Senate HELP Committee- Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak

November 15, 2012: Dr. Marion Kainer

On behalf of the Tennessee Department of Health, I would like to thank Senator Alexander for the opportunity to comment on the recent fungal meningitis outbreak. I hope to provide some insights from this tragic outbreak to the Health, Education, Labor and Pensions (HELP) Committee which I hope will assist the Committee to gain an understanding of potential opportunities to prevent and respond to such devastating outbreaks in the future.

As of November 13, Tennessee reported 81 cases and 13 deaths. Behind each one of these numbers is a lot of suffering of the patients affected, their loved ones and the communities in which they participated. One example: The death of Diana Reed who, according to her brother, was her husband's arms, legs and voice, has been devastating. Her husband has Lou Gehrig's Disease and Diana was instrumental in keeping his accounting business going and in helping her husband get in and out of bed, the shower and his wheelchair. The family is trying to figure out how they will carry on and enable her husband the ability to maintain his dignity and to keep his work without her; they shared their story with the New York Times.

Fungal meningitis is extremely rare. One of our great challenges was knowing just what we were dealing with as more and more patients fell ill. Even though we were looking for a fungus because the initial patient reported to us had been diagnosed with a fungal meningitis, none of the diagnostic tests yielded confirmed results until October 3, 15 days after we initiated our investigation of the first case.

Below is an outline of the timeline of major events of this outbreak and the role of the Tennessee Department of Health in this investigation. I will also discuss lessons learned in the context of this investigation.

Timeline of Major Events:

Date	**Major Events**	**Case Count as Known at That Time**
Day 1: Tuesday Sept 18	Dr. Marion Kainer, Director of the Tennessee Department of Health (TDH) Healthcare Associated Infections and Antimicrobial Resistance Program, receives an email sent by Dr. April Pettit, Infectious Diseases Physician, Vanderbilt University Medical Center (VUMC) about a patient with meningitis caused by a fungus, *Aspergillus fumigatus,* who had a recent epidural injection at a pain clinic. Dr. Kainer and Dr Pettit discuss the case. Dr. Kainer speaks with Ms. Candace Smith, infection preventionist (IP) at St Thomas Hospital (STH), which is organizationally affiliated with the St Thomas Outpatient Neurosurgical Center (STONC) where the patient received the injection. Dr. Kainer requests details of the procedure, states that the infection is a sentinel	1 case of Aspergillus meningitis

	event of concern, which deserves a careful investigation and requests that Ms. Smith commence an inspection of the pain clinic (e.g., evidence of any construction, water damage) and to inquire about any potential additional cases.	
Day 3: Thursday, Sept 20	IP from STH contacts Dr. Kainer and confirms that index case had an epidural steroid injection (ESI) at STONC; provides details of the procedure. Because the Facility Manager of STONC is on vacation, the IP at STH continues to help in the investigation. Dr. Kainer contacts Dr. Perz at the Division of Healthcare Quality Promotion (DHQP), Centers for Disease Control and Prevention (CDC) to ask whether any cases of Aspergillus meningitis had been reported to CDC from any other ambulatory surgery centers (ASC) or pain clinics. Fungal meningitis is rare, but is not required to be reported to the CDC. Even without any requirement, clinicians or states often contact CDC about unusual infections; however, no one had recently contacted the Mycotics Branch at CDC to report any cases of Aspergillus meningitis. STH reports two additional patients with meningitis with high levels of white blood cells but no known cause. Both had undergone ESIs at STONC. Diagnoses were complicated because the patients appeared to be getting better and the cause of their meningitis was unknown. Dr. Kainer worked with clinicians to request exhaustive diagnostic tests. They also had ESI performed by same anesthesiologist at STONC. The preservative-free methylprednisolone acetate used in their ESIs was obtained from New England Compounding Center (NECC). Arrange for one on Dr Kainer's staff to visit STONC the next morning, with the IP and the ID physician from STH. ***On this day, STONC closes voluntarily, sequesters supplies and orders new supplies from other distributors.***	1 case of Aspergillus meningitis 2 cases of meningitis, unknown cause, both seeming to be improving No national reports of Aspergillus meningitis
Day 4: Friday Sept 21	Visit to STONC by TDH staff for a careful review of all procedures and the physical environment: no evidence observed of environmental conditions that would have led to fungal contamination of procedures. TDH contacts CDC and describes findings of site visit. TDH asks CDC to help with laboratory testing of patients with meningitis of unknown cause (because fungus is very hard to diagnose) and also for testing of environmental samples from the clinic, if needed. Another patient with meningitis and stroke with a history of ESI at STONC is identified, while VUMC also reports yet another patient who had a stroke and had an epidural injection, but at the time it was not clear where the ESI was done (it was confirmed as STONC on	1 case of Aspergillus meningitis 2 cases of meningitis of unknown cause 1 case of stroke and meningitis, unknown cause

	Day 7). TDH sent out a Health Alert using our TN Health Alert Network (THAN), asking clinicians to look for and report any cases of meningitis following epidural injection to the TDH. At this time, the leading suspected causes of meningitis were the contrast media and methylprednisolone acetate (MPA) from NECC because both were used in each patient (and are commonly given together for an ESI). Other less likely possibilities included local anesthetic, local skin preparation and needles used for the injection.	1 case of stroke, no spinal tap was done.
Day 6 Sunday Sept 23	IP at STH contacts Dr. Kainer about one new patient and one patient readmitted with meningitis; both had ESI at STONC.	
Day 7 Monday Sept 24	Facility manager from STONC has returned from vacation and provides additional information on the facility practices. TDH staff arrange to begin collecting data on patients to try to find out what distinguishes the case patients from those who did not get sick. TDH and CDC communicating closely. Dr. Kainer contacts State epidemiologist at Massachusetts Department of Health, Dr. Al DeMaria, to request a conference call with TDH, CDC, MA staff and NECC to obtain distribution list of clinics that got MPA from NECC in order to look for other cases of meningitis among patients who received ESI with MPA compounded by NECC.	1 case Aspergillus meningitis 4 cases of meningitis unknown cause 1 case of stroke, but no spinal tap done.
Day 8 Tuesday Sept 25	2 new cases of meningitis reported to TDH. Both had ESI using MPA from NECC at STONC; however, one of the patients did not receive the suspected contrast and the procedure was done by a different anesthesiologist. Conference call with TDH, CDC, Massachusetts Department of Health and Board of Registration in Pharmacy (MABRP) and NECC. NECC stated no adverse events reported, no new suppliers of ingredients or changes in procedures. TDH described severity of cases and that preservative free MPA was leading hypothesis. TDH requested distribution list and verified that voluntary recall procedures were in place. TDH staff begin collecting all the medical information needed to conduct their epidemiologic studies. STONC starts contacting potentially exposed patients. A new patient who had an ESI at STONC was admitted to STH with numbness and bowel/bladder control problems, but no headache or fever. Her spinal tap shows signs of meningitis of unknown cause, but with a much lower white blood cell count than the other cases of meningitis.	1 case Aspergillus meningitis 6 cases of meningitis unknown cause 1 case of stroke, but no spinal tap done. 1 case of other neurologic problems and abnormal spinal tap (unknown cause)

Day 9 Wednesday Sept 26	**NECC issues voluntary recall for 3 lots of preservative free MPA and provides distribution list of consignees to MABORP and FDA.** TDH and CDC draft an Epi-X Alert (national emergency alert system for public health professionals) to report cases of meningitis related to epidural injections. TDH continues to follow up on patients who received ESI at STONC to look for any other unusual illnesses or complications. CDC helps TDH by making available a medical doctor with expertise in treating fungus to assist TN clinicians in caring for patients.	
Day 10 Thursday Sept 27	TDH staff complete first round of epidemiologic studies; preliminary findings supports that MPA is likely source. TDH asks STONC to contact all patients who had procedures since July 30. Analysis of the NECC distribution list shows two other clinics in TN received MPA. These clinics are contacted and all MPA is sequestered. Both clinics cease performing ESIs. The first clear evidence that the meningitis cause is not related to the STONC clinic: North Carolina (NC) reports a patient with meningitis exposed to MPA from NECC.	
Day 11 Friday Sept 28	It is still not absolutely clear that the MPA from NECC is the only possible source of contamination: the NC case patient had also received lidocaine and povidone iodine from the same manufacturers used by STONC. The lidocaine was the same lot number. CDC notifies all State Health Departments of situation and urges them to contact clinics who do ESIs to ask them to contact and check on the health of recipients of MPA using a script prepared by CDC. They ask that this be done immediately, not waiting until after the weekend. CDC issues another national Epi-X alert indicating that this now is a multi-state outbreak and requesting reports of meningitis, other neurological infections, and stroke. TDH sends its own alert through THAN to clinicians and hospitals in TN to look for and report meningitis, stroke and focal infections in patients who have had epidural injections. Still, all diagnostic tests on these cases remain negative. The only patient with a confirmed diagnosis remains the first case patient reported. This highlights the difficulty of diagnosing a fungal infection, even when one is looking very hard to find it.	

	TDH continues to work on epidemiologic studies to learn more about these patients, despite not yet having a confirmed diagnosis. TDH requests assistance from CDC to abstract clinical data from patient records (help arrives on Day 14)	
Day 13 Sunday Sept 30	TDH and STONC staff continue to abstract data on patients who had procedures since July 1	
Day 14 Monday Oct 1	TDH holds its first press conference and initiates a daily scheduled press briefing. TDH partners with the state Poison Control Center to assist in responding to questions from the general public Other TN clinics continue to contact patients exposed to MPA from NECC. CDC and TDH staff work on gathering patient data to continue studies. TDH participates on call with expert fungal clinical panel convened by CDC, discuss need for CDC to provide interim suggestions/ advice to clinicians on diagnosis and treatment	11 cases, 2 deaths
Day 15 Wednesday Oct 3	CDC issues interim guidance on diagnostics and clinical management using input from an expert fungal clinical panel convened by CDC. **For the first time since the initial report, a tissue biopsy from a case patient shows a fungus.** However, the fungus looks different than Aspergillus. More tests must be done to identify it. TDH issues another alert through THAN to clinicians to help them identify, diagnose and treat ill persons exposed to MPA from NECC. TDH analysis of STONC patients suggests that one particular lot of the 3 NECC MPA lots present at STONC is the most likely to make patients sick: Lot 06292012.	18 cases, 2 deaths
Day 16 Thursday Oct 4	A final identification of the fungus causing illness is still not made, but a specimen from another patient who died shows a fungus that is not Aspergillus. **FDA announces fungus was seen on microscopic examination of an unopened vial of MPA from Lot 08102012.** This now is very strong evidence that MPA is the cause of the outbreak. TDH alerts TN healthcare facilities using THAN to cease use of all medications and products from NECC.	25 cases 3 deaths
Day 17 Friday Oct 5	TDH opens state health operations center to assist in case tracking, active surveillance (contacting, reaching out to all persons who received MPA from NECC at any of the 3 Tennessee clinics- a total	29 cases, 3 deaths

	of 1009 persons). Mobilize regional health operations centers and use public health nurses to contact hard to reach patients, going door to door when necessary. Public health nurses maintained regular phone and in person contact with affected patients for weeks, changing messaging as required to adjust to a fluid and constantly changing scientific understanding and related patient needs. The CDC has another meeting of its expert fungal panel.	
Day 18 Saturday Oct 6	NECC announces voluntary recall of all NECC products FDA issues Medwatch alert asking providers to stop using any NECC products.	29 cases, 3 deaths
Day 24 Friday Oct 12	MMWR (CDC publication) is published on clinical presentation of cases.	50 cases, 6 deaths
Day 26 Sunday Oct 14	FDA call with States and CDC on concerns about sterility of any product from NECC.	53 cases, 6 deaths
Day 27 Monday Oct 15	FDA issues Medwatch alert. TDH works with the Tennessee Hospital Association (THA), the TN medical association (TMA), the ambulatory surgery center association and the TN pharmacist association to assist in alerting hospitals, providers and clinics to identify and notify patients who received NECC products	53 cases, 6 deaths
Day 29 Wednesday Oct 17	TDH identifies that patients who received older vials are much more likely to get sick. Questions begin about whether or not to test these patients even if they are not sick, if testing might prevent serious illness such as stroke.	61 cases, 8 deaths
Day 30 Thursday Oct 18	TDH works with CDC experts to develop a mathematical model used for decision analysis by CDC about what to do for high risk patients. **For the first time, CDC and FDA confirm presence of *Exserohilum rostratum* in unopened vials from Lot 0810210@51** This is now definitive evidence that contaminated MPA is the cause of the outbreak.	63 cases, 8 deaths
Day 35 Tuesday Oct 23	MA Board of Registration in Pharmacy issues report of initial preliminary findings.	70 cases, 9 deaths
Day 38 Friday Oct 26	FDA releases copy of FDA form **483.** All 50 vials of MPA tested showed contamination (likely fungal).	74 cases, 10 deaths
Day 48 Tuesday Nov 6	The New England Journal of Medicine publishes an article written by TDH and CDC investigators on this outbreak: http://www.nejm.org/doi/full/10.1056/NEJMoa1212972 A copy of the article is attached.	78 cases, 13 deaths
Day 51 Friday	TDH invited to provide testimony to the Senate HELP committee.	81 cases, 13 deaths

Nov 9	TDH requests on site assistance again from CDC to describe later complications of fungal infection, such as epidural abscess, arachnoiditis and risk factors. Two EIS officers will arrive on site on Nov 13.	

Lessons Learned:

1) Compounding and/or repackaging of medications must be performed safely. Patients and healthcare providers should expect safe and effective medications. Compounding pharmacies provide a needed service. If compounded products are unavailable to meet the unique needs of some patients, providers may perform compounding or repackaging themselves at the bedside and may also put patients at risk.

2) Recent investments in public health infrastructure through cooperative agreements from the CDC have supported building public health capacity at the TDH. This capacity was invaluable in identifying and responding to the outbreak, determining the cause resulting in product recall only eight days after initial notification saving lives and limiting the number of patients administered the contaminated injections. Specific examples are provided below:
    a. Six members of the Healthcare Associated Infections (HAI) team are funded through the Prevention and Public Health Fund Epidemiology and Laboratory Capacity Cooperative agreement and the Emerging Infections Program. In addition, the team has a CDC/ Council of State and Territorial Epidemiologists (CSTE) fellow. The only person not funded by CDC is the director of the HAI program, Dr. Kainer.
        i. The team had the expertise to ask the right questions, conduct on-site visits, create relevant standardized investigation forms, create a database, enter and analyze the data swiftly to determine the cause of the outbreak and those at highest risk of getting sick.
        ii. In Tennessee, if the recall had been delayed by 9 days, we estimate that at this time we would have seen an additional 59 cases and at least 5 additional deaths. If treatment guidance from CDC had been delayed, the number of deaths would be even higher.
        iii. To prevent healthcare associated infections, the team has built very close relationships with infection preventionists at hospitals, the Tennessee Hospital Association and is building relationships with the ambulatory surgery center community. These relationships are built on mutual trust and have been invaluable in promoting open communication.
    b. Surge capacity was provided by staff funded under the Epidemiology and Laboratory Capacity (ELC) grant and the Public Health Emergency Preparedness (PHEP) cooperative agreements as well as an additional CDC/CSTE fellow and an Epidemic Intelligence Service (EIS) officer assigned to Tennessee.
        i. These staff funded provided assistance in reviewing clinical information on suspect and confirmed cases, and in tracking down 1,009 exposed patients. Contact by phone or in person was made by local public health department staff, funded by the state of Tennessee, sometimes with assistance from law

enforcement. Outreach included frequent telephone calls and door to door tracking, including home visits whenever necessary. Some exposed patients were living in or traveling in other states or were overseas when they developed symptoms.

ii. The State Health Operations Center provided the necessary infrastructure to coordinate activities among the 170 public health staff in Tennessee.

iii. The alert network (THAN) connecting TDH with clinicians and staff at hospitals was invaluable in rapidly getting information out.

iv. We were able to use a database designed for tracking persons in shelters to track patients who were exposed.

3) Relationships with Federal partners were critical in the response to this outbreak.

a. CDC provided invaluable assistance throughout the outbreak including weeknights and weekends. Some examples include:

i. Laboratory support: CDC developed a diagnostic test to assist in the outbreak investigation and provided laboratory support for confirming the identities of fungal isolates. The infectious diseases pathology branch has been providing valuable insights on how this fungus behaves and the type of damage it does to tissues. This has greatly assisted the clinicians on the fungal expert working group.

ii. Clinical support: TDH was fortunate to have CDC Epidemic Intelligence Service Officers on site to assist in clinical data abstraction. CDC regularly convenes the expert fungal panel to develop diagnostic and management guidance that has been constantly updated with the latest clinical information. This has been very helpful to clinicians, many of whom have never treated fungal meningitis before, and this guidance without a doubt saved a lot of lives. Of the 33 Tennessee patients who sought medical care before October 3, 9 (27.3%) died. Of the 48 patients who sought medical care on, or after October 3, when the first CDC treatment guidance was issued, four (8.3%) died.

iii. Communications: CDC has provided relevant, up-to-date information on case counts, diagnostic and treatment guidance, case definitions etc… on their website, through EPI-X alerts and the Health Alert Network. They have hosted regular conference calls with State partners and other Federal partners to ensure accurate dissemination of information.

iv. Epidemiologic support: CDC has provided technical support (e.g., reviewing logistic regression models, running survival analyses) as well as coordinated the aggregation of data across multiple states to provide a complete national picture. Examples of critical information include distribution of incubation periods. CDC provided expertise in mathematical modeling to review whether guidance needed to be changed for asymptomatic patients at high risk of infection in order to prevent strokes or death.

v. Coordination: CDC has coordinated the national response with other States and the FDA

vi. Funding through cooperative agreements—please see above note #2 on how these funds were used to build capacity at the TDH.

b. FDA provided valuable information on local inspection findings, as well as laboratory testing of products
    i. The information provided by FDA was extremely helpful. It also would have been helpful if FDA had shared interim findings with TDH and other State health departments to allow them a better understanding of the extent of the problem at the compounding pharmacy. This type of information is very helpful as state health departments attempt to gauge the level of risk and consider surveillance strategies.

4) Relationships and Infrastructure
    a. By focusing on emergency preparedness and on reducing healthcare associated infections, we have made much progress in enabling rapid communication between public health and hospitals; however challenges remain, especially with providers who do not work in hospitals (e.g., ambulatory surgery centers) and with medical specialists who are not traditional emergency response partners.
    b. Use of electronic health records allowed tremendous savings in time in allowing us to monitor the clinical progress of patients and saved time and resources at the affected hospitals.
    c. This outbreak illustrated the tremendous importance of inter-facility communication when patients may seek medical services in multiple facilities for complications that arise from treatment at another facility. Reporting to public health is critical, as Dr. Pettit's email illustrated.
    d. Communication with exposed patients during periods of great uncertainty was very important. Public health played a vital role in finding exposed patients that were difficult to reach and when clinic staff were overwhelmed with the task at hand.
    e. Communication with media: Frequent press-briefings allowed TDH to effectively communicate important public health messages in a dynamic and rapidly evolving outbreak while allowing staff to continue to do critical work.

Conclusion:

This has been a devastating outbreak for patients, their families and friends, healthcare providers and clinics. In Tennessee we still have many patients hospitalized and suffering from complications and others who are exposed and frightened that they may become infected. Sustained commitment to funding for emergency preparedness and reduction of healthcare associated infections through cooperative agreements from the CDC has supported our productive relationships with our partners and healthcare providers across the state. These pre-existing relationships allowed us to respond quickly because we trusted each other. We all need to work together to do our best to prevent such a tragedy from occurring again and to ensure that we have the public health capacity to detect and rapidly respond to any future outbreaks.

Thank you for your time and attention.