research) performed on humans in the United States through CLIA. The objective of the CLIA program is to ensure quality laboratory testing. Although all clinical laboratories must be properly certified to receive Medicare or Medicaid payments, CLIA has no direct Medicare or Medicaid program responsibilities. CLIA covers approximately 180,000 laboratory entities. The Division of Laboratory Services/CMS Survey and Certification Group/ Center for Medicaid and State Operations has the responsibility for implementing the CLIA Program. CDC provides technical consultation to CMS regarding CLIA.

The CAP is one of the approved providers CMS uses to administer proficiency testing programs, and Meridian Biosciences, Inc, the company that actually supplied the samples of influenza A (H2N2) for proficiency testing, is a CAP contractor.

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Security Testing Issues

What is the select agent program?
The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Act) requires entities to register with HHS or the U.S. Department of Agriculture (USDA) if they possess, use, or transfer biological agents or toxins (i.e., select agents and toxins) that could pose a severe threat to public health and safety, to animal or plant health or to animal or plant products. In addition to ensuring that laboratories safely handle these select agents and toxins, the Act also requires increased safeguards and security measures of these agents, including controlling access, screening entities, and personnel (i.e., security risk assessments) and establishing a comprehensive and detailed national database of registered entities.

The Secretary of Health and Human Services has tasked CDC with the responsibility of promulgating and implementing these regulations. At CDC, the Division of Select Agents and Toxins in the Coordinating Office of Terrorism Preparedness and Emergency Response oversees these activities and registers all laboratories and other entities in the United States that possess, use, or transfer a select agent or toxin.

What is a select agent?
A select agent is a biological agent or toxin that has the potential to pose a severe threat to public health and safety. There are currently 40 agents and toxins listed in the CDC regulation, Title 42 Part 73 Possession, Use, and Transfer of Select Agents and Toxins. In addition, the USDA is responsible for establishing a list of agents and toxins that has the potential to pose a severe threat to animal or plant health, or to animal or plant products. Those that are regulated by both CDC and Animal and Plant Health Inspection Service of USDA are referred to as “overlap” select agents and toxins.

How was the select agent list established?
The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Act) requires the Secretary of Health and Human Services by regulation to establish and maintain a list of each biological agent and toxin that has the potential to pose a severe threat to public health and safety. In determining whether to include an agent in the list the Act requires that the following criteria be considered:

(I) the effect on human health of exposure to the agent or toxin;
(II) the degree of contagiousness of the agent or toxin and the methods by which the agent or toxin is transferred to humans;
(III) the availability and effectiveness of pharmacotherapies and immunizations to treat and prevent any illness resulting from infection by the agent or toxin; and
(IV) any other criteria, including the needs of children and other vulnerable populations, that the Secretary considers appropriate

In 2002, CDC convened an inter-agency workgroup of subject matter experts from Federal government entities to determine which biological agents and toxins required regulation based on the criteria specified in the Act. Members of the working group included representatives from HHS/Office of the Secretary (DHHS/OS), CDC, the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Department of the Army (DoD/Army), the Department of the Navy (DoD/Navy), the Department of the Air Force (DoD/AF), USDA, the Environmental Protection Agency (EPA), the Agency for Toxic Substances and Disease Registry (ATSDR), the Department of Labor/Occupational Safety and Health Administration (OSHA), the National Institute of Occupational Safety and Health (CDC/NIOSH), the Department of Transportation (DOT), the Department of Commerce (DOC), the Department of Energy (DOE), the Department of Justice (DOJ), the Federal Bureau of Investigation (FBI), the Central Intelligence Agency (CIA), the Defense Intelligence Agency (DoD/DIA), and the U.S. Postal Service (USPS). In addition, thirteen professional organizations were invited to address the workgroup. The recommendations from

that workgroup were published in a Federal Register notice of intent to issue regulations on August 23, 2002 requesting public comments on the proposed list of select agents and toxins.

As was required by the Act, the list was published as part of an interim final rule on December 13, 2002. This list was recently re-reviewed by the inter-agency workgroup and published on March 18, 2005 as part of a final rule that became effective on April 18, 2005.

Is H2N2 a select agent?
No.

Why not?
The 2002 inter-agency workgroup recommended that influenza strains that might potentially be capable of causing a pandemic not be added to the list. Among the considerations at the time was the concern that the registration, additional security measures, and prior approval of the movement of these samples may adversely impact the need to quickly identify a pandemic strain and to respond to this potential public health emergency with the rapid development of effective therapeutics and vaccines.

One of the actions that CDC will take as a result of this incident is to consult with scientific experts to identify what additional safety and security measures should be implemented to ensure that this does not happen again. This would include re-evaluating whether influenza strains that might potentially be capable of causing a pandemic should be added to the select agent list.

Who has the authority to include influenza A (H2N2) on the list of select agents?
As outlined above, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 authorized the Secretary of Health and Human Services to establish and maintain this list of biological agents and toxins that have the potential to pose a severe threat to pubic health and safety.

In establishing this list and in determining which agents should be included on the list, the Secretary has to consider (1) the effect on human health of expose of the agent or toxin; (2) the degree of contagiousness of the agent or toxin and the methods by which the agent or toxin is transferred to humans; (3) the availability and effectiveness of pharmacotherapies and immunizations to treat and prevent any illness resulting from infection by the agent or toxin; and (4) any other criteria, including the needs of children and other vulnerable populations, that the Secretary considers appropriate.

The Secretary must also consult with appropriate Federal departments and agencies and with scientific experts representing appropriate professional groups, including groups with pediatric expertise. The Secretary reviews the list biennially, or more often as needed. Additions or deletions, to the select agent list would be made by amending part 73 of Title 42 of the Code of Federal Regulations after public notice in the Federal Register and the opportunity for public comment.

Are there other select agent pathogens in storage that may present a problem in the future?
Laboratories that knowingly possess, use, or transfer the defined select agents are required to register with the Select Agent Program. There are stringent controls on laboratories that knowingly store specimens containing select agents, requiring that the specimens are secured or destroyed.

In some instances, all laboratories that may have infectious agents have been contacted. For example, as part of the polio eradication program at the behest of the World Health Organization (WHO) and HHS, CDC made concerted efforts to contact all research and clinical laboratories that may have stored specimens containing polio virus.

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On the other hand, there are facilities that have frozen and lyophilized clinical samples which were never fully characterized.

Laboratory Safety Issues

Who has the authority to designate influenza A (H2N2) a biosafety level 3 (BSL3) agent?
Biosafety levels for different substances are determined through a risk assessment of working with the organism in a laboratory. A group of experts convenes to do this and the resulting decisions are published in the CDC/NIH publication, Biosafety in Microbiological and Biomedical Laboratories (BMBL).
Over the past year, a group of flu experts from government and academia have discussed the risk assessment for various strains of influenza, including human H2N2 viruses. A revised BMBL manual is scheduled for release in the fall of 2005 and will include a recommendation that such strains of flu be worked with using BSL3 practices, procedures, and facilities with enhancements. CDC will work with NIH to publish interim recommendations for work with flu strains that have the potential for a pandemic.

What was the public health risk of this situation?

Does CDC have authority to order destruction of specimens?
Under section 361 of the Public Health Service Act (42 USC 264), the HHS Secretary has broad authority to enact rules and regulations to prevent the introduction, transmission, and spread of communicable diseases from foreign countries into the United States and from one state or possession into another. Regulations promulgated under this statutory authority may be found at 42 CFR Parts 70 (Interstate Quarantine) and 71 (Foreign Quarantine). Under 42 CFR 70.2, whenever the CDC Director determines that the measures taken by the health authorities of any state or possession are insufficient to prevent the spread of communicable diseases from one state or possession into another, the Director may take such measures to prevent the spread of the disease as the Director deems reasonably necessary, including inspection, fumigation, disinfection, and destruction of animals or articles believed to be sources of infection. This section does not apply to measures taken by health authorities outside the United States.