Board of Scientific Counselors, Office of Infectious Diseases
Centers for Disease Control and Prevention

Teleconference on August 19, 2014

A 2-hour open teleconference of the Board of Scientific Counselors (BSC), Office of Infectious Diseases (OID), was held on August 19, 2014, from 1:00 to 3:00 PM, Eastern Time. The meeting was announced in the Federal Register on July 29.

The meeting included reports from the BSC/OID Antimicrobial Resistance Working Group, Food Safety Modernization Act (FSMA) Surveillance Working Group, and Infectious Disease Laboratory Working Group, followed by updates on the Ebola outbreak in West Africa, the spread of chikungunya fever in the Americas, and the humanitarian crisis involving thousands of unaccompanied children entering the United States from Central America. A presentation was also provided on CDC's intensified efforts to improve laboratory safety, following the recent laboratory incidents involving improper handling, transfer, and storage of select agents at CDC and other federal agencies

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 Designated Federal Officer. Dr. Berkelman welcomed four new BSC members: Mike Brady, MD, Associate Medical Director, Nationwide Children's Hospital, Columbus, Ohio; Tim Jones, MD, State Epidemiologist, Tennessee Department of Health; Ruth Lynfield, MD, State Epidemiologist and Medical Director, Minnesota Department of Health; and Lee Riley, MD, Professor and Chair, Division of Infectious Diseases and Vaccinology, School of Public Health, University of California, Berkeley.

Dr. Khabbaz described recent OID and national center staffing changes, including the appointments of Michael Shaw, as OID Senior Advisor for Laboratory Science; Inger Damon,[*] as Director, Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID); Philip LoBue, as Director of the Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP); and Eugene McCray, as Director, Division of HIV/AIDS Prevention, NCHHSTP.

WORKING GROUP REPORTS

1. Antimicrobial Resistance Working Group (ARWG)

A slide set provided by BSC member Dr. Robert Weinstein, the AR Working Group chair, is posted at http://www.cdc.gov/oid/docs/arwg_bsc_report_slides.pdf

Dr. Weinstein provided an update on the May 6th meeting of the ARWG, which included presentations on the development of a framework for prevention of carbapenem-resistant Enterobacteriaceae (CRE), on judicious use and antibiotic stewardship activities, on AR funding in the President's FY 2015 budget, and on drug-resistant gonorrhea. Following discussions of each topic, the ARWG drafted a working plan for FY 2014–16 with three focus areas: Laboratory Capacity and Surveillance; Improving Antibiotic Use and Stewardship; and Promoting Evidence-based Prevention Practices. The working group will hold conference calls for each focus area on a monthly or bi-monthly basis.

[*] Currently serving as Incident Manager of CDC's Ebola Response

The aim of the Laboratory Capacity and Surveillance focus area is to identify gaps in laboratory testing and consider how they might be filled. The ARWG discussed the need for new methods to

- Identify patients colonized with multidrug-resistant organisms (MDRO) like CRE
- Conduct molecular typing of MDRO (e.g., to provide outbreak data and better understand transmission dynamics)
- Detect resistance mechanisms for MDRO pathogens such as CRE
- Identify extreme-drug-resistant (XDR) or pan-drug-resistant (PDR) pathogens and determine their susceptibility to new drugs or older drugs like polymyxin B and fosfomycin.

The aims of the Antibiotic Use and Stewardship focus area are to promote adoption of a CDC-proposed National Quality Forum (NQF) antibiotic stewardship measure; identify knowledge gaps regarding practices and policies that can improve antibiotic use, especially in outpatient and long-term care (LTC) facilities; identify "easy wins" that can demonstrate the effectiveness of interventions to improve antibiotic use; recommend strategies to increase public awareness and acceptance of antibiotic stewardship; and promote the use of reimbursement policies and/or incentives that can help change prescribing behaviors.

The aims of the AR Prevention focus area include developing criteria for identifying effective prevention strategies for improving antibiotic use and stewardship in different settings (e.g., in acute care, LTC, and outpatient facilities); identifying adaptations that can broaden uptake of regional prevention strategies; considering the potential of future AR prevention strategies that do not require changes in prescribing behavior (e.g., treating infections by restoring gut microbiota and developing vaccines against drug-resistant diseases); and assessing the pros and cons of requiring notifiable disease reporting and/or public reporting of selected AR infections.

Discussion

- In response to a question about emergence of resistance due to over-use of antibiotics in animal husbandry, Beth Lautner, USDA, reported that USDA is developing an action plan to reduce AR use in agriculture. It was also noted that improved surveillance data on antibiotic resistance in foodborne pathogens (as discussed by the FSMA Surveillance Working Group) can help guide and measure the outcomes of initiatives to reduce the use of antibiotics in food animals.
- Another major issue is improving capacity to detect resistance through culture-independent molecular testing, as clinical laboratories move away from culture-dependent testing. At the present time, for example, there are no FDA-approved PCR-based methods for detection of CRE, so laboratories rely on culture-based screening, which takes days. Jean Patel, CDC Office of Antimicrobial Resistance, noted that methods for identification of patients colonized by CRE and other MDRO will be one of the first testing gaps discussed as part of the ARWG's Laboratory Capacity and Surveillance focus area.
- In response to a question about turnaround times, Dr. Weinstein agreed that faster provision of resistance information to clinicians—who are likely to default to use of broad-spectrum antibiotics in the absence of data—is a major issue for ARWG discussion. Specimens may be sent to off-site laboratories for rapid molecular testing, which may result in delayed turnaround time, which in turn may result in less diagnostic testing and greater use of empiric therapy.

2. Food Safety Modernization Act (FSMA) Surveillance Working Group

A slide set provided by BSC member Dr. Harry Chen, the FSMA Surveillance Working Group chair, is posted at http://www.cdc.gov/oid/docs/fsma_bsc_report_slides.pdf

Dr. Chen provided an update on the May 5–6 meeting of the FSMA Surveillance Working Group, which included review and discussion of CDC initiatives to address gaps in foodborne disease surveillance, with special emphasis on foodborne diseases caused by antibiotic-resistant bacterial pathogens. Updates were provided on initiatives

to improve 1) culture-independent diagnostic testing for foodborne pathogens and 2) surveillance for foodborne cycloporiasis.

The working group considered the public health use of surveillance data on drug-resistant foodborne pathogens for 1) tracking changes in resistance over time; 2) detecting, investigating, and controlling outbreaks of resistant infections; 3) measuring harm to public health caused by resistant infections; and 4) attributing drug-resistant outbreak pathogens to specific sources and reservoirs.

The working group also discussed areas for growth and enhancement of the National Antimicrobial Resistance Monitoring System (NARMS; http://www.cdc.gov/narms/), which is a collaboration among CDC, USDA, and FDA. In 2013, data from the NARMS retail meat surveillance program helped identify multidrug-resistant *Salmonella* Heidelberg associated with frozen chicken as the cause of a multistate outbreak (http://www.cdc.gov/salmonella/heidelberg-10-13/timeline.html). In addition to providing timely data during outbreaks, NARMS collects susceptibility data that can be used to manage risks associated with antibiotic use in food animals. Areas for enhancement include improving data quantity and quality (e.g., testing a greater variety of sources, including non-food sources); improving the interpretation of AR findings (e.g., to better understand linkages between virulence and AR); increasing stakeholder engagement (e.g., tailoring public health messages to target audiences); and further aligning resources (e.g., identifying and utilizing other existing clinical and regulatory data sources).

In terms of future directions, the Working Group noted that whole genome sequencing (WGS) may supplant multiple testing methods now in use (e.g., serotyping, PFGE, and culture-based susceptibility testing). In the future, WGS could enhance many aspects of disease surveillance, providing information on gene sequences, resistance mechanisms, virulence profiles, phage-typing of *Salmonella*, and genetic markers for source attribution. Use of WGS may lead to a better understanding of emerging trends and may also provide cost savings.

Next steps include drafting the working group's Annual Report to the HHS Secretary and developing an FY 15 agenda, whose items may include tools for investigating foodborne outbreaks; improving surveillance for *Vibrio cholerae*, toxoplasmosis, cyclosporiasis, or cryptosporiasis; identifying environmental factors that contribute to foodborne outbreaks; and updates on how CDC is making use of the working group's guidance.

Discussion

- BSC ex officio member Steve Ostroff (FDA) reported that FDA held a 2-day meeting last week to consider future directions for NARMS. FDA issued voluntary guidance last December on use of antibiotics in food animals, which stated that medically important antibiotics should be labeled as not to be used for growth promotion. Dr. Ostroff observed that NARMS is ideally suited to monitor the impact of FDA guidance by examining changes in patterns of antibiotic resistance in response to changes of antibiotic use on farms.
- BSC ex officio member Carole Heilman (National Institute of Allergy and Infectious Diseases [NIAID]) noted that adding databases to NARMS to increase its data quality and quantity will require infrastructure-building and modeling to validate the integration of each additional database. Dr. Chen said that this question will be addressed at the December meeting of the FSMA Surveillance Working Group, with further information shared with the BSC as appropriate.
- In response to a question about monitoring resistance in animal isolates, it was noted that animal isolates are tested at the time of slaughter, so that both healthy and ill animals are tested.

3. Infectious Disease (ID) Laboratory Working Group

A slide set provided by BSC members Drs. Jill Taylor and Susan Sharp, ID Laboratory Working Group co-chairs, is posted at http://www.cdc.gov/oid/docs/idlwg_bsc_report_slides.pdf

The May 7 meeting of the ID Laboratory Working Group focused on the CDC Advanced Molecular Detection(AMD) initiative (http://www.cdc.gov/amd/index.html) . The meeting included an overview of CDC's AMD activities; updates on AMD activities conducted by FDA, NIH, and state health laboratories; and a review of federal data-sharing policies and data-sharing issues that require additional discussion (e.g., ensuring data quality and addressing privacy issues related to the use of metadata).

In discussing the AMD initiative, the working group made these observations:

- **Collaborations**
  - Some state health departments are already using AMD techniques, most often in partnership with academic institutions or as part of the FDA GenomeTrakr network. CDC should be involved in these collaborations as soon as possible.
  - NIH supports development of new cutting-edge AMD tools and should work with FDA to create a framework to facilitate their evaluation and approval
  - Clinical laboratories are rapidly transitioning from culture-dependent to PCR-based tests. In the near future, they are likely to transition to other non-traditional and closed-system technologies.
- **Staying ahead of the curve.** In view of the rapid rate of technologic change, by the end of 2018, CDC needs to be poised to lead into the future (not plateau or become obsolete). CDC should
  - Work with academic, clinical, state, and industry partners to make the best possible public health use of this evolving technology
  - Ensure that the CDC Core Bioinformatics Program benefits from the experiences of others and avoids obstacles already overcome by others
  - Consider staggering its purchases of hardware to ensure that each purchase involves the most current technology
- **Future directions**
  - Over time, AMD testing will provide more accurate knowledge of the "universe" of microbes
  - Data standards and reference databases developed today may still be useful in a few years, although they will have evolved
  - Cloud bioinformatics is likely to become an important AMD tool, making it unnecessary to purchase new software and hardware. In the near future, cloud-based surveillance data on reportable diseases may help us identify outbreaks by automatically flagging possible disease clusters.
  - Over time, AMD databases may incorporate additional types of metadata (e.g., immunologic data, environmental data, and data on microbiomes)

Discussion

- In response to a question about the One Health approach to disease surveillance, Dr. Taylor noted that the ID Lab Working Group might benefit from adding an animal health expert. Dr. Khabbaz suggested to the BSC that a representative from USDA be considered for the working group.
- In response to a question about FDA GenomeTrakr network, Dr. Ostroff agreed that it is a good model for building AMD capacity at additional state laboratories.

- In response to working group concerns that CDC has not been part of the states' earliest AMD efforts, Dr. Khabbaz reported that CDC has responded to these concerns (which were raised at the May meeting) by putting end-of-fiscal-year 2014 funds into state projects.[†]
- In response to a question about sharing data with academic partners—who could provide CDC with valuable feedback and assistance on AMD projects—Dr. Khabbaz noted that CDC is working to overcome barriers to data-sharing, including privacy issues related to sharing state-level public health data.
- In response to a question about the lack of PCR-based tests for resistance markers, Dr. Sharp agreed that this is a major issue. The working group will continue to consider how to work with industry partners to ensure that laboratories, physicians, and epidemiologists obtain the information that they need.

SELECTED OID PRIORITY ACTIVITIES

Beth Bell, NCEZID Director, provided the following updates on selected OID priority activities:

West Africa Ebola Outbreak. This outbreak is the largest Ebola outbreak in history as well as the first in West Africa. The number of cases (2,200 as of the date of the teleconference) is larger than the total number of cases detected since Ebola was first identified in the 1970s, and half of the cases have been fatal. Three countries are affected—Liberia, Sierra Leone, and Guinea—and there is a cluster of cases in Nigeria. The outbreak has been designated by WHO as a Public Health Emergency of International Concern (PHEIC) under the 2005 International Health Regulations (IHR). Therefore, all member countries are required to report Ebola cases and conduct response planning.

The scale-up of the outbreak response includes

- Detection, which requires adequate laboratory facilities and testing capabilities in each country.
- Treatment, which requires adequate healthcare facilities. This is an acute issue in Liberia and Sierra Leone, where many areas lack facilities to isolate and care for patients. There is also a lack of personnel and capacity for managing cases, for providing supportive care, and for conducting contact-tracing and follow-up.
- Prevention, which requires 1) improving hospital infection control, 2) preventing transmission during burial practices, and 3) preventing transmission when handling bush meat.

The CDC Emergency Operations Center (EOC) has been activated at the highest level, which has only been done a few times before (e.g., for the H1N1 pandemic). CDC is sending more than 50 personnel overseas to help with case identification, contact-tracing, and data management; to provide laboratory support; and to train healthcare workers to improve infection control in hospitals. CDC personnel are also providing assistance with exit screening, in accordance with IHR requirements.

The risk of Ebola transmission to the United States is very low, although we might see a few imported cases. In past years, imported cases of other viral hemorrhagic fevers—including Marburg (which is very similar to Ebola) and Lassa–were managed effectively in U.S. hospitals using well-established protocols. CDC has posted guidance on laboratory detection and infection control for state and local partners.

Chikungunya Fever. The first case of chikungunya fever in the Americas was reported in St. Martin in December 2013. As of last week, local transmission had been reported in 29 countries and territories in North, Central, and

[†] These projects include providing resources and training via the Epidemiology and Laboratory Capacity (ELC) program to help state health departments pilot the use of next-generation PulseNet techniques and of AMD technologies for characterizing strains *Cyclospora*, TB, and influenza. CDC is also working with APHL to develop a strategic state-level AMD roadmap and is convening a group that will help coordinate CDC/state AMD activities.

South America, with more than half a million suspected cases. This remarkable spread is likely to continue. Over the past few years, CDC worked with PAHO, the Caribbean Health Agency, and other partners to lay the groundwork for addressing outbreaks of chikungunya fever by developing regional surveillance and response plans and distributing diagnostics testing protocols and reagents to 25 countries.

In recent years, about 30 cases of chikungunya were detected in the United States each year among travelers returning from endemic areas. Not surprisingly, the number of travel-related U.S. cases has increased this year, due to cases among travelers to the Caribbean. Chikungunya is not currently reportable in the United States but will be as of January 2015. Current cases (reported via ArboNET) include several hundred in Puerto Rico. Local transmission of chikungunya has also been reported in Florida.

Unaccompanied Children from Central America. In July, CDC's EOC was also activated to address public health aspects of the humanitarian crisis caused by the entry of tens of thousands of unaccompanied minors—mostly from El Salvador, Guatemala, and Honduras—into the United States, via Mexico. Most were initially housed in Department of Defense (DoD) holding facilities until additional long-term facilities were opened by the HHS Office of Refugee Resettlement (ORR); transition to the new ORR facilities occurred over several weeks and has been completed. CDC worked with DoD and the Department of Homeland Security (DHS), providing guidance on such health issues as disease screening and vaccination (e.g., use of pneumococcal conjugate vaccine and influenza vaccine). On August 15, scientists from NCEZID and the National Center for Immunization and Respiratory Diseases (NCIRD) published a description of an outbreak of respiratory disease among these children.[‡] CDC is continuing to work with ORR, as needed.

Discussion

- A BSC member noted that CDC's activities with the Ebola and chikunyunga outbreaks demonstrate the importance of communications as a major public health tool
- In response to a question about the availability and use of ZMapp (the experimental drug used to treat two Americans who fell in in Liberia), Dr. Bell noted that no Ebola treatments have been tested in humans and that the use of ZMapp and other experimental treatments presents a range of ethical issues. The WHO Ethics Committee met in August to begin developing guidance and recommendations on how to approach the use of these treatments.[§]
- In response to a question about explaining the importance of public health to Congress and the public, Dr. Bell agreed that Ebola is a clear example of the importance of global health security—providing a stark illustration of what can happen when countries lack basic public health functions for preventing, detecting, and responding to disease.
- In response to a question about working with partners in Liberia, Sierra Leone, and Guinea (including local medical societies) to overcome communication challenges and alleviate mistrust of health personnel, Dr. Bell said that each CDC Ebola response field team includes a health communicator. These persons identify trusted local leaders and work with them to disseminate health messages via radio, videos, and texting. Dr. Bell also noted that the Ebola response effort is deepening CDC's collaboration and involvement with ministries of health in West African countries. CDC is also working with other countries contributing to the Ebola response.

[‡] Nyangoma EN, Arriola CS, Hagan J, et al. Notes from the field: hospitalizations for respiratory disease among unaccompanied children from Central America - multiple states, June-July 2014. MMWR 2014;63:698-9.

[§] Ethical considerations for use of unregistered interventions for Ebola virus disease (EVD). Summary of the panel discussion. WHO statement. 12 August 2014 (http://www.who.int/mediacentre/news/statements/2014/ebola-ethical-review-summary/en/).

UPDATE ON CDC LABORATORY SAFETY IMPROVEMENTS

Michael Bell, the interim CDC Director of Laboratory Safety, reported that CDC has released reports of its internal investigations into the recent laboratory incidents involving select agents (http://www.cdc.gov/about/lab-safety/). These events have highlighted the need to move toward an overall culture of laboratory safety—not just to address individual events, but to understand underlying issues and make sustainable changes.

Following the anthrax laboratory incident, Dr. Frieden declared a moratorium on any biological material leaving any CDC BSL-3 or BSL-4 laboratory, pending a lab-by-lab review of policies and procedures for laboratory safety and security. Dr. Bell stated that the reviews are being conducted by an internal biosafety workgroup—the Laboratory Safety Improvement Workgroup (LSIW), which he leads. The workgroup will determine when the moratorium can be lifted in each laboratory, based on demonstration that appropriate protocols are in place to ensure laboratory safety. Reviews of applications to lift the moratorium in a particular laboratory are prioritized toward laboratories that provide clinically actionable results (e.g., TB laboratories) or participate in public health responses (e.g., laboratories that provide outbreak support for addressing Ebola or Chikungunya). The review process includes identification and documentation of critical control points and laboratory safety protocols.

Dr. Bell said that the LSIW is also considering sustainable ways to enhance laboratory safety in all CDC laboratories, including non-infectious-disease laboratories, and is reviewing examples of successful practices at CDC and at other institutions (e.g., use of CLIA certification in infectious disease laboratories and International Organization for Standardization (ISO) certification in environmental labs). Aims include codifying procedures that make it easy for laboratories to follow safety protocols and bolstering laboratory safety training.

CDC has also established an external advisory group of 11 laboratory safety experts (http://www.cdc.gov/about/lab-safety/workgroup.html), as a workgroup under the CDC Advisory Committee to the Director (ACD) (http://www.cdc.gov/about/advisory/advCharter.htm). The Laboratory Safety Workgroup is co-chaired by Joseph Kanabrocki, Associate Vice President for Research Safety and Professor of Microbiology, University of Chicago, and Kenneth Berns, Distinguished Professor Emeritus, Department of Molecular Genetics and Microbiology, College of Medicine, University of Florida, Gainesville. The workgroup is reviewing current protocols and advising CDC through the ACD on which ones to adopt. It has met once by phone and will have its first in-person meeting in October. Dr. Bell stated that, in the meantime, CDC is gathering information on safety issues and obstacles directly from our laboratory staff. The goal is to make laboratory safety another point of laboratory excellence at CDC.

Discussion

- In response to a question about borrowing safety training practices from other disciplines, Dr. Mike Bell noted that CDC is reaching out to groups with worker-safety experience in areas such as mine safety and engineering.
- In response to a question about determining whether laboratory protocols are necessary and scientifically sound—as well as safe—Dr. Michael Shaw, OID Senior Advisor for Laboratory Science, agreed that we need thoughtful approaches to laboratory safety that require a focus not only on physical safety but also on the safety inherent in a protocol. Due diligence in reviewing an old protocol or adopting a new one includes considering all aspects of the procedure, especially when new machines are used in new locations by new people.
- Dr. Taylor noted that building a culture of laboratory safety requires multiple approaches and redundant procedures so that if a mistake is made, there are multiple layers of protection.

OPEN PHONE LINES—QUESTIONS/COMMENTS FROM PARTNERS AND THE PUBLIC

Scott Becker, Executive Director, Association of Public Health Laboratories (APHL), expressed appreciation to CDC for its ongoing work on the Ebola outbreak and for addressing laboratory incidents. He emphasized the importance of health communications and thanked CDC for working with partners to advance these efforts.

FINAL BSC COMMENTS/DISCUSSION

- In regard to whether protocols for the review of dual-use research should be included as a possible future BSC agenda item, Dr. Khabbaz said that many other groups are already considering this issue. While CDC is not engaged in research that could result in increased influenza virus transmissibility, CDC is involved in other types of gain-of-function studies on influenza for public health purposes, including research to monitor for and better understand naturally occurring resistance to antiviral therapies. Dr. Shaw added that CDC is working with other government agencies to develop dual-use protocols, and that CDC has a dual-use protocol in place. An update on this issue can be provided at the next BSC meeting.
- In regard to lessons learned about laboratory safety that might be of use to others, Dr. Khabbaz noted that CDC's reports on the anthrax and influenza incidents have been sent to the BSC and are available online (http://www.cdc.gov/about/lab-safety/). An update on laboratory-safety lessons learned can be provided at the next BSC meeting.
- Dr. Anne Schuchat, NCIRD Director, noted that the laboratory incidents may serve as a major transition point—causing us to examine laboratory safety from a broader, systems-wide point of view. Dr. Taylor commended CDC for its transparency and agreed that lessons learned about laboratory safety may be valuable to many partners.

CLOSING REMARKS

Dr. Berkelman thanked everyone for their attendance and participation. The next BSC meeting will be held on December 10 and 11, 2014.

While CDC does not engage in GOF transmissibility studies with highly pathogenic avian influenza H5N1 viruses, CDC is involved in other types of GOF studies for public health purposes including research to monitor for and better understand naturally occurring resistance to antiviral therapies and studies to develop better diagnostic capacities.

BSC Member and CDC Staff Participants

BSC Members

Ruth Berkelman
Jack Bennett
Kristy Bradley
Mike Brady
Harry Chen
Frank Cockerill
Bruce Gellin
Carole Heilman
Tim Jones
Mohamed Karmali *(representing Public Health Agency of Canada on behalf of Judy Bossé)*
Beth Lautner
Ruth Lynfield
Laurene Mascola
José Montero
Steve Ostroff
Andy Pavia
Scott Ratzan
Lee Riley
Bob Sautter
Susan Sharp
Jill Taylor
Judy Wasserheit
Bob Weinstein

CDC Staff

Beth Bell
Mike Bell
Kim Distel
Marta Gwinn
Ellen Kersh
Rima Khabbaz
Alexandra Levitt
Gladys Lewellen
Tonya Martin
Susan McClure
Jonathan Mermin
Nancy Messonnier
Dale Morse
Robin Moseley
Ed O'Neill
Mark Pallansch
Jean Patel
Anne Schuchat
Michael Shaw
Sarah Wiley

Identified Partner Representative

Scott Becker, *Association of Public Health Laboratories*