Multi-State Outbreak of Fungal Meningitis and Other Infections Associated with Contaminated Methylprednisolone Acetate, 2012–2013
Multistate Outbreak of Fungal Meningitis and Other Infections

- Largest healthcare-associated infection outbreak reported in the United States

- Massive undertaking
  - Response was a joint effort at CDC
    - Division of Healthcare Quality Promotion
    - Mycotic Diseases Branch
  - Over 300 staff at CDC HQ
  - Likely more than 1000 staff nationally
    - State and local health departments
    - Clinicians, nurses, administrative staff

- Collaborations
  - State HDs, FDA, CMS, clinicians
## Acknowledgements

<table>
<thead>
<tr>
<th>State Health Departments:</th>
<th>New Hampshire</th>
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<td>California</td>
<td>New Jersey</td>
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<th>Local Health Departments</th>
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<td>State boards of pharmacy</td>
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<th>Professional Organizations</th>
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<td>Clinical community</td>
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For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333  
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348  
E-mail: cdcinfo@cdc.gov  Web: http://www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Tennessee Department of Health (TNDOH) contacted CDC about a hospitalized patient with culture-confirmed *Aspergillus* meningitis
- Patient was immunocompetent (unusual for *Aspergillus* infection)
- Received epidural steroid injection (ESI) at Clinic A in TN on July 30, 2012
Early epidemiologic investigation

- TNDOH identified seven additional patients with meningitis from Clinic A
Initial eight patients

- Recent onset of meningitis with marked elevation of white blood cells in the cerebrospinal fluid (CSF)
- Four (50%) had a posterior circulation stroke
  - Unusual site in brain for stroke
- CSF cultures from seven patients were negative
Commonalities among initial eight patients

- Injection at Clinic A with one of three lots (lot 5, 6, or 8) of methylprednisolone acetate (MPA), a steroid, from the New England Compounding Center (NECC)

- Contrast material, povidone-iodine, lidocaine, spinal needles, epidural tray kits
Early epidemiologic investigation

- NECC notified of the initial investigation and potential involvement of three lots of MPA (lot 5, 6, and 8) associated with initial patients

- NECC stated they received no reports of adverse events, and results of routine sterility testing were negative
Drug recall and outreach

- NECC voluntarily recalled lots 5, 6, and 8 of MPA, though its contribution to patient illnesses remained unconfirmed; provided customer list to CDC

- CDC continued to investigate other products

- CDC initiated outreach to states to evaluate scope of problem
North Carolina Department of Health and Human Services reported another patient with meningitis

- Received ESI with MPA from NECC at North Carolina clinic
- Posterior circulation stroke
- CSF specimen also culture-negative

Exposure not limited to TN Clinic A
CDC recommended states begin notification of patients that received injection of lots 5, 6, or 8 of MPA from NECC
Contaminated MPA

- FDA announced that unopened vials of MPA were contaminated with fungi.
Compounding pharmacies

- Prepare customized medications that are not commercially available for individual patients with specialized medical needs
  - Prescription required for compounded product

- Regulated by state boards of pharmacy

- Exempt from good manufacturing practice regulations that ensure quality of FDA-approved products

- Compounded products not evaluated for clinical safety and efficacy
Products prepared at compounding pharmacies

- **Non-sterile**
  - Oral
  - Inhaled
  - Nasal
  - Topical
  - Transdermal

- **Sterile**
  - Ophthalmic solutions
  - Irrigation solutions
  - Cardioplegia solutions
  - Dialysis solutions
  - Injectables
    - Anesthesia
    - Antibiotics
    - Electrolytes
    - Flushes
    - Intraoculars
    - Parenteral nutrition
    - **Steroids**
Scope of problem with compounding pharmacies

Compounding pharmacies intended to provide customized medication on small scale

Production en masse without regulatory oversight for good manufacturing practices might result in compromised quality assurance
Methylprednisolone acetate (MPA)

- Anti-inflammatory glucocorticoid

- Available with or without preservative
  - Preservative extends shelf life and inhibits bacterial/fungal growth

- MPA with preservative is approved by FDA
  - Indicated for intramuscular, intra-articular, soft tissue, or intralesional injection
  - Preservative has toxicity in central nervous system tissue

- Physicians prefer to use preservative-free MPA for ESI
Preservative-free MPA

- Not approved by FDA
- Prepared at compounding pharmacy and used for ESI
- Lots 5, 6, and 8 of MPA recalled by NECC were preservative-free
Epidural steroid injections (ESI)

- Steroids injected into epidural space around spinal cord to relieve inflammation and pain
  - Spinal stenosis or disc herniation
  - Chronic neck or back pain

- Efficacy is unproven

- Over 2 million among Medicare beneficiaries in 2008
  - Median injections was 2 per patient

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1 Bart Staal J., et al., Injection Therapy for Subacute and Chronic Low-back Pain. Cochrane Database Sys. Rev. 2008; (3)
Intra-articular steroid injections

- MPA used in intra-articular (joint) injections for relief of pain and inflammation from osteoarthritis

- Peripheral joints
  - Knees, shoulders, wrists

- Sacroiliac joint
  - Proximal to spine

www.centenoschultz.com
Outbreaks of post-procedural fungal meningitis

- *Exophiala dermatitidis* meningitis–2002
  - Contaminated MPA from compounding pharmacy
  - Four cases; one death

- *Aspergillus fumigatus* meningitis–2005
  - Inadequate storage of syringes used for spinal anesthesia
  - Six cases; three deaths
EPIDEMIOLOGIC INVESTIGATION METHODS
Case definitions

- **Probable:** illness in person who received injection with MPA from NECC and developed any of the following:
  - Meningitis
  - Parameningeal infection
  - Peripheral joint infection
  - Posterior circulation stroke in absence of a normal CSF profile

- **Confirmed:** probable case with laboratory evidence of fungi from a clinical specimen
Case-patient information

- Standardized case report form completed for each patient meeting the case definition by
  - State health departments
  - Local health departments
  - Clinicians treating patients
  - EISOs on Epi-Aids
MPA distribution

- NECC provided a list of facilities that received MPA
- 17,675 vials
- 76 facilities
- 23 states
Notification of exposed persons

- **High morbidity and mortality among initial patients**
  - Early notification and diagnosis might result in better outcomes
  - Notified of exposure to contaminated medication and informed of symptoms requiring medical attention

- **Injection facilities identified potentially exposed patients**
  - MPA lot numbers not consistently recorded
  - Facilities often established a period of risk when MPA was in use
  - All patients who received MPA were potentially exposed
Notification of exposed persons

- Injection facilities, state and local health departments and CDC contacted patients by telephone, letter and/or home visit
- CDC opened call center to supplement efforts
Case Finding Information Flow

Surveillance Team

Desk Manager

Desk 1
8 states
Clinics and Hospitals

Desk 2
9 states
Clinics and Hospitals

Desk 3
8 states
Clinics and Hospitals

Desk 4
9 states
Clinics and Hospitals

Desk 5
8 states
Clinics and Hospitals

Desk 6
9 states
Clinics and Hospitals

Desk 7
1 state
Clinics and Hospitals
Attack rate calculation

- **State-specific attack rate***
  \[
  = \frac{\text{no. of cases in state}}{\text{no. of exposed persons in state}} \times 100\%
  \]

- **Case definition-specific attack rate**
  \[
  = \frac{\text{no. of cases meeting case definition}}{\text{no. of persons receiving relevant injection}} \times 100\%
  \]

*calculated for persons with meningitis, parameningeal infection, or stroke who received ESI
Incubation period calculation

| 2012 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Sept |   |   |   |   |   |   |   |   |   | Injection #1 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Oct  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Nov  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | Meningitis diagnosed by lumbar puncture |   |   |   |
| Dec  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
Incubation period calculation

| 2012 |  1 |  2 |  3 |  4 |  5 |  6 |  7 |  8 |  9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Sept |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | Injection #1 |
| Oct  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | Meningitis diagnosed by lumbar puncture |
| Nov  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dec  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
Incubation period calculation

| Year | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
|      |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sept |   |   |   |   |   |   |   |   |   | Injection #1 | Injection #2 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Oct  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Nov  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | Parameningeal infection diagnosed by MRI |
| Dec  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
Incubation period calculation

| 2012 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Sept |   |   |   |   |   |   |   |   |   | Injection #1 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Oct  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Nov  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | Parameningeal infection diagnosed by MRI |
| Dec  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
Microbiologic methods

- **Specimens**
  - Fungal isolates from unopened vials of MPA
  - Clinical specimens (CSF, tissue, aspirate fluid) or fungal isolates from case-patients

- **Identification methods**
  - PCR and sequencing of ribosomal DNA ITS-2 regions
  - Histopathology, including polyfungal immunohistochemistry, used to detect fungal elements
Epidemiologic Investigation Results
Exposed persons notified

- 13,534 persons potentially exposed
  - 12,069 (89%) by epidural, spinal, or paraspinal injection
  - 1,648 (12%) by peripheral joint or other injection
Case-patients by April 1, 2013 (n=730)

- **584 met a single case definition**
  - 308 had parameningeal infection
  - 236 had meningitis
  - 33 had peripheral joint infection
  - 7 had stroke

- **146 met multiple case definitions**
  - 144 had parameningeal infection and meningitis
  - 2 had parameningeal infection and peripheral joint infection
## Case-patient characteristics (n=696)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Median age, years (range)</td>
<td>62</td>
<td>(16-97)</td>
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<tr>
<td>Female (%)</td>
<td>410</td>
<td>(59)</td>
</tr>
<tr>
<td>Median no. injections (range)</td>
<td>1</td>
<td>(1-6)</td>
</tr>
<tr>
<td>MPA lot exposure known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lot 5</td>
<td>68</td>
<td>(10)</td>
</tr>
<tr>
<td>Lot 6</td>
<td>414</td>
<td>(59)</td>
</tr>
<tr>
<td>Lot 8</td>
<td>88</td>
<td>(13)</td>
</tr>
<tr>
<td>Case definition</td>
<td>Median (days)</td>
<td>(range)</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td>Overall (n=675)</td>
<td>44</td>
<td>(0 - 190)</td>
</tr>
<tr>
<td>Parameningeal infection (n=403)</td>
<td>49</td>
<td>(7 - 182)</td>
</tr>
<tr>
<td>Meningitis (n=231)</td>
<td>36</td>
<td>(0 - 146)</td>
</tr>
<tr>
<td>Peripheral joint (n=34)</td>
<td>62</td>
<td>(22 - 190)</td>
</tr>
<tr>
<td>Stroke (n=7)</td>
<td>24</td>
<td>(3 - 157)</td>
</tr>
</tbody>
</table>
### Attack rates (n=730)

<table>
<thead>
<tr>
<th>Case definition</th>
<th>Cases</th>
<th>Exposed</th>
<th>AR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameningeal*</td>
<td>452</td>
<td>12,069</td>
<td>3.7</td>
</tr>
<tr>
<td>Meningitis*</td>
<td>380</td>
<td>12,069</td>
<td>3.1</td>
</tr>
<tr>
<td>Peripheral joint*</td>
<td>35</td>
<td>1,648</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*Per case definition, with or without multiple infections*
Distribution of cases by case definition (n=730)

- Spinal Infection: 308 (42%)
- Meningitis: 236 (32%)
- Meningitis + Spinal Infection: 144 (20%)
- Peripheral Joint Infection: 33 (5%)
- Stroke: 7 (1%)
- Spinal Infection + Peripheral Joint Infection: 2 (0.3%)
### Case-fatality rates

<table>
<thead>
<tr>
<th>Case Definition</th>
<th>Cases</th>
<th>Deaths*</th>
<th>CFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All case-patients</td>
<td>730</td>
<td>53</td>
<td>7.3</td>
</tr>
<tr>
<td>Meningitis</td>
<td>236</td>
<td>26</td>
<td>11.0</td>
</tr>
<tr>
<td>Meningitis + parameningeal</td>
<td>144</td>
<td>11</td>
<td>7.6</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>Parameningeal</td>
<td>308</td>
<td>9</td>
<td>2.9</td>
</tr>
<tr>
<td>Peripheral joint</td>
<td>33</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*all cause mortality among case-patients
Exserohilum isolated from unopened MPA vials

- **Exserohilum rostratum** (lots 5, 6, and 8)
  - Predominant organism from clinical specimens and vials of MPA
  - Environmental mold
  - Rare cases of clinical illness
  - No reported cases of infection of central nervous system

*Exserohilum rostratum*
Other organisms isolated from unopened MPA vials

- Other organisms identified
  - Cladosporium cladosporioides
  - Paecilomyces formosus
  - Rhodotorula laryngis
  - Rhizopus stolonifer
  - Bacillus subtilis and B. pumilus

- Aspergillus not found in MPA vials
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

- Highlighted regulatory questions for compounding pharmacies
Fungi Confirmed in Patients

- *Exserohilum rostratum*
- *Aspergillus fumigatus* identified in 1 patient
- Variety of other fungi of unclear clinical significance identified in 11 patients
Other fungi detected in case-patient specimens

- Aspergillus
- Bipolaris
- Coelomycete
- Stachybotrys
- Alternaria
- Epioccum
- Paecilomyces
- Penicillium
- Scopulariopsis
- Chaetomium
Multistate Outbreak of Fungal Meningitis and Other Infections
Laboratory Support

- Fungal diagnostics for cerebrospinal fluid (testing for meningitis) do not exist
- Novel PCR test developed in 2 days
- >1,000 specimens processed during outbreak

L Gade, et al., Eukaryotic Cell, 1 March 2013
Detection of fungal DNA in human body fluids and tissues during a multistate outbreak of fungal meningitis and other infections
Epidemic Curve as of March 4, 2013

Week of Diagnosis of Case-Patients
(665 Case-Patients, 788 Dates of Diagnosis)

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

Week of Diagnosis:
8-Jul-12 22-Jul-12 5-Aug-12 12-Aug-12 22-Aug-12 2-Sep-12 9-Sep-12 16-Sep-12 23-Sep-12 30-Sep-12 7-Oct-12 14-Oct-12 21-Oct-12 28-Oct-12 4-Nov-12 11-Nov-12 18-Nov-12 25-Nov-12 2-Dec-12 9-Dec-12 16-Dec-12 23-Dec-12 30-Dec-12 6-Jan-13 13-Jan-13 20-Jan-13 3-Feb-13 10-Feb-13

Total Cases:
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
Multi-State Meningitis Outbreak - Current Case Count

Persons with Fungal Infections Linked to Steroid Injections, by State

APRIL 8, 2013 3:30 PM EST

[Map showing cases by state, with color coding for different case counts: 1-11 cases, 12-40 cases, ≥41 cases.]
Patient notification challenges

- Relied on injection facilities to identify persons exposed
  - Required human resources for rapid and accurate identification and patient notification
  - Some injection facilities did not record MPA lot number

- State and local health departments ensured each exposed person was contacted and sufficiently notified
  - In some cases, numbers of exposed persons exceeded capacity

- Activation of CDC Emergency Operations Center necessary to ensure rapid patient notification
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
Multistate Outbreak of Fungal Meningitis and Other Infections

Health Communication

- Health communication strategy relied on
  - Risk communication principles
  - Websites
  - Traditional and social media
  - Targeted outreach to clinicians, patients, partners

- Communication Metrics 10/4 – 11/7
  - 1M web page views
  - 430K total news stories
  - 290K social media views
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
Communication strategies

- Direct patient communication
- Electronic communication dissemination
  - Epi-X posting
  - Emerging Infections Network
  - ClinMicroNet
  - Blast emails to professional societies and listservs
  - Dedicated CDC website
- Health Alert Network
- Clinical Outreach Communication Activity (COCA) calls
- Media press releases
Outbreak Summary (April 8, 2013)

- **Exserohilum rostratum** predominant fungus identified in patients
  - Also isolated from unopened vials of MPA from NECC
- **733 infections in 20 states, 53 deaths***
  - Meningitis
  - Localized spinal or paraspinal infections (e.g., epidural abscess, phlegmon, arachnoiditis)
  - Peripheral joint infections
- **Treatment**
  - Adequate duration of antifungal treatment is unknown
  - Minimum of 3 months with more severe disease likely needing 6 months to 1 year.

*Deaths reported are from all causes among persons who meet the case definition and may not be directly attributed to a fungal Infection

http://www.cdc.gov/HAI/outbreaks/meningitis.html
Unprecedented outbreak

- Largest outbreak of healthcare-associated infections in US

- Severity and complexity of clinical disease

- Large number of exposed persons required rapid patient identification and notification
Remaining questions

- **Why did attack rates vary between states?**
  - Injection techniques between injection facilities
  - Age of MPA vials shipped to injection facilities
  - Degree of contamination among vials

- **What is the upper limit for incubation?**
  - Longest incubation period is 190 days

- **How do we capture case-patients going forward?**
  - Patient dispersal
  - Waning awareness of risk
EXTRA SLIDES
What happened?

- September 18: TN DOH notified by physician treating patient with *Aspergillus* meningitis who had recent epidural injection at ambulatory surgical center (ASC)
- TN DOH contacts CDC to determine if similar cases had been reported to CDC
- Local investigation identifies additional cases of meningitis, of unknown etiology, in patients who had received epidural injections at the same ASC
- All had undergone epidural steroid injection with Methylprednisolone acetate (MPA) from New England Compounding Center (NECC) and had other common exposures
- FDA notified about investigation and there was joint call with NECC to discuss the investigation
- NECC issues voluntary recall of 3 lots of MPA used by the TN ASC and provides list of all 76 facilities in 23 states that these 3 lots to CDC
- CDC uses list to initiate case-finding in other states while also pursuing other possible sources of the outbreak
- NC DOH identifies patient with meningitis of unknown etiology following ESI at NC clinic; suggests exposure may not be limited to TN ASC
What happened next?

- Widespread notification through various networks and listservs, notification of patients exposed to recalled MPA initiated by health departments in collaboration with clinics
- Exposure still not confirmed; Pathogen not identified except index case
- VA’s Public Health laboratory identifies the fungal species *Exserohilum* in an unexplained death and relays a verbal report from the medical examiner that the neuropathology on the patient was consistent with stroke.
- October 4: FDA announces that unopened vials of MPA were contaminated with fungus
- CDC activates Emergency Operations Center and ongoing urgent efforts to directly notify ~14,000 exposed persons
- October 6: CDC identifies *Exserohilium rostratum* in a patient sample and confirms VA finding by microscopy. All NECC products compounded at and distributed from its Framingham, MA facility are recalled.
- October 18: *Exserohilium rostratum* recovered from unopened vials of methylprednisolone acetate
Engaged clinical expert mycologists with experience in fungal infections
  - Best practices for diagnosis, treatment, and management
  - Based on little to no data, but likely theoretical benefit

Resulted in real-time development, dissemination of recommendations for patient care
  - Able to evolve with the rapidly changing outbreak

CMS
  - CDC guidance used as the basis for modifying indications for diagnostic testing and treatment and eligibility for reimbursement

Clinical course unknown
  - Recruited group of ID specialist volunteers to provide ongoing consultation to treating physicians
CDC Health Alert Network (HAN):

Update: Notice to Clinicians: Continued Vigilance Urged for Fungal Infections Among Patients Who Received Contaminated Steroid Injections, March 4, 2013
Update: Multistate Outbreak of Fungal Infections among Persons Who Received Injections with Contaminated Medication, December 20, 2012
Update: Additional Contamination Identified in Medical Products from New England Compounding Center, December 3, 2012
Update: Multistate Outbreak of Fungal Meningitis and Other Infections Associated with Contaminated Steroid Medication, November 20, 2012
Contamination Identified in Additional Medical Products from New England Compounding Center, November 1, 2012
Voluntary Recall of All Ameridose Medical Products, November 1, 2012
Issuance of Guidance on Management of Asymptomatic Patients Who Received Epidural or Paraspinal Injections with Contaminated Steroid Products, October 23, 2012
Update: Multistate Outbreak of Fungal Meningitis and Joint Infections Associated with Contaminated Steroid Medications, October 17, 2012
Multistate Outbreak of Meningitis and Stroke Associated with Potentially Contaminated Steroid Medication, October 8, 2012
Meningitis and Stroke Associated with Potentially Contaminated Product, October 4, 2012
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:
  - Clinician
  - Healthcare setting (clinic, hospital)
  - Local and state health departments
  - Federal agencies
Attack rate calculation

- **State-specific attack rate**
  \[
  = \frac{\text{no. of cases in state}}{\text{no. of exposed persons in state}}
  \]

- **State-specific attack rate with ESI**
  \[
  = \frac{\text{no. of meningitis, stroke and parameningeal cases in state}}{\text{no. exposed persons receiving ESI in state}}
  \]
Case-finding results

- Case-patients initially presented with single-site infections

- As outbreak progressed, many patients developed infection at an additional sterile site
  - Patients met multiple case definitions
Clinical characteristics at initial presentation (n=696)

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median white blood cell count in CSF (cells/mL)</td>
<td>21</td>
<td>(range: 0-15,400)</td>
</tr>
<tr>
<td>Headache</td>
<td>419</td>
<td>(62)</td>
</tr>
<tr>
<td>Back pain</td>
<td>195</td>
<td>(30)</td>
</tr>
<tr>
<td>Fever</td>
<td>139</td>
<td>(21)</td>
</tr>
<tr>
<td>Neck pain or stiffness</td>
<td>104</td>
<td>(15)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>97</td>
<td>(14)</td>
</tr>
</tbody>
</table>
Limitations

- Data pertaining to symptom onset are subject to recall bias and might be complicated by underlying morbidities
- Data for analyses are collated from multiple databases and may not be available for all cases reported
- Longitudinal or follow-up data have not been collected
<table>
<thead>
<tr>
<th>State</th>
<th>Total Case Count</th>
<th>Meningitis Only</th>
<th>Meningitis + Paraspinal/Spinal Infection</th>
<th>Stroke w/out Lumbar Puncture Only</th>
<th>Paraspinal/Spinal Infection only</th>
<th>Peripheral Joint Infection Only</th>
<th>Paraspinal/Spinal Infection + Peripheral Joint Infection</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florida (FL)</td>
<td>25</td>
<td>22</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Georgia (GA)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Idaho (ID)</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Illinois (IL)</td>
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<td>2</td>
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<tr>
<td>Indiana (IN)</td>
<td>84</td>
<td>31</td>
<td>16</td>
<td>1</td>
<td>36</td>
<td>1</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Maryland (MD)</td>
<td>26</td>
<td>25</td>
<td></td>
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<td>3</td>
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<td>Michigan (MI)</td>
<td>258</td>
<td>22</td>
<td>43</td>
<td>2</td>
<td>164</td>
<td>25</td>
<td>2</td>
<td>14</td>
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<tr>
<td>Minnesota (MN)</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
<td>2</td>
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<td></td>
<td>1</td>
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<tr>
<td>North Carolina (NC)</td>
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<td>2</td>
<td>2</td>
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<td>13</td>
<td></td>
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<tr>
<td>New Hampshire (NH)</td>
<td>14</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
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<td>5</td>
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<tr>
<td>New Jersey (NJ)</td>
<td>49</td>
<td>31</td>
<td>10</td>
<td>7</td>
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<tr>
<td>New York (NY)</td>
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</tr>
<tr>
<td>Ohio (OH)</td>
<td>20</td>
<td>12</td>
<td>3</td>
<td>5</td>
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<tr>
<td>Pennsylvania (PA)</td>
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<tr>
<td>Rhode Island (RI)</td>
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</tr>
<tr>
<td>South Carolina (SC)</td>
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<tr>
<td>Tennessee (TN)</td>
<td>150</td>
<td>21</td>
<td>58</td>
<td>3</td>
<td>66</td>
<td>2</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Texas (TX)</td>
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<td></td>
</tr>
<tr>
<td>Virginia (VA)</td>
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<td>44</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>West Virginia (WV)</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>GRAND TOTAL</strong></td>
<td><strong>727</strong></td>
<td><strong>238</strong></td>
<td><strong>140</strong></td>
<td><strong>7</strong></td>
<td><strong>306</strong></td>
<td><strong>34</strong></td>
<td><strong>2</strong></td>
<td><strong>50</strong></td>
</tr>
</tbody>
</table>
Multi-State Case Finding Approach

- 23 states received contaminated MPA, but cases may reside in states other than where injection received.

- Case “belonged” to state where patient received injection, not where patient resided.

- All state, Puerto Rico, and Washington DC health departments, were assigned a contact number at an EOC desk to report cases efficiently.
  - Prevented case reporting from clinics/physicians
  - Created a directional flow of information to CDC.
Case Finding

- Public health analysts and EISO manned EOC desks for seven day shifts

- All case reporting funneled through EOC desks where CDC Unique ID was assigned for each case

- CDC Unique ID required for CDC laboratory testing and case discussion with clinical team
  - Allowed separate databases to be linked with CDC Unique ID
  - Prevented duplication of case reporting
  - Ensured consistent communication and accurate case counts
Surveillance Team Objectives

- Accurately identify case-patients

- Communicate outbreak information to state partners
  - Epidemiologic
  - Clinical
  - Laboratory
  - FDA investigation

- Communicate surveillance information to incident command leadership and teams
Lot-specific Attack Rates (n=505)\(^1\)

<table>
<thead>
<tr>
<th>Lot #</th>
<th>Cases ever exposed</th>
<th>Volume administered (mL)</th>
<th>AR (per 1,000 mL administered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>67</td>
<td>11,622</td>
<td>5.8</td>
</tr>
<tr>
<td>B</td>
<td>410</td>
<td>10,665</td>
<td>38.4</td>
</tr>
<tr>
<td>C</td>
<td>88</td>
<td>4,304</td>
<td>20.4</td>
</tr>
</tbody>
</table>

\(^1\)179 persons were missing data on lot exposure and not included in this analysis