Testimony
Before the Health, Education, Labor and Pensions Committee
United States Senate

The CDC and Public Health Response to the 2012 Fungal Meningitis and Other Infections Outbreak

Statement of

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Chairman Harkin, Ranking Member Enzi, members of the committee, thank you for the opportunity to speak to you today about CDC's response and ongoing activities related to the multi-state outbreak of fungal meningitis and other infections. CDC works 24-7 to save lives and protect people from harm and this outbreak illustrates the power of public health in action both to identify serious health problems and to coordinate a targeted response that protects our nation and its citizens from infectious disease threats.

I want to extend my sympathies to the patients affected by this outbreak. Our hearts go out to the patients and families impacted by the debilitation and death from these infections.

My remarks today will focus specifically on the identification of, and subsequent public health response to, the outbreak associated with injections of contaminated preservative-free methylprednisolone acetate (MPA), an injectable steroid produced by the New England Compounding Center (NECC). Specifically, I will cover three critical areas related to the outbreak:

- a summary of the response by CDC and our partners in state public health agencies;
- a description of the fungal infections involved in this outbreak and how these infections are affecting patients; and
- a discussion of several early lessons learned.

As of November 14th at noon (EST), a total of 461 cases, including 32 deaths, have been reported in 19 states. The cases include fungal meningitis, stroke, or other central nervous system-related infections plus 10 peripheral joint infections (i.e. knee, hip, shoulder, elbow). CDC and our partners at state and local health departments marshaled an enormous effort nationwide to determine the source and scope of the outbreak, rapidly contact patients at risk, and enlist the individual input of leading experts to help us develop novel diagnostic and treatment guidance to achieve the best possible patient outcomes. In this outbreak, local infectious disease officials, including state epidemiologists, healthcare associated infection (HAI) prevention coordinators, and others whose positions are directly supported through CDC's Epidemiology and Laboratory Capacity (ELC) cooperative agreement and CDC's Emerging Infections Program (EIP) were pivotal in the original identification of the outbreak and the substantial patient notification that followed. Their efforts at the state and local level have been extraordinary and in many cases undoubtedly contributed directly to saving the lives of exposed patients.

I would like to highlight some specific efforts by CDC and state health agencies:

- The Tennessee Department of Health (TN DOH) identified and sounded the alarm on the initial cluster of cases. The TN DOH official who alerted others about these cases serves as the state's HAI Program Director and is a graduate of CDC's Epidemic Intelligence Service (EIS) program. Tennessee also is one of CDC's 10 Emerging Infections Program (EIP) sites and as such receives additional resources that helped support their response in this outbreak.
- The Virginia Department of Health laboratory, whose staff had been trained by CDC in identifying fungi, was the first to identify the very rare fungal pathogen, *Exserohilum*. This discovery saved valuable time and provided the nation with a critical piece of information to guide diagnostic and treatment recommendations.
- The Michigan Department of Community Health identified the first case of a joint infection associated with these products.
- Over 250 Federal disease control specialists have been working out of CDC's Emergency Operations Center to coordinate the multistate fungal outbreak response efforts with Federal, state,

local, tribal, and territorial public health partners. CDC coordination was helpful to ensure patient notification, development and dissemination of treatment guidance, and rapid communication to the public and the health professions community.

- State and local public health departments, health care facilities, and CDC tracked down and contacted over 14,000 exposed patients in 23 states with facilities which received the implicated medication.
- CDC engaged the nation's leading clinical fungal disease experts to receive their individual input on the development of diagnostic and treatment guidance appropriate for identifying and treating patients that develop infections. This panel has met repeatedly as the outbreak has evolved to adjust clinical advice to very complex and rare infections. CDC has educated over 4,200 clinicians through our clinician conference calls (COCA calls) on the interim diagnostic and treatment guidance.
- CDC has prioritized transparent and rapid communication with the public in this outbreak. To date, CDC's meningitis outbreak and fungal diseases web pages have been accessed over one million times and have sourced media outlets with direct links and resources to ensure accurate reporting and broad dissemination of health messages. CDC has used the Health Alert Network (HAN) to release multiple health advisories as the outbreak has unfolded. HANs are directly distributed to health care providers nationwide. CDC has also responded to over 4,500 calls to our public inquiry line (CDC-INFO).

- CDC's mutually reinforcing laboratory and surveillance systems have been critical in confirming the cause of the outbreak:
  - CDC's fungus laboratory is the national reference laboratory and in this outbreak has served as an indispensable resource to public health and FDA laboratories to identify and confirm the variety of fungal species recovered from patient, product, and environmental samples. Because there were no available rapid diagnostic tests to identify the fungal organism(s) associated with this outbreak, CDC scientists developed and refined a real-time polymerase chain reaction (PCR) to detect fungal ribosomal DNA, and then performed DNA sequencing to identify the specific fungus by its DNA barcode.
  - CDC's HAI laboratory is working with FDA to identify other microorganisms from sealed medication vials. Few laboratories nationwide have the technical expertise and capacity to perform such complicated and exact testing to assess the presence of any bacterial contamination.
  - CDC's Infectious Diseases Pathology laboratory has been testing biopsy and autopsy samples from the outbreak. Information from these analyses provides vital clinical information on how this rare disease is affecting patients, and such information is used to inform development of CDC's interim clinical guidance.

Evolution of the Outbreak:

On September 18th, an astute clinician alerts the Tennessee Department of Health (TN DOH) of a patient with culture-confirmed *Aspergillus fumigatus* meningitis after epidural steroid injection at an ambulatory surgical center (ASC).[1] The patient received an epidural steroid injection on July 30th and was admitted to the hospital in late August.

[1] www.cdc.gov/mmwr/preview/mmwrhtml/mm61e1012a1.htm?s_cid=mm61e1012a1_w

This type of infection is exceedingly rare, and we are extremely fortunate that the clinician chose to test the patient's cerebrospinal fluid (CSF) for a possible fungal infection (which is not a routine test ordered by clinicians) and then notify the state health department when those results came back positive. After further consultation with the clinician in Tennessee, the TN DOH contacts CDC on September 20th to ask if CDC has received similar reports of unexplained fungal meningitis infections. CDC relays that it had not received reports of unexplained fungal meningitis infections and recommends that the TN DOH conduct a site visit to the ambulatory surgical center where the epidural injection was administered.

On Friday, September 21st, the TN DOH follows up with CDC about the results of the site visit. TN DOH relays that multiple products and exposures could be the source of the infection, including epidural injection tray kits, preservative-free contrast media, povidone-iodine, lidocaine, and preservative-free MPA from NECC.[2] External contamination of supplies in a common storage area at the ASC was also considered as a possible source of infection. CDC recommends that TN DOH continue to gather detailed information, including lot numbers on all of the products and sources of exposure, to facilitate further investigation. Over the weekend, the TN DOH works with the ASC and area hospitals to gather additional information and checks if there are any other *Aspergillus* or unexplained meningitis cases.

On Monday, September 24th, CDC and TN DOH discuss the investigation. The discussion focuses on additional patients with meningitis from the same ASC with similar procedures and product exposures uncovered by the TN DOH over the weekend. CSF cultures from the additional patients with meningitis were negative, but all presented with a clinical picture similar to the index patient. CDC and TN DOH coordinate on next steps of the investigation. The TN DOH contacts the Massachusetts Department of Public Health (MA DPH) in an effort to obtain more information about NECC and its products. TN DOH notifies MA DPH about its cluster of meningitis cases following epidural steroid injections[3] and that use of MPA distributed by NECC is one of the common exposures under investigation.

On Tuesday, September 25th, CDC notifies FDA that CDC and the TN DOH are investigating a cluster of meningitis cases in a single ASC in Tennessee that may be related to product contamination. CDC notes that they are investigating several product exposures as possible sources of infection. Also on Tuesday, the MA DPH and the MA Board of Pharmacy organize a call with NECC, the TN DOH, and CDC to inform NECC of the ongoing investigation and inquire about product information and adverse event reporting. Public health authorities learn about how the MPA steroid is prepared, request distribution lists for the three lots[4] identified by the TN DOH and inquire about any reports of illnesses related to MPA.[5] NECC states that it has not received reports of illnesses and that sterility testing, as well as environmental monitoring, has not demonstrated any concerning results. The MA Board of Pharmacy asks if NECC has a voluntary recall process in place if the investigation confirms contamination. NECC affirms that it does have a voluntary recall process in place.

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[2] Kainer, M., et al Outbreak of Neuroinvasive Fungal Infections Associated with Epidural Steroid Injections, Tennessee, 2012
[3] Kainer, M., et al Outbreak of Neuroinvasive Fungal Infections Associated with Epidural Steroid Injections, Tennessee, 2012
[4] Lot #05212012@68, BUD 11/17/2012; Lot #06292012@26, BUD 12/26/2012; Lot #08102012@51, BUD 2/6/2013
[5] www.cdc.gov/mmwr/preview/mmwrhtml/mm61e1012a1.htm?s_cid=mm61e1012a1_w

The following day (September 26th), the MA Board of Pharmacy initiates an inspection of NECC[6] and NECC issues a voluntary recall of the three lots of MPA identified by the TN DOH. Approximately 3,000 doses of MPA are quarantined or returned.[7] CDC is provided an invoice list of all facilities that received possibly contaminated lots and begins work with TN DOH and other state health departments to contact other clinics from the NECC distribution list to see if they are aware of any meningitis cases of unknown etiology. CDC also provides an update to FDA about the NECC call and informs FDA that NECC initiated a voluntary recall of the three lots of MPA though there was no specific evidence of product contamination. CDC asks FDA to query MedWatch reports for any related cases; the MedWatch query ultimately identifies the previously known cases from the Tennessee ASC. During this time, CDC continues to pursue other possible sources of the outbreak and contacts the New York Department of Health for assistance in contacting the company that produced the epidural injection trays used at the Tennessee ASC.

On September 27th, FDA and MA DPH begin coordination for a collaborative investigation of NECC.[8] A case is identified in another state[9] as North Carolina reports its first patient with meningitis of unknown etiology following epidural spinal injection to CDC late that evening. This is significant because it is the first evidence that the exposure may not be isolated to the TN ASC. CDC begins working with the TN DOH and NC DOH to identify common exposures in new cases from both states which include MPA from NECC as well as the same brands of povidone iodine and lidocaine. Of the patients identified thus far, only one has a culture-confirmed *Aspergillus* fungal meningitis infection. The additional patients have a similar clinical presentation of meningitis as the index case with *Aspergillus*, but no microbiological data yet link them together. The microbiological key comes later in the outbreak when the Virginia Department of Health (VA DOH) in consultation with CDC's infectious disease pathology laboratory links an unexplained death to the outbreak and identifies *Exserohilium* as the fungal pathogen related to that case.

On Friday, September 28th, CDC requests all 23 states with clinics that received the three MPA lots from NECC begin contacting patients who received epidural injections to see if there are any other meningitis cases of unknown etiology. Through the weekend of September 29-September 30th, CDC posts outbreak information to ClinMicroNet (a network of clinical labs) and the Emerging Infections Network (EIN, a network of infectious disease physicians) to help identify any additional *Aspergillus* meningitis cases or meningitis cases of unknown etiology.

On Monday, October 1st, FDA and MA Board of Pharmacy initiate a joint inspection of NECC.[10] Investigators find violations of MA pharmacy regulations[11] and the MA DPH issues a formal quarantine notice.[12]

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[6] MA DPH NECC Preliminary Investigation Findings: "…investigators found NECC employees cleaning sterile compounding areas and conducting environmental testing. MA DPH investigators also detected signs of bleach decontamination in the compounding areas."
[7] MA DPH NECC Preliminary Investigation Findings
[8] MA DPH NECC Preliminary Investigation Findings
[9] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm61e1012a1.htm?s_cid=mm61e1012a1_w
[10] http://www.cdc.gov/media/releases/2012/t1004_meningitis_outbreak.html
[11] MA DPH NECC Preliminary Investigation Findings – Investigators found that methylprednisolone products labeled as patient specific were not individual prescriptions but lists of patients generated by a clinic and provided to NECC to obtain the product which is a violation of MA pharmacy regulations.

The following day, CDC initiates a call with the 23 states that received the three NECC lots of MPA to provide updates on the investigation and share information on meningitis cases of unknown etiology as well as common exposures. While NECC products are considered the likely source of the outbreak, the investigation does not find conclusive evidence of NECC product contamination until October 4th when FDA announces it has identified by microscopy visible fungal contamination of previously sealed vials of MPA from NECC from one of the three lots identified by TN DOH.

With conclusive identification of fungal contamination, CDC activates its Emergency Operations Center on October 4th and intensifies outreach to patients and clinicians to ensure appropriate patient diagnosis and treatment. CDC also launches a fungal meningitis outbreak website to provide continual updates to patients, clinicians, and the public, and by October 5th, CDC posts the lists of the clinics that had received the three implicated lots of MPA to facilitate patient follow-up. Additionally, CDC and FDA laboratories work on pathogen identification in patient, product, and environmental samples. This combined laboratory effort ultimately recovers multiple bacterial and fungal contaminants from sealed NECC products labeled as sterile.

The Patient Experience with Fungal Meningitis and Related Infections

We do not yet have a full picture of the extent of the impact of this tragic outbreak, which clearly has devastating impacts on patients and their families. Contaminated medication was administered by injection to thousands of people, resulting in an outbreak of fungal meningitis and other infections. *Exserohilum rostratum,* the predominant fungal species in this outbreak, is a common brown-black mold found in soil and on plants, especially grasses, that thrives in warm and humid climates. Fungal infection caused by *Exserohilum rostratum* is rare and when it does occur it has generally been documented as a cause of sinus and skin infections. Diagnosis of fungal meningitis, particularly with molds, is extremely difficult because traditional diagnostic methods such as culture have limited yield.

The clinical syndromes of these infections are rare and thus lack clinical trials or other experience that provide evidence for optimal treatment. Available treatments are not straight-forward because of potential adverse events and variability among patients. With little literature describing these types of infections and limited clinical experience available, CDC solicited the individual input of outside mycology experts to help develop novel diagnostic and treatment guidance for patients at risk for these fungal infections. CDC has worked with these experts throughout the outbreak to update our interim guidance as more information has become available about the clinical experience of patients. Adequate duration of antifungal treatment is unknown although we expect a minimum of three months' treatment be considered. CDC has sent staff to states and worked with state and local health departments to abstract medical charts and gather information on patients' ongoing clinical experiences. CDC has disseminated our treatment guidance through web postings, blast emails to professional societies, and multiple clinician-specific conference calls.

As of November 13, the median age of the patients is 65 years (range: 16-92 years) and over 60 percent are female. While most of the cases have presented with meningitis, we have also seen cases of stroke,

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[12] MA DPH NECC Preliminary Investigation Findings – "The Notice directed that all methylprednisolone acetate raw materials (chemicals), all non-sterile products located at NECC used in the compounding of methylprednisolone acetate, and all inventory on the premises prepared for dispensing and stored at the pharmacy, or received by recall should be quarantined and not disposed of without the express approval of the DPH."

epidural abscess (infection between the outer covering of the brain and spinal cord and the bones of the skull or spine), osteomyelitis (bone infection), and septic arthritis (joint infection). Many patients with meningitis had only a few mild symptoms, such as headache and/or nausea or vomiting.

The incubation period has ranged from 0 to 120 days with a median of 20 days. Based on current data, the highest risk is likely to be in the first 42 days (six weeks) after last injection. Maximum incubation period for infection is not known, and the incubation period could be longer for some patients. Thus, asymptomatic but exposed patients should remain vigilant for symptoms and seek medical attention should symptoms develop. The clinical situation is still evolving. Even with treatment, we are seeing many patients return after being discharged from the hospital with new symptoms and other conditions such as arachnoiditis (inflammation of the membranes that surround nerves) and abscesses at the original injection sites. This suggests that there may be long-term complications for patients that have not yet become apparent.

To support ongoing clinical efforts, CDC has developed a Clinicians Consultation group consisting of a network of leading clinical infectious disease and fungal disease experts nationwide who have volunteered to provide consultation with clinicians providing direct patient care. CDC is also planning to continue to follow cases to help track the course of treatment and provide ongoing information on patient outcomes.

Early Lessons Learned

Outbreak responses require skilled, trained public health personnel in state and local agencies. In this outbreak, we were fortunate that trained individuals were already "on the ground" in key positions, reinforced by already-established surveillance and laboratory capacity. Personnel cuts at the state and local levels have made CDC support to state infectious disease programs key to these efforts. CDC's Epidemiology and Laboratory Capacity (ELC) cooperative agreement and the Emerging Infections Program (EIP) support this critical infectious disease capacity and networking.

This outbreak is also a reminder of the importance of CDC's infectious disease epidemiologists and laboratories to rapidly respond to and characterize outbreaks of unexplained death and illness. This outbreak exemplifies the work of CDC's disease detectives to track down and solve public health problems. CDC's laboratory capacity for infectious diseases has been a critical element in the response, identifying rare or obscure pathogens and providing added capacity as a backstop to states. With declining local resources, many states have cut back on maintaining fungal testing and instead rely upon CDC's fungus laboratory. During the peak of laboratory testing, CDC's fungus laboratory was operating 7 days a week to test the hundreds of outbreak-related samples. This outbreak has also underscored the importance of bioinformatics and genomics technologies that can help CDC and states more rapidly and decisively detect, respond to, and control large outbreaks like this one.

CDC plays a vital role not only in responding to these outbreaks but in preventing them as well. For years, CDC and its state public health partners have been the first-responders to multiple outbreaks stemming from suboptimal practices in handling sterile medications in clinics and in pharmacies. We are learning that many of these outbreaks are the result of a widespread lack of knowledge of or adherence to well-recognized regulatory and professional standards for properly handling sterile medications.

Concluding Remarks

This outbreak demonstrates the essential role that public health plays in identifying and responding to infectious disease outbreaks large or small. Our national public health capacity is disseminated to state and local responders who work on a daily basis to keep our country safe from infectious diseases – whether they are from naturally emerging threats such as a new influenza pandemic or from human-made problems such as contaminated medicines. CDC will continue to work with state partners, national experts, front-line clinicians and others to respond to the critical public health needs related to this outbreak.