

# Multi-state Outbreak of Fungal Infections Associated with Contaminated Steroids 2012-2013

## A National Perspective

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CDC

The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention

*“... one of the most shocking outbreaks  
in the annals of American medicine.”*

*Lawrence Altman  
New York Times  
November 5, 2012*

## Acknowledgments

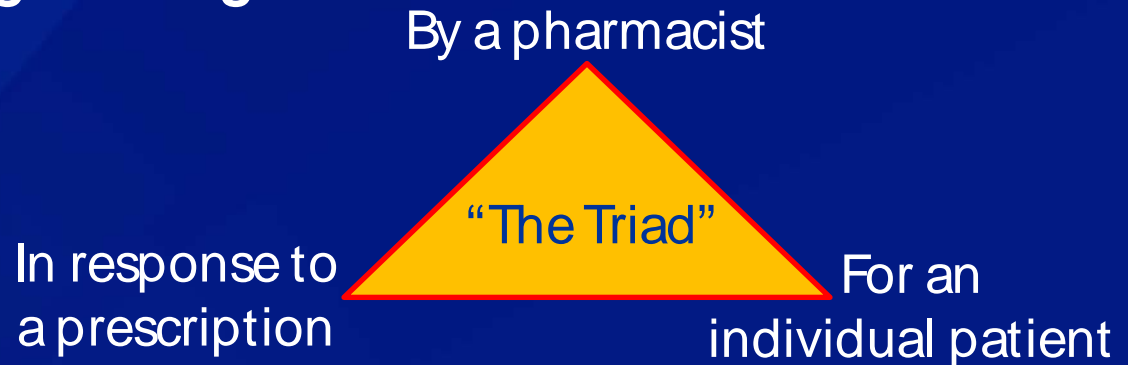
- ❑ Hundreds of employees at 23 state health departments
- ❑ 300+ CDC employees
- ❑ FDA and DHHS employees
- ❑ Experts in fungal infection
- ❑ Physicians and others responsible for patient care

# The Call

- ❑ September 20, 2012
- ❑ Tennessee Department of Health called CDC
- ❑ Discuss an unusual case reported by an astute physician
  - Patient with *Aspergillus* meningitis
  - Had received an epidural steroid injection for pain
  - Somewhat strange infection
    - Meningitis due to molds are very rare
    - Concern for contamination somehow
    - Steroid was a compounded medication

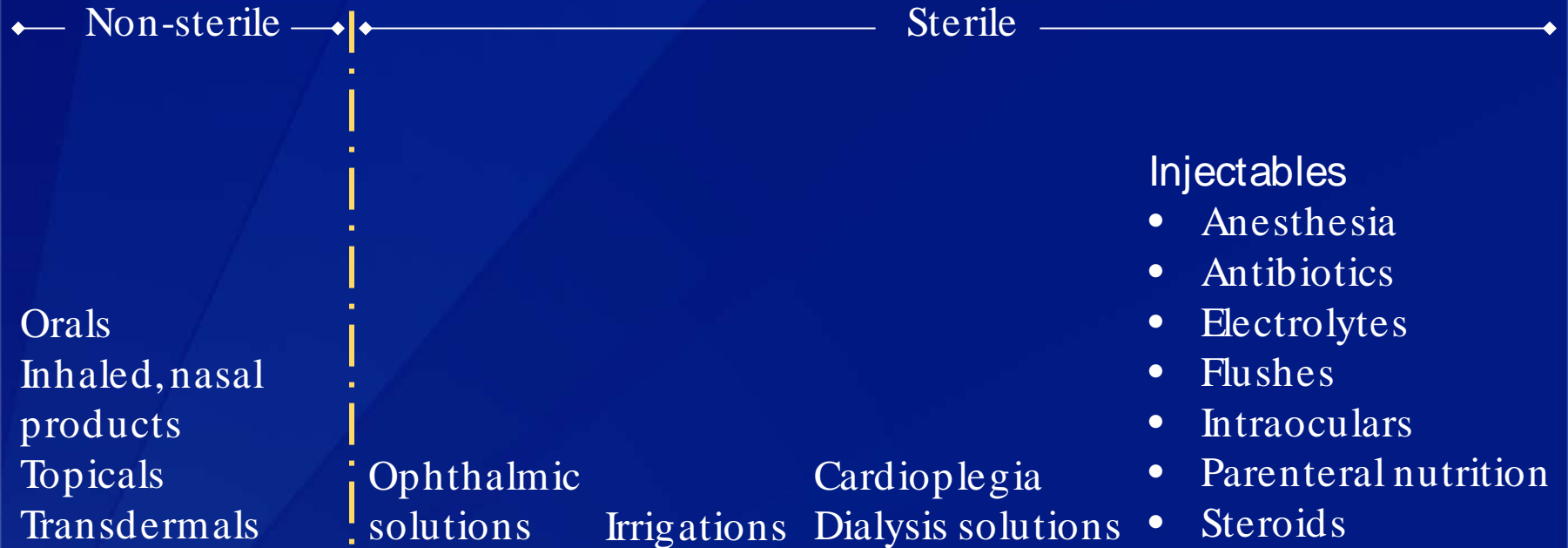
# What is Pharmacy Compounding?

- ❑ Extemporaneous combining, mixing, or altering of drug ingredients:\*



- ❑ Traditional component of pharmacy practice
  - Eg., local pharmacy making oral suspension for children
- ❑ Meets needs that cannot be met with commercially-manufactured drug products

# Compounding Has a Broad Scope



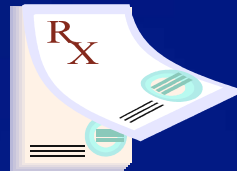
# Compounded Medications More Common

- Recent expansion in scope and nature of activities
  - In 2012, 7500 U.S. pharmacies specializing in advanced compounding services\*
    - ~3000 provide sterile compounding services

OLD



In-house



Individual prescription



Orals, Topicals



Local



NEW



Outsourcing



Bulk

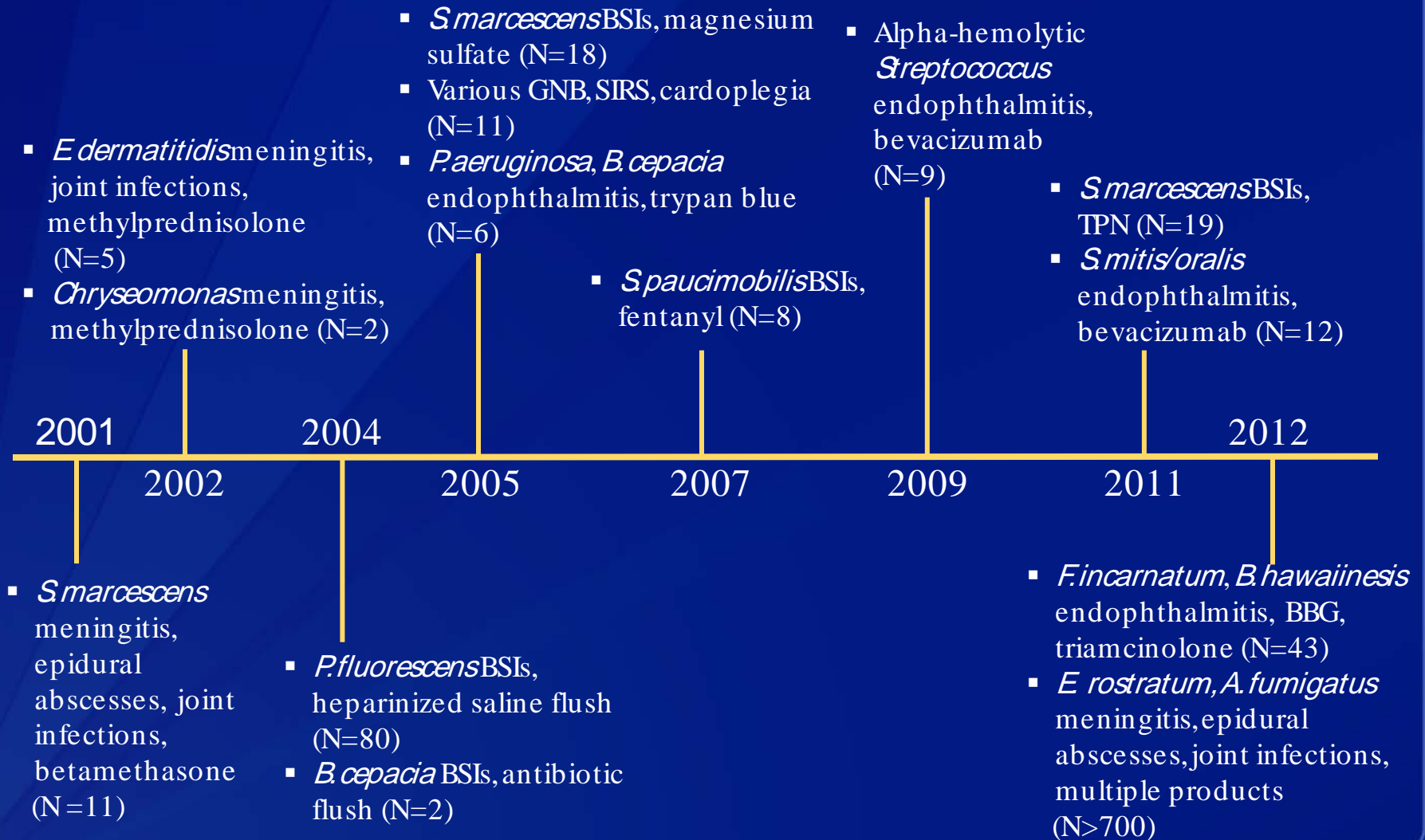


Sterile Products



Multi-state Distribution

# Outbreaks Linked to Compounding Pharmacies 2000 – Present (U.S.)



# Compounding Industry Regulation

- ❑ **Regulation is complex**
  - Ambiguous authority, fragmented oversight
- ❑ **States (Boards of Pharmacy)—primary authority**
  - Sterile compounding subject to state regulatory/professional standards
  - Not subject to federal pharmaceutical manufacturing standards
  - Highly variable enforcement
- ❑ **Federal (FDA) enforcement considered when scope of pharmacy activities “raise the kinds of concerns normally associated with a drug manufacturer” \***



# Timeline- Two Weeks

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

OCTOBER

## Timeline- Two Weeks

CDC contacted by TN DOH about a single patient with culture-confirmed *Aspergillus meningitis* following epidural steroid injection at an ASC.

Patient had injection on July 30<sup>th</sup> and was admitted to the hospital in late August



# Timeline- Two Weeks

Further investigation by TN DOH identified 7 additional patients with meningitis from same ASC



## Timeline- Two Weeks

Further investigation by TN DOH identified 7 additional patients with meningitis from same ASC

Unusual clinical cluster:

All characterized by subacute onset of meningitis with marked CSF pleocytosis

4 had posterior circulation strokes

CSF cultures from additional patients all initially negative



SEPTEMBER

OCTOBER

## Timeline- Two Weeks

Further investigation by TN DOH identified 7 additional patients with meningitis from same ASC

### Common links:

All had undergone epidural steroid injection

Methylprednisolone acetate (MPA) from New England Compounding Center (NECC)

Other common exposures included: contrast material, povidone-iodine, lidocaine, spinal needles, epidural tray kits



SEPTEMBER

OCTOBER

## Very Unusual Cluster

- ❑ Immediate concern for some type of contamination
- ❑ Two main types of contamination
  - Extrinsic
    - Packaging
    - Surgical site
    - Air (HVAC, nearby construction)
  - Intrinsic
    - Medication itself

# Prior Fungal Meningitis Outbreaks

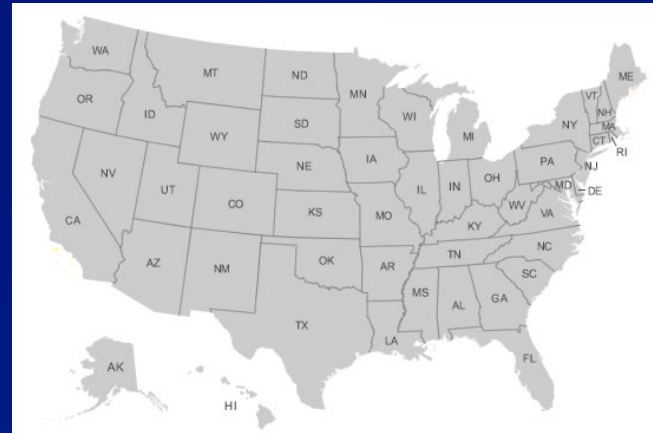
- ❑ Surprisingly, there have been a few:
- ❑ **Extrinsic contamination**
  - Sri Lanka following 2005 Indian Ocean tsunami
  - Moldy closet led to *Aspergillus* meningitis in pregnant women undergoing spinal anesthesia
  - Case fatality 60%
- ❑ **Intrinsic contamination**
  - 2002 outbreak in NC of 5 cases of *Exophiala* meningitis
  - Compounded steroid medication
  - Distributed locally

# Some Initial Hypotheses



## Clinic-based contamination?

- No new construction
- No problems with HVAC
- No flooding
- No change in practices
- No clustering by physician
- Many common products



## Product-based contamination?

- Many common products
- Compounded steroid probably most likely
- But many others national distribution

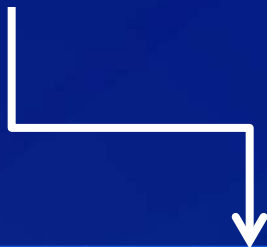


# Timeline- Two Weeks

FDA notified about investigation

Call with NECC to discuss the investigation

NECC states it had not received any reports of illnesses and no concerning results with sterility testing or environmental monitoring



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OCTOBER

## Timeline- Two Weeks

NECC issues voluntary recall of 3 lots of MPA used by the TN ASC

NECC provides list of all 76 facilities in 23 states that received MPA from these 3 lots to CDC

CDC uses list to initiate case-finding in other states while also pursuing other possible sources of the outbreak



## Timeline- Two Weeks

NC DOH identifies patient with meningitis of unknown etiology following ESI at NC clinic

Suggested exposure may not be limited to TN ASC



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OCTOBER

## Timeline- Two Weeks

Notification of patients exposed to recalled MPA initiated by health departments in collaboration with clinics

- Exposure still unknown
- Pathogen not identified except index case



SEPTEMBER

OCTOBER

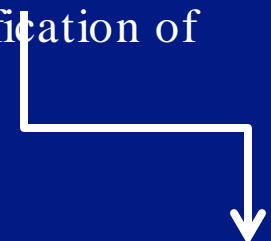
## Timeline- Two Weeks

FDA announced that unopened vials of MPA were contaminated with fungus

Virginia state lab found *Exserohilum* in case

CDC activated Emergency Operations Center

CDC began direct patient notification of ~14,000 exposed persons



SEPTEMBER

OCTOBER

# Major Outbreak Response

- ❑ Largest healthcare-associated outbreak reported in the United States
- ❑ Massive undertaking
  - Over 300 staff at CDC HQ
  - Thousands of staff nationally
    - State and local health departments
    - Clinicians, nurses, administrative staff

## Thousands Exposed to Tainted Steroid, C.D.C. Says

By DENISE GRADY  
Published: October 8, 2012

About 13,000 people may have been exposed to the tainted steroid that has been linked to a growing outbreak of fungal [meningitis](#), a spokesman for the [Centers for Disease Control and Prevention](#) said on Monday. The outbreak has killed 8 people and sickened 97 others in 23 states. More cases are expected.

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The figure, the first estimate of how many people were injected with any of the 17,676 doses shipped around the country, is based on reports from state health departments and clinics that used the drug, methylprednisolone acetate. It was injected near the spine to ease back and neck pain, a treatment that about five million people in the United States undergo every year.

### Multimedia



### Tracking an Outbreak

The company that made the drug, the [New England Compounding Center](#) in Framingham, Mass., has shut down, surrendered its license and recalled all its products, not just the steroid.

### Related

*New York Times, October 8, 2012*

## The Concern

- ❑ Almost 14,000 persons exposed to contaminated MPA
- ❑ Delayed diagnosis in many patients → adverse events
- ❑ Of the initial 9 patients identified
  - 4 developed posterior circulation stroke
  - 3 died
- ❑ Limited experience with this type of infection
- ❑ Known outbreaks had ~40% mortality

# Public Health Actions: Major Components

- ❑ Patient Notification
- ❑ Clinical Guidance
- ❑ Laboratory Support
- ❑ Communications



# Patient Notification

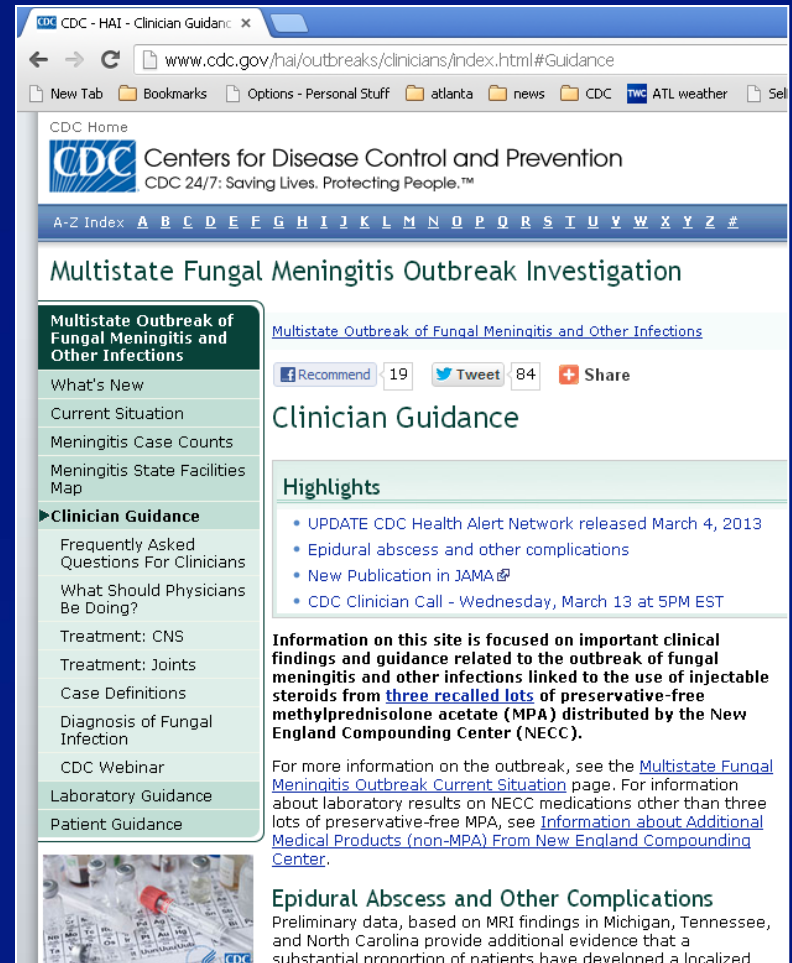
- ❑ Medication recalled on 9/26/12
  - Not enough
- ❑ CDC launched a collaborative effort to notify all exposed persons
  - Nature of the exposure
  - Indications to seek medical care
- ❑ Conducted mainly through clinic staff, state, local HDs
- ❑ The Goal: early diagnosis and treatment to reduce poor outcomes
- ❑ Within 10 days, >90% of all exposed persons were notified



CDC Emergency Operations Center

# Development of Clinical Guidance

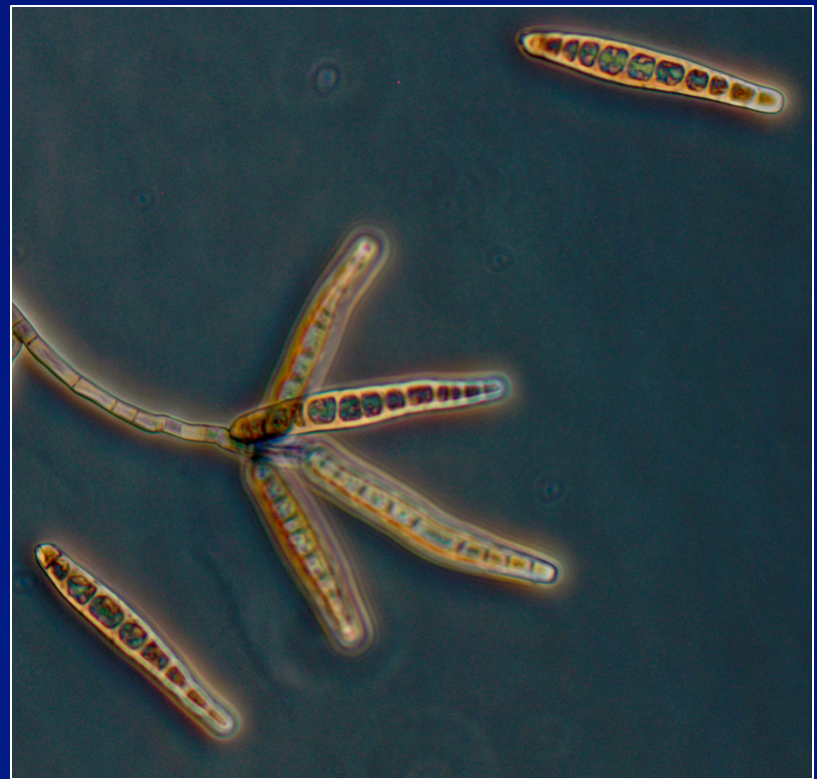
- Engaged clinical expert mycologists with experience in fungal infections
  - Best practices for diagnosis, treatment, and management
  - Based on little to no data, but likely theoretical benefit
- Resulted in real-time development, dissemination of recommendations for patient care
  - Able to evolve with the rapidly changing outbreak



The screenshot shows the CDC website page for the Multistate Fungal Meningitis Outbreak Investigation. The page is titled "Multistate Fungal Meningitis Outbreak Investigation" and features a sidebar with a "Clinician Guidance" section highlighted. The main content area includes a "Clinician Guidance" section and a "Highlights" section. The "Highlights" section lists several updates, including a CDC Health Alert Network release on March 4, 2013, and a CDC Clinician Call on Wednesday, March 13 at 5PM EST. The "Clinician Guidance" section includes a "Frequently Asked Questions For Clinicians" link and a "What Should Physicians Be Doing?" link. The "Information on this site" section provides details about the outbreak, mentioning the use of injectable steroids from three recalled lots of preservative-free methylprednisolone acetate (MPA) distributed by the New England Compounding Center (NECC). The "Epidural Abscess and Other Complications" section mentions preliminary data based on MRI findings in Michigan, Tennessee, and North Carolina, indicating that a substantial proportion of patients have developed a localized abscess.

## Laboratory Support

- ❑ Fungal diagnostics for CSF do not exist
- ❑ Novel PCR test developed in 2 days
- ❑ Quickly identified main fungus as *Exserohilum rostratum*
- ❑ >1,000 specimens processed during outbreak



*Exserohilum rostratum*

# Communications

## □ Integral components of outbreak response

- Website
- Media
- Health Alerts to clinicians
- Blast emails
- Scientific publications

## □ Goal

- Transparent, timely, trustworthy

The screenshot shows the CDC website page for the Multistate Fungal Meningitis Outbreak Investigation. The page includes a navigation bar with the CDC logo and the text "Centers for Disease Control and Prevention CDC 24/7: Saving Lives. Protecting People.™". Below the navigation bar is a search bar and a list of links (A-Z Index). The main content area features a large heading "Multistate Fungal Meningitis Outbreak Investigation" and a sub-heading "CDC Responds to Multistate Outbreak of Fungal Meningitis and Other Infections". A photograph shows a person in a lab coat working in a laboratory. The text describes the outbreak and includes a "Current Situation Update" link. To the right is an "At-A-Glance" box with key statistics: Status: Ongoing Investigation, Infection: Fungal, Facility Type: Outpatient Setting, Case Count: 720\*, States: 20\*, Deaths: 48\*, and Laboratory Results. Below this are two maps: "Case Count" and "Healthcare Facilities". The "Case Count" map shows the distribution of cases across the United States, and the "Healthcare Facilities" map shows the locations of facilities. The page also includes sections for "Clinician Guidance" and "Patient Guidance", each with a "More »" link. At the bottom, there is a "What's New on this Website" section with a link to a CDC Health Alert Network (HAN) update from March 4, 2013.

CDC Home  
Centers for Disease Control and Prevention  
CDC 24/7: Saving Lives. Protecting People.™

A-Z Index: A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

### Multistate Fungal Meningitis Outbreak Investigation



**CDC Responds to Multistate Outbreak of Fungal Meningitis and Other Infections**  
The Centers for Disease Control and Prevention (CDC), in collaboration with state and local health departments and the [Food and Drug Administration \(FDA\)](#), is investigating a multistate outbreak of fungal meningitis and other infections among patients who received contaminated steroid injections. **This form of meningitis is not contagious.** The investigation also includes fungal infections associated with the injection site, both spinal and peripheral joints, such as a knee, shoulder or ankle. [See Current Situation Update »](#)

THIS WEBSITE WAS LAST UPDATED MARCH 4, 2013 3:00 PM EST

#### At-A-Glance

- Status: Ongoing Investigation
- Infection: Fungal
- Facility Type: Outpatient Setting
- Case Count: 720\*
- States: 20\*
- Deaths: 48\*
- Laboratory Results

\* Case counts are updated every Monday.

#### Clinician Guidance

- Frequently Asked Questions and Answers
- Health Alert Network
- Management and Treatment
- Case Definitions
- Diagnostic Testing
- Publications and Resources

[More »](#)

#### Patient Guidance

- Frequently Asked Questions for Patients
- What Should Patients Do?

[More »](#)

#### Case Count



[View case count map.](#)

#### Healthcare Facilities



[View facilities map.](#)

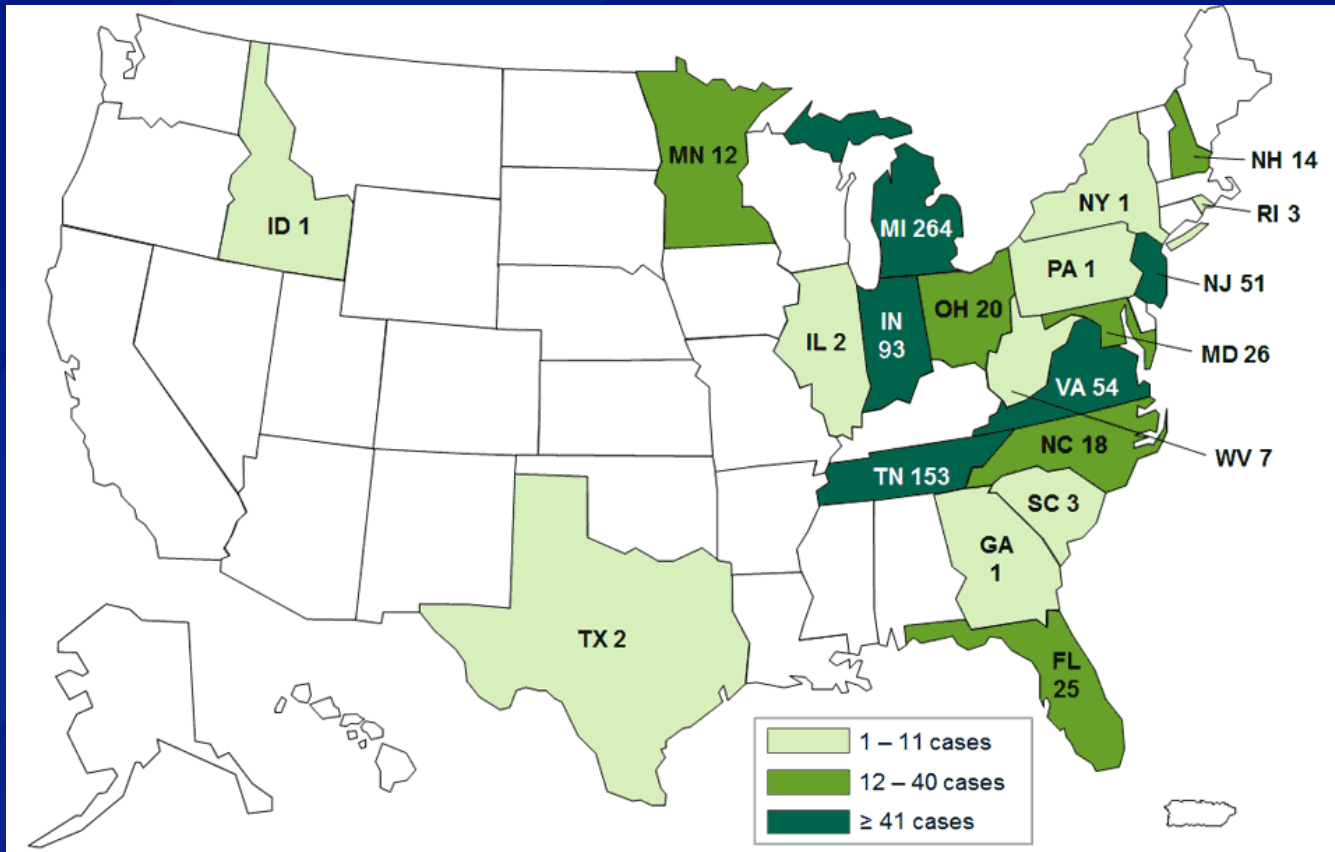
#### What's New on this Website

- 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

3/5/2013 9:31 AM

# OUTBREAK- CURRENT STATUS

# Outbreak as of October 23, 2013



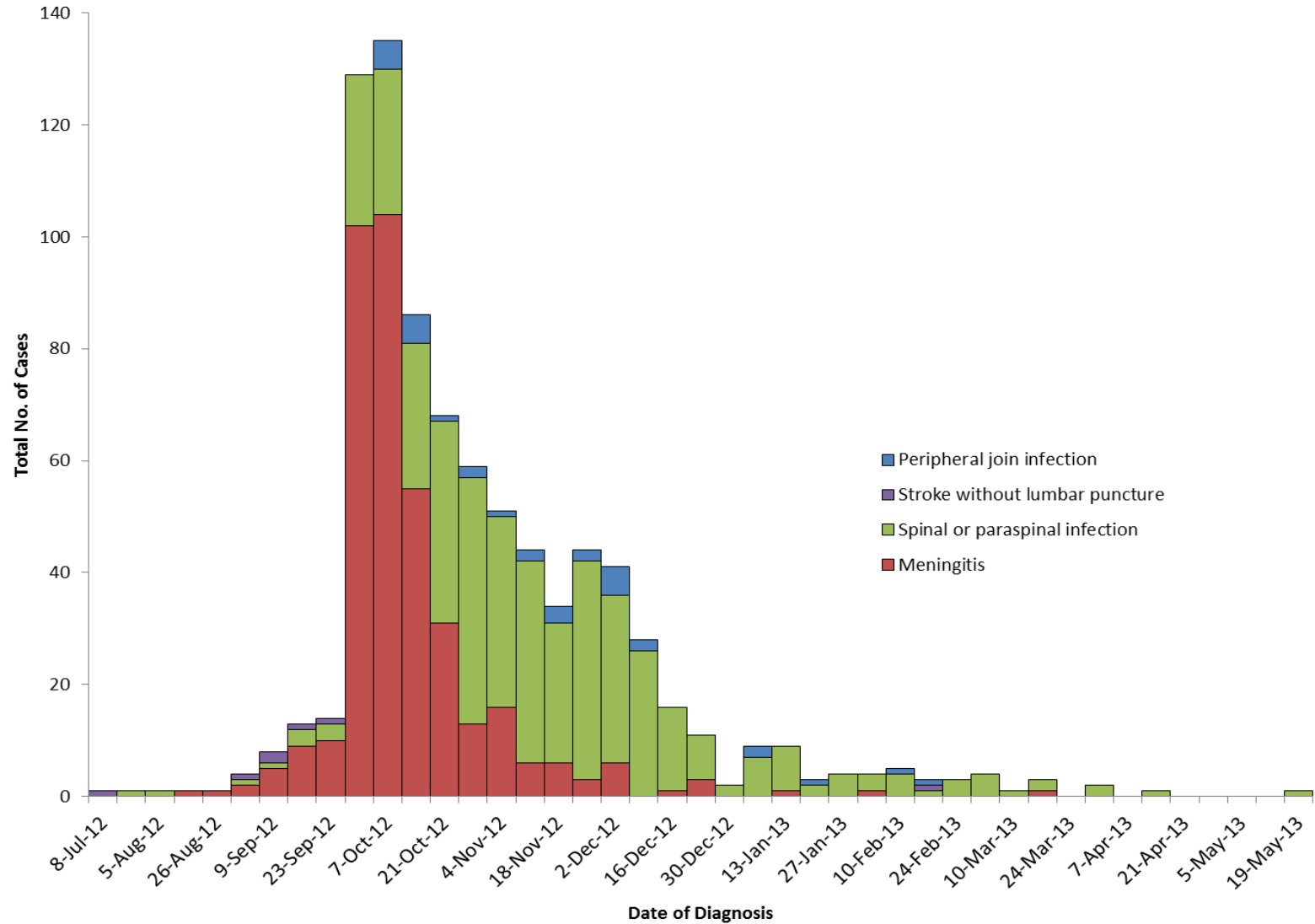
**751 cases in 20 states**

**64 deaths**

## Sites of infection

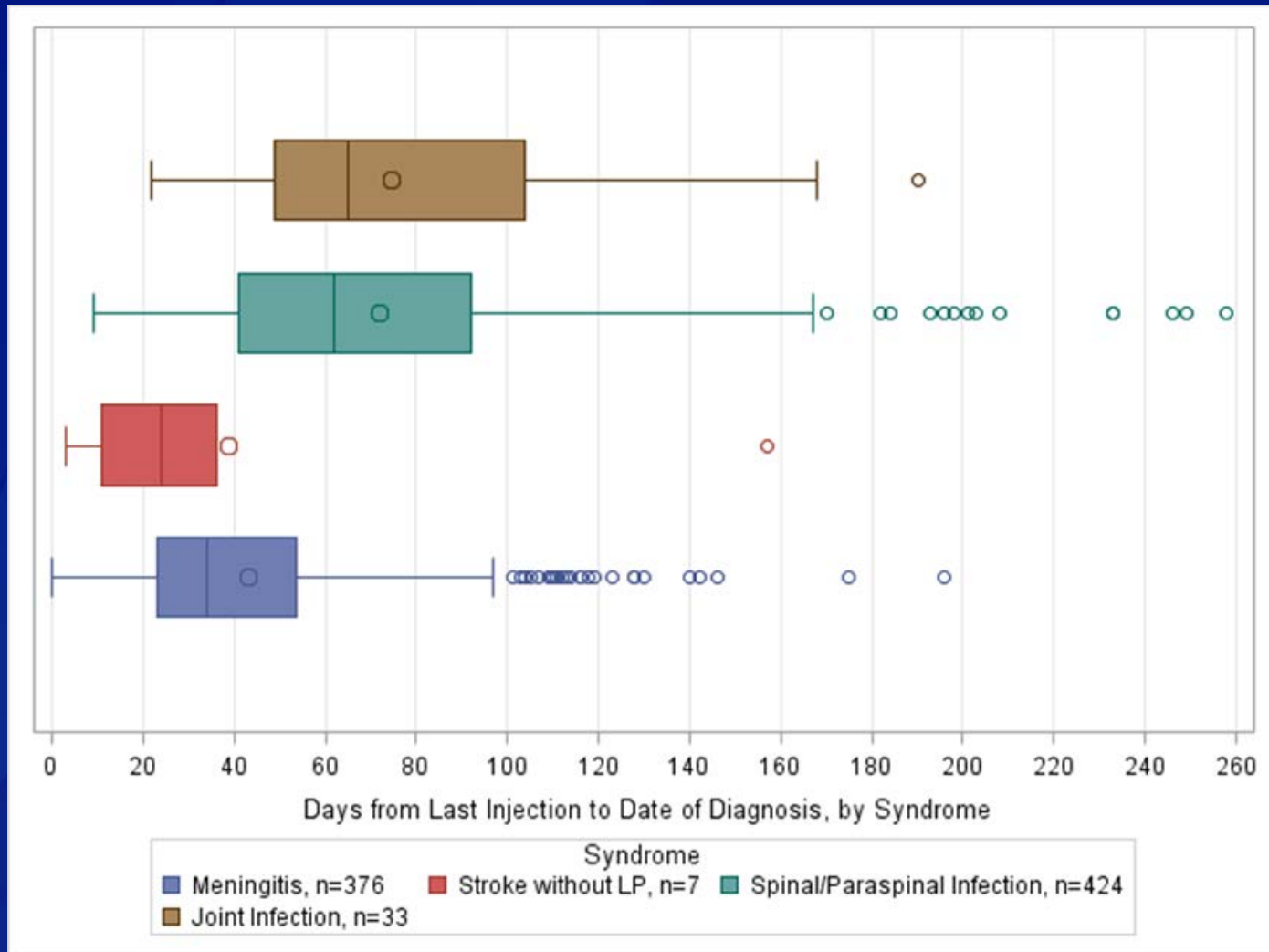
- ❑ **Meningitis**
- ❑ **Parameningeal infection**
  - Epidural abscesses, vertebral osteomyelitis
- ❑ **Peripheral joint infection**
- ❑ **Posterior circulation stroke in absence of CSF examination**
  - Presumed to be due to undiagnosed meningitis
- ❑ **20% of patients have more than one site of infection**
  - Most common: parameningeal disease and meningitis

# Epidemic curve by diagnoses





# Incubation period by diagnosis



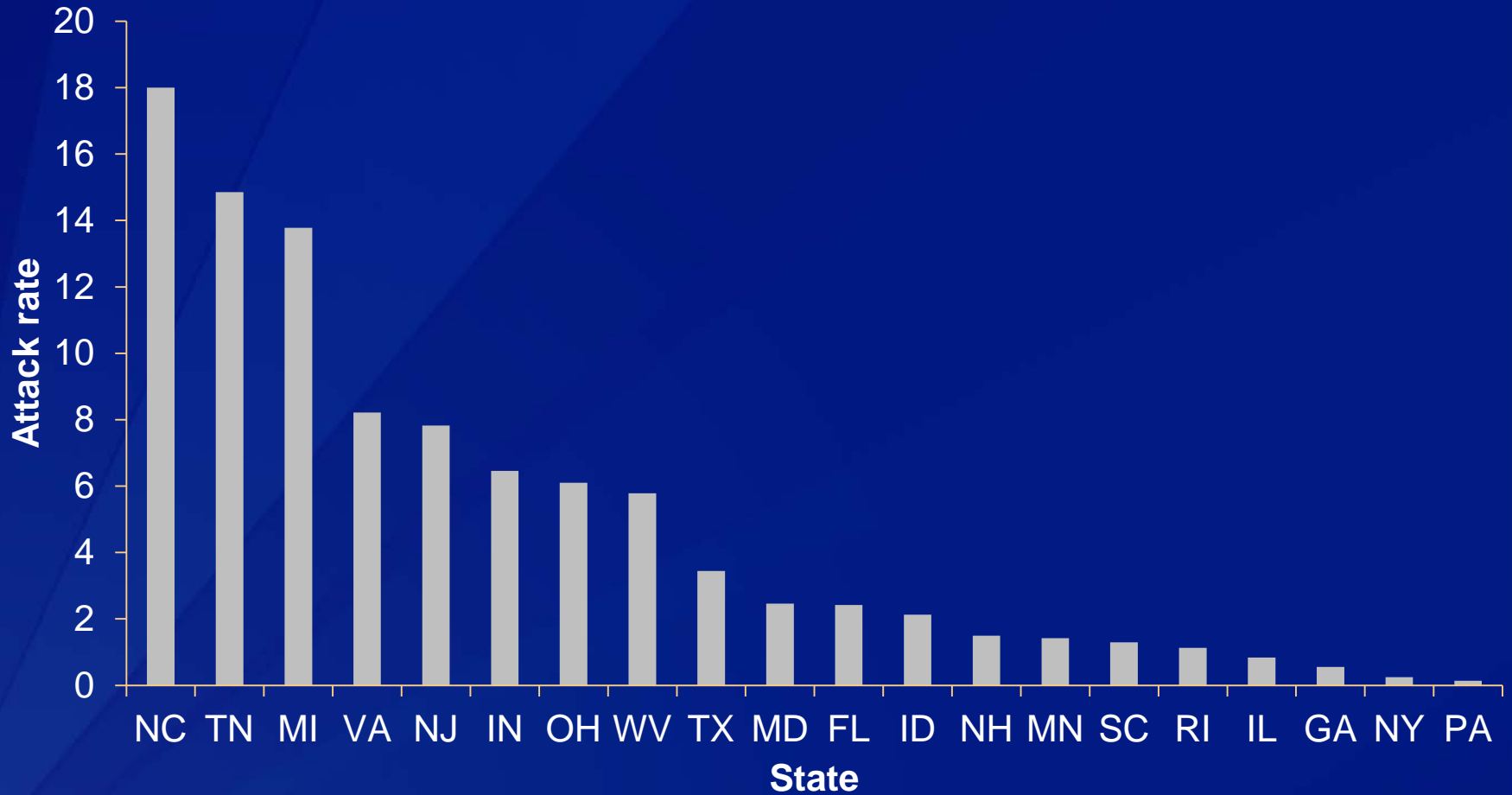
Median incubation to first diagnosis: 47 days (0-249)

## National attack rates

<b>Injection type</b>	<b>Cases</b>	<b>Exposed</b>	<b>Attack rate*</b>
All injections	749	13,534	5.5
Epidural/paraspinal injections	716	12,069	5.9
Peripheral joint injections	35	1,648	2.1

\* Per 100 persons exposed

## State-specific attack rates



**States with exposures but no cases: CA and NV**

## Case-patient characteristics (n=728)

Characteristic	n (%)
Female	432 (59)
Median Age (range)	64 (15-97)
Initial symptoms <sup>1</sup>	
Headache	428 (61)
Back pain	319 (46)
Neck stiffness/pain	211 (30)
Lot exposure <sup>2</sup>	
05212012@68	74 (14)
06292012@26	429 (80)
08102012@51	95 (18)

<sup>1</sup>n=701; <sup>2</sup>n=536

## Case-patient laboratory results

Result	n (%)
Case-patients with specimens at CDC	519 (69)
Positive result	173 (33)
<i>Exserohilum</i> spp.*	153 (88)
<i>Aspergillus</i> spp.	4 (2)
<i>Cladosporium</i> spp.	6 (4)
Other fungi	10 (6)

\*With or without other fungi

## Case-fatality rates\*

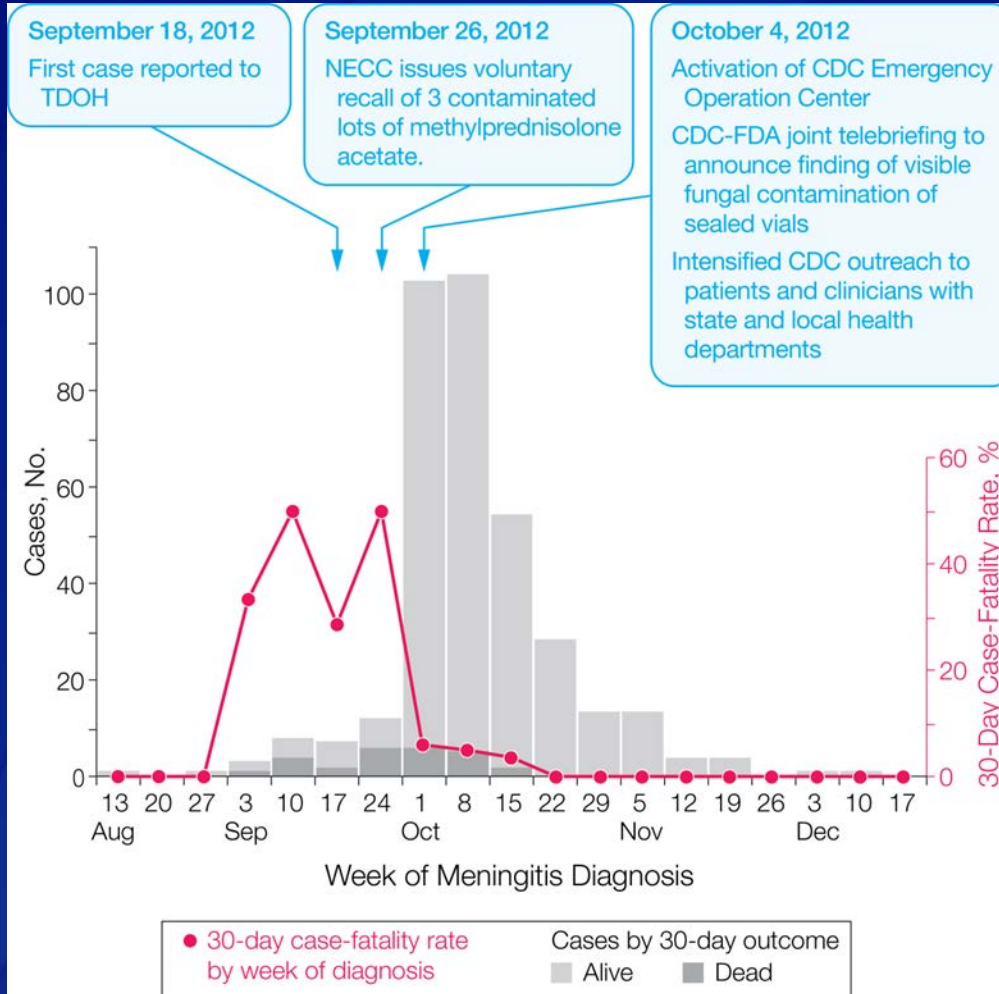
	Cases	Deaths	CFR
All cases	749	63	8.4
Meningitis only	233	32	13.7
Meningitis + Parameningeal	151	13	8.6
Parameningeal only	323	11	3.4
Peripheral joint	33	0	0

\*all-cause mortality among case-patients

## Public health efforts led to early diagnosis

Characteristic	On/before October 4	After October 4	p
Median CSF			
WBC	1,064	31	<0.01
Glucose	38	55	<0.01
Protein	117	71	<0.01
Number of symptoms	5	4	<0.01
Antifungal treatment within 48 hours	58%	84%	<0.01

# Public health efforts reduced case-fatality



**Public health response saved >100 lives**

Responding to the Outbreak of Invasive Fungal Infections: The Value of Public Health to Americans  
 Beth P. Bell, MD, MPH; Rima F. Khabbaz, MD. *JAMA*. 2013;309(9):883-884.



## Keys to Success

- ❑ **Close collaboration among numerous partners**
  - Federal (FDA, CMS)
  - State
  - Local
  - Clinicians
- ❑ **Strong state health department public health infrastructure was essential**
  - Coordinate patient notification
  - Conduct case-finding, case reporting, and follow-up
  - Communicate changing clinical guidance

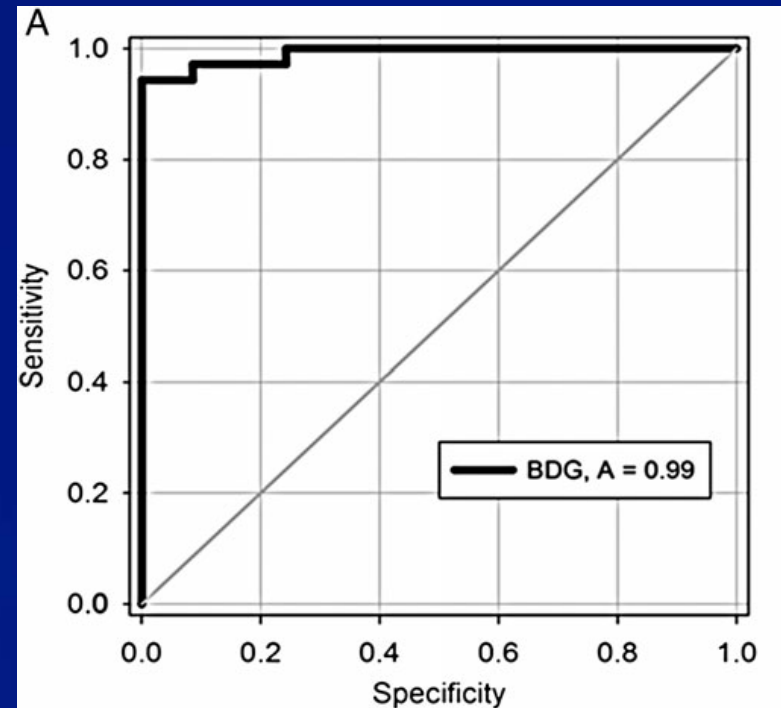
# **CHALLENGES AND NEXT STEPS**

## Ongoing challenges in this outbreak

- ❑ **Patients are completing therapy, returning to community providers**
  - Difficult to determine clinical status
- ❑ **Difficult clinical questions remain**
  - Length of treatment, when to discontinue therapy
  - Reports of relapsed infection
- ❑ **Patients' face tremendous anxiety**
  - Infected and exposed

## Next steps: Diagnostics?

- ❑ **Beta-D-glucan (BDG)**
  - A cell wall polymer found in fungi
  - Available as commercial assay (Fungitell) for use in serum
- ❑ **CSF BDG is sensitive and specific**
  - For the diagnosis of *Exserohilum meningitis*
  - As a marker for treatment response



ROC curve for BDG cutoff values

Lyons JL et al., Cerebrospinal fluid (1,3)-B-D-Glucan detection as an aid for diagnosis of iatrogenic fungal meningitis. *J Clin Microbiol* 2013 (51)4:1285-7

Litvintseva et al., Utility of (1-3)-B-D-glucan testing for diagnostics and monitoring response to treatment during the multistate outbreak of fungal meningitis and other infections. *Clin Infect Dis* 2013; first published online December 12, 2013 doi:10.1093/cid/cit808

## Relapses?

- ❑ Five relapses have been reported to CDC
- ❑ All had received at least 3 months of antifungal therapy
- ❑ Most were complicated infections with arachnoiditis, toxicities
- ❑ 3 of 3 retrospectively tested had a CSF BDG identified as positive (>500 pg/mL)
  - BDG has promise for patient follow-up

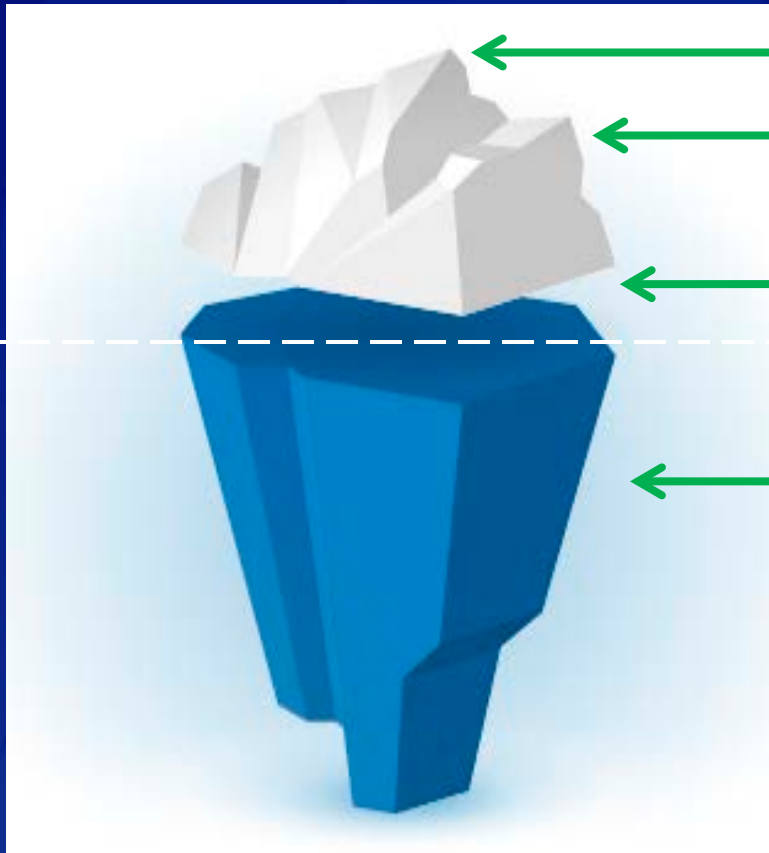
Smith RM, Tipple M, Chaudry M, Schaefer MK, Park BJ. Relapse of fungal meningitis associated with contaminated methylprednisolone (letter). *N Engl J Med* 2013;368(26):2522-3

Litvintseva et al., Utility of (1-3)-B-D-glucan testing for diagnostics and monitoring response to treatment during the multistate outbreak of fungal meningitis and other infections. *Clin Infect Dis* 2013; first published online December 12, 2013  
doi:10.1093/cid/cit808

## **Next steps: Long term follow-up study**

- ❑ **Aim to track long term outcomes of case-patients**
  - Antifungal medications
  - Side effects
  - Outcomes including relapse, treatment failure
- ❑ **Goal to enroll 400-500 patients**
- ❑ **CDC and Mycoses Study Group**
- ❑ **Patients not enrolled – limited follow-up data collected by clinicians and state HDs**

# What About Compounding?



Outbreaks

FDA, state enforcement actions  
(e.g., product recalls, license  
revocation)

FDA "Warning Letters"

?

# Attention Turned to Compounding Industry

The Washington Post | Politics | Opinions | Local | Sports | National | World | Business | Tech | I

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March 7, 2013

#### Preview: Lethal Medicine

Scott Pelley investigates the source of tainted pain medication that caused fungal meningitis that has so far killed 48 Americans and sickened hundreds more. Watch Pelley's report on Sunday, March 10 at 7:00 p.m. ET/PT.

Watch Video Read Story

Preview: Lethal Medicine

Preview: Sheryl Sandberg

Preview: God's Architect

Christopher Long  
Wash. Long's...

own as compounders  
manufacturers to  
standards enforced by



# Compounding Quality Act

- ❑ Signed into law as part of the Drug Quality and Security Act on November 27, 2013
- ❑ Amends the Federal Food, Drug, and Cosmetic Act (FDCA) in relation to human drug compounding
- ❑ **Section 503A: “Traditional compounding”**
  - Primarily regulated by states
- ❑ **Section 503B:**
  - Creates a new category of “registered outsourcing facility”
  - Pharmacies that register as an “outsourcing facility” will be primarily regulated by FDA
  - Will be inspected by FDA (risk-based schedule)
  - Subject to registration and re-inspection fees
  - Registration is voluntary

## The Future?

- ❑ No new cases since summer
- ❑ Patients face tremendous anxiety
  - Infected and “worried well”
- ❑ Starting to hear of more and more patients “cured”
- ❑ New legislation to expand FDA oversight may help
- ❑ Outbreaks will continue
  - Strong public health system is essential

**THANK YOU**