Fungal Meningitis:
Anatomy of an Outbreak

Meredith Kanago, MSPH
Epidemiologist, HAI Coordinator
Tennessee Department of Health
Illinois Statewide Conference on HAIs
November 21st, 2013

“... one of the most shocking outbreaks
in the annals of American medicine.”
Larry Altman, New York Times, November 5, 2012
Steps In an Outbreak Investigation

1. Establish case definition(s)
2. Confirm cases are “real”
3. Establish background rate of disease
4. Find cases, decide if outbreak, define scope
5. Examine descriptive features of cases
Steps In an Outbreak Investigation

6. Generate hypotheses
7. Test hypotheses
8. Collect and test environmental samples
9. Implement control measures
10. Communicate (staff, patients, press/ public)
Dr. Jones,

We have a case of a \[
\]
yo immunocompetent man with Aspergillus fumigatus meningitis. He had been receiving lumbar epidural steroid injections at an outside facility which is the only explanation we can find to explain this. He also has an L4-L5 1cm epidural abscess which supports this theory. I wanted to inform you of this in case you feel that an investigation is warranted. I am happy to discuss it further if you like.

Thanks!
April Pettit
Day 1: Tue, Sept. 18th

• Dr. Pettit from VUMC notifies TDH regarding unusual case of Aspergillus meningitis following epidural steroid injection at a clinic (STONC). Case is discussed.

• TDH contacts IC at STH associated with STONC
  – “Sentinel event-- please look into this”
  – Confirm ESI was performed at STONC, and provide procedure details
  – Review if any construction or water damage at STONC, any change in procedures, etc...

September 2012
Fungal Meningitis

• Extremely uncommon
• Occurs when fungus spreads to the spinal fluid
• Usually occurs in immunosuppressed patients
  – AIDS or cancer
  – Post-transplant
  – Rheumatoid arthritis
  – Other immunosuppressive therapy
• Not contagious (not transmitted from person to person)

http://www.cdc.gov/meningitis/fungal.html
Day 3: Thurs. Sept. 20th

- IC confirmed index patient had ESI at STONC
  - Clinic facility manager on vacation; IC at STH happy to help out
  - “They get meds from an out-of-state pharmacy”
  - Obtain procedure note

- TDH requests name of the out-of-state pharmacy
  - New England Compounding Center (NECC) supplied methylprednisolone acetate (MPA)
  - According to clinician A, “no reports of issues from anyone” when he contacted NECC

September 2012
Safe Preparation and Administration of Intravitreal Bevacizumab Injections

Beth Anne Frost, M.P.H.
Marion A. Kainer, M.B., B.S., M.P.H.
Tennessee Department of Health
Nashville, TN
marion.kainer@tn.gov
Exophiala Infection from Contaminated Injectable Steroids Prepared by a Compounding Pharmacy — United States, July–November 2002

Outbreak of Serratia marcescens Infections following Injection of Betamethasone Compounded at a Community Pharmacy

Rachel Civen,¹ Duc J. Vugia,² Richard Alexander,⁴ Wendel Brunner,⁴ Sirlura Taylor,⁴ Nancy Parris,⁵ R. Wasserman,⁵ Sharon Abbott,³ S. B. Werner,³ and Jon Rosenberg²

¹Los Angeles County Department of Health Services, Acute Communicable Disease Control Program, Los Angeles, ²Infectious Diseases Branch and ³Microbial Diseases Laboratory, Division of Communicable Disease Control, California Department of Health Services, Richmond, ⁴Contra Costa County Public Health Department, Martinez, and ⁵John Muir Hospital, Walnut Creek, California
Day 3: Thurs. Sept. 20th

- TDH contacts CDC whether received any similar reports of Aspergillus meningitis (not reportable or notifiable)
  - DHQP & Mycotics- not aware of any reports
- IC notifies TDH of 2 additional cases of culture negative neutrophilic meningitis at STH who also had ESI at the clinic
  - Appear to be clinically improving, one discharged home
  - Same clinician performed ESI on all 3 patients; no changes in staff, technique or supplies
  - Request fungal cultures and extended incubation on current specimens
  - Consider repeat LP for fungal culture (large volume)
- Arrange on-site visit of STONC next day together with IC and ID physician

Meningitis: 3
Aspergillus: 1
Day 4: Fri. Sept. 21

• Visit to the Clinic
  – Closed (voluntary); sequestered all supplies
  – No obvious signs of construction or water damage
  – Single-use Omnipaque (contrast) vials used as multi-use vial throughout course of day
  – All cases had also received preservative-free methylprednisolone acetate (MPA) from New England Compounding Center (NECC)
Day 4: Fri. Sept. 21

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Operating Room at Clinic A

September 2012
Omnipaque contrast

September 2012
Methylprednisolone acetate vial from NECC

September 2012
Day 4: Fri. Sept. 21st

- Additional Cases?
  - Pt presented with posterior circulation stroke. Sub-acute meningitis case (reported by IC at STH, then ID physician at VUMC). Also had ESI at same clinic → requested records
  - Fungal culture in progress; started on anti-fungal therapy
  - Contacted IC at VUMC
    - Mentioned another out of state resident who presented with stroke who had MSSA bacteremia. Also had ESI (? which clinic) → requested records
Day 4: Fri. Sept. 21st

- Contact CDC
  - Update on new case count and on-site visit findings
  - Confirm no other reports from any other states of Aspergillus meningitis or other complications following ESI
  - CDC will notify FDA wrt. compounding pharmacy
  - Arrange conference call next Monday to discuss potential laboratory testing of patient and/or environmental samples

September 2012

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Report meningitis following epidural injections

Severity: Moderate
Time Sent: 9/21/2012 4:50:20 PM
Expires: 9/28/2012 4:50:20 PM
Delivery Time: 1 hr (60)
From: Marion Kainer
Signature: Marion Kainer, Tennessee Department of Health, marion.kainer@tn.gov

Since July 30th, 2012, there have been 5 cases of meningitis among immunocompetent patients that had previously received lumbar epidural steroid injections (ESI). At least four are associated with one outpatient surgical facility in Tennessee. All persons were admitted to the hospital within 1 month of the lumbar transmaminal ESI procedure with signs of meningitis, including: headache, neck stiffness, and fatigue. All had high CSF protein levels, low CSF glucose and high polymorph white cell count (in the thousands). One case is culture positive for Aspergillus fumigatus; other cultures are pending/negative to date. At least 4 of the 5 cases received injections of Depo-Medrone (methylprednisolone acetate), 1% lidocaine, and Omnipaque (Iohexol) during the procedure. Please report any cases of suspected meningitis occurring within 1 month of an epidural injection (since July 1, 2012) to the TDH on (615) 741-7247 or marion.kainer@tn.gov. Please do not discard any associated CSF specimens. Thank you for all that you do in protecting Tennesseans.
Day 6: Sun. Sept. 23rd

• Additional meningitis case reported - STH
  – Txt message and E-mail from IC at STH

Meningitis: 5
? Stroke (no LP): 1
Aspergillus: 1
Day 7: Mon. Sept. 24th

• Clinical Update
  – Index case doing poorly
  – Case 2 was readmitted
  – Case 3 not doing so well
  – Case 4 (posterior circulation stroke with subacute meningitis)- marked improvement after IV antifungals (from ICU on Friday to walking on a general ward on Monday)
  – Case 5 discharged to rehab facility out of state
    • Contacted ID fellow in evening– strongly consider performing LP to rule out meningitis

Meningitis: 5
? Stroke (no LP): 1
Aspergillus: 1

September 2012
Day 7: Mon. Sept. 24th

- Conference call with CDC: DHQP and Mycotics
  - Describe clinical features of cases
  - All agree suggestive of fungal etiology
  - Sensitivity of culture for Aspergillus may be low
  - Guidance on culturing CSF (large volume, cytospin)
  - Await galactomannan CSF results
  - Continue case finding in TN, including contacting pts who had procedures on same day as cases
  - Need to reach out to compounding pharmacy (via MA DOH)– get distribution list to perform targeted surveillance
Day 7: Mon. Sept. 24th

• Call with Facility Manager at Clinic (just returned from vacation)
  – Denominator data on procedures- types, volumes, clinicians, clinician preferences
  – Variation in number of procedures, equipment and steroid used (not just MPA)
  – Arrange to perform cohort study to begin data collection on the next day

• Call with Anesthesiologist A
  – Has done 30-40K ESIs, only ever had 1 superficial infection in a diabetic patient

• Contacted MA DOH State epidemiologist to arrange call with NECC, MABORP and CDC on Tuesday
  – Leading hypothesis is preservative-free MPA; (contrast less likely)
Day 8: Tue. Sept. 25th

2 new cases
- 1 case-- different anesthesiologist and no exposure to contrast

Call MADOH: increased urgency to have call with NECC

Call: TDH, CDC, MADOH, MABORP, NECC
- No adverse events reported
- Requested distribution list of consignees
- No new supplier of API, no change in procedures
- Described severity of cases to NECC and that MPA was leading hypothesis and others far less likely
- Had voluntary recall procedures in place

Meningitis: 7
? Stroke (no LP): 1
Aspergillus: 1

September 2012
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Procedure Data Collection

• TDH staff worked closely with clinic staff to abstract all procedure information using standardized collection form

• Cohort of all patients with a procedure on the same day as a case procedure

• Prioritized active surveillance outreach by clinic to call all patients with procedures on same day as a case
Data Collection Form

Demographics:
1. What is the patient’s Medical Record Number (MR#): ______
2. Patient’s Age (yrs): ______
3. Patient’s DOB: ___/___/_____ 4. Patient’s Sex: ___M/___F
5. Patient’s Last Name: ______
6. Patient’s First Name ______
7. List any of the patient’s allergies: ________________
8. Did the patient receive more than one steroid epidural injection since July 1st, 2012?  Yes/No
9. What was the procedure that was performed?

L ESI  C ESI  T ESI  L Facet  C Facet
NRB  SI Joint  Bld Patch  SGB  Sel/Symp  Other

10. Date of procedure?  _____/_____/_____

11. What time was the procedure started (patient entry into room)?
   _____:_______ AM / PM

12. What time was the procedure completed (record printed)?  __:__

13. In what procedure room within the clinic was this procedure completed?
   PR OR1 OR2

14. Indicate the technician(s) that completed the procedure ________

15. Indicate which anesthesiologist(s) performed the procedure: ______

16. What was the location of the injection
   (1= lumbar, 2= cervical, 3= thoracic): ___

17. What was the approach to the procedure
   (1= transforaminal, 2= translaminar): ___

18. What was the product name of the steroid injected
   (1= depo-medrol, 2= celestone): ______

19. What was the dose of the steroid provided: ___

20. Did the procedure include the injection of omnipaque: Yes / No
Translaminar vs Transforaminal

- Epidural space
- Neural Foramen

Translaminar

Transforaminal
Day 9: Wed. Sept. 26th EPI-X Alert

Call for Cases: Meningitis Following Epidural Injections -- Tennessee, 2012

Access and Notification: Make available to all Epi-X users
Click to see who has viewed this report.

Distribution: Release outside of Epi-X as needed
Contributor's instructions for distributing this report.

Brief Summary of Report: Please report suspected cases of clinical meningitis/other neurologic infection with onset within 1 month of epidural injection since July 1 to Marion Kainer - 615-741-7247 or marion.kainer@tn.gov.
Day 9: Wed. Sept. 26th

- NECC performed nationwide recall of 3 lots of MPA
  - The only lots of MPA ever linked to the outbreak
- NECC provided distribution list of MPA
- 17,675 vials
- 76 facilities
- 23 states
- 2,520 vials to TN

![Map of affected states]

**September 2012**

18 19 20 21 22 23 24 25 26 27 28 29 30 1 2 3 4

**October**
Strong Sense of Urgency: Parallel Efforts

- Chart abstraction (TDH & Clinic A)
- Database construction (TDH)
- Data entry (TDH)
- Preparation of SAS code (TDH)
- Outcome ascertainment (case/not a case): (Clinic A & TDH)

- Labor intensive manual process (data on 306 patients, 586 procedures) in newly created database within 60 hours
Why Cohort (vs. Case-Control) Study?

- Outbreak rapidly evolving (ongoing outreach, patients were becoming cases), with cohort study could easily change outcome from non-case to case as new information became available
- Lot number allocation could only be performed if obtained information on every exposed patient (lot numbers not recorded in patient charts)
- Avoid introduction of bias through control selection
- Allows for calculation of attack rates (important for risk communication, prioritization of patient outreach)
• First preliminary results from cohort study: no clinic related factors – implicates MPA (dose response) [Outcomes known for 181 patients]
  MPA <80 mg       RR=1.0 (Ref)
  MPA 81-160 mg RR=1.9
  MPA >160 mg     RR=2.7

• Asked STONC to contact all patients since July 30th

Day 10: Thurs. Sept. 27th

Meningitis: 7 +1
? Stroke (no LP): 2
? Cauda equina: 1
Aspergillus: 1

18 19 20 21 22 23 24 25 26 27 28 29 30 1 2 3 4
Day 10: Thurs. Sept. 27th

- North Carolina reports potential case
  - Meningitis (next day: posterior circulation stroke)
  - Shared exposures with TN cases:
    - MPA from NECC (recalled lot number)
    - Lidocaine (same lot, same manufacturer)
    - Povidone iodine (same manufacturer)
- Better understanding of spectrum of clinical presentations (subacute, ranging from few objective clinical signs (fever, meningism) to devastating stroke; cauda equina syndrome)
Update: Multi-state Outbreak of Meningitis following Epidural Injections

Brief Summary of Report:
10 patients developed meningitis after epidural steroid injection. Please report cases of neurologic infection or CVA - within 1 mo. of epidural since 7/1/12 to Rachel Smith-vih9@cdc.gov/404-639-7738.

Access and Notification:
Click to see who has viewed this report.

Distribution:
Contributor's instructions for distributing this report.

Release outside of Epi-X as needed
Laboratory Tests

• Index case: Aspergillus fumigatus; galactomannan (Aspergillus Ag) +ve

• CSF: High protein, low glucose, high WCC (predominately neutrophils)

• ALL other tests on ALL other cases NEGATIVE, (including all galactomannan/Aspergillus Ag)
  — despite attempts to optimize recovery (obtaining high volume of CSF and culturing pellet after spinning down CSF)
Clinical Picture Consistent With Fungal Meningitis

Posterior circulation stroke:
Suggestive of angioinvasive fungus such as Aspergillus or Mucormycosis

Concern that patients may not seek care & that physicians may not perform LP/ fungal tests or start empiric Rx with antifungals
Case Finding and Investigation

• 3 clinics in TN, 1021 patients exposed to 3 lots of MPA from NECC

• Two resource-intensive outreach efforts to all exposed individuals
  – Initial outreach for case finding & follow-up and second effort to identify additional local infections
  – Joint effort between public health and clinics
  – Engaged local and regional public health nurses
  – Use of Tennessee Countermeasures and Response Network (TN CRN) Patient Tracking Module

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Assignment of Lot Numbers

• Lot numbers NOT recorded in patient charts
• Dates of invoices and lot numbers associated with invoices
• Number of vials used per procedure
  – No sharing of vials between patients
  – 1 vial: 40 mg, 80 mg
  – 2 vials: 120 mg, 160 mg
  – 3 vials: 200 mg
• Number of vials still on hand
• Assumed no wastage
• Usage followed “First in, first out”
• Walked back and assigned lot numbers until all vials for that lot number were accounted for, then started with next lot number (08, then 06 then 05)
• Calculated lot specific attack rates
Description of Clinical Cases

• Clinical Epi-Aid: ID trained EIS officer and medical student
  – Assist in abstraction of charts to describe the clinical features of cases, including incubation periods

• Incubation Period
  – Symptom onset subtle in some patients
    • Difficulty in assigning precise date of onset of symptoms
  – Patients had multiple procedures
    • Which date should count as the exposure?
October 1 (Day 14)

Press release and press briefing by TDH.
Day 16: Wed. Oct 3  12:15, THAN Alert

Adverse events including meningitis following methylprednisolone epidural steroid injections

Severity: Severe
Time Sent: 10/3/2012 12:15:33 PM
Expires: 10/10/2012 12:15:33 PM
Delivery Time: 15 min (15)
From: Marion Kainer
Signature: Marion Kainer, Tennessee Department of Health, marion.kainer@tn.gov

This THAN message is for wide distribution including: ED, infectious disease, neurology, hospitalists, radiology, laboratory, infection control to update TDH and healthcare providers regarding the ongoing meningitis outbreak investigation. To date, eighteen patients with meningitis with or without epidural abscess; or stroke have been reported following epidural steroid injection (ESI) in Tennessee. Cases are under investigation in other states including North Carolina. CDC and FDA and coordinating multistate aspects of the investigation. Please review and share the attached documents (under News on THAN) regarding the history, clinical examination findings, diagnostic and treatment guidance, and reporting instructions. Patients who had ESI and abnormal lumbar puncture results (CSF with high WBC count, high protein, or low glucose) should be reported immediately to the Tennessee Department of Health at (615 741-7247).
THAN: Adverse Events following epidural steroid injections of methylprednisolone from NECC (http://www.neccrx.com/)

**History:** fever, new symptoms of headache (not necessarily severe or associated with meningism or photophobia), nausea with or without vomiting, new neurological deficit (associated with impairment of posterior circulation, e.g., basilar artery), cauda equina syndrome, neuritis or involvement of the spinal cord), weakness, impaired gait, slurred speech, sensory deficits, dizziness and falls, sphincter problems or worsening or previous symptoms, including in the severity of their back pain at the site of injection.

**Examination** findings: careful neurological examination to examine for impairment of posterior circulation (including cranial nerves, cerebellar signs, long tract motor signs, sensory deficits)* and or impairment of spinal cord, nerve root problems.

**Lumbar puncture** should be considered unless contraindications exist. **Lumbar puncture is the single most helpful diagnostic test.**

Posterior circulation cerebrovascular syndromes
October 3 (Day 16)

- CDC publishes interim treatment guidance
- First confirmation that disease process was due to FUNGUS (other than index case)
- Biopsy of dura (enhancement on imaging)
- Appeared to be invading/direct extension of infectious process through dura
- Did not look like Aspergillus
Histopathology & Autopsies

Collaboration:

- Surgeons/OR staff
- Pathology departments at healthcare facilities
- Office of Chief Medical Examiner
- County Medical Examiner
- Across jurisdictions/state-lines
- State Public Health Lab
- CDC: Mycotics and Infectious Diseases Pathology Branch
State Public Health Lab from Virginia isolates and identifies *Exserohilum rostratum* from the CSF in an unknown death investigation

- Patient was exposed to MPA from NECC

- Black mold (melanin), found in soil, on plants
- Thrives in warm, humid environment
- Very rare case reports in literature,
- No reports of meningitis, CNS infection
October 4 (Day 17)

FDA has observed fungal contamination by direct microscopic examination of foreign matter taken from a sealed vial of MPA collected from NECC.
Day 17: Thurs Oct 4; 16:03 THAN Alert: CEASE use of all NECC medications/products
Clinical Challenges

- Patient notification resulted in thousands of patients seeking care
- Many physicians had never seen or treated fungal meningitis
- Often difficult for patients to distinguish new symptoms from baseline symptoms
- Diagnostic tests not without risk
Clinical Guidance

- Engaged clinicians with experience in fungal infections
- Established best practices for diagnosis, treatment and management
- Resulted in real-time development, dissemination of guidelines for patient care
  - Evolved with the constantly changing outbreak
Who Covers Costs of Diagnostic Work up & Treatment?
Centers for Medicare & Medicaid Services (CMS)

- Worked to remove prior approvals and any other barriers to expedite treatment for patients
- Reached out to Americas Health Insurance Plans (AHIP) early, communicated the serious nature of the outbreak and noted what CMS was doing to ensure access to treatment
  - October 16: Coverage for Medicare Part D prescriptions
  - October 25: Items and services to diagnose and treat patients . . . qualify for the Medicare Part A or Part B benefit. . . Due to the severity of this situation, CMS advises providers that Medicare contractors are expected to expedite all coverage determination requests for these items and services to include antifungal medication.
Day 18: Fri. Oct. 5th

- State Health Operations Center (SHOC) activated
  - Case tracking
  - Active surveillance among all patients exposed to MPA at 3 clinics that received NECC MPA
  - Allow for coordination with Regional Health Operations Centers (RHOCs)
TDH Epidemiology Snapshot: Oct. 7

• 31 cases from Clinic A in Tennessee as of 10/7/2012 4:30pm
  – 51 procedures performed on cases from Clinic A since 7/1/2012
• 798 patients underwent procedures at Clinic A since 7/1/2012
• 1,313 procedures performed at Clinic A since 7/1/2012

LOT B (06)
• 25 cases/449 patients receiving lot B (06)
  – 56 cases per 1,000 patients receiving lot B (06)
• 25 cases/619 procedures using lot B (06)
  – 40 cases per 1,000 procedures using lot B (06)
• 40 procedures/619 total procedures using lot B (06)
  – 65 case-procedures per 1,000 procedures using lot B (06)
• 25 cases per 1,000 vials of lot B (06)
# TDH Lot Analysis on Oct 7, 2012

<table>
<thead>
<tr>
<th>Comparison of Exposure to Lot B (06)</th>
<th>Test</th>
<th>p-value</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 80mg vs. 80mg or less</td>
<td>Chi-square</td>
<td>p=0.046</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fisher’s Exact</td>
<td>p=0.034</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.41 (0.98-5.93)</td>
</tr>
<tr>
<td>High to Low Exposure (Greater than 160mg vs. 80mg or less)</td>
<td>Chi-square</td>
<td>p=0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fisher’s Exact</td>
<td>p=0.004</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.94 (1.52-10.21)</td>
</tr>
<tr>
<td>Medium to Low Exposure (120mg/160mg vs. 80mg or less)</td>
<td>Chi-square</td>
<td>p=0.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fisher’s Exact</td>
<td>p=0.34</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.46 (0.50-4.26)</td>
</tr>
</tbody>
</table>
Figure 1. Number of Epidural and Paraspinal Glucocorticoid Injections and Attack Rate.
Shown are the number of epidural and paraspinal glucocorticoid injection procedures performed in case patients, as well as the attack rates among persons who received methylprednisolone acetate from the implicated lots during these procedures. Data are shown according to 5-day time periods.

Figure 1. Number of Epidural and Paraspinal Glucocorticoid Injections and Attack Rate. Shown are the number of epidural and paraspinal glucocorticoid injection procedures performed in case patients, as well as the attack rates among persons who received methylprednisolone acetate from the implicated lots during these procedures. Data are shown according to 5-day time periods.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases (%)</th>
<th>Non-Cases (%)</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>41/431</td>
<td>17/346</td>
<td>1.9 (1.1-3.4)</td>
</tr>
<tr>
<td></td>
<td>9.5%</td>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>47/400</td>
<td>11/380</td>
<td>4.1 (2.1-7.7)</td>
</tr>
<tr>
<td></td>
<td>11.8%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Translaminar approach</td>
<td>47/488</td>
<td>11/291</td>
<td>2.5 (1.3-4.8)</td>
</tr>
<tr>
<td></td>
<td>9.6%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>Multiple procedures</td>
<td>41/355</td>
<td>17/425</td>
<td>2.9 (1.7-5.0)</td>
</tr>
<tr>
<td></td>
<td>11.5%</td>
<td>4.0%</td>
<td></td>
</tr>
<tr>
<td>MPA 06 lot &gt;50 days old</td>
<td>29/149</td>
<td>6/190</td>
<td>6.2 (2.6-14.5)</td>
</tr>
<tr>
<td></td>
<td>19%</td>
<td>3.0%</td>
<td></td>
</tr>
</tbody>
</table>

TDH Communication

• Patient contacts, working along with clinics
  • Phone, certified mail, home visits, neighbors, etc.
  • More contacts as outbreak progressed

• Medical community
  – Clinics involved, hospitals caring for patients
  – Other states, especially Kentucky
  – Federal partners (CDC, FDA, Senate hearing)
  – The medical community at large

• Media - Prompt and insightful reporting
  – TDH web site updated daily

• Legislative partners, state and federal
Fungal Infections Associated with Contaminated Methylprednisolone in Tennessee

Marion A. Kainer, M.B., B.S., M.P.H., David R. Reagan, M.D., Ph.D.,
Duc B. Nguyen, M.D., Andrew D. Wiese, M.P.H., Matthew E. Wise, Ph.D.,
Jennifer Ward, M.S., Benjamin J. Park, M.D., Meredith L. Kanago, M.S.P.H.,
Jane Baumblatt, M.D., Melissa K. Schaefer, M.D., Brynn E. Berger, M.P.H.,
Ellyn P. Marder, M.P.H., Jea-Young Min, Pharm.D., M.P.H., John R. Dunn, D.V.M., Ph.D.,
Rachel M. Smith, M.D., John Dreyzehner, M.D., M.P.H., and Timothy F. Jones, M.D.,
for the Tennessee Fungal Meningitis Investigation Team*

This article was published on November 6, 2012, at NEJM.org.
Current Status of the Outbreak
Unprecedented Outbreak

• Severity and complexity of clinical disease
• Large number of exposed persons required rapid patient identification and notification
• Largest healthcare-associated outbreak reported in US history
MPA Distribution/Exposures

- 17,675 vials
- 76 facilities
- 23 states

- 13,534 persons exposed
  - 12,069 (89%) by epidural, spinal, or paraspinal injection
  - 1,648 (12%) by peripheral joint or other injection
Case Count and Distribution as of Sept 6 (N=750)

64 deaths
Case-patients reported to CDC as of May 15, 2013 (n=742)

- 593 met a single case definition
  - 321 had parameningeal infection
  - 232 had meningitis
  - 33 had peripheral joint infection
  - 7 had stroke only

- 149 met multiple case definitions
  - 144 had parameningeal infection and meningitis
  - 2 had parameningeal infection and peripheral joint infection
Case Definition (n)

- Stroke without LP
- Spinal/Paraspinal Infection
- Meningitis
- Joint Infection

Epidemic curve*

CDC EOC activated

Patient notification

MPA was distributed from May 21, 2012

First case diagnosed

Week of Diagnosis

Case Definition (n)
Number of Fungal Infections by Symptom Onset in Tennessee  N=152

- Meningitis only 21
- Meningitis + spinal 58
- Spinal only 68
- Stroke w/o LP 3
- Peripheral joint 2

Mostly Meningitis

Mostly Localized Infections
Fungal hyphae within granulomas
Results of FDA Testing of MPA

• FDA tested a total of 8 different lots ranging in production time from March 12, 2012 to August 13, 2012.

• 2/8 lots demonstrated contamination; 343/484 vials tested were positive.
  – 08102012@51: 218/262 (83%) vials tested were positive for fungal growth.
  – 06292012@26: 125/130 (96%) vials tested were positive for fungal growth.
  – 05212012@68: 0/17 vials tested were positive.
Impact of Public Health Action on TN Case Numbers and Deaths

Current: 153 cases; 16 deaths
Without PH action: 368 additional exposed
251 [+99] cases; and potentially 84 [+69] deaths

• # persons not exposed: 368
  – Clinics A (337); B (31) if no additional shipments

• Applying TN attack rates to 368 exposed persons:
  # of additional cases prevented = 99

• Case fatality rate in patients presenting
  before Oct. 3 = 31.3%; since Oct. 3: 4.2%

• TN now reports 153 cases; applying the 31.3% case fatality rate to the cases who presented after Oct. 3, N = 219 (120+99) = 69 additional deaths
Bell BP, Khabbaz RF Responding to the Outbreak of Invasive Fungal Infections: The Value of Public Health to Americans; JAMA 2013; 309(9):883-884
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- **September 18, 2012**
  - First case reported to TDOH

- **September 26, 2012**
  - NECC issues voluntary recall of 3 contaminated lots of methylprednisolone acetate.

- **October 4, 2012**
  - Activation of CDC Emergency Operation Center
  - CDC-FDA joint telebriefing to announce finding of visible fungal contamination of sealed vials
  - Intensified CDC outreach to patients and clinicians with state and local health departments

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**Week of Meningitis Diagnosis**

- **30-day case-fatality rate by week of diagnosis**
- Cases by 30-day outcome: Alive, Dead
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September 18, 2012
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Outbreak Response Coordination

- Collaboration among public health partners at multiple levels allowed for rapid response
  - Identification of exposed patients
  - Patient notification
  - Case-finding
  - Treatment and diagnosis
  - Communications
Some Lessons Learned in TN

1. Investments in public health infrastructure, including healthcare associated infection (HAI), informatics and data management were critical for an effective response (ELC, ARRA, ACA, EIP, EP, EIS, CSTE fellow).

2. Timely communication is essential
   - Labs, IC, Clinicians, Imaging, Pharmacists, Chief Medical Examiner’s office, PH staff, Office of General Counsel, PIO, exposed patients, other State HDs, CDC, FDA
   - Greatly facilitated by pre-existing relationships
   - Interfacility communication is important
   - Access to Electronic Health Records

3. Preexisting relationships key

4. Compounding pharmacy regulation complex but essential
Summary

- Contaminated medication was administered in normally sterile sites to thousands of people
- An outbreak of fungal meningitis and other syndromes of unprecedented scope and magnitude resulted
- Demonstrated public health impact of healthcare associated infections
- Effective response required
  - Clinicians
  - Healthcare setting (hospitals, clinics)
  - Local and state health departments
  - Federal agencies
Postscript on NECC

- NECC recalled more than 2,000 products in addition to MPA and ceased operations in October 2012
  - Filed for Chapter 11 bankruptcy in December 2012
- Multitude of bacterial and fungal organisms were isolated from NECC products labeled as sterile
  - No outbreaks associated with other NECC products
Acknowledgements

• Tennessee Department of Health (180+)
• The 3 affected clinics and their staff
• Clinicians, infection preventionists, laboratories, hospitals
• Officer of Chief Medical Examiner, county medical examiners
• CDC (eg., mycotics, DHQP, IDPB, EIS, EOC)
• Other State Health departments (esp. MA, NC, MI, VA)
• FDA, CMS