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Examining the U.S. Public Health Response to Seasonal Influenza

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INTRODUCTION

Good morning Chairman Murphy, Ranking Member DeGette, and Members of the Subcommittee. I am Dr. Anne Schuchat, Director of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention (CDC). Influenza continues to be a significant public health burden and has proven, time and again, to be a worthy adversary to our best science; especially in a season where a change in the virus has presented unusual challenges to our control efforts.

Influenza is a contagious respiratory illness caused by influenza viruses. Risk of hospitalization and death from influenza is greater among the elderly, children under two years, pregnant women and others with chronic medical conditions. Each year between five percent and 20 percent of Americans are sickened by the virus, hundreds of thousands of hospitalizations occur and direct medical costs for hospitalizations and outpatient visits from complications of influenza exceed $10 billion.[1] The influenza virus is continually changing, necessitating new formulations of vaccine to be prepared and produced each year, thus requiring people receive annual vaccination in order to be protected.

Predicting influenza season requires constant public health and clinical vigilance to get the best information as rapidly and accurately as possible. Continual laboratory-based surveillance is needed to identify newly circulating viruses. The predominant circulating flu virus this year is the H3N2 subtype of Influenza A. H3N2 viruses, tend to cause more severe illness, particularly among the elderly. Influenza vaccination is, by far, the best available tool to prevent influenza. Since 2010, in the United States annual influenza vaccine has been recommended for everyone six months of age and over.

[1] Molinari et al. 2007, http://www.ncbi.nlm.nih.gov/pubmed/17544181

My colleagues and I represent the Agencies that comprise the collaborative partnerships that are essential for responding to both seasonal and pandemic influenza. The National Institutes of Health (NIH) supports research on influenza to inform the design of new and improved influenza vaccines, diagnostic tools, and antiviral drugs applicable to both seasonal and pandemic influenza strains. The Food and Drug Administration (FDA) is responsible for regulating influenza vaccines, and in this role, brings together public health and influenza disease experts to recommend which influenza virus strains should be included in FDA-licensed vaccines. The Biomedical Advanced Research Development Authority (BARDA) is mandated to support advanced research and development and procurement of novel and innovative medical counter measures such as vaccines, therapeutics, antiviral and antimicrobial drugs, diagnostics, and medical devices to address the medical consequences of man-made and emerging infectious diseases such as pandemic influenza and Ebola for the Nation.

At CDC we have spent decades building the surveillance and diagnostic capacity to monitor seasonal flu and rapidly detect novel influenza strains. Our systems are used to provide the scientific basis for vaccine virus selection – both for each season's flu vaccine as well as for pandemic vaccine stockpiling. We diligently monitor for genetic changes in the flu virus, and identify how those genetic changes affect disease transmission and severity. Our team builds public awareness and provider knowledge about the importance of vaccination, other prevention measures, and early treatment for influenza infection. These critical communication tools and partner networks are put to the test each influenza season, and are also crucial in the event of pandemic emergency. We work with public health and governmental partners at a global, Federal, state, and local level to respond to annual influenza epidemics as well as emerging novel and pandemic influenza threats. Just a decade ago, in October 2004, problems at one of the two manufacturers producing the great majority of flu vaccine for the United States resulted in a sudden loss of half of the Nation's expected supply of seasonal vaccine. This experience exposed the

Nation's vulnerability in preparedness for seasonal influenza and a possible pandemic, and exposed communication and programmatic challenges related to vaccine distribution. Since then, collaborative efforts across the Federal Government and the private sector, have led to improved influenza vaccine technologies that have either expanded vaccine supply or improved vaccine effectiveness, and in some cases, accomplished both of these goals. Today seven different companies produce flu vaccine for the U.S. market, offering newer formulations such as live attenuated influenza vaccines, thimerosal preservative-free, high dose inactivated, intradermal, cell-based, recombinant, and quadrivalent products. A network of improved domestic and international surveillance and monitoring systems provides timely vaccine virus updates and vaccine coverage and effectiveness estimates; more treatment options exist than before; and progress is being made towards the development of a longer-lasting and more broadly protective universal flu vaccine.

CURRENT SEASON

Influenza activity often increases in October and can extend as late as May. While flu seasons are unpredictable in terms of their timing, peak, duration, and severity, they have lasted an average of 13 weeks each year of the past decade.

The current influenza season began the week of November 23, 2014, and flu quickly became widespread across most of the country. To date, this season has been severe, with hospitalizations among the elderly exceeding that observed in the past five years through this point in the season, and the vast majority of illness caused by influenza A H3N2. These patterns are characteristic of a flu season where the dominant circulating strain is H3N2.

STRAIN SELECTION

The flu viruses selected for inclusion in seasonal flu vaccines are updated each year based on data collected by 142 national influenza centers in 112 countries, conducting influenza surveillance. These laboratories send influenza viruses to one of the five World Health Organization (WHO) International Collaborating Centers for influenza; CDC's Influenza Division is one of these WHO collaborating centers. These data show us which influenza viruses are circulating, how they are spreading, and detect whether circulating viruses are drifted away from vaccine strains. They also help us generate surveillance-based forecasts about which viruses are most likely to cause illness during the coming season.

Twice each year, CDC and other global public health partners participating in the WHO network review data on thousands of influenza viruses to select four representative candidate vaccine viruses (1 influenza A H3N2 virus, 1 influenza A H1N1 virus, 1 influenza B Yamagata lineage virus, and 1 influenza B Victoria lineage virus). For the Northern Hemisphere, these viruses are selected in late February of each year. For the Southern Hemisphere, these viruses are selected in September. These decisions are made many months before the influenza season starts to provide time for vaccine manufacturers to prepare and harvest vaccine viruses and produce vaccines that can be released for use.

WHO recommends specific vaccine viruses for inclusion in influenza vaccines based on all of the surveillance information; however, each individual country must decide which vaccine candidate viruses should be included in influenza vaccines licensed in their country. . In the United States, the U.S. Food and Drug Administration (FDA) determines which vaccine viruses will be used in U.S.-licensed vaccines for the upcoming influenza season, taking into consideration recommendations made by the WHO and FDA's Vaccines and Related Biological Products Advisory Committee. It takes at least six months to produce large quantities of influenza vaccine. Because of these production schedules and the variable

timing and duration of influenza seasonal activity, the selection of vaccine viruses for the next season is often made in the middle of the current season. For example, the 2014-2015 season is ongoing, but decisions about the viruses to be included in the vaccine for the 2015-2016 season will be discussed at WHO later this February, followed by a meeting of the FDA's advisory committee, which makes recommendations for the FDA-licensed influenza vaccines. CDC and the WHO influenza surveillance network will continue throughout the year to collect and characterize new viruses as potential vaccine candidates.

DRIFTED VIRUSES

Antigenic drift happens when there are small changes in the genes of influenza viruses that gradually occur over time as the virus moves through the millions of people that are infected each year. These small genetic changes are inevitable and occur, in a sense, as a way for the virus to evade the protection afforded by past infection or vaccination. These genetic changes can occur at any time, and in any location around the globe. The 2014-2015 Northern Hemisphere vaccine viruses were selected in February 2014, and were based on strains that were circulating worldwide at that time. In the months following the annual virus selection, CDC's routine surveillance identified a small number of influenza H3N2 strains which had drifted and were not covered by the vaccine viruses chosen in February. The first of these drifted viruses was detected on March 8, 2014. Through the spring of 2014 (March through the end of May), drifted viruses represented only 17 percent of the hundreds of specimens collected and tested at CDC during that time.

Drift variants emerge and die out frequently. When a drifted virus first emerges, there is no way to predict if and when it will die out or circulate widely. Over the summer of 2014, the drifted H3N2

viruses were detected in greater proportions and became more common among H3N2 viruses in the United States and abroad. Forty-nine percent of the 47 H3N2 viruses collected worldwide in September 2014 and characterized by CDC were drifted from the H3N2 Northern Hemisphere influenza vaccine virus component. Based on CDC and other WHO Collaborating Center surveillance data, one representative virus of these drifted H3N2 viruses was selected in September 2014 for inclusion in the Southern Hemisphere vaccine. As of January 23, 2015, 64 percent of H3N2 viruses collected in the United States and characterized by CDC were drifted from the H3N2 vaccine virus component. Interim vaccine effectiveness estimates available at the beginning of January confirmed our concerns of reduced protection from this year's seasonal influenza vaccine. These mid-season CDC studies determined that receiving an influenza vaccine reduced a person's risk of going to the doctor for laboratory-confirmed influenza illness by about 23 percent, a level that was less than half the effectiveness of vaccines in years where the match was much better. While these mid-season estimates are preliminary, they help CDC and others tailor prevention and control messages and policies during the season, helping make the public health response more nimble and appropriate to the evolving situation.

While we sometimes see that antibodies made in response to vaccination with one flu virus can provide protection against different but related viruses, our early vaccine effectiveness estimates this season suggest that there is little cross-protection against the drifted H3N2 viruses. However, vaccinated people are still better protected than those not vaccinated—the vaccine is preventing some illness caused by H3N2, and because the flu vaccine protects against other influenza types (H1N1, B), people who got vaccinated are likely to be protected against other viruses that may circulate later in the season. For these reasons, CDC continues to recommend flu vaccination, however we have increased alerts about the importance of other approaches to mitigate the complications of the severe influenza season.

ANTIVIRAL MEDICATIONS

Antiviral drugs become even more important when circulating flu viruses vary from the vaccine viruses. Antivirals can reduce duration of illness by a day, improve patient outcomes in the hospital, and reduce spread, especially if given within 48 hours of illness onset. These are not perfect drugs and they have limitations, however they are the only drugs available for the specific treatment of influenza infection. Antiviral drugs are approved by the FDA for the treatment of uncomplicated influenza, based on data submitted during the licensure process from randomized controlled trials, which have generally targeted relatively healthy populations and outpatient illness. A large and growing body of data from various studies shows that these drugs can prevent more serious flu outcomes, such as pneumonia and hospitalizations. Among hospitalized patients, the risk of death was reduced when antiviral drugs were used. These drugs are especially important for populations at increased risk for complications from the flu, including young children, pregnant women, and the elderly.

We also know that these drugs are underused by physicians.[2] As soon as CDC determined that the vaccine might have less benefit than usual, CDC increased its communication efforts around the appropriate use of influenza antiviral drugs, by issuing health alerts and media updates, convening clinician networks, and disseminating messages and guidance through public health, clinician organization, and community-based partners. Antiviral drug manufacturers have stated they have sufficient product on hand to meet the projected high demand during the 2014-2015 influenza season.

PREPARING FOR THE NEXT PANDEMIC

Investments in strengthening control of seasonal influenza contribute to pandemic preparedness. The systems we have in place for seasonal influenza are a part of the same systems we use to prepare for and respond to an influenza pandemic. For example, CDC's robust surveillance network identified the

[2] http://www.cdc.gov/flu/news/influenza-prescribing-study.htm: http://cid.oxfordjournals.org/content/early/2014/07/09/cid.ciu422.abstract

emergence of the drifted H3N2 seasonal virus, but also aids in detection of novel, avian, and swine-origin influenza viruses causing disease in humans. CDC's increased surveillance has led to a greater number of viral specimens received, viruses of concern identified, and candidate viruses created for seasonal and pandemic vaccine manufacturing. Our systems allow us to detect new viruses; assess virus' transmissibility; provide information to enable vaccine production; promote treatment with antiviral drugs; and communicate with the public and medical community.

Improvements to our seasonal influenza response also serve to strengthen the effectiveness of our pandemic response. Pandemic influenza is a formidable security threat due to the potential for substantial excess illness and death as well as multisector disruption. Pandemics can emerge anywhere, and early detection of novel influenza is critical to an effective response. Robust networks of global partners are critical in helping to protect the Nation. CDC has 57 bilateral cooperative agreements with partner nations to enhance their capacity to detect and respond to influenza. Of note, this capacity-building effort is also benefiting other respiratory pathogen detection and prevention work. CDC provides technical assistance to help these countries collect data. These data provide an evidence base to adopt robust influenza vaccination policy and recommendations. We have seen an impact from supporting our global partners as evidenced by the increasing number of vaccine virus candidates from these countries, as well as the detection and response to avian influenza cases.

The wide distribution of CDC's diagnostic test kits to hundreds of partner laboratories around the globe helps to monitor seasonal influenza and provide vaccine viruses for use in annual vaccines. This capability also can detect novel avian and swine influenza viruses which occasionally cause illness in humans. CDC has designed its diagnostic tests to detect both seasonal and novel infections, leading to first detections of the newly emerging pandemic H1N1 in 2009, and more recent infections with swine

influenza viruses occurring in fair-goers in the U.S. Because of the ability to detect novel influenza virus infections, CDC is prepared to test for any possible human infection with the recently identified avian H5N8 and H5N2 influenza viruses that have been detected for the first time in the U.S. in the Pacific Northwest.

Progress over the Past Decade

Substantial improvements have occurred during this past decade. In 2005, in response to the emerging, highly pathogenic H5N1 influenza in Asia, the National Strategy for Pandemic Influenza was released; and one year later, the Pandemic and All-Hazards Preparedness Act (PAHPA) was signed into law. These set the standard for the US Government response to influenza preparedness and response. Response to the 2009 H1N1 influenza pandemic further strengthened the nation's capacity to detect and respond to influenza threats.

In 2004, CDC fully sequenced 241 virus specimens compared to 1,832 in 2014. In 2005, there were no FDA-approved PCR (**polymerase chain reaction)** kits to test for influenza; today, CDC has submitted and received FDA-approval for 11 different influenza diagnostic PCR test applications. State and local public health labs are capable of detecting novel influenza strains including H5 and H7N9 strains. As a result of the 2004 flu vaccine shortage, approximately 58 million doses of vaccines were available in the U.S. market that season; to date, more than 147 million doses of vaccine have been distributed in the United States this flu season. Over the past few years, through the combined efforts of USG agencies working closely with manufacturers, we now have 14 influenza vaccines produced by seven manufacturers. This is an increase from five seasonal influenza vaccines that were available in the US market in 2006.

In 2005, 19 percent of Americans were vaccinated against influenza; last season, the coverage rate was up to 46 percent. In the 2005-2006 flu season, we averted 1,300,309 cases of influenza through vaccination; last year's season saw 6,787,615 cases of flu averted.[3,4] Finally, CDC has expanded the number of countries supported through international cooperative agreements to build influenza surveillance capacity from nine in 2004, to 57 today.

The Future Fight Against Influenza

Rapid laboratory identification of influenza, such as advanced molecular detection (AMD) using next-generation molecular sequencing to reveal a virus' complete genetic information, make it easier to identify changes in an influenza virus' genome. This has improved the speed of our detection and response to new variants of influenza. Using AMD methods to obtain complete genetic data without growing cultures in the lab has reduced the time needed to detect emerging threats and reduce response times. These methods are being applied to enhance virus genetic data that informs influenza vaccine virus selection, vaccine development, risk assessment, and investigation of the source of the disease.

CDC participates in the Biomedical Advance Research and Development Authority (BARDA)-led initiatives to improve manufacturing of current vaccines and support development of better influenza vaccines. Part of this effort is the development of a "universal vaccine" that would offer better, broader, and longer-lasting protection against seasonal and novel influenza viruses. A number of government agencies and private companies have begun work to advance development of universal flu vaccines.

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[3] Kostova D, Reed C, Finelli L, Cheng PY, Gargiullo PM, Shay DK, Singleton JA, Meltzer MI, Lu PJ, Bresee JS. Influenza Illness and Hospitalizations Averted by Influenza Vaccination in the United States, 2005-2011. PLoS One. 2013 Jun 19;8(6):e66312. Print 2013. PubMed PMID: 23840439; PubMed Central PMCID: PMC3686813.

[4] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6349a2.htm

In support of U.S. universal influenza vaccine efforts, CDC used cutting edge genomic technologies to develop two candidate vaccine viruses for use in universal influenza vaccine human clinical trials sponsored by the National Institutes of Health (NIH). In July 2014, CDC sent these vaccine viruses to an Australian vaccine manufacturer contracted by BARDA to produce the clinical lots for vaccine trials. Phase 1 clinical trials to be conducted by NIH are scheduled to start in 2016.

CONCLUSION

Influenza viruses present us with unique challenges. Unlike other vaccine preventable diseases, influenza is constantly changing. The investments made by the U.S. government for the diagnosis, prevention, and control of influenza have led to increased domestic and global viral surveillance, an increase in knowledge about how the flu virus works, more choices of vaccine types, increases in the number of cases averted due to vaccination, and expanded recommendations of influenza vaccination to all age groups (above the age of six months) and increased use of influenza vaccine among children and pregnant women.

Although many gains in seasonal and pandemic influenza preparedness and control have been made over the years, continued improvements are needed. We will work, along with our government, academic, and industry partners, to improve use of antiviral treatment, to make more effective influenza vaccines, and to speed production of existing vaccines for all Americans.

As we work together toward the goal of universal influenza vaccines, CDC will continue to work 24/7 to identify ways to improve methods of diagnosis, prevention, and control of influenza and respond to influenza threats here and around the world.