Meeting of the Board of Scientific Counselors, Office of Infectious Diseases
Centers for Disease Control and Prevention
Tom Harkin Global Communications Center
Atlanta, Georgia

May 8, 2013

A one-day, open public meeting of the Board of Scientific Counselors (BSC), Office of Infectious Diseases (OID), was held on May 8, 2013, at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. In addition to Board members and CDC staff, the meeting was attended by representatives of several public health partner organizations (Appendix).

The meeting began with a report from the Influenza Coordination Unit on the emergence of avian influenza A (H7N9) in China, which was followed by updates from the National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), the National Center for Immunization and Respiratory Diseases (NCIRD), and the Center for Global Health (CGH). Next, presentations were made on two issues on which BSC guidance was requested: (1) monitoring the health impact of the national human papillomavirus (HPV) vaccination program and (2) modernizing public health laboratory and bioinformatics capacity for improving infectious disease outbreak detection and response.

Following these presentations and related discussions, the BSC members voted to establish a BSC working group to provide guidance on the use of advanced molecular diagnostics and bioinformatics technologies to improve public health. The meeting also included reports from the BSC Food Safety Modernization Act (FSMA) Surveillance Working Group and the BSC Antimicrobial Resistance Working Group.

OPENING REMARKS

BSC Chair Ruth Berkelman, Rollins Professor, Emory University, called the meeting to order and was joined in welcoming participants and facilitating introductions by Rima Khabbaz, CDC Deputy Director for Infectious Diseases, and Robin Moseley, the BSC/OID Designated Federal Officer.

DECEMBER 2012 BSC MEETING FOLLOW-UP

Dr. Khabbaz reported on several actions taken following the December 2012 BSC meeting:

- A BSC letter regarding the proposed U.S. Preventive Services Task Force (USPSTF) recommendations on hepatitis C testing was submitted to HHS Secretary Kathleen Sebelius in January. USPSTF is currently reviewing public comments, including comments from HHS and CDC, and will issue a final recommendation later this year. [Update: USPSTF published revised recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspshepc.htm) on June 24.]

- A BSC teleconference was held on April 18 that included updates on the Advanced Molecular Detection and Response to Infectious Disease Outbreaks (AMD) initiative and the emergence of avian influenza A (H7N9) in China, as well as consideration of a proposal to establish a BSC working group to provide guidance to CDC in expanding the application of advanced molecular tools and bioinformatics technologies to improve public health.

Dr. Berkelman noted that it is necessary to re-do the vote taken on April 18 regarding establishing this working group, since technical difficulties prevented the votes of some BSC members from being heard by all teleconference participants. (The new vote was taken at the end of the discussion on CDC's work on advanced molecular diagnostics and bioinformatics technologies; see page 23.)

CDC UPDATES

- **ICU Update: Avian Influenza A(H7N9) in China**

Sonja Rasmussen, ICU Deputy Director, reported that, as of May 7, human cases of avian influenza A (H7N9) have been reported in eight contiguous provinces in southeastern China, two municipalities (Beijing and Shanghai), and Taiwan; 132 cases were laboratory-confirmed by the Chinese Center for Disease Control (China-CDC) or by provincial centers for disease control. Of the 132 patients, 126 were hospitalized (95%), 42 were discharged from the hospital, and 31 (23%) died. Most cases were sporadic, with no evidence of sustained human-to-human transmission.

The first case was reported in mid-February, with most cases occurring in March and April, with few thus far in May. The closure of live bird markets in several affected provinces may have been an effective disease control measure. Another possibility is that the decreased number of cases is part of the seasonal drop-off in influenza cases that typically occurs at the beginning of summer.

Epidemiologic investigation. The source of the human infections is presumed to be exposure to infected birds, possibly at live bird markets. Seventy-seven percent of patients reported exposure to animals (76% chickens and 20% ducks). The median age of the patients was 61 years, with 21% of cases occurring in people older than 74. Very few cases occurred among children, and those that did were mild. Seventy-one percent of patients were male, and 76% had at least one underlying health condition. Most patients had severe respiratory illness, involving pneumonia that progressed to acute respiratory distress syndrome.

Laboratory investigation. CDC-China has posted 19 partial or complete genome sequences of H7N9 virus isolates online. Twelve are from human isolates, 5 from birds, and 2 from environmental specimens. All eight genes are of avian origin and are closest phylogenetically to three Eurasian influenza virus lineages from birds. The viral sequences include genetic determinants associated with enhanced virus binding to (and replication in) mammalian respiratory cells, as well as with increased severity of infection.

CDC received H7N9 virus isolate A/Anhui/1/2013 from CDC-China on April 11, as well as a second isolate (A/Shanghai/1/2013) more recently. These viruses exhibit robust replication in eggs, in cell culture, and in the respiratory tracts of laboratory animals. The A/Anhui/1/2013 virus is susceptible to oseltamivir and zanamivir; the drug susceptibilities of the A/Shanghai/1/2013 virus have not yet been determined.

Animal investigation. The H7N9 virus is considered a low-pathogenic avian influenza virus because (unlike H5N1) it does not cause disease in chickens. As of April 26, reports from the Chinese Ministry of Agriculture indicate that only 46 (0.07%) of >68,000 bird and environmental specimens were positive for H7N9, using culture-dependent tests. It is unclear whether the low percentage is accurate or the result of a problem with the testing methods. In any case, the H7N9 virus has been found in chickens, ducks, pigeons (feral and captive), and environmental specimens; swine samples have been negative.

CDC response. CDC activated its Emergency Operations Center on April 8 to Level 2 and is continuing to coordinate its response with other federal agencies and to provide domestic and international partners with information as the situation evolves. Response actions include

- Sending a CDC team to China in early May to assist Chinese health authorities and WHO in investigating and monitoring the evolving situation
- Issuing guidance (April 5) to U.S. clinicians and public health departments on which persons should be tested for H7N9 virus. As of May 6, 52 patients from 21 states have been tested; all tests results were negative
- Characterizing the H7N9 virus in terms of antiviral susceptibility, transmissibility, and pathogenicity
- Developing and distributing a laboratory diagnostic test for H7N9 to national and international partners, beginning on April 24
- Posting a CDC travel notice (April 5) to help travelers and Americans living in China protect themselves from exposure to H7N9 virus (e.g., by staying away from live bird markets)
- Developing informational and training materials for Customs and Border Protection Officers about identifying and notifying CDC about ill international travelers

CDC is also working with the Strategic National Stockpile to ensure the availability and effectiveness of medical countermeasures (antiviral medications, respirators, and ventilators) that might be needed if the H7N9 virus were introduced into the United States. Other preparedness activities include

- Developing and distributing H7N9 treatment guidelines (April 18), as well as interim guidance for infection control within healthcare settings (April 11)
- Holding conference calls with public health officials and clinicians to help states and localities prepare for the response to a potential future influenza pandemic

Vaccine development. On May 1, CDC announced the availability of a potential H7N9 candidate vaccine virus developed in partnership with WHO and BARDA. The candidate vaccine virus, which was created using reverse genetics, is available to qualified laboratories and manufacturers to expedite vaccine development. (Qualified laboratories must have BSL-3 and BSL-3-enhanced facilities.) NIH is preparing to conduct vaccine trials.

In summary, Dr. Rasmussen stated the following:

- Although H7N9 causes severe disease in humans, there is no evidence of sustained human-to-human transmission.
- Good progress has been made on diagnostics and vaccine development, but a vaccine will not be available for several months.
- CDC and partners are planning for other interventions, including non-pharmaceutical interventions.
- Many questions remain about how the virus is transmitted, about its animal reservoir, about risk factors for human disease, and about the scope of the outbreak.

Discussion

North American collaboration. In accordance with the *North American Plan for Animal and Pandemic Influenza* (www.phe.gov/napapi), Canada and Mexico are working with the United States to ensure public health preparedness to detect and control H7N9 if it should enter North America.

Treatment. In response to a question about treatment of the 132 confirmed cases in China, Dr. Rasmussen said that, according to an article in the *New England Journal of Medicine* (published online April 24, 2013; http://www.nejm.org/doi/full/10.1056/NEJMoa1304617), two-thirds were treated with oseltamivir or zanamivir. However, it is not clear whether treatment occurred early enough for the medication to be effective.

Diagnostics. In response to questions about using PCR-based tests or rapid antigen tests to detect H7N9 infection (e.g., in travelers), Dr. Rasmussen noted that

- The H7N9 diagnostic kits distributed to partners by CDC are PCR-based kits
- CDC has posted H7N9 primer sequences on the Internet that can be used by public and private laboratories to develop PCR tests (http://www.cdc.gov/flu/avianflu/h7n9-detecting-diagnostics.htm)

Surveillance for cases of mild disease. In response to a question about whether mild cases of H7N9 infection are going undetected, Dr. Rasmussen said that this possibility has not been ruled out. However, enhanced disease surveillance in affected Chinese provinces has not detected mild cases of disease. Dr. Rasmussen noted that CDC faced similar uncertainties during the early stages of the H1N1 pandemic in Mexico.

Migratory fowl as disease carriers. In response to a question about the role of migratory water fowl in spreading disease (a suggestion mentioned in the Chinese press), Dr. Rasmussen said that she is unaware of any data on this topic. An assessment of whether migratory fowl are likely to spread H7N9 virus to the United States concluded that the likelihood is low.

Social media. In response to a question about communications and surveillance efforts involving social media, Dr. Rasmussen noted that CDC is monitoring public interest in H7N9 by conducting a social media scan and tracking hits on the CDC website. Thus far, the social media scan indicates low interest in H7N9.

Vaccine development. BSC ex officio member Bruce Gellin (HHS/National Vaccine Program Office) reported that it will take at least a few months before an H7N9 vaccine can be made available in the United States using the candidate vaccine virus developed by CDC. Due to excess manufacturing capacity, this vaccine could be manufactured (at least in limited amounts) without affecting the regular supply of seasonal influenza vaccine. It is as yet unclear whether two doses will be needed for protection.

The interagency machinery to support vaccine development (including clinical trials) as part of a robust response is already in place, with interagency calls made on a weekly or biweekly basis to discuss epidemiology, vaccine development, communications, and all other relevant topics. Dr. Gellin said that he will keep the BSC informed of progress in this area.

Transmissibility. In response to a question about whether CDC is conducting gain-of-function experiments to assess potential transmissibility of H7N9 viruses, Dr. Rasmussen said that CDC has not begun such experiments.

➢ NCEZID Update

Beth Bell, NCEZID Director, provided the following updates:

- **Multistate outbreak of fungal infections linked to contaminated steroid injections.**[1] As of May 6 the outbreak has included 741 cases with 55 deaths in 20 states. Of the 741 cases, 234 patients presented with meningitis only; 319 with paraspinal or spinal infection only; 146 with both meningitis and paraspinal or spinal infection; 33 with peripheral joint infection only; 2 with paraspinal or spinal infection and peripheral joint infection; and 7 with stroke. Outbreak cases continue to be identified, with about 10 new cases reported every few weeks.

  In collaboration with Peter Pappas at the University of Alabama at Birmingham, CDC is planning a long-term follow-up study to assess clinical features and answer questions about clinical management of *Exserohilum rostratum* infection (e.g., determining the optimal duration of treatment to avoid relapses of fungal meningitis and other symptoms). Currently, CDC's interim clinical guidance recommends 3–6 months of antifungal therapy for parameningeal infections, with longer treatment for severe disease. However, it was recently reported that an outbreak patient suffered a relapse of meningitis about 18 weeks after his course of antifungal therapy ended.

- **Foodborne illness attribution report.** CDC issued its first-ever set of estimates for food source attribution of foodborne illness in March 2013 (http://wwwnc.cdc.gov/eid/article/19/3/11-1866_article.htm). The estimates build on 2011 estimates of foodborne illness in the US (~48 million people / year), and include data from >1200 foods implicated in outbreak investigations, divided into 17 food categories, or "commodities." Among the key findings,
  - Produce was the dominant source (46%) for illnesses, driven by norovirus and by leafy vegetables
  - Poultry and meat together were the dominant source (29%) for deaths

  These findings will help industry partners and regulatory agencies target prevention efforts to help keep food safe. Additional work on food-source attribution is conducted by Interagency Food Safety Analytics Consortium, which includes USDA/Food Safety and Inspection Service (FSIS), FDA, and CDC (*see also* BSC minutes for December 2012).

- **Healthcare-associated infections (HAI): SIR report.** The National and State HAI Standardized Infection Ratio (SIR) Report analyzes national and state-level HAI data to help identify gaps in HAI prevention. The SIR report for 2011 (http://www.cdc.gov/hai/national-annual-sir/) documented a
  - 41% reduction in central line-associated bloodstream infections (CLABSIs)
  - 17% reduction in surgical site infections (SSIs)
  - 7% reduction in catheter-associated urinary tract infections (CAUTIs)

  CDC is working with state health departments to target prevention efforts to healthcare facilities that have seen little progress in reducing CAUTIs or other HAIs, as documented by National Healthcare Safety Network (NHSN) reporting.

[1] A detailed account of the outbreak response is provided in the December 2012 BSC minutes.

- **Healthcare-associated infections: CRE.** CDC has issued a national call to action to stop carbapenem-resistant Enterobacteriaceae (CRE), whose incidence is increasing. In 2012, about 4% of U.S. hospitals reported at least one patient with a CRE infection, as described in the March 2013 issue of CDC Vital Signs (http://www.cdc.gov/vitalsigns/hai/cre/). To advance this effort, CDC has created a CRE toolkit (http://www.cdc.gov/hai/organisms/cre/cre-toolkit/) based on CDC prevention guidelines that have been used to reduce CRE rates in healthcare facilities in Colorado and Florida.

- ***CDC Health Information for International Travel* (The 2014 Yellow Book).** CDC's new Travelers' Health website will launch mid-May 2013, and the new Yellow Book will be released at the International Society of Travel Medicine meeting on May 19–23, 2013. New Yellow Book features include malaria risk maps for 10 destinations and country-by-country vaccine and malaria recommendations. The first mobile app version of the Yellow Book is scheduled for release in summer 2013. [http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014]

- **Mosquito-borne diseases**
  - ***Dengue outbreak in Puerto Rico.*** The 2013 case counts for dengue in Puerto Rico exceeded the epidemic threshold on April 26, with more than 4750 suspected cases, of which 2317 (49%) are laboratory confirmed. Thirteen cases involved dengue hemorrhagic fever, but fortunately none have been fatal. CDC recently assisted in investigations of outbreaks in the Virgin Islands, Kenya, Angola, and the Solomon Islands.
  - ***West Nile guidelines.*** CDC plans to release updated U.S. guidelines for West Nile virus surveillance, prevention, and control on June 7, 2013.

- **Tickborne diseases**
  - ***Heartland virus*.** Field and laboratory investigations are underway to elucidate the epidemiology of the Heartland phlebovirus (e.g., identify patients with acute disease, find any new locations, and conduct a human serosurvey) and identify the vertebrate host.
  - ***Rocky Mountain spotted fever (RMSF)*.** The RMSF Rodeo pilot project on Arizona tribal lands is testing a comprehensive public health intervention that combines tick control activities with community-based education. The plan is to expand the intervention reservation-wide in summer 2013.

NCEZID budget. Dr. Bell also reported on the NCEZID budget request for FY2014, which includes $432.414 million for emerging and zoonotic infectious diseases, which represents an increase of $70.271 million above the FY2012 level. The proposed increases include (1) $16.605 million for Food Safety (including support for FoodCORE and for Integrated Food Safety Centers of Excellence in five states); (2) $12.491 million for NHSN (including support for providing HAI data to the Centers for Medicare & Medicaid Services [CMS], implementing the NHSN Antimicrobial Resistance (AR) module, and addressing CRE); and (3) $40 million for the AMD initiative. The FY2014 budget also includes a request to maintain FY2012 funds from the Prevention and Public Health Fund (PPHF) of the Affordable Care Act (ACA). The PPHF funds would include $40 million for programs that build state-level infectious disease public health capacity and $11.75 million for state-level HAI reduction efforts.

Discussion

In response to a question about whether increases in dengue and the West Nile virus can be correlated with temperature trends, Dr. Bell said that some modeling work was conducted last year on the effects of climate change on the incidence of West Nile disease. However, in general, we lack sufficiently robust surveillance data to understand the bigger picture. ArboNET, which tracks West Nile virus in mosquitoes and bird as well humans, has been adversely affected by budget cuts. Given this reduced funding, CDC has prioritized ArboNET funding for certain states, while other states have needed to curtail some activities due to budget shortfalls.

In response to a question about regulation of compounding pharmacies, Dr. Bell noted that a Senate bill has been introduced to improve quality assurance and clarify relevant FDA authorities. A hearing on the bill will be held on May 9. Bob Sautter, Director of Microbiology, Carolinas Pathology Group, noted that some compounding pharmacies have asked hospital administrators to conduct quality assessment (QA) testing of their products. This is difficult because hospital laboratories normally work with clinical samples only and do not have established QA protocols for testing medical products. He asked if CDC could provide assistance in this area and also suggested that the American Society for Microbiology might develop such protocols. While this may more likely be an issue for FDA rather than CDC, FDA does not currently have this type of regulatory authority. Jesse Goodman, FDA Chief Scientist and Deputy Commissioner for Science and Public Health, said that existing QA protocols for sterile drug products may suffice. He agreed that FDA needs further clarification of its authority to regulate compounding pharmacies.

- **NCHHSTP Update**

Dr. Khabbaz has served as Acting Director of NCHHSTP since January. A new NCHHSTP director may be arriving by the end of summer. Dr. Khabbaz also mentioned that Howell Wechsler, Director of the Division of Adolescent and School Health (DASH), NCHHSTP, is retiring from CDC and joining the Alliance for a Healthier Generation in New York. John Moore will be serving as Acting Director of DASH.

Selected NCHHSTP program updates include

- **STDs**
  - ***Social media and web-based communications.*** CDC's Twitter account @CDCSTD reached 15,000 followers in March, and the Division of STD Prevention (DSTDP) homepage was CDC's most popular website, visited 28 million times in 2012. In addition, the topic of the February CDC Public Health Grand Rounds was *Reducing the Burden of HPV-Associated Cancer and Disease through Vaccination in the U.S.* (http://www.cdc.gov/about/grand-rounds/archives/2013/february2013.htm).
  - ***STD incidence and costs.*** According to CDC's national STD estimates (updated in March 2013), 20 million new infections occur in the United States each year,[2] costing the U.S. healthcare system nearly $16 billion.[3]

[2] Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. Sex Transm Dis 2013;40(3):187–93.
[3] Owusu-Edusei K Jr, Chesson HW, Gift TL, et al. The estimated direct medical cost of selected sexually transmitted infections in the United States, 2008. Sex Transm Dis 2013;40(3):197–201.

- ***Drug-resistant gonorrhea.*** As discussed by DSTDP Director Gail Bolan at the December 2012 BSC meeting, CDC is continuing to monitor drug-resistant gonorrhea through the Gonococcal Isolate Surveillance Project (GISP; http://www.cdc.gov/std/gisp/) and to collaborate with WHO to improve detection and communication about drug-resistant gonorrhea on a global basis.
- ***Collaborative projects.*** DSTDP is currently working with
  - CDC's Office of Antimicrobial Resistance (CDC/OAR) on a CDC-wide report on AR issues
  - CDC/OAR and FDA to support inclusion of *Neisseria gonorrhoeae* on the list of pathogens that require urgent attention under the 2011 Generating Antibiotic Incentives Now (GAIN) Act (*see also* report from the AR Working Group, page 28)
  - NIH/NIAID on a clinical trial of two antimicrobial combination treatments for gonorrhea
  - The Harvard School of Public Health on whole-genome sequencing of isolates collected by GISP

- **HIV/AIDS**
  - ***Public health campaigns.*** NCHHSTP has expanded the HIV awareness and anti-stigma campaign *Let's Stop HIV Together* and launched a Spanish-language version. The campaign now includes new participants, more materials in both Spanish and English, and HIV awareness and testing information in Spanish through a new website.
  - ***Research findings.*** At the 2013 Conference on Retroviruses and Opportunistic Infections held in Atlanta March 3–6, the following data were presented by NCHHSTP staff:
    - A significantly greater share of HIV-positive men who have sex with men (in 20 cities) were aware of their infections in 2011 (66 percent), compared with 2008 (56 percent).
    - Health insurance coverage correlates with rates of viral suppression among patients receiving HIV care.
  - ***Matching prevention funds to the epidemic.*** NCHHSTP is pursuing a high-impact approach to preventing HIV infections that targets proven, cost-effective, and scalable interventions to high-risk groups. These efforts are supported by $359 million in health department prevention funding provided to 68 health departments, with allocations based on HIV prevalence. The goal is to use individual and community-level data to improve diagnosis, linkage to care, retention in care, and provision of antiretroviral therapy. CDC's efforts to measure and drive improvements in quality of care are helping to advance the CDC priority of ensuring increased collaboration between the public health and healthcare communities to improve U.S. health.

- **Tuberculosis**
  - ***Outbreak investigations.*** Although the number of TB cases in the United States is very low, outbreaks continue to pose challenges.[4] CDC is currently assisting Dallas and Los Angeles with outbreak investigations and is using whole-genome sequencing to identify TB transmission pathways of TB isolates obtained during a hospital outbreak in Duval County, Florida.
  - ***TB drug shortages.*** CDC is working with FDA and pharmaceutical manufacturers to address shortages of isoniazid and other TB drugs and introduce bedaquiline, a newly approved drug that can be used to treat multidrug-resistant (MDR) TB in the United States.

[4] CDC. Trends in tuberculosis—United States, 2012. MMWR 2013;62:201–5.

- **Division of Adolescent and School Health activities**
  - ***CDC Vital Signs*.** The November 2012 CDC Vital Signs on youth and HIV (http://www.cdc.gov/vitalsigns/HIVAmongYouth/index.html) noted that
    - Young people ages 13–24 accounted for one quarter of new HIV infections in 2010, with about 1000 young people becoming infected every month. Most of these young people do not know that they are infected
    - Young men who have sex with men were more likely to engage in HIV-related risk behaviors than other males and females, and too few of them have been tested for HIV
  - ***National Youth HIV & AIDS Awareness Day.*** The first National Youth HIV & AIDS Awareness Day was held on April 10, 2013, and Dr. Wechsler participated in a Capitol Hill Event.

- **Viral hepatitis.** Examples of recent CDC activities include the following:
  - Hepatitis testing and referral to care activities have begun in all 35 sites supported through the PPHF.
  - With support from the Viral Hepatitis Action Coalition, CDC has begun a series of meetings to engage stakeholders in helping to implement CDC's birth cohort hepatitis C testing recommendations (http://www.cdc.gov/features/hepatitisctesting/).
  - In partnership with the National Institute on Drug Abuse, CDC has organized a conference to determine the best way to respond to the recent increase in HCV infections among injection drug users generally and young persons (<30).
  - The May 2013 CDC Vital Signs (http://www.cdc.gov/vitalsigns/hepatitisc/) focuses on hepatitis C testing, and May 19 has been designated as Hepatitis Testing Day.

- **Other NCHHSTP updates**
  - The new Internet-based Atlas tool has increased the public's access to NCHHSTP data on HIV/AIDS, viral hepatitis, STDs, and TB (http://www.cdc.gov/nchhstp/atlas/).
  - NCHHSTP is developing a Prevention Through Health Care website to help public health departments take advantage of key provisions in the Affordable Care Act.
  - The recently released *Public Health Reports* supplement entitled *Understanding Sexual Health* (http://www.publichealthreports.org/issuecontents.cfm?Volume=128&Issue=7) contains multiple articles by CDC authors.

NCHHSTP budget. Dr. Khabbaz noted the following**:**

- Due to sequestration, each of NCHHSTP budget lines has decreased by 5%.
- The total request for FY2014 is $1.177 billion, which (if provided in full) would be a net increase of $14 million over FY2012. The increase would support HIV surveillance activities and an evaluation of school-based health prevention efforts.
- The proposed funding for STDs, TB, and viral hepatitis would be roughly level with that for FY2012. However, the funding for viral hepatitis provided in FY2012 as part of the PPHF would be moved to the base budget.

Discussion

Actions suggested by individual BSC members for CDC included the following:

- Measure the health impact of increased health coverage by comparing infectious disease rates in states that expand Medicaid coverage (in accordance with ACA provisions) with rates in states that do not expand it.

- Track and investigate late diagnoses of HIV or STDs, as part of helping healthcare partners assessing quality assurance.
- Promote the establishment of school-based healthcare programs as an effective way to reach adolescents with HIV or STDs.
- Assess how well states target disease prevention resources to communities with greatest need.
- Improve health literacy about HIV, STD, and viral hepatitis issues.
- Provide feedback to the Board on areas where sequestration cuts have a major health impact.

➢ **NCIRD Update**

Dave Swerdlow, NCIRD Acting Deputy Director, provided the following updates:

- **2012–13 influenza season.** The end of this year's flu season was overshadowed by news about human cases of avian influenza H7N9 in China (*see also* ICU update, page 2).

  Dr. Swerdlow noted that the intensity of influenza activity in the two seasons following the 2009–10 H1N1 pandemic was low. However, the 2012–13 influenza season started 4 weeks earlier than usual and involved high rates of hospitalization, an increase in deaths attributed to pneumonia and influenza in seniors, and an increase in pediatric deaths. Most influenza isolates were either H3N2 or B, with few cases of H1N1; H3N2 seasons tend to be more severe. Although about half of the population was vaccinated this year, vaccine effectiveness estimates were low for people over 65 years of age.

- **New coronavirus in the Middle East.** A novel human coronavirus causing severe disease in humans was identified in the Middle East in 2012. A formal name has not been adopted as yet; the new virus has variously been called novel coronavirus (nCoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). [Note: MERS-CoV is now the designated name of the virus.]

  Human coronaviruses, which were first isolated in the 1960s, include four that cause mild disease (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1). In 2003, a human coronavirus that causes severe disease (SARS-CoV) was identified as the causative agent of the global outbreak of severe acute respiratory syndrome.

  As of the first week of May, the outbreak includes 30 laboratory-confirmed cases, 18 of them fatal, with onsets between April 2012 and May 1, 2013. Twenty-three cases involved males; the median age of the 30 cases was 53. Twenty-two cases were reported in Saudi Arabia, 3 in the United Kingdom, 2 in Jordan, 2 in Qatar, and 1 in the United Arab Emirates. Of the 30 cases, 23 were associated with five clusters, including a hospital cluster of two cases in Jordan (retrospectively identified among healthcare workers) and a family cluster of three cases in the United Kingdom that occurred when a traveler returned to the United Kingdom after visiting Saudi Arabia and Pakistan. Saudi Arabia reported three clusters: a family cluster of 3 cases; a close-contact cluster of 2 cases; and a hospital cluster currently under investigation that so far includes 13 cases. These clusters suggest that the new virus may spread from person to person, although no sustained person-to-person transmission has been observed.

  CDC has developed real-time PCR diagnostic assays and deployed them to partners around the world, and provided epidemiologic and laboratory support to WHO and the ministries of health of Saudi Arabia and Jordan, sending a team to Saudi Arabia in October 2012 and a team to Jordan in

May 2013. CDC's Global Disease Detection (GDD) Regional Center in Egypt and the U.S. Naval Medical Research Unit No. 3 (NAMRU-3) are working with the Eastern Mediterranean Acute Respiratory Infection Surveillance (EMARIS) Network to test suspected cases of severe acute respiratory illness among travelers. Thus far, EMARIS has tested and ruled out 3329 cases in Egypt, 572 cases in Jordan, and 34 cases in Oman.

In the United States, CDC has alerted the public health and medical communities to prepare for possible importation of the novel virus and has helped identify and rule out 15 suspected cases among travelers. CDC has also issued a travel notice (http://wwwnc.cdc.gov/travel/notices/watch/coronavirus-arabian-peninsula) and two *MMWR*s about the outbreak:

— CDC. Update: severe respiratory illness associated with a novel coronavirus—worldwide, 2012–2013. MMWR 2013;62:194–5 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6210a4.htm?s_cid=mm6210a4_w)
— CDC. Severe respiratory illness associated with a novel coronavirus—Saudi Arabia and Qatar, 2012. MMWR 2012;61:820 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a5.htm)

- **Impact of the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) on invasive pneumococcal disease in the United States.** The PCV13 vaccine was licensed in February 2010, on the basis of immunogenicity data, without studies with clinical endpoints. Between 2010 and 2012, the Active Bacterial Core surveillance (ABCs) system documented a decrease of 59% in invasive pneumococcal disease in children less than age 2 years, as well as a decrease of 28% in adults over 65 years that was apparently due to the indirect effects of the childhood immunization program. The ABCs study focused on five serotypes present in both the PV13 and PV5 vaccines (19A, 7F, 3, 1, and 5) and excluded 2009 data to avoid artifacts due to the H1N1 pandemic.

Discussion

In response to a question about explaining to patients why persons over 65 should receive seasonal flu vaccine, in spite of low vaccine effectiveness in this population, Dr. Swerdlow said that the basic message remains the same: the seasonal influenza vaccine is helpful in reducing severe illness, and it is the best tool we have so far. We are always trying to improve vaccine effectiveness, and in the future, we may develop a universal vaccine that is effective against most or all influenza strains.

In response to a question about how the childhood immunization program is affected by the sequester and cuts to Section 317[5] funds, Kristin Pope, NCIRD Associate Director for Policy, noted that the budget situation is complicated because the final budget numbers for 2013 and 2014 are not yet known. While NCIRD received $18 million in transfer funds from HHS for immunization, PPHF funds allocated for immunization activities in 2013 have not yet been received. Also, the CDC Office of Public

[5] The Section 317 immunization grant program provides funding for immunization operations and infrastructure necessary to implement a comprehensive immunization program at the federal, state, and local levels (http://www.hhs.gov/recovery/programs/cdc/immunizationgrant.html).

Health Preparedness and Response made one-time investments in immunization infrastructure in FY2012 (e.g., to improve vaccine registries, support interoperability between registries and electronic medical records, and expand the CDC Vaccine Tracking System [VTrckS]). Immunization priorities for FY1013 and FY2014 include the following:

- Preserving core public health immunization infrastructure at the local, state, and federal levels.
- Maintaining an adequate supply of vaccines to provide a vaccination safety net for uninsured adults and to respond to outbreaks of vaccine-preventable diseases (VPDs). While higher rates of insurance coverage due to ACA implementation will reduce the number of people without access to vaccines, CDC will continue to reserve a supply of vaccine for those who remain uninsured. CDC will also continue to use Section 317 funds to respond to VPD outbreaks.
- Making strategic investments to enhance the immunization infrastructure and evidence base and to improve efficiency.

Ms. Pope concluded that, without the final numbers for FY2014, it is difficult to comment on possible reductions in funding to the states or in vaccine purchase amounts.

In response to a question about the indirect effects of childhood immunization on the elderly, Dr. Swerdlow mentioned ongoing research efforts in this area, especially in regard to the impact of the PV13 vaccine and seasonal influenza vaccines. He noted that CDC does not presently recommend social distancing (or cocooning) of elderly people during the influenza season.

In response to a question about outbreaks of pertussis (a major topic at the December 2012 BSC meeting), Dr. Swerdlow said that in 2012 the United States had the highest number of pertussis cases since 1995. Case-control studies conducted in Washington State indicate that vaccine effectiveness wanes each year following administration. CDC has organized a consultation with a group of experts that will address this issue and present its conclusions to the CDC Advisory Committee on Immunization Practices (ACIP). Possibly the experts will recommend development of a new vaccine or use of a booster shot. Dr. Swerdlow confirmed that there are no plans to return to using the whole-cell vaccine, because of the potential for adverse events.

Dr. Goodman said that the substantial reduction in pneumococcal disease due to the PCV13 vaccine is a valuable achievement. Dr. Swerdlow noted that no evidence has been found to indicate that use of the PCV13 vaccine leads to increased incidence of non-vaccine serotypes. Dr. Gellin said that we need to continue addressing patients' concerns about both efficacy and safety. We also need to explain that current disease prevention tools like the acellular pertussis vaccine may be superseded by new and improved ones.

In response to a question about monitoring the new coronavirus, Dr. Swerdlow said that CDC's assay—which is available to public health departments under an FDA Emergency Use Authorization—can also be used for disease surveillance purposes. Commercial kits are also available. Mark Pallansch, Director, NCIRD Division of Viral Diseases, added that test kits have been distributed internationally via WHO and other partners. In the United States, public health departments are using the test to monitor respiratory disease in travelers after common illnesses like influenza have been ruled out. In some cases, CDC has been contacted for follow-up testing.

➢ CGH Update

Pattie Simone, CGH Deputy Director, provided the following updates:

- **Organizational improvement.** CGH, which was established as a new center in 2010, commissioned an organizational improvement assessment in 2012. In response to the assessment, CGH is undertaking several activities, including the following:
  - Establishing a cross-center working group to implement key recommendations for improving communication and coordination
  - Reorganizing to reduce overlap between two divisions and combine and integrate activities that build capacity and enhance global security

  As part of these efforts, CGH has created the new Division of Global Health Protection (proposed), which will include the center's Non-Communicable Disease Unit, as well as four branches: Emergency Response and Reconstruction, Field Epidemiology Training Programs, Global Disease Detection (including the GDD Operations Center and GDD Regional Centers), and Global Health Security (focusing on implementation of core capacities under the International Health Regulations [IHR]).

- **PEPFAR: scaling up programs and services.** Between 2004 and 2012, the President's Emergency Plan for AIDS Relief (PEPFAR) has scaled up services for treatment and care, services for orphans and vulnerable children, and prevention of mother-to-child transmission (PMTCT) in countries with a significant burden of HIV/AIDS. Substantial progress has been made in reaching targets established in 2010 for provision of PMTCT and antiretroviral therapy (about 6 million patients). Numbers of voluntary medical male circumcisions were initially low, but rose in 2012, approaching 75% of the PEPFAR target.

- **President's Malaria Initiative (PMI).** As reported in the seventh annual PMI report, submitted to Congress in April 2013, all-cause mortality in children under 5 years of age decreased significantly (by 23–50%) in malaria-endemic countries between 2002 and 2011. Use of insecticide-treated nets has increased in these countries, moving towards achievement of the PMI target of bednet use of 85% among children under 5. Progress made in FY2012 also includes increased provision of intermittent malaria treatment for pregnant women.

- **Polio eradication.** Dr. Simone noted that the world is closer than ever to polio eradication. In 2011, 11 polio outbreaks occurred in 16 countries. In 2012, only one outbreak occurred, in Pakistan, and sporadic cases were detected in only five countries: Chad, Niger, Nigeria, Afghanistan, and Pakistan.

- ***CDC Global Health Strategy.*** CDC is developing targets and measures to monitor implementation of the *CDC Global Health Strategy* 2012–15 (http://www.cdc.gov/globalhealth/strategy/). The Strategy includes four goals:
  - Goal 1. Health Impact: Improve the health and well-being of people around the world
  - Goal 2. Health Security: Improve capabilities to prepare for and respond to infectious diseases, other emerging public health treats, and public health emergencies
  - Goal 3. Health Capacity: Build country public health capacity
  - Goal 4. Organizational Capacity: Maximize potential of CDC's global programs to achieve impact

CGH budget. The President's proposed CGH budget for FY2014 is $393 million, which is about the same as for FY2012. The budget includes $22 million for parasitic diseases and malaria; $46 million for global disease detection and emergency response; $52 million for global measles and other vaccine-preventable diseases; $131 million for polio eradication; $10 million for global public health capacity development; and $132 million for global HIV/AIDS. It includes an additional request for polio. The cuts due to the sequester and continuing resolution are having a significant impact on the CGH travel budget.

New CGH director. Dr. Thomas Kenyon will join CDC as CGH Director in May. He is planning to attend the World Health Assembly with HHS Secretary Sebelius.

Discussion

In response to a question about collaboration on global health issues, Dr. Simone said that the GDD Regional Centers work closely with the Department of Defense (DoD) and its overseas laboratories (e.g., NAMRU-3), under a CDC–DoD interagency agreement. The DoD laboratories support GDD capacity-building work, with diagnostics and IHR implementation as major focus areas. Dr. Berkelman asked about progress in treating tuberculosis and MDR-TB among HIV-infected patients.

In response to a question about CDC's partnering with industries or universities to monitor travel-related case of respiratory disease that might be due to the new coronavirus or to the avian influenza A(H7N9) detected in China, Dr. Bell said that CDC's Division of Global Migration and Quarantine focuses on travelers' health, working with many travel industry partners. CDC has not suggested restrictions on travel to China, but does recommend that travelers avoid live poultry markets. CDC and public health departments also monitor respiratory illness in airplane travelers returning from China or the Middle East. Dr. Simone noted that CDC has staff in 60 countries who can provide travel health information to U.S. embassy personnel.

In response to a question about whether the inclusion of the Non-Communicable Disease Unit in the new CGH Division of Global Health Protection (proposed) has led to greater focus on the interactions between infectious and chronic diseases, Dr. Simone said that this area is high priority but underfunded. Future areas are likely to include joint treatment of TB and diabetes and promoting HPV vaccination programs to prevent cervical cancer.

In response to a question about partnerships and health diplomacy, Dr. Simone noted that all CGH activities involve partnerships, especially with ministries of health and with USAID, DoD, and other U.S. agencies. CGH hopes to establish additional public/private partnerships, which are important to CGH's AIDS work. CGH partners tend to focus principally on HIV reduction, polio eradication, childhood immunization, and malaria, with less emphasis on capacity building.

FOCUSED DISCUSSIONS

Following program updates, the meeting shifted to focused discussions on two topics on which BSC input was specifically requested: (1) monitoring the health impact of the national HPV vaccination program and (2) modernizing public health laboratory and bioinformatics capacity for improving detection and response to infectious disease outbreaks. Both of these issues cross multiple programs and centers across CDC and require strong internal and external collaborations/partnerships.

➢ U.S. HPV Vaccine Program and Monitoring Efforts

Dr. Lauri Markowitz, Team Lead, Division of STD Prevention, NCHHSTP, spoke about CDC's current efforts and plans for monitoring the impact of vaccines against HPV, which can cause cervical cancer, some other anogenital and oropharyngeal cancers, and genital warts. She began by providing background information on the two HPV vaccines licensed for use in the United States:

- Gardasil, a quadrivalent vaccine that protects against HPV types 6, 11, 16, and 18 (licensed for use in females and males)
- Cervarix, a bivalent vaccine that protects again HPV types 16 and 18 (licensed for use in females)

Both vaccines are given in three doses. Both provide protection against about 70% of cervical cancers and the majority of other HPV-associated cancers; Gardasil also provides protection against 90% of genital warts.

ACIP recommendations. When introduced in 2006, Gardasil was recommended for routine use in females 11–12 years of age, and in females 13–26 years of age who had not been previously vaccinated. In 2009, after Cervarix was licensed, either Gardasil or Cevarix was recommended for routine use in females. Also in 2009, Gardasil was licensed for use in males. While it was not recommended for routine use at that time, it could be used in males. More recently, in 2011, Gardasil was recommended for routine use in males 11–12 years of age, and in males aged 13–21 years who had not been previously vaccinated. Gardasil may be given to males 22–26 years of age.

Vaccine coverage. Thus far, HPV vaccine coverage has lagged behind adolescent coverage for other recommended adolescent vaccines (e.g., Tdap and MCV4). Coverage varies by state (with an overall one-dose coverage of 54% and the highest rates in California, Oregon, Washington, Wisconsin, New Hampshire, and Rhode Island); by poverty status (with girls from families below poverty level having higher coverage); and by ethnicity (with highest first-dose coverage in Hispanics). Nationally, 71% of girls who start the three-dose series complete it.

HPV is included as a middle school vaccination requirement in two states, with broad opt-out provisions, while Tdap (or the tetanus and diphtheria vaccine) is required in 41 states and MCV4 in 13 states. CDC is investigating other factors that might influence vaccination coverage. So far, no association has been found between coverage rates and state policies that affect access to care (e.g., insurance coverage), or between coverage rates and parent's education level. However, the strength of a recommendation from a pediatrician or family physician does appear to matter. According to a CDC survey, only 51% of physicians strongly recommended HPV vaccination for 11- to 12-year-olds. That percentage rises to 79% for 13- to 15-year-olds and to 85% for 16- to 18-year-olds. Other studies[6,7] found that

- HPV vaccine is often presented as "optional," whereas other adolescent vaccines are recommended as needed
- Some physicians expressed mixed or negative opinions about the vaccine (e.g., concerns about the safety and efficacy of a new vaccine)

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[6] Goff SL, Mazor KM, Gagne SJ, Corey KC, Blake DR. Vaccine counseling: a content analysis of patient-physician discussions regarding human papilloma virus vaccine. Vaccine 2011;29(43):7343–9.

[7] Hughes CC, Jones AL, Feemster KA, Fiks AG. HPV vaccine decision making in pediatric primary care: a semi-structured interview study. BMC Pediatr 2011;11:74.

- When parents expressed reluctance, providers were hesitant to engage them in discussion
- Some providers shared a parent's views that a teen was not at risk for HPV and could delay vaccination until older

A CDC survey of parents of adolescent girls found that 25–28% say they are unlikely to have their daughters vaccinated over the next 12 months. The most common reasons for not vaccinating included the following: the vaccine is not needed or not necessary; the adolescent is not sexually active; the parent is concerned about side effects; the parent lacks knowledge about the vaccine; and no recommendation was made by the adolescent's healthcare provider.

CDC is conducting multiple activities to address this challenge:

- Continuing to analyze vaccine coverage data via the National Immunization Survey-Teen (http://www.cdc.gov/vaccines/stats-surv/nisteen/articles.htm)
- Awarding funds to eight public health departments to use CDC's Immunization information Systems (IIS) to provide patients with vaccination reminders and assess vaccination coverage among the patients of providers who report vaccinations to the IIS (http://www.cdc.gov/vaccines/programs/iis/index.html)
- Providing a tip sheet for physicians to help them talk with parents about HPV vaccine (http://www.cdc.gov/vaccines/who/teens/for-hcp-tipsheet-hpv.html
- Developing a speakers bureau to provide vaccine presentations at professional meetings
- Continuing to evaluate barriers to vaccination and better understand the safety concerns of parents and patients
- Developing more effective ways of communicating safety data to providers and parents

Monitoring the impact of the HPV vaccine. CDC typically monitors the impact of vaccination to demonstrate population health impact and collect data to improve vaccine policies and other health policies (e.g., data on vaccine effectiveness, the duration of protection, and the number of doses required for protection).

Efforts to monitor the impact of HPV vaccination can focus on

- Early outcomes, occurring within years after infection, which include HPV prevalence and genital warts
- Mid-outcomes, occurring years to decades after infection, which include pre-malignant cervical intraepithelial neoplasias (CINs) and other precancerous lesions
- Late outcomes, occurring over decades, including HPV-associated cancers

The first data on early outcomes due to HPV vaccination were reported from Australia, where Gardasil was provided through a school-based program to 12- to 13-year-old girls, starting in 2007. More than 70% of the targeted age group received three doses of vaccine. In 2011, declines were documented in the number of young people diagnosed with genital warts[8] and in the prevalence of HPV types 6, 11, 16, and 18.[9]

[8] Ali H, Guy RJ, Wand H, et al. Decline in in-patient treatments of genital warts among young Australians following the national HPV vaccination program. BMC Infect Dis 2013;13:140.

[9] Tabrizi SN, Brotherton JM, Kaldor JM. Fall in human papillomavirus prevalence following a national vaccination program. J Infect Dis 2012;206(11):1645–51.

Challenges to monitoring the impact of the HPV vaccination programs in the United States include the lack of routine tracking systems (e.g., incomplete state vaccination registries, no national vaccine registry, and only one state-level Pap registry). CDC efforts to monitor early outcomes include using the National Health and Nutrition Examination Survey (NHANES; http://www.cdc.gov/nchs/nhanes.htm), which covers a representative sample of the U.S. population through home interviews and examinations conducted in a mobile medical center. Since 2007, NHANES has included HPV-related questions about vaccination history and sexual behavior; the mobile medical center examinations have included HPV testing of genital swabs for females (since 2003) and for males (beginning in 2013). A comparison of NHANES HPV data obtained in the periods 2003–06 and 2007–10 documents a 56% decline in HPV vaccine types in 14- to 19-year-olds but in no other age group.[10] This decline was larger than expected and might indicate the effect of herd immunity.

Other early-outcome monitoring efforts include

- Working with a managed care organization to monitor type-specific HPV prevalence in cervical specimens from Pap testing
- Monitoring the incidence of genital warts by analysis of administrative data (IC-9 codes) from a large claims database. Early results indicate a downward trend in genital warts since 2007 in females aged 15–19[11]

Ongoing efforts to monitor mid-outcomes include working with

- Cancer registries in Kentucky, Louisiana, Michigan, and Los Angeles County to monitor CIN grade 3 and adenocarcinoma in situ (AIS)
- Emerging Infections Program (EIP; http://www.cdc.gov/ncezid/dpei/eip/) sites in California, Connecticut, New York, Oregon, and Tennessee to monitor CIN grades 2 and 3 and AIS

The EIP data gathered from 2008–10 found that most CINs are associated with HPV type 16 and are therefore potentially preventable via HPV vaccination.[12] The EIP study also documented a reduction in the percentage of cervical pre-cancer lesions due to vaccine-type HPV among woman who initiated vaccination at least 24 months prior to their diagnosis.[13] Dr. Markowitz mentioned that a 9-valent vaccine is currently in phase 3 clinical trials.

Ongoing efforts to monitor late outcomes include working with cancer registries in all 50 states to track the incidence of HPV-associated cancers (cervical, vaginal, vulvar, penile, anal, and oropharyngeal), overall and by state.[14] CDC is also working with selected state registries to conduct HPV typing of HPV-associated cancers reported between 2007 and 2011. Dr. Markowitz noted that the impact of HPV vaccination on trends in the incidence of cervical pre-cancers over time may be difficult to assess due to changes in screening practices.

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[10] Markowitz LE, Hariri S, Lin C, et al. Reduction in HPV prevalence among young women following vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003–2010. J Infect Dis 2013;208(3):385–93.

[11] Flagg EW, Swartz R, Weinstock H. Prevalence of anogenital warts among participants in private health plans in the US, 2003–2009: potential impact of HPV vaccination. Am J Public Health 2013;103(8):1428–35.

[12] Hariri S, Markowitz L. Monitoring HPV vaccine impact: early results and ongoing challenges. J Infect Dis 2012;206(11): 1633–5.

[13] Powell SE, Hariri S, Steinau M, Bauer HM, Bennett NM, Bloch KC, Niccolai LM, Schafer S, Unger ER, Markowitz LE. Impact of human papillomavirus (HPV) vaccination on HPV 16/18-related prevalence in precancerous cervical lesions. Vaccine 2012;31:109–13.

[14] CDC. Human papillomavirus-associated cancers—United States, 2004–2008. MMWR 2012;61:258–61.

Taken together, these early, late, and mid-outcome HPV monitoring efforts will not only document the impact of HPV vaccination but also help answer questions about vaccine effectiveness, duration of protection, and whether HPV vaccine types are replaced by other types as vaccine coverage increases.

In summary, Dr. Markowitz said that a variety of early, mid and late outcomes of HPV vaccination are being monitored and that data on the impact on early and mid outcomes are already becoming available, despite low vaccine coverage. Other monitoring products are still being evaluated; trends in cervical pre-cancers will be difficult to interpret due to changes in screening. Data on effectiveness and on duration of protection depends on quality of vaccination data.

Discussion

HPV coverage

- Dr. Markowitz said that CDC is continuing to survey healthcare providers about their attitudes toward recommending HPV vaccine. Physicians may recommend HPV vaccination more strongly as they learn more about its effectiveness in preventing cancer.
- Shannon Stokley, Associate Director for Science, Immunization Services Division, NCIRD, added that CDC is issuing an FY2013 Funding Opportunity Announcement for studies that evaluate ways to improve physicians' communications skills and comfort level with talking about and recommending HPV vaccines. Dr. Markowitz noted that the National Vaccine Advisory Committee has established a working group on this topic.
- In regard to a question about why girls in families below poverty level have a higher rate of HPV coverage, Dr. Markowitz suggested that parental concerns and cost factors could affect vaccination rates. The vaccine is provided free under the Vaccines for Children (VFC) program but is expensive if purchased in pharmacies. (The school-based program in Australia provided vaccines purchased by the government.)
- Ms. Stokley added that teens who are VFC-eligible have higher first-dose HPV coverage rates (but lower completion rates) than those with private insurance. Although first-dose coverage rates are lower among teens with educated and older mothers (who may question vaccine safety), those who begin the vaccination series tend to complete it.
- The high vaccine coverage rate in Australia was likely due, in part, to the vaccine program being school-based.
- Data on HPV vaccine coverage should always specify the number of doses to ensure that coverage rates are comparable between studies.
- Because adolescents typically do not get regular check-ups, it would be good to provide clinicians with guidance on whether HPV doses may be administered off-schedule.
- Health management organizations (HMOs) may see HPV vaccination as cost-ineffective, because cost savings due to cancer prevention will not be realized for many years.
- A National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set (HEDIS; http://www.ncqa.org/HEDISQualityMeasurement.aspx) measure is being tested that would require girls to receive three doses of HPV vaccine by age 13. Vaccination may become a reportable measure for HMOs.

Monitoring HPV outcomes

- Prevention of HPV-associated cervical cancer is "low-hanging fruit," and monitoring HPV outcomes at different stages is a very good approach.
- Genital warts in women can be monitored via a variety of data sources (e.g., STD clinics, private medical offices, and HMOs).

- Data on genital warts in men, including men who have sex with men, is available from STD clinics, via HMO data. Warts are a valuable short-term measure of HPV vaccine impact, especially in males.
- An ideal setting for HPV monitoring over long periods of time might be HIV clinics where men who have sex with men receive antiretroviral therapy. CDC may follow this approach if funding is available.

Communications

- It is important that providers and parents understand how common HPV infections are and that vaccination is needed before exposure to prevent cancers.
- The HPV vaccine should be "marketed" as an anti-cancer vaccine.
- In regard to a question about whether parents are concerned that HPV vaccination will lead to unsafe sex, Dr. Markowitz said that although this issue was raised in the media as a major concern, it has not been borne out by studies as being a major parental concern.
- A survey of teens and healthcare providers conducted by the National Foundation for Infectious Diseases found that teens are more interested in health issues than their parents or providers perceive them to be. Therefore, CDC might survey teens as well as parents about how providers' recommendations are received.
- Ms. Stokley said that CDC is conducting research on patients' decision-making about other vaccines. Although manufacturers may be marketing the vaccine to adolescents, CDC's materials mostly target parents, because parents must give consent for vaccination of 11- to 12-year-olds.
- HPV, like HBV, is sexually transmitted and causes cancer. However, because HBV vaccine is provided to infants rather than teens, it presents different communication challenges.
- Teens might be reached through social media sites, phone apps (e.g., an adolescent health checklist), and/or linkages to other outlets visited by teens. Pharmacies or providers could also be engaged to text reminders to obtain second and third doses.
- Countering misinformation from anti-vaccine groups is also a communication challenge.
- HPV vaccine discussions should be included with other communication efforts on the need for adult vaccination

Vaccine and cancer registries to track vaccine coverage

- Vaccine and cancer registries are part of the "meaningful use" effort to promote interoperability and support electronic health information exchange.
- Vaccine registries tend to be more complete for childhood vaccines than for adolescent vaccines, although completeness varies from state to state.
- One reason for the incompleteness of vaccine registries is that a person included at birth may move out of the state by adolescence.
- The New Hampshire public health department began to partner with insurance companies 11 years ago to facilitate reimbursement for vaccination.

Partnerships

- HPV activities at CDC involve offices and centers that address infectious diseases, global health, non-communicable diseases, and cancer prevention. These offices work closely with state-level partners. Other partners include professional societies, universities, and pharmaceutical manufacturers.
- Dr. Carolyn Deal, Chief of the Sexually Transmitted Diseases Branch, NIH/NIAID, agreed that HPV prevention cuts across the usual "silos." CDC has identified questions that are guiding NIH's research efforts to improve HPV prevention (e.g., about adolescent attitudes and behaviors and about vaccine cost-effectiveness).

- **Advanced Molecular Detection and Response to Infectious Diseases**

Duncan MacCannell, Science Officer, NCEZID, described the AMD initiative as combining traditional epidemiology with genomic sequencing and bioinformatics. He noted that the speed of DNA sequencing has gone from 500 base pairs per day in 1993 to about 50 billion per day in 2013. Because each human genome includes 3 billion base pairs, one machine can now sequence 16 human genomes per day. Moreover, the cost of DNA sequencing began to drop around 2008—from ~$10,000 per megabase in 2001 to ~$100 in 2012. Instrumentation also got much smaller.

Although workflow procedures are increasingly standardized—no matter which pathogen's genome is being sequenced—the hardware and software involved in analyzing and making sense of this huge amount of DNA data ("Big Data") is rapidly evolving. There are many bioinformatics software programs but few consistent standards. A new workforce and skill set is needed to address Big Data.

Blue Ribbon Panel. In June 2011, OID convened a panel of external expert consultants to review the current state of bioinformatics resources across CDC's infectious diseases laboratories, to identify critical gaps, and to provide recommendations for improvement. The panel found that CDC's ability to meet its public health mission was threatened by not keeping up with growing bioinformatics requirements that have paralleled major advances in laboratory technology (e.g., high-throughput genomic sequencing).

The panel's short-term recommendations included the following:

- Develop a core bioinformatics activity to collaborate with and support program science across the infectious disease centers
- Leverage other resources by fostering collaborations with genomics and bioinformatics groups in other government agencies, academia, and private industry
- Provide leadership to state public health departments on using genomics and bioinformatics to meet core public health missions

In response, CDC established a "Bioinformatics Core Support" activity with three organizational components:

- OID Core Bioinformatics (led by Dr. MacCannell)
- NCIRD Influenza Division (Elizabeth Neuhaus)
- NCEZID Division of Scientific Resources (Scott Sammons)

The activity includes laboratory branches in NCEZID, NCIRD, NCHHSTP, and CGH and encompasses

- Scientific computing infrastructure (hardware, software, databases, storage, networking)
- Expert bioinformatics support, including
  - Development and administration of collaborative projects
  - Consultation and coordination on bioinformatics and genomics projects
  - Training, resource development, and user/desktop support
- Collaboration, partnerships, outreach, and advocacy

CDC is currently collaborating in this area with the following partners:

- The Advanced Biomedical Computing Center (http://isp.ncifcrf.gov/abcc/) to optimize bioinformatics applications

- The TGen North facility (in Arizona) of the Translational Genomics Research Institute (https://www.tgen.org/research/tgen-north.aspx) on the molecular epidemiology of HAIs, mycotic diseases, and other diseases
- The Broad Institute of Harvard University and MIT (http://www.broadinstitute.org/) on whole-genome sequencing and genomic analysis of malaria parasites, gonococcus, and other microbes
- Oak Ridge National Laboratory, Los Alamos National Laboratory, and the Lawrence Livermore National Laboratory on projects requiring high performance computing (HPC; e.g., involving metagenomics and sequence-based pathogen identification and characterization)
- The Wellcome Trust Sanger Institute on whole-genome sequencing and genomic analysis projects

CDC scientists are also contributing to:

- 100,000 Genomes Project of the PHG Foundation, which aims to sequence and analyze the genomes of 100,000 patients of the U.K. National Health Service (http://www.phgfoundation.org/news/13721/)
- Global Microbial Identifier project, which aims to develop a global system to aggregate, share, mine, and use microbiological genomic data to address global public health and clinical challenges (http://www.g-m-i.org/)

CDC scientists are also working with the Georgia Institute of Technology and Emory University to develop bioinformatics graduate programs that provide MS and PhD degrees. As part of these efforts, CDC is developing a bioinformatics fellowship and other training mechanisms that will place bioinformatics graduates and graduate students in public health programs.

Examples of ongoing bioinformatics projects include

- Investigation of outbreaks strains of CRE, including those that carry the New Delhi metallo-beta-lactamase 1 (NDM1) gene
- Characterizing the *Exserholium* strains involved in the 2012–13 multistate outbreak of fungal meningitis (*see also* NCEZID update, page 5)
- Performing a metagenomic survey of bacterial species associated with needleless catheter access devices
- Assessing the importance of genetic drift on the stability of measles hemagglutinin genes, with special regard to antigens and epitopes used in measles vaccines

Budget for bioinformatics activities. The President's proposed FY2014 budget for CDC includes $40 million to support an AMD initiative designed to

- **Improve pathogen identification and detection** by expanding capacity for rapid DNA sequencing and molecular characterization and improving capabilities for data analysis and interpretation. CDC experts and collaborators will develop tools for genome-scale molecular epidemiology and apply them to CDC's laboratory and surveillance activities.
  - ***Outcome:*** Rapid progress toward modernizing PulseNet and other critical laboratory-based surveillance systems

- **Adapt new diagnostics to meet evolving public health needs** by leading public health efforts to adapt the next generation of rapid, semi-automated, point-of-need molecular tests.
  - ***Outcome:*** Enhanced ability to detect outbreaks early, develop new tests during outbreaks, and better characterize infectious disease threats
- **Help states meet future reference testing needs in a coordinated manner** by assisting state and local public health laboratories in transitioning from culture-based methods to molecular technologies. CDC and collaborators will help expand capacity for rapid DNA sequencing and bioinformatics analysis to the state and local level.
  - ***Outcome:*** More effective and better integrated outbreak response activities
- **Implement enhanced, sustainable, and integrated laboratory information systems.** Big Data present new challenges to manage, interpret, and integrate laboratory results quickly.
  - ***Outcome:*** Ability of laboratories inside and outside CDC to share information quickly and seamlessly, including information from CDC databases such as MicrobeNet and PulseNet
- **Develop prediction, modeling, and early recognition tools** by modifying and upgrading modeling systems to facilitate the use of new kinds of laboratory data.
  - ***Outcome:*** Better capacity to prevent, detect, and respond to infectious disease threats

AMD funds will be used to make investments in

- **Scientific infrastructure** at CDC, state and local health departments, and key overseas laboratories. Examples include investing in sequencers, mass spectrometers, HPC workstations, and software for data storing and management.
- **Workforce development.** Examples include bioinformatics training for CDC and state and local laboratory staff, development of fellowship programs, and recruitment of staff with new skill sets.
- **Consortia, partnerships, and alignment of efforts.** Partners may include academic institutions, state and federal laboratories, private companies, non-governmental organizations, and international partners.
- **Pilot projects** with state and local health departments and other partners to improve laboratory-based surveillance and outbreak detection, investigation, and response.

In conclusion, Dr. MacCannell said that the use of advanced molecular and bioinformatics technologies will allow CDC to detect outbreaks sooner and respond more effectively, saving lives and reducing costs.

Discussion

Dr. Khabbaz introduced Jan Nicholson, OID Senior Advisor for Laboratory Science; members of the OID Bioinformatics Working Group who were in attendance; and Bob Cottingham, OID Senior Consultant, who served on the 2011 Bioinformatics Blue Ribbon Panel. Dr. Berkelman noted that CDC's bioinformatics activities will continue to be funded "on a shoestring" unless the AMD initiative is funded in FY2014.

Comments from BSC members and meeting participants included the following:

- **General comments**
  - It is essential to avoid "analysis paralysis" by focusing on important public health questions. Dr. Bell agreed that CDC's work in bioinformatics must be totally in sync with our public health

priorities, especially in view of funding issues. Dr. MacCannell noted that CDC is building on our partners' innovations to apply bioinformatics to specific public health needs.
  - Next-generation DNA sequencing is only one part of this rapidly changing field. Dr. MacCannell noted that genomics will underpin CDC's future work in proteomics. An important first step for CDC in this area is to sequence the genomes of microbes in CDC's reference collection.
  - CDC should not lose its capacity for culture-based testing. In some cases, DNA testing may not be able to identify novel species (e.g., new taxa of viruses found in mosquitoes). Dr. MacCannell agreed that CDC must ensure capacity for culture-based testing (e.g., to conduct AR testing and other functional assays).

- **Partnerships and collaboration**
  - The world of bioinformatics and Big Data is necessarily collaborative, because the amounts of data are so large. The number of partnership opportunities for CDC laboratories in this area could be overwhelming. CDC must focus on doing what it has always done, but make use of bioinformatics tools to do it better.
  - Widespread use of testing methods based on bioinformatics may create a chasm between the public health and medical communities, because clinicians are not familiar with these methods.
  - CDC is planning to pursue bioinformatics collaborations with federal food and veterinary laboratories.
  - CDC is also reviewing standards for universal data exchange, including those used by the Public Health Agency of Canada and other international partners.
  - In response to a question about partnering with the bioinformatics industry, Dr. MacCannell said that CDC is working with software and hardware venders to outline database requirements for public health applications.

- **Database issues**
  - CDC and partners can make use of existing microbial databases created by domestic and international partners.
  - Dr. MacCannell said that FDA is developing standards for DNA databases used in diagnostics, as well as certifying software applications that run on new sequencing machines.
  - Dr. Deal said that it is important to develop shared language and nomenclature for DNA databases. Dr. Bell agreed that a "Tower of Babel" situation could easily develop, impeding the application of bioinformatics tools to public health. CDC and NIH can take a lead role in this area.
  - The creation of a database on resistance mutations (with standardized definitions) could provide immediate help to hospitals coping with CRE. Dr. Bell agreed that this is a priority area for public health that is not currently funded.

- **State-level issues**
  - In the future, state health laboratories will need to consider whether to maintain their own bioinformatics capabilities or support a regional or shared-service mechanism for DNA testing.
  - Jane Getchell, Senior Director of Public Health Programs, Association of Public Health Laboratories (APHL), said that APHL looks forward to working with CDC to transfer bioinformatics tools and techniques to state and local public health laboratories—an effort that must go forward with or without FY2014 AMD funding. If no funds are forthcoming, APHL and CDC will work together to figure out what steps should be taken.

Outcome of the discussion. Dr. Berkelman asked the BSC members to vote on establishing a BSC/OID working group to provide consultation and advice on the AMD initiative and CDC's activities in this area. The motion passed unanimously by show of hands.

Dr. Berkelman asked that BSC members let her know by next week if they would like to participate in the new working group. BSC member Jill Taylor, Interim Director, Wadsworth Center, New York State Department of Health, has volunteered to serve as chair, and NIH and FDA will be asked to designate expert consultants.

BSC WORKING GROUP REPORTS

- **FSMA Surveillance Working Group Report**

James Hadler, Public Health Consultant, reported on the activities of the BSC FSMA Surveillance Working Group, which met on May 6–7 in Atlanta. Working group members include two representatives from the BSC (Dr. Hadler and Harry Chen, Commissioner, Vermont Department of Health) and 19 representatives from USDA, FDA, academia, consumer groups, industry, and state and local health organizations.

Annual report. In January, the working group submitted its annual report to the BSC/OID, which reviewed, approved, and submitted it to HHS Secretary Sebelius, as required under FSMA. The annual report summarized the group's efforts between October 2011 and September 2012. In the report's cover letter, Drs. Berkelman and Hadler (the BSC/OID chair and FSMA Surveillance Working Group chair, respectively) emphasized the potential challenges of culture-independent diagnostic tests (CIDTs), as well as surveillance and resource gaps. Secretary Sebelius acknowledged the important efforts of the working group in providing advice to help prioritize actions to improve foodborne disease surveillance and in highlighting the challenges of CIDTs.

At the May 6–7 meeting, working group topics included the following:

- **CDC updates on foodborne illness surveillance activities**
  - ***Attribution of foodborne illness***. Data were presented from a March 2013 paper on attribution of foodborne illness, hospitalizations, and deaths to particular types of food, based on outbreak data compiled from 1998 to 2008[15] (*see also* NCEZID update, page 5). Thirty-six disease agents and 17 food categories were included in the analysis. The major findings were that the dominant source of illness was contaminated produce (fruits and vegetables), with most illness caused by norovirus. However, poultry and meat together were the dominant source of illness leading to deaths.
  - ***Communications and data-sharing.*** Rob Tauxe, Deputy Director, NCEZID Division of Foodborne, Waterborne, and Environmental Diseases, described CDC efforts to improve communication and data-sharing on foodborne diseases between federal agencies (i.e., for disease attribution, outbreak investigation, and monitoring of antimicrobial resistance) and with industry, policymakers, public health partners, and consumer groups. CDC has developed and improved websites for the five Integrated Food Safety Centers of Excellence (in Colorado, Florida, Minnesota, Oregon, and Tennessee; http://www.cdc.gov/foodsafety/centers/); for FoodCORE

[15] Painter JA, Hoekstra RM, Ayers T, et al. Attribution of foodborne illnesses, hospitalizations, and deaths to food commodities by using outbreak data, United States, 1998–2008. Emerg Infect Dis 2013;19(3):407–15.

(http://www.cdc.gov/foodcore/about.html); and for FoodNet (http://www.cdc.gov/foodnet/). CDC has also expanded outreach to non-governmental partners prior to data releases and issuance of new publications.

- **Guidance on CDC's initiative on developing performance measures to enhance federal, state, and local foodborne illness surveillance.** The aim of this initiative is to improve nationwide capacity for foodborne disease surveillance, working with FoodNet and FoodCORE partners. The working group considered the following questions:
  - ***What is the value of performance measures for foodborne illness surveillance?***
    The working group believes that standardized performance measures could promote common understanding of key elements of foodborne disease surveillance and improve performance by identifying performance gaps within and between states, as well as the reasons for those gaps and measures to address them. Performance measures could also help states justify ongoing and future investments and inform priority setting.
  - ***How should performance measures be selected?***
    The working group suggested that measures be chosen in collaboration with state and local health departments based on their importance in achieving food safety goals related to disease prevention, disease surveillance, and outbreak response. Disease-specific performance measures could be prioritized based on the burden and severity of the disease and should take into account the type of data necessary to attribute the disease to a particular food source. Where applicable, performance measures could be linked to the guidelines of the Council to Improve Foodborne Outbreak Response (CIFOR; http://www.cifor.us/).[16]
  - ***What are the key factors in implementing performance measures?***
    The working group agreed that key factors in developing performance measures include developing a shared vision of their importance; involving state and local health departments in their development and implementation; and ensuring mutual accountability between federal and state partners. The development of these measures could be an iterative process with regular review, discussion, and modification. The working group agreed that measures should be easy to record and report, and health departments should be prepared to invest dedicated staff time and resources to their implementation.
  - ***What are additional factors that could support performance measure implementation in low-resource states?***
    The working group suggested that low-resource states could partner with high-performance states (e.g., those that host Integrated Food Safety Centers of Excellence) and that low-resource states could be a priority group for funding by CDC. In the future, if the performance measures are used in accreditation reviews, incentives could be provided to support their implementation in low-resource states.
  - ***What are the barriers to implementing performance measures?***
    The working group believes that implementation barriers include
    - Disagreement on which measures are most important
    - Lack of human and financial resources
    - Insufficient incentives and lack of "champions" to move things forward
    - Political ramifications if measures reveal poor performance

[16]CIFOR is a multidisciplinary working group convened to increase collaboration across the country and across relevant areas of expertise to reduce the burden of foodborne illness in the United States. The Council of State and Territorial Epidemiologists (CSTE) and the National Association of County and City Health Officials (NACCHO) co-chair CIFOR with support from CDC and FDA.

    - Difficulties in gathering performance data (e.g., technical issues involved in sharing or gaining access to data)
    - Difficult and complicated reporting
    - Different state structures for gathering disease surveillance (e.g., centralized versus decentralized)

- **Guidance on addressing CIDTs.** The benefits of CIDTs for detection of enteric pathogens include rapid results and lower costs. Many CIDTs probe for multiple antigens, and their widespread use could lead to increased data on the causes of gastrointestinal illnesses, which often go undiagnosed. The challenges of CIDTs include less sensitivity and specificity than culture-based tests. In addition, if multiple pathogens are detected, it may not be clear which one is causing disease. Finally, the public health community must figure out how best to incorporate CIDT results into public health surveillance (e.g., which cases to count and how to count them).

  In the next decade, CIDTs are likely to replace most culture-based and antigen-based tests, leading to sharply decreased availability of isolates for public health surveillance. At the current time, most national and multistate outbreaks of foodborne disease are detected by CDC's PulseNet surveillance system, whose member laboratories culture microbial isolates and use pulsed-field gel electrophoresis (PFGE) to subtype and compare them. Unless PulseNet is able to incorporate newer technology, the reduced availability of isolates will negatively impact PulseNet and decrease our ability to detect and solve outbreaks. Industry and regulators would lose the information they use to identify gaps in food safety, which will likely lead to increasing numbers of cases. The decrease in (or loss of) culture-based testing will also have a negative impact on FoodCORE, OutbreakNet, FoodNet , the National Antimicrobial Resistance Monitoring System (NARMS), the FDA Coordinated Outbreak Response and Evaluation (CORE) Network, and the predictive analytics component of the USDA/FSIS Public Health Information System.

  APHL has developed a draft white paper on CIDTs aimed at technical audiences, and the Center for Food Integrity has developed a draft white paper aimed at political and policy audiences.

  The working group presented overarching needs, as well as short-, mid-, and long-term actions needed to address these concerns:

  - ***Overarching action.*** We need a comprehensive strategy for developing and adopting a culture-independent typing system that meets public health needs while preserving the current capabilities in the interim.
  - ***Short-term actions***
    - Preserve isolates and culture. Possible approaches include
      - Requiring clinical laboratories to culture specimens that are positive by CIDT (reflex-culturing) or to transport them to public health laboratories for culturing
      - Working with FDA to ensure that public health needs are addressed during the approval process for CIDTs (e.g., requiring reflex culturing)
    - Enhance the quality and quantity of exposure information by improving exposure assessments and reporting tools (e.g., as soon as a diagnosis is made, patients should be systematically interviewed to identify the source of exposure, using a standardized questionnaire).
    - Adapt surveillance to new types of data (e.g., using enhanced case definitions that provide information on disease exposure).

- ***Mid-term actions.*** Develop genomic and metagenomic molecular methods for disease surveillance. These efforts will require increased bioinformatics capacity at public health departments. It will be necessary to build a consensus on how to implement this approach with shared standards and consistency.
- ***Long-term actions.*** Modernize foodborne illness surveillance systems by implementing the new genomic and metagenomic methods for pathogen identification and characterization.

Next steps. The working group plans to complete its annual report by early November and send it to the BSC for approval. The BSC can vote on and/or endorse the actions proposed by the working group at the December 2013 BSC meeting.

New topics for discussion at the working group's December meeting include surveillance for norovirus infections and for antimicrobial resistance in foodborne pathogens.

Discussion

BSC members made several comments regarding the suggested actions. Comments regarding the requirement for clinical laboratories to culture specimens that are positive by CIDT or to transport them to public health laboratories for culturing included the following:

- These options are not likely to be implemented at a time of low resources.
- Submission of isolates to public health laboratories by clinical laboratories might have to be voluntary in some states, due to existing state laws.
- It is unclear who would pay for culture testing that is performed for public health purposes rather than for the benefit of individual patients.
- The cost of additional culture testing by public health laboratories will pose an additional burden on state health departments. States are likely to approach this challenge in different ways. Reflex testing would be a less expensive approach, because it involves culture-based testing only of specimens that are positive by CIDT, which (based, for example, on data from the Utah Department of Health) would mean culture-based testing of only about 15% of specimens. Costs might be further reduced if state health departments provided culturing materials for tests performed at clinical laboratories or covered transportation costs for submission of clinical specimens to public health laboratories. Another option might be to regionalize culture testing (e.g., by having it performed by Integrated Food Safety Centers of Excellence or on contract by one or more private laboratories).

Additional comments were made across several other areas:

- **The need to work with FDA to ensure that public health needs are addressed during the approval process for CIDTs *(comments as follows)***
  - Perhaps FDA could require that CIDTs include in their package insert a requirement for reflex testing at state health departments when results are positive. However, package inserts are unlikely to be effective for several reasons (e.g., the sentence requiring reflex testing of positive specimens may not stand out in a package insert, clinicians may not read the inserts. Some combination of legal, regulatory, and educational approaches might work best.

- **Problems in arranging confirmatory testing *(comments as follows)***
  - Frontline healthcare providers understand that it is important to address the needs of the community as well as the patient. During an outbreak in Oklahoma, for example, when cases of *Escherichia coli* infection involving a new serogroup were not identified by tests used in hospital laboratories, the state health department contacted physicians through its ongoing physician training plan and had them send specimens from suspected cases of *E. coli* infection to public health laboratories for additional testing. This example of partnering with frontline healthcare providers might be a good model to follow in arranging for confirmatory culture-based testing of specimens that test positive for foodborne diseases by CIDT.
  - During the 2012 West Nile virus outbreak, some commercial tests did not work properly, and some states requested specimens be forwarded to public health laboratories for confirmatory testing using a test developed at CDC. This process was labor intensive, required repeated requests to clinical laboratories, and provided a low number of specimens for testing.
  - Because West Nile rates are low except during outbreaks, West Nile virus is a good candidate for regionalized testing.
- **CIDT-specific issues *(comments as follows)***
  - The transition from culture-based to molecular technology is not likely to happen rapidly during a time of healthcare crisis.
  - Dr. Goodman noted that without specific legal authority FDA cannot require clinical laboratories to submit samples to public health laboratories for reflex testing. He suggested taking a pathogen-specific approach to advancing the transition that involves: (1) identifying which information is most critical for public health surveillance (e.g., incidence of pathogens of public health importance and their drug susceptibilities); (2) what proportion of isolates must be tested to obtain that information; and (3) whether genetic testing can provide this information or whether culture-based testing remains critical.
  - A pathogen-specific approach might also make sense because of reimbursement issues. As multi-pathogen CIDTs come into use at private laboratories, reimbursement rates for their use will differ from state to state. Especially in the short term, these disparities in reimbursement may influence the decisions of clinical laboratories regarding adopting CIDT testing for a given pathogen.

➢ **Antimicrobial Resistance Working Group Report**

BSC member Andy Pavia, Chief, Division of Pediatric Infectious Diseases, University of Utah, reported on the May 7 meeting of the Antimicrobial Resistance Working Group (ARWG), which included an update on CDC's ongoing AR threat assessment and a review of the CDC Framework for Antimicrobial Stewardship and Appropriate Antibiotic Use.

Update on CDC's AR threat assessment. At the December 2012 BSC meeting, the ARWG expressed support for CDC's efforts to develop a methodology for AR threat assessment, in fulfillment of the 2011 Generating Antibiotic Incentives Now (GAIN) Act (H.R. 2182). The assessment includes bacterial threats in the United States. When the assessment is complete, CDC's Office of Antimicrobial Resistance plans to publish the results in the scientific literature or in a CDC AR report.

CDC has proposed three categories of AR threats:

- **Urgent.** These are high-consequence AR threats because of significant risks identified across several criteria. These threats may not be currently widespread in all populations but have the potential to become so and require urgent public health attention to identify infections and to limit transmission. An example of an "Urgent" threat is CRE.
- **Serious.** These are significant AR threats but for varying reasons are not considered urgent threats at this time. These are threats that require public health monitoring and prevention activities. An example is extensively drug-resistant (XDR) *Mycobacterium tuberculosis* infections, which have significant clinical and economic impact and very limited treatment options, but the current and projected U.S. incidence of these infections is low. Other examples of "Serious" threats include methicillin-resistant *Staphylococcus aureus* (MRSA), nontyphoidal *Salmonella* (ceph –R, FQ-R), and MDR-TB.
- **Emerging.** These threats include the bacterial pathogens in which the incidence of resistance is low and/or there are multiple therapeutic options for resistant infections. These bacteria are important human pathogens causing serious infections. Threats in this category require monitoring and, in some cases, rapid incident or outbreak response. Examples of "Emerging" threats include *Neisseria meningitidis* (with resistance to recommended therapy or prophylaxis) and *Streptococcus agalactiae* (with resistance to recommended therapy).

Pathogens currently under review by CDC include *Acinetobacter* spp., *Campylobacter* spp., *Candida* spp., *Clostridium difficile,* Enterobacteriaceae (including CRE and extended-spectrum β-lactamases), *Enterococcus* spp., *M. tuberculosis, Neisseria gonorrhoeae, N. meningitidis, Pseudomonas aeruginosa, Salmonella* spp., *Shigella, S. aureus, Streptococcus agalactiae, Streptococcus pneumoniae,* and *Streptococcus pyogenes.* Criteria for categorizing each pathogen as "Urgent," "Serious," or "Emerging" include clinical impact, economic impact, availability of limited treatment options, current incidence, 10-year incidence, transmissibility, and prevention barriers. The transmissibility criteria include transmissibility of mutations conferring resistance, as well as transmissibility of the pathogen itself.

Issues under discussion include whether to replace "Emerging" with a better term and how to communicate the assessment data and its implications to medical and public health partners and to the public. Gaps in our knowledge of how to prevent some of the "Urgent," "Serious," and "Emerging" pathogens remain significant.

CDC Framework for Antibiotic Stewardship and Appropriate Antibiotic Use. The proposed program goal for the CDC Framework for Antibiotic Stewardship and Appropriate Antibiotic Use is to ensure the implementation of effective strategies to improve antimicrobial use in all U.S. healthcare settings. Proposed program objectives include

- Developing target percentages for uptake of stewardship activities in different healthcare settings
- Developing an annual report on implementing stewardship activities in U.S healthcare settings that includes process and outcome metrics
- Setting national, and perhaps state-level, goals for reducing inappropriate and overall use of antibiotics in outpatient settings

Dr. Pavia noted that antibiotic stewardship is in its infancy, with important indicators still to be developed. Current data suggest that antibiotic use in the United States continues to be high, with an average of four outpatient prescriptions for every five persons per year.[17] This average masks considerable regional variation in the use of antibiotics that might be addressed via improved stewardship. CDC suggests five 5-to-10-year action items for framework implementation:

1. Promote implementation of appropriate use strategies in all U.S. health settings
2. Conduct surveillance of antimicrobial use in all U.S. health settings
3. Establish and evaluate indicators of appropriate antibiotic use
4. Establish structure and process indicators for stewardship and appropriate use activities
5. Strengthen the scientific basis for program evaluation

CDC's ongoing implementation of action item #3 (*Establish and evaluate indicators of appropriate antibiotic use*) involves several ongoing outpatient studies. Examples include

- An HEDIS quality measures analysis that examines appropriate testing for children with pharyngitis; appropriate treatment for children with upper respiratory infection; and avoidance of antibiotic treatment in adults with acute bronchitis
- National Ambulatory Medical Care Survey studies that examine antibiotic prescribing practices for community-acquired pneumonia in adults, for pharyngitis in adults and children, and for otitis media in children

CDC's efforts to improve antibiotic stewardship in hospitals include evaluating the effectiveness of an "antibiotic time-out" and conducting a pilot program with five hospitalist groups and the Institute for Healthcare Improvement to explore roles that hospitalists might take in leading stewardship interventions.

Future regulatory or accreditation approaches to implementing antibiotic stewardship programs in hospitals include

- Working with the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America to develop potential quality measures for antibiotic use for submission to the National Quality Forum
- Continuing to work with CMS to evaluate antimicrobial stewardship quality measures and incentives
- Conducting an initial outreach to The Joint Commission to consider accreditation measures related to antibiotic stewardship

To advance implementation of action item #4 (*Establish structure and process indicators for stewardship and appropriate use activities*), CDC is developing an evaluation tool that will help hospitals document and assess their stewardship activities and infrastructure. CDC hopes to pilot test this tool during field investigations at hospitals. At the present time, CDC is also pilot testing audit and evaluation tools that can help hospitals assess appropriate antibiotic use to treat community-acquired pneumonia, urinary tract infections, and MRSA.

[17] Hicks LA, Taylor TH Jr, Hunkler RJ. U.S. outpatient antibiotic prescribing, 2010. N Engl J Med 2013;368(15):1461–2.

At the ARWG meeting, CDC staff presented an overview of CDC programs that are contributing to implementation of action item #4. These activities include

- The National Healthcare Safety Network (www.cdc.gov/nhsn/), whose Antimicrobial Use and Resistance Module includes summary measures for hospitals that allow inter-facility comparisons
- The Emerging Infections Programs (www.cdc.gov/ncezid/dpei/eip/), whose HAI-Community Interface activity can provide a national estimate of antibiotic usage patterns from a sample of hospitals, based on hospital-wide prevalence surveys of HAIs and antimicrobial use
- *Get Smart for Healthcare (*http://www.cdc.gov/getsmart/healthcare/), whose audit tools provide facility-specific assessments of appropriate antibiotic use for internal purposes

Following the presentation, the ARWG discussed the following five questions:

1. What methods may be useful in measuring the uptake and implementation of stewardship and appropriate use activities in U.S. healthcare settings?

   ARWG suggestions included the following:
   - Measurement of stewardship implementation will require identifying specific activities that constitute stewardship
   - Stewardship programs should offer recognition to facilities meeting certain criteria (e.g., a "certificate" program)
   - Ideally, accreditors, payers, licensing agencies, and public health agencies should all have an interest in establishing stewardship programs

2. What process indicators would be useful in measuring success in achieving widespread adoption of stewardship?

   ARWG suggestions included the following:
   - Both process and patient-centered outcome (quality of care) measures are needed
   - Indicators should help assure that reasonable procedures are followed (obtaining necessary cultures, assuring necessary documentation, etc.)
   - Indicators should target specific diagnoses or syndromes (e.g., asymptomatic bacteriuria)

3. What are the best clinical indicators to demonstrate that stewardship and appropriate use activities are succeeding?

   The ARWG agreed that
   - No single measure is ideal because outcomes are multifactorial
   - Risk-adjusted use rates remain important
   - The development of National Quality Forum measures would be very useful
   - Measures similar to CMS Surgical Care Improvement Project measures (https://www.premierinc.com/safety/topics/scip/) might also be useful
   - Lower rates of *C. difficile*, risk-adjusted resistance rates, and rates of adverse events are interesting to know but difficult to measure and not directly tied to stewardship efforts

4. How do the approaches for ensuring widespread uptake of stewardship/appropriate antibiotic use activities differ between inpatient and outpatient settings?

   The ARWG believes that it is helpful to consider stewardship approaches in inpatient and outpatient settings as part of a continuum. However, flexibility is required in applying particular approaches due to significant differences in the availability of information and the ability to intervene in these settings.

5. What is the right mix of policies and strategies to achieve the improvements that we want to measure?

   The ARWG agreed that
   - Education and messaging—of both providers and patients—are vital but are unlikely to produce significant impact in the absence of financial motivators
   - Payers, accreditors, and regulators need to get involved

The ARWG also suggested that it is important to emphasize and understand the role of the laboratory in achieving stewardship goals (e.g., the use of diagnostics for situational awareness) and to take advantage of Accountable Care Organizations and other aspects of the new financial environment for healthcare to promote financial and quality incentives for antibiotic stewardship.

Next steps. The ARWG plans to hold two conference calls prior to the BSC meeting in December 2013. Topics for review and discussion will include (1) identification of evidence gaps for the development of stewardship guidelines; (2) identification of infection control paradigms to prevent transmission of AR threats; and (3) AR issues related to the animal/human interface.

Discussion

Comments on these issues from BSC members and meeting participants included the following:

- The words that describe categories of AR threats (e.g., "Urgent" and "Serious") should be carefully chosen.
- Data on the effectiveness of antibiotic stewardship are limited. Studies are needed to determine which interventions are most effective in decreasing the use of particular antibiotics or in reducing their volumes in particular settings.
- A routine diagnostic tool is needed to confirm that a patient with uncomplicated illness does not have a bacterial infection. Development of technology to distinguish between viral and bacterial infections should be a priority.
- A workshop on antibiotic use in animals held in January as part of the North American Veterinary Conference presented data on the large amount of antibiotics administered to large animals. Veterinary associations are starting to devise their own antibiotic use guidelines.

CONCLUSION

Drs. Berkelman and Khabbaz thanked the Board members for their service and their support of CDC's mission. Before closing, Dr. Berkelman mentioned several issues that arose during the meeting that might benefit from further discussion: (1) the use of school-based programs in increasing HPV vaccination rates and improving other health outcomes; (2) CDC's role in helping compounding pharmacies prevent contamination; and (3) establishment of the BSC working group on the use of advanced molecular diagnostics and bioinformatics technologies to improve public health.

The next BSC meeting will be held December 11–12, 2013. One or more phone meetings may be held over the course of the year to follow up on today's discussion.

The meeting was adjourned at 3:30 pm.

APPENDIX

Meeting Participants

BSC Members

Ruth Berkelman
Jack Bennett
Kristy Bradley
Harry Chen
Carolyn Deal *(representing National Institute of Allergy and Infectious Diseases on behalf of Carole Heilman)*
Rainer Engelhardt
Matt Erdman *(representing U.S. Department of Agriculture on behalf of Beth Lautner)*
Bruce Gellin
Jesse Goodman
Jim Hadler
Kent Kester *(participated by phone)*
Jeanne Marrazzo
Laurene Mascola
Andy Pavia
Scott Ratzan
Bob Sautter
Kim Smith
Julio Sotelo
Jill Taylor
Jon Temte
Bob Tesh
Judy Wasserheit

Partners and Public Visitors

Timothy Baker *(Northrop Grumman Health IT)*
Frank Cockerill *(Mayo Clinic; Mayo Medical Laboratories)*
Jeff Engel *(Council of State and Territorial Epidemiologists)*
Tom File *(National Foundation for Infectious Diseases)*
Jane Getchell *(Association of Public Health Laboratories)*
Joe Hilinski *(Pediatric Infectious Diseases Society)*
Lilly Kan *(National Association of County and City Health Officials)*
Harry Keyserling *(American Academy of Pediatrics)*
Jennifer Lemmings *(Council of State and Territorial Epidemiologists)*
Ruth Lynfield *(Infectious Diseases Society of America)*
José Montero *(New Hampshire Department of Health and Human Services)*
Mark Raizenne *(Public Health Agency of Canada)*
Ken Scott *(Public Health Agency of Canada)*
Susan Sharp *(Kaiser Permanente Northwest)*
Kathy Talkington *(Association of State and Territorial Health Officials)*
Christine Vaupel *(GlaxoSmithKline)*

CDC Staff

Bishwa Adhikari
Yusra Ahmad
Ronny Alford
Jorge Arana
Jill Barr-Walker
Beth Bell
Elise Beltrami
Stuart Berman
Gwen Biggerstaff
Carolyn Black
Sharon Bloom
Gail Bolan
Anna Bowen
Brad Bowzard
Gary Brunette
Courtney Callahan
Roberta Carey
Heather Carleton
Evelyn Cater
Joanne Cono
Bob Cottingham
Angela Coulliette
Sean Courtney
Emily Cramer

CDC Staff (cont.)

Reneé Crawford
Peter Crippen
Cecilia Curry
Kim Distel
John Douglas
Richard Draut
Scott Fridkin
Katie Fullerton
Jon Gentsch
Stephen Hadler
Rana Hajjeh
Susan Hariri
Tom Hearn
Angela Hernandez
Marsha Houston
Rima Khabbaz
Lindsay Kim
John Kools
Wendi Kuhnert
George Lathrop
Miriam Lawson
Alexandra Levitt
Brandi Limbago
Duncan MacCannell
Eva Margolies
Lauri Markowitz
Cliff McDonald
Pierre Michel
Jennifer Mitchell
Steve Monroe
Dale Morse
Robin Moseley
Anna Newton
Jan Nicholson
John O'Connor
Steve Oberste
Cheryl Ocfemia
Clint Paden
Mark Pallansch
Jean Patel
Larry Pickering
Bob Pinner
Kristin Pope
Krista Queen
Sonja Rasmussen
John Ridderhof
Lisa Rotz
Catherine Sager
Don Sharp
Pattie Simone
Sharon Slocumb
Nicole Smith
Steve Solomon
Jessica Soper
Aijun Srinivasan
Erin Stone
Dave Swerdlow
Deborah Talkington
Rob Tauxe
Angela Thompson
Suxiang Tong
Ron Van Duyne
Travis Wagner
John Ward
Todd Weber
Cindy Weinbaum
Sarah Wiley
Michelle Wilson
Lyna Zhang
Beth Unger

I hereby certify that to the best of my knowledge, the foregoing minutes of the proceedings of the meeting of the Board of Scientific Counselors, Office of Infectious Diseases, on May 8, 2013, are accurate and complete.

_____ _____

Ruth Berkelman, M.D. Date
Chair, BSC, OID