

Cepheid

ON

DEMAND

report

A Quarterly Publication
by Cepheid

Influenza today: Still a hot topic on many fronts

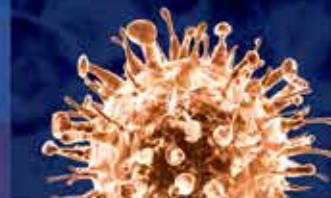
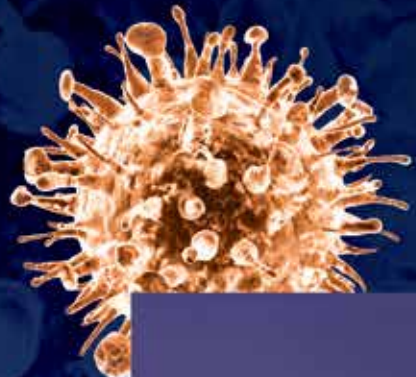
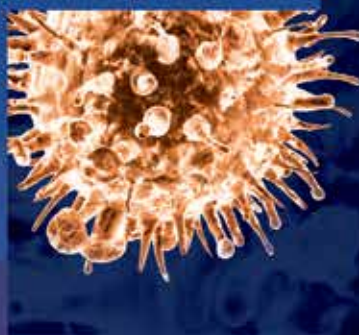
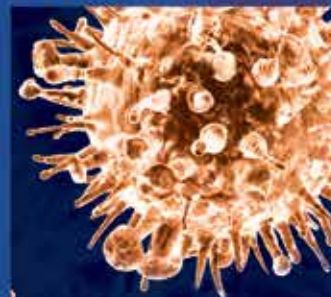
Case Study Award:

Cepheid Xpert® Flu Assay Results:
Positive in More than One Way

More
Accurate

Faster

Positive



Volume 6, Issue 1

 **Cepheid®**
A better way.

CONTENTS WINTER 2013

Executive Editor

David Persing, M.D., Ph.D.

Lead Author

Ellen Jo Baron, Ph.D.

Contributing Authors

Fred Tenover, Ph.D.

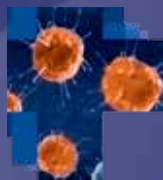
Cepheid's ON DEMAND Report is distributed four times a year. We welcome communication from users of Cepheid systems and tests and invite suggestions for articles in future issues. Send correspondence to:
Cepheid ON DEMAND Report
1327 Chesapeake Terrace
Sunnyvale, CA 94089

editor@cepheidondemand.com

To sign up for e-mail notification of new issues of Cepheid's ON DEMAND Report, visit www.cepheidondemand.com

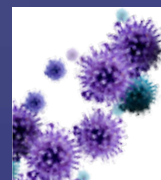
Contents are ©2013 by Cepheid unless otherwise indicated. Rights reserved on all guest columns. The contents of this publication may not be reproduced in any form without written permission of the editor. The mention of trade names, commercial products, or organizations does not imply endorsement by Cepheid.

COVER STORY 3



Influenza today:
Still a hot topic on
many fronts

INSIDE 8



Case Study Award:
Cepheid Xpert® Flu Assay
Results: Positive in More
than One Way



David Persing
M.D., Ph.D.

Chief Medical and
Technology Officer, Cepheid

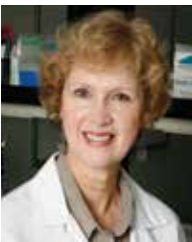
From the Editor

In this issue of On Demand, Dr. Ellen Jo Baron provides a wealth of information on our perennial foe, the influenza virus. If you want to get up to speed on this subject quickly, read this issue; it encapsulates much of the recent research on the flu viruses, their virulence factors, and approaches to their detection. As many of you know, rapid detection of this virus during the flu season is of significant medical value, but until recently, most of the rapid tests have not been sensitive enough to rule out influenza infection with a high degree of confidence. Next-generation molecular diagnostic testing for influenza virus and specifically the Xpert® Flu cartridge represent game-changing technologies. I hope you enjoy reading this issue as much as I have.

David H. Persing



Influenza today: Still a hot topic on many fronts



Ellen Jo Baron
Ph.D., D(ABMM)

Prof. Emerita, Stanford University
Director of Medical Affairs, Cepheid

It seems like just yesterday that influenza was on everyone's minds, but it has been almost a year since we featured influenza in an edition of On Demand. The novel influenza A H1N1 strain that caught everyone by surprise in 2009 seems to have become a very minor component of the circulating strains now, except in the Middle East and India, where it still predominates. This season, influenza B is prominent in the Americas and Africa, and influenza A H3N2 comprises half the reported cases in Europe and Australia, and more than 75% of strains in China^A. The World Health Organization reported that the most common strain worldwide, A(H3N2), is again targeting the traditional at-risk age groups of >60 years and <2 years. In temperate South America, numbers of influenza cases began to increase in May, peaking around July with the largest numbers seen for A(H3N2), but showing a second peak in August with more influenza B strains and untyped influenza A strains (Figure 1). There was a sharp drop-off in September, heralded by the disappearance of almost all influenza A reports. Africa peaked in July, but numbers remained high into September, with influenza B assuming the majority of cases. The United States is just beginning its influenza season, so the epidemiology is not known yet (Figure 2). Overall, influenza activity is lower than historical levels. This may be a result of increasing numbers of Americans receiving their annual flu vaccine. However, a new virus, variant H3N2 (H3N2v), associated with pigs and originally discovered in 2011, has cropped up this year in some human outbreaks periodically since July, 2012.^{1,B} Although the strains of influenza circulating globally now are genetically slightly different from those in the current vaccine, the CDC feels that there will be significant cross-reactive protection, so they recommend that the vaccines not be changed. The common viruses causing disease are generally susceptible to both neuraminidase inhibitor antiviral agents oseltamivir (Tamiflu®) and zanamivir (Relenza®). This correlates with the seeming disappearance of the previously circulating H1N1 strain (called "seasonal") that was resistant to oseltamivir. Of course, occasional resistance can arise and patients who fail to improve after a week of therapy should be evaluated for drug resistant strains, as well as for other complications. Zanamivir is not recommended for patients <7 years old or for those with underlying respiratory disease. The CDC treatment guidelines state that antiviral therapy should not be delayed while waiting for diagnostic test results when clinical indications suggest influenza and antiviral treatment is indicated.^C

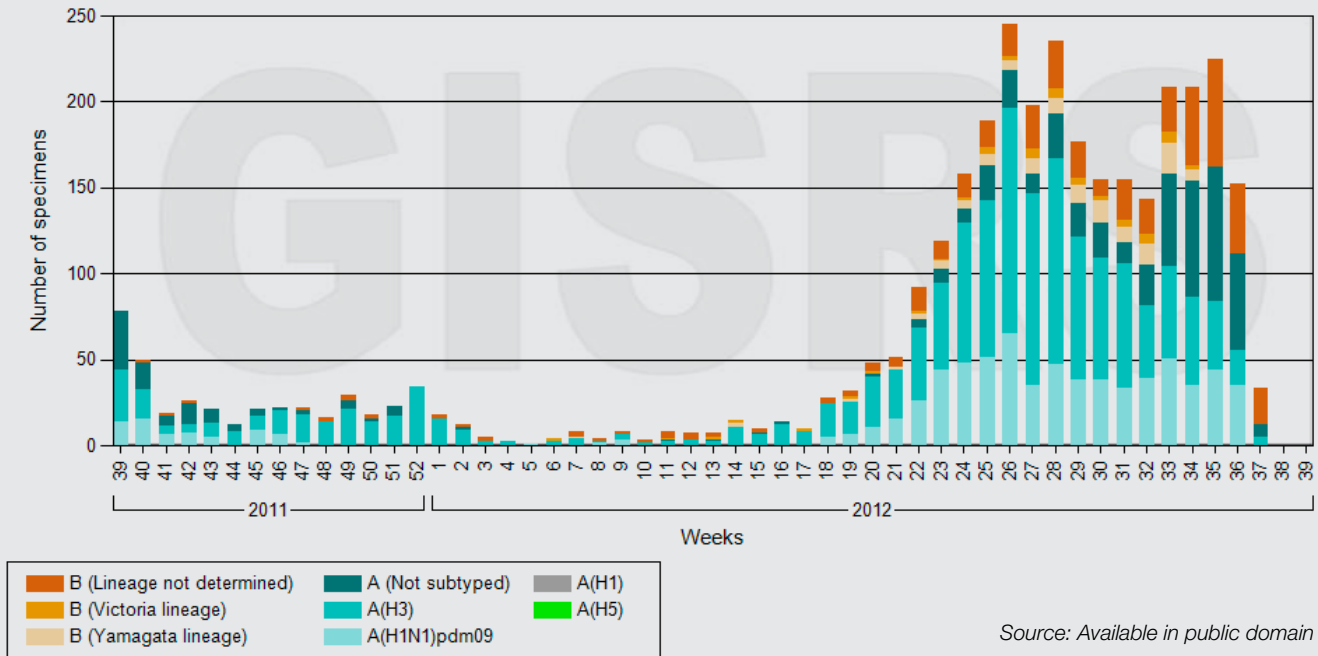
The current influenza activity is interesting to public health authorities and of paramount importance to individual patients and their caregivers and those close to them, but the topic of most discourse in the literature this year is the ethics of performing certain types of research involving influenza. The debate over this activity rose to the highest levels of academia and the national science community. Some readers may remember back in 1996 when reports started trickling out of China about a new strain of avian influenza that had a surprisingly high mortality rate in chickens, H5N1. In 1997 in Hong Kong there were 18 cases of the same virus infecting people who were in contact with sick poultry; and most unusual for influenza, one-third of the patients died. No one was particularly alarmed because all patients had contact with poultry and it was not thought that such viruses could transmit an infection from human to human, and there were no more cases reported for several years. But in 2003, the virus resurfaced in Hong Kong.

...if the current widely circulating strains of HPAI could acquire the genetic determinants that would allow the virus to infect humans more easily...Such ability would surely contribute to the possibility of a great pandemic of lethal influenza, resembling that of 1918.

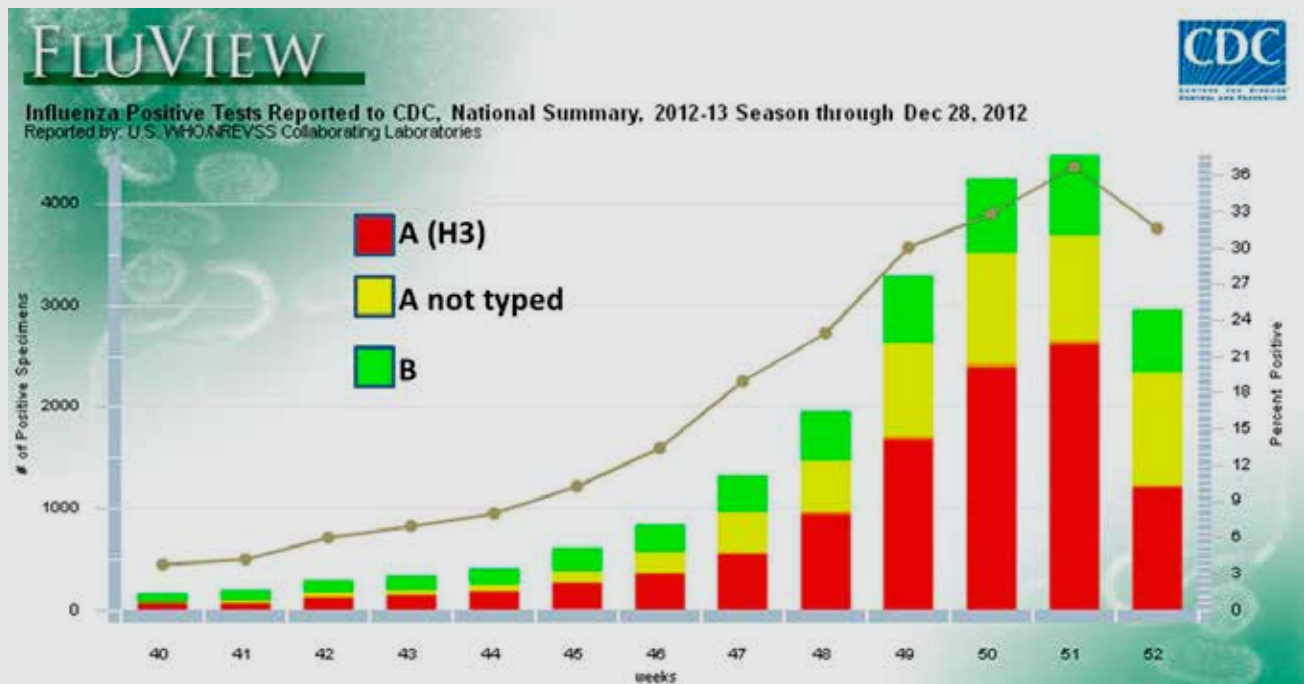
After that, cases began to spring up elsewhere and in other species of animals. A zoo in Thailand fed fresh chicken carcasses to two leopards and two tigers, all four of which died of fulminant disease in a short period of time. Poultry in both Korea and Vietnam were dying and influenza A H5N1 was identified as the culprit. Human cases resulting in many deaths in Vietnam began and continued, caused by the same virus. By 2004, the virus was widely disseminated throughout Southeast Asia. In early 2004, 9 million poultry were culled in China to stem the epidemic. A study published in January, 2005 reported the first well-documented case of human to human transmission, in which a young Thai girl passed the infection to her mother. Sadly, the mother died.

In 2005, a huge die-off of wild birds in a large lake populated by numerous migratory species (Qinghai Lake) was determined to be due to a new, more lethal variant of H5N1. Japan and Philippines also reported disease in poultry and illness seemed to have spread to migratory birds as far away as Russia, Mongolia, and to poultry, pigs, and then humans in Indonesia. Throughout the next few years, cases in humans or animals were reported throughout the world, moving to Europe, India, and other areas. It appeared that children and young adult patients were more susceptible to infection than the elderly and very young patients, in whom influenza is typically more common. Research was initiated to explore the pathogenesis of the virus, now known as Highly Pathogenic Avian Influenza (HPAI) and one study showed that human disease was diverted at least partly because the virus preferentially adhered to epithelial cells deep in the lungs rather than those cell types that it is most likely to encounter in the upper respiratory tract. By June, 2006, there had been 205 laboratory-confirmed human cases reported to the World Health Organization. By spring of this year (2012), several hundred human cases had been reported worldwide. WHO publishes a timeline of events that is updated often.^D A major human outbreak has not occurred, but many people are concerned, and some scientists are studying this virus with new technological and molecular tools.

Two specific groups of researchers, one collaboration between the University of Wisconsin and several Japanese institutions and the other a collaboration between the National Institutes of Health, the Erasmus Medical Center in Netherlands and the University of Cambridge in UK, endeavored to determine if the current widely circulating strains of HPAI could acquire the genetic determinants that would allow the virus to infect humans more easily, including factors that would facilitate binding to upper respiratory tract epithelial cells. Such ability would surely contribute to the possibility of a great pandemic of lethal influenza, resembling that of 1918. The virus of the 1918 pandemic was similar to this virus, in that it preferentially affected relatively healthy children and young adults. In fact, a number of genetic characteristics of the HPAI H5N1 resembled those of the 1918 strain.² Those scientists who were studying the characteristics that would allow inter-species transmission by the airborne route had chosen ferrets as the animal model for their research. Ferrets are often used for this type of respiratory virus research because they can develop a respiratory infection similar to human influenza; in fact, ferrets sneeze just like people do. The experiments were carried out with utmost care under rigorous scientific protocols. Mutations that developed in the viral strains grown in the laboratory were carefully controlled and characterized. Finally, the two independent groups of scientists were able to modify A/H5N1 enough to allow ferret-to-ferret respiratory transmission. Does this mean that those genetic changes could occur naturally in nature? Does it mean that even if such changes were to occur, that they would behave the same way in humans? Nobody knows the answers, but the prospect

FIGURE 1. Chart of influenza subtypes in temperate South American zone.

Source: Available in public domain

FIGURE 2. United States Influenza isolates for flu season beginning end of 2012. (<http://www.cdc.gov/flu/weekly>)

Source: Available in public domain

is disconcerting. Both manuscripts were submitted for publication at the same time to *Nature* and *Science*, among the most prestigious and widely read scientific journals in the world. These manuscripts were to generate a huge amount of public and private dialogue and controversy.³

After 9/11 and the anthrax distribution in the U.S., many scientists and government officials felt that the information necessary to weaponize anthrax spores could have been found in legitimate scientific literature (much like the information on how to build a bomb is available on the internet), and they wanted to censor any future publications that could be seen as helping potential bioterrorists achieve their goals. This type of research is called Dual-Use Research of Concern (DURC), meaning that both peaceful and military applications are possible based on the results. The academic and government communities agreed that bioterrorism was a threat sufficient to warrant serious concern and put an official oversight function in place. The government created an advisory board, the National Science Advisory Board for Biosecurity (NSABB), peopled by eminent and respected scientists, whose job was to review publications of research findings that could lead to potentially dangerous information becoming available and being exploited for the wrong purposes. The Board's focus was to decide how to protect the public from harm while not inhibiting the advancement of science.

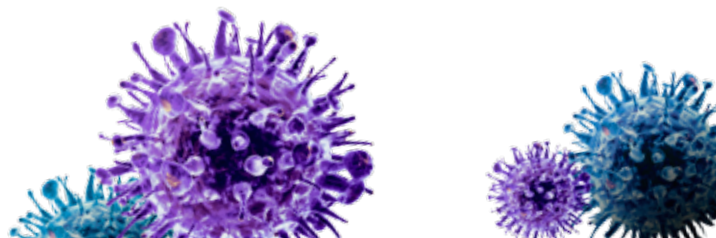
Clearly, the two submitted manuscripts describing the genetic manipulations of the HPAI virus that allowed it to infect ferrets by the airborne route merited review by this board. After much deliberation, the NSABB decided that the full protocols should be published and available to the general public. This decision provoked an outcry from some scientists who felt that potential security risks outweighed the free dissemination of research findings. The supporters of total publication felt that partial publication (holding back key experimental details) would have a detrimental effect on other scientists contemplating similar research. They felt that the information presented could potentially lead to better control, and perhaps a better vaccine. The final upshot of this highly vocal and visible rift within the influenza research community and the broader scientific community was the publication, in full, of both manuscripts.^{2,4} Amidst many calls for better decision-making in the future, the safeguards and oversight activities have been modified.^{5,6,E} Still, at this time, the HPAI has not moved into the general population. Could our currently available rapid influenza tests detect H5N1 if it suddenly swept into the human population? At least one group studied two lateral flow antigen assays with samples from infected poultry.⁷ Rectal/genital (i.e., cloacal) swabs were less sensitive for detection of HPAI H5N1 than feathers and neither sample was very sensitive compared with a molecular assay. Cloacal samples are appropriate, since infected birds shed the virus via the gastrointestinal tract. However, this result does not bode well for detection of the virus in human samples.

The inevitable emergence of new strain variants fueled by genetic reassortments among existing strains has important implications for diagnostic tests.

Can the rapid antigen tests developed for circulating strains at the time of test creation detect the new variants? Clearly they have challenges, as illustrated by the very public failure of existing rapid antigen tests to detect the influenza A 2009 novel strain⁸ and the H3N2v strain.⁹

Both the rapid antigen tests and the antibodies used in the direct fluorescent antibody stains used by those laboratories performing DFA assays were developed before avian influenza was considered to be a threat. Genetic tests have the advantage, as they can be tailored with the addition and subtraction of specific primers and probes to match the circulating strains.

How do the current diagnostic tests fare with the influenza strains currently in circulation? The general laboratory population was surprised to learn that the novel A H1N1 2009 was not detected very well by the commonly used rapid antigen tests. Current recommendations from the CDC about which diagnostic tests to use are based on that experience. First of all, patients should be tested as early in their disease as possible. Test results are less reliable at 4 days after onset of illness. The CDC recommendations state that rapid influenza diagnostic tests (RIDT) are not very sensitive, averaging sensitivities from 40-70% with a range of 10-80%.^F A negative test should be confirmed with a more sensitive test, such as reverse transcriptase PCR or viral culture. These tests are more sensitive, but slower. Although a truly rapid test (15-20 minutes) that could unequivocally rule out influenza would be ideal, the state of our technology still falls short of that goal. Whether the patient presents at the height of influenza season or in the middle of the summer, major decisions will be made based on the test results. Should the patient be admitted into a respiratory isolation room? Should the patient be sent home? Should the patient be given antiviral medication or antibiotics? An accurate test result in a timely fashion is important to that individual patient, his or her family, and the institution. Fortunately, there are options available for the laboratory, although all have pros and cons.



Some laboratories continue to use rapid antigen tests, usually immunochromatographic lateral flow format. A group from the Stanford University Medical School laboratory of Dr. Benjamin Pinsky, led by first author Dr. Mike Dimaio (**Figure 3**), has recently published an evaluation of two of the most popular such assays, BinaxNOW and BD Directigen, along with Cepheid Xpert Flu for their sensitivity and specificity with today's circulating virus strains.¹⁰ The Stanford laboratory, with its highly skilled and experienced virology staff, routinely used direct fluorescent antibody (DFA) testing and its own laboratory-validated real-time reverse-transcriptase PCR assays for influenza A (based on the CDC published protocol) and the primary mutation that confers oseltamivir resistance. In 2008, the laboratory had performed a comparison of the rapid direct antigen tests that it had been using in previous years and found the sensitivity and specificity to be so low (unpublished data) that it had discontinued use of those tests even before the novel H1N1 virus outbreak began in the spring of 2009, instead ramping up the number of times per day that DFA testing was performed. But physicians wanted a more rapid turnaround time. The group used 200 previously submitted samples (frozen) including 84 from children <18 years old. Samples had been previously identified by DFA



FIGURE 3. Dr. Mike Dimaio, the first author of the Stanford influenza study, hard at work at the Stanford Hospital GeneXpert® System.



FIGURE 4. Alejandro DeTorres, CLS, testing a sample in the Kaiser-Permanente North Hollywood Microbiology Laboratory.



The ease of use, the rapid turnaround time, and the random access nature of the assay, which helps diminish the chance of cross-contamination, all serve to make the Xpert® Flu an attractive test.

as positive for influenza A, influenza B, respiratory syncytial virus, human metapneumovirus, adenovirus, or parainfluenza viruses or were negative for the above agents (57 samples). Results for the 74 influenza A positive specimens yielded sensitivity of 97.3% for Xpert® Flu, 95.9% for direct fluorescent antibody testing, 62.2% for BinaxNOW, and 71.6% for BD Directigen. All specimens positive for influenza A by rapid antigen testing were detected by the Xpert Flu assay. Specificity for influenza A was 100% (126/126) for Xpert Flu, BinaxNOW, and BD Directigen, and 99.2% for direct fluorescent antibody testing. In this study, there were five samples with seasonal H1N1. All five were detected by Xpert Flu, BD Directigen detected one, but BinaxNOW failed to detect any. For the 33 influenza B positive samples, sensitivity was 100% for Xpert Flu and direct fluorescent antibody testing, 54.5% for BinaxNOW, and 48.5% for BD Directigen. Specificity for all three tests was 100%. The authors concluded that the Xpert Flu was more accurate but as easy to use as the rapid antigen tests, and could eliminate the need for reflex testing. In addition, with a turnaround time of <90 minutes, results could be delivered in sufficient time to influence clinical decision-making.¹⁰ For laboratories using molecular multi-analyte respiratory virus panels for certain at-risk patients, especially during influenza season, the Xpert Flu might be used as the assay of choice to triage influenza-positive patients and eliminate the need for the additional more expensive panel assay.

Novak-Weekley and colleagues (Figure 4) from five institutions in the U.S. and Australia provided another evaluation of Cepheid's new Xpert Flu test.¹¹ Both nasopharyngeal swabs and nasal aspirates/washes, prospective and previously frozen, were included. More than 1500 samples were included, divided almost equally between fresh and frozen. The ProFlu+ molecular assay, viral cultures, and sequencing of viruses were all used as reference tests. Compared to the ProFlu+ molecular assay, frozen nasal wash samples tested by Xpert Flu had sensitivities of 98-100% for all influenza A and B viruses. For nasopharyngeal swabs, there were somewhat lower sensitivities (93.8%) for influenza B containing samples, although the results for influenza A were comparable to those seen with washings. Specificities were 99-100% for both aspirates and swabs. The prospective samples had 100% sensitivities for all samples except for nasal washings, for which slightly lower sensitivities were seen with seasonal influenza A, not including the 2009 H1N1 strains. The PCR assay performed better than culture, after discrepant analysis by sequencing. Novak-Weekley and colleagues noted that the ease of use, the rapid turnaround time, and the random access nature of the assay, which helps diminish the chance of cross-contamination, all serve to make the Xpert® Flu an attractive test for laboratories that lack molecular expertise or that require rapid turnaround time and do not wish to wait to accumulate a batch of samples for testing.¹¹

The recently newsworthy influenza A H3N2v, another pig to human influenza virus, was probably not included in either of the Xpert Flu publications described above. This virus has become a risk especially for patients who tend pigs for prolonged periods, and who frequent county fairs. H3N2v is likely not well detected by any current FDA-cleared tests. In fact, a recent study shows that a number of variant viruses were not detected by current rapid antigen tests at all.¹² So far, these viruses have all been detected by the current GeneXpert assay, including the H5N1 highly pathogenic strain, which is reported as “influenza A.” Cepheid scientists are working now on the next generation influenza assay, which embodies our commitment to continuously improve our assays, and in the case of influenza, to try to keep up with this wily virus as it evolves.

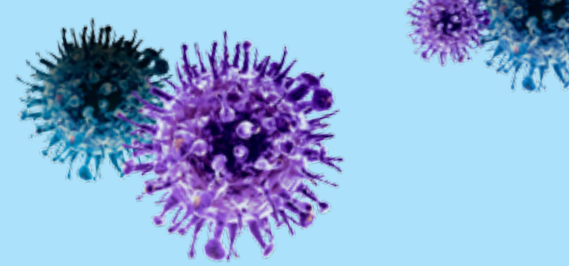
The flu season has started, and laboratories have several choices of tests to employ. Knowing the pros and cons of the options can help microbiologists and physicians choose the best tests and testing algorithms for their needs. The case report in the next section of this edition of On Demand describes one laboratory’s approach.

Call for Case Studies

Sharing your interesting patient cases where GeneXpert made a difference can be a rewarding experience. David Persing, Fred Tenover, and Ellen Jo Baron invite you to send us your case for publication in On Demand.

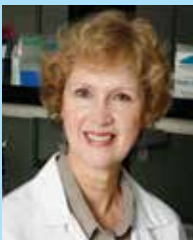
- The best case of the quarter will win a copy of the new definitive reference on Molecular Microbiology from ASM Press, signed by Dr. David Persing and Dr. Fred Tenover.
- Your case and a photo of your lab will be published in On Demand, Cepheid’s quarterly newsletter: <http://www.cephheidondemand.com/>
- Write up the case including history, symptoms, initial findings, sample type received, assay(s) performed (including routine laboratory tests), time to results, and outcomes.
- Describe how the GeneXpert® System made a difference.
- Photos or other images are especially welcome.
- Send it to editor@cephheidondemand.com.





Case Study Award: Cepheid Xpert® Flu Assay Results: Positive in More than One Way

Jack L. Brothers, MT(ASCP), Microbiology Technical Supervisor, works at a surprisingly beautiful hospital (Figure 1) in an unlikely place: Anchorage, Alaska. The Joint Base Elmendorf-Richardson is the largest U.S. military installation in Alaska and was created when former Elmendorf Air Force and Fort Richardson Army bases were merged in 2010.



Ellen Jo Baron
Ph.D., D(ABMM)

Prof. Emerita, Stanford University
Director of Medical Affairs, Cepheid

The base medical facility has 60 inpatient beds but its larger mission is to provide medical care to over 35,000 joint service members, dependents, Veterans Administration (VA) patients, and retirees throughout Alaska. One usually does not think about VA hospitals as receiving many pediatric patients, but in this case, families of service members are a large component of the population served. For allowing us to benefit from his experience with a GeneXpert assay, Jack will receive a copy of the recently published second edition of the popular book published by ASM Press, *Molecular Microbiology: Diagnostic Principles and Practice*, hand signed by the two co-editors David Persing and Fred Tenover. Jack Brothers elegantly described the situation and how the Cepheid Xpert Flu assay, with final results delivered less than 2 hours from sample collection, saved one tiny patient and his family a lot of grief and potential further trauma (notably enabling the cancellation

of a spinal tap). This is Jack's case description.

“The parents of a two month old male infant brought their child to the 673rd Medical Group DOD/VA Joint Venture Hospital Emergency Department late one night in March of 2012. The chief complaint was a high fever with intermittent shortness of breath and “gasping for air with a dry cough.” Vital signs revealed a rectal temperature of 101.1°F, pulse of 194, respirations of 40 per minute, and O₂ Saturation of 98% on room air. In addition to the tachycardia and dyspnea, the physical exam noted pharyngeal erythema, and a blanchable rash on the cheeks and chest. Blood was collected for a complete blood count (CBC) and culture, and an intravenous line was inserted. A nasal washing (using normal saline) was also obtained and sent to the laboratory for viral testing, and a chest X-ray was ordered.



FIGURE 1. The 673rd medical group Joint Venture Department of Defense/Veterans Administration hospital

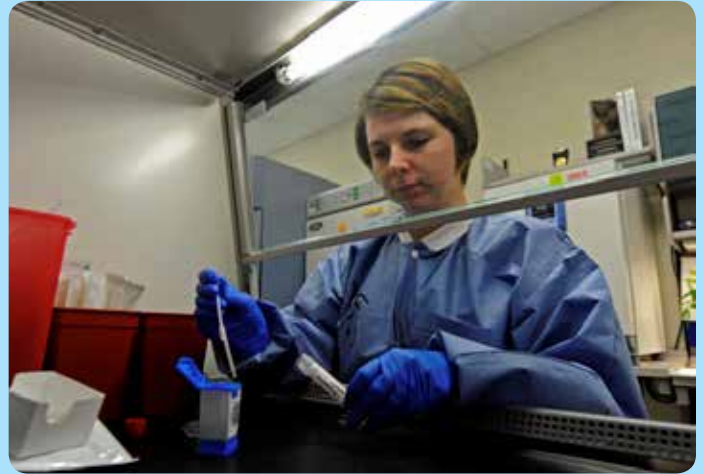


FIGURE 2. Senior Airman Jessica Green performing the Xpert® Flu test, adding the sample to the cartridge in a biosafety cabinet

The CBC was essentially normal, as was the chest X-ray. A rapid antigen detection assay for respiratory syncytial virus (RSV) was performed on the nasal washings and was negative. Rapid antigen detection assays for influenza A and influenza B performed on the same sample were also negative and were reported to the physician handling the case in the Emergency Department.

EJB comment: Luckily for the baby, Jack's laboratory policy requires reflexing samples from some patients that are negative by the rapid influenza antigen assay to testing with the Cepheid Xpert® Flu assay, designed to detect both influenza A, B, and A[2009 H1N1], as he explains further below.

Per laboratory policy, Senior Airman Jessica Green pipetted 600µl of the original nasal wash into 3ml of Universal Transport Medium (UTM), and then used 300µl of the diluted sample to set up a Cepheid Xpert® Flu assay (Figure 2). The Cepheid® RT-PCR assay was “influenza A positive, no influenza B detected, no influenza A 2009 H1N1 (A/California/7/2009-like) detected”, and was certified. A few minutes later, she received a call from the doctor. He wanted to make absolutely sure that he was interpreting the results correctly, and that the PCR test was indeed positive for Influenza A. Jessica explained that the rapid antigen tests can sometimes give false negative results, and that the PCR is much more sensitive and also more accurate. He thanked her, and said that there was no longer a need to do a spinal tap on the baby since they now knew the origin of his fever. The child was given Tamiflu and sent home.

The policy at the 673rd Medical Group Laboratory is to confirm the results of rapid influenza antigen tests by performing reflex PCR testing on all samples obtained from patients considered at high risk for respiratory distress, and on all samples

collected from inpatients. We define high risk for influenza testing to be patients less than one year of age, patients over 65 years of age, and those with known conditions that would make them more vulnerable to viral infections, such as chronic obstructive pulmonary disease (COPD) or immune suppression. We perform reflex testing using the real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) Xpert Flu assay on a Cepheid 4-well GeneXpert instrument.

Most PCR testing requires an extraction procedure that necessitates batching of samples. In this case the Cepheid GeneXpert® enabled a busy Technician to perform an accurate, sensitive RT-PCR flu assay at 2:30 in the morning, while the patient was still in the Emergency Department. Less than 2 hours elapsed from the time the sample was collected until the final PCR result was certified and sent to the provider. As a result, additional expensive testing to determine the cause of a fever of unknown origin was avoided, and the relieved parents were able to return home with an accurate diagnosis for their child in minimum time. The Alaska State Virology Laboratory in Fairbanks confirmed the Cepheid Xpert Flu result (A/H3), but those results were not available until the following week. ”

REFERENCES

Influenza today: Still a hot topic on many fronts

1. Lindstrom, S., et al., Human infections with novel reassortant influenza A(H3N2)v viruses, United States, 2011. *Emerg Infect Dis.* 18(5): p. 834-7.
2. Imai, M., et al., Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. *Nature.* 486(7403): p. 420-8.
3. Osterholm, M.T. and D.A. Relman, Creating a mammalian-transmissible A/H5N1 influenza virus: social contracts, prudence, and alternative perspectives. *J Infect Dis.* 205(11): p. 1636-8.
4. Herfst, S., et al., Airborne transmission of influenza A/H5N1 virus between ferrets. *Science.* 336(6088): p. 1534-41.
5. Fauci, A.S. and F.S. Collins, Benefits and risks of influenza research: lessons learned. *Science.* 336(6088): p. 1522-3.
6. Lipsitch, M., et al., Evolution, safety, and highly pathogenic influenza viruses. *Science.* 336(6088): p. 1529-31.
7. Slomka, M.J., et al., Evaluation of lateral flow devices for identification of infected poultry by testing swab and feather specimens during H5N1 highly pathogenic avian influenza outbreaks in Vietnam. *Influenza Other Respi Viruses.* 6(5): p. 318-27.
8. Control, C.f.D., Performance of rapid influenza diagnostic tests during two school outbreaks of 2009 pandemic influenza A (H1N1) virus infection - Connecticut, 2009. *MMWR Morb Mortal Wkly Rep.* 2009. 58(37): p. 1029-32.
9. Centers for Disease Control and Prevention. Evaluation of Rapid Influenza Diagnostic Tests for Influenza A (H3N2)v Virus and Updated Case Count - United States, 2012. *Morbidity and Mortality Weekly Report*, 2012. 61: p. 1-3.
10. Dimaio, M.A., et al., Comparison of Xpert Flu rapid nucleic acid testing with rapid antigen testing for the diagnosis of influenza A and B. *J Virol Methods.* 186(1-2): p. 137-140.
11. Novak-Weekley, S.M., et al., Evaluation of the Cepheid Xpert Flu Assay for rapid identification and differentiation of influenza A, influenza A 2009 H1N1, and influenza B viruses. *J Clin Microbiol.* 50(5): p. 1704-10.
12. Balish, A., et al., Analytical detection of influenza A(H3N2)v and other A variant viruses from the USA by rapid influenza diagnostic tests. *Influenza Other Respi Viruses.*
- A. http://www.who.int/influenza/surveillance_monitoring/updates/2012_09_28_update_GIP_surveillance/en/index.html
- B. <http://www.cdc.gov/flu/swineflu/h3n2v-outbreak.htm>
- C. <http://www.cdc.gov/flu/antivirals/index.htm>
- D. http://www.who.int/influenza/human_animal_interface/H5N1_avian_influenza_update150612N.pdf
- E. <http://ebookbrowse.com/united-states-government-policy-for-oversight-of-durc-final-version-032812-pdf-d340636360>
- F. http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm



1327 Chesapeake Terrace
Sunnyvale, CA 94089
toll-free: 1.888.336.2743