Multistate Outbreak of Fungal Infections associated with Contaminated Steroids 2012 – 2013

Lessons Learned

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CDC

"… 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

September 20, 2012

- **Tennessee Department of Health called CDC to discuss a case reported by an astute physician**
  - Patient with *Aspergillus* meningitis
  - Had received an epidural steroid injection for pain
- **Somewhat unusual case**
  - Meningitis due to molds are very rare
  - Patient was not immunocompromised
- **Steroid was a <u>compounded medication</u>**
  - Concern for contamination

What is Pharmacy Compounding?

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

By a pharmacist

In response to a prescription

For an individual patient

- **Traditional component of pharmacy practice**
- **Meets needs that cannot be met with commercially-manufactured products**

*U.S. Food and Drug Administration:
http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm

Compounding Has a Broad Scope

Non-sterile | Sterile

Orals
Inhaled, nasal products
Topicals
Transdermals

Ophthalmic solutions

Irrigations

Cardioplegia
Dialysis solutions

Injectables
- Anesthesia
- Antibiotics
- Electrolytes
- Flushes
- Intraoculars
- Parenteral nutrition
- Steroids

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 <u>sterile</u> compounding services

OLD

In-house

Individual prescription

Orals, Topicals

Local

NEW

Outsourcing

Bulk

Sterile Products

Multi-state Distribution

*International Academy of Compounding Pharmacists: http://www.iacprx.org

Timeline- Two Weeks

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

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.

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

SEPTEMBER OCTOBER

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

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

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

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

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
  - Case fatality 20%

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?

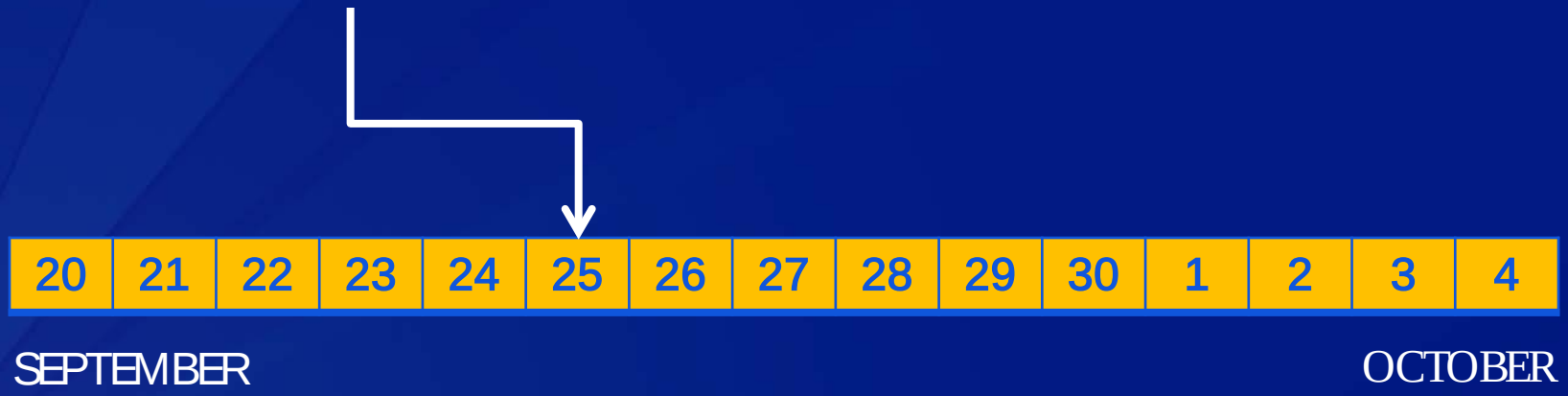
- Many common products
- Most nationally distributed
- Immediate concern about compounded steroid

Timeline- Two Weeks

FDA notified about investigation

Call with NECC to discuss concerns re: steroid

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

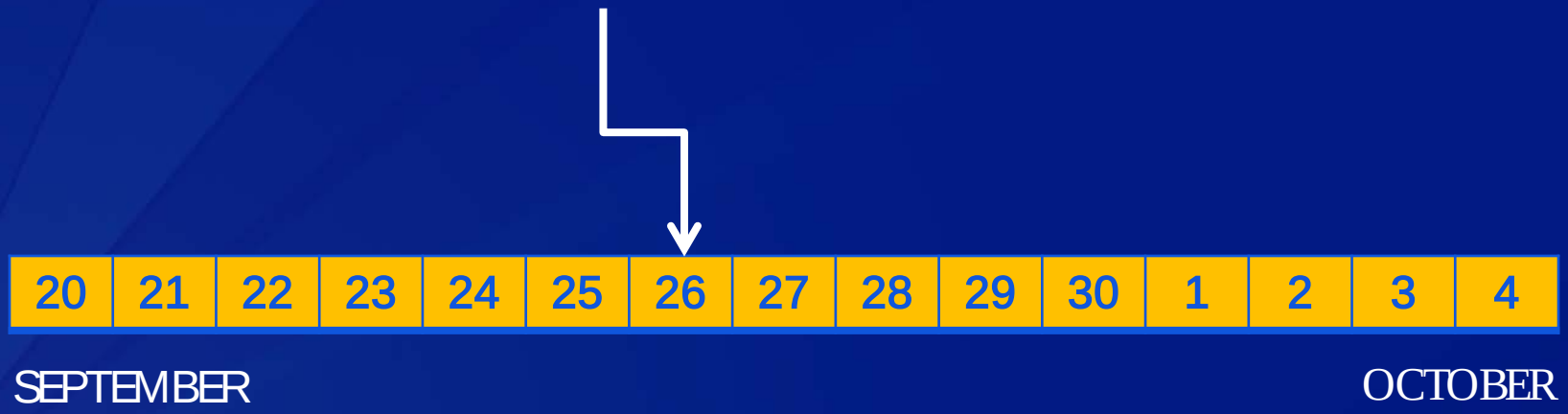


Timeline- Two Weeks

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

NECC provided list of all 76 facilities in 23 states that received recalled MPA to CDC

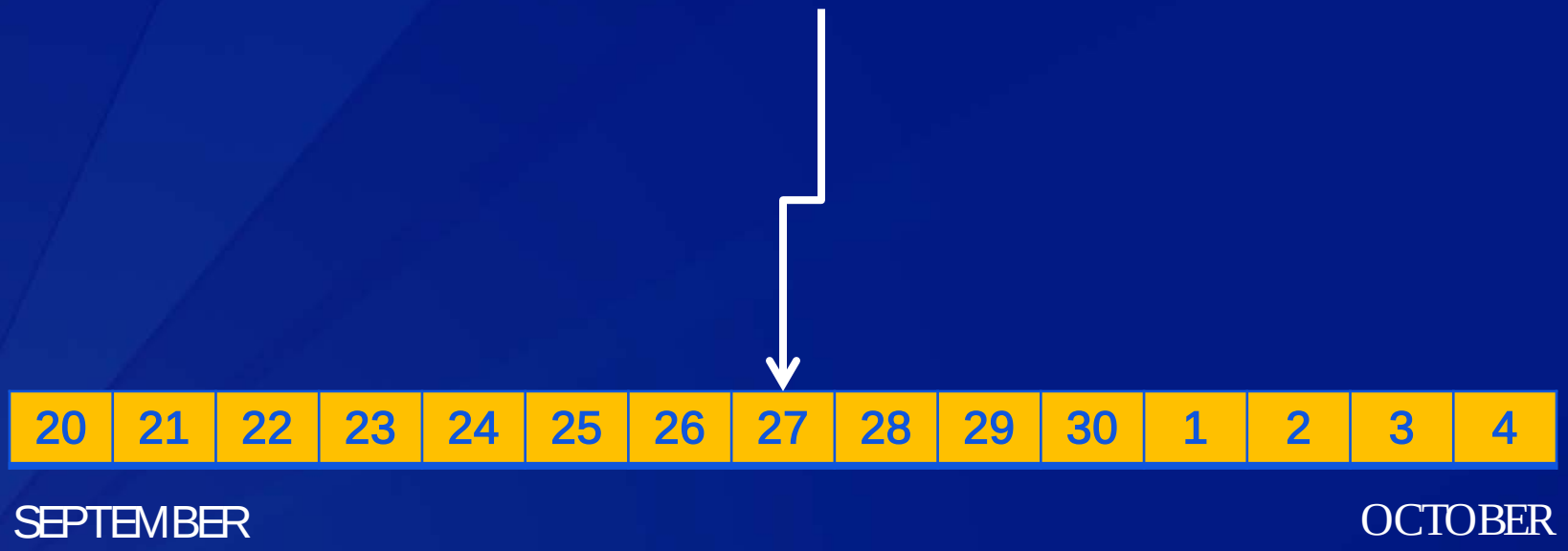
CDC used list to initiate case-finding in other states while also pursuing other possible sources of the outbreak



Timeline- Two Weeks

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

Suggested exposure may not be limited to TN ASC

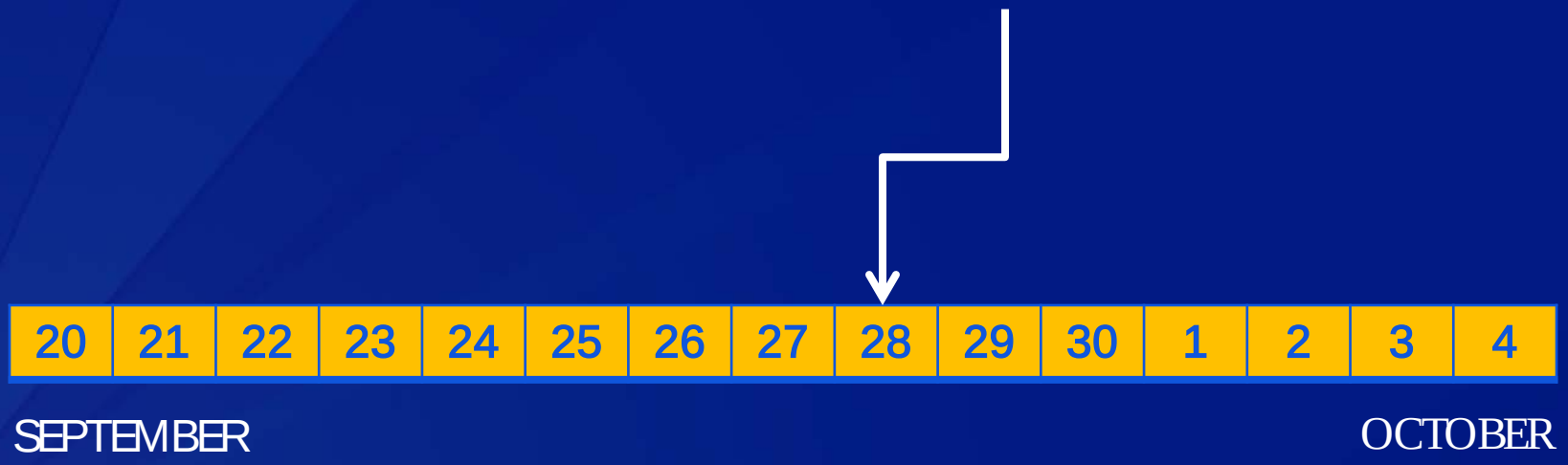


Timeline- Two Weeks

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

- Exposure still unknown

- Pathogen not identified except index case



Timeline- Two Weeks

FDA announced that unopened vials of MPA were found to be contaminated with fungus

Virginia state lab identified *Exserohilum* in deceased case

CDC activated Emergency Operations Center

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

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

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.

FACEBOOK
TWITTER
GOOGLE+
E-MAIL
SHARE
PRINT
REPRINTS

THE EAST
COMING SOON
WATCH TRAILER

Multimedia

Tennessee
• 35 cases, including 4 deaths
• 3 facilities

PA. OHIO W.VA. VA. N.C. TENN. S.C.

Interactive Map

Tracking an Outbreak

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.

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 20-60% mortality**

Public Health Actions: Major Components

- Patient Notification
- Clinical Guidance
- Laboratory Support
- Communications

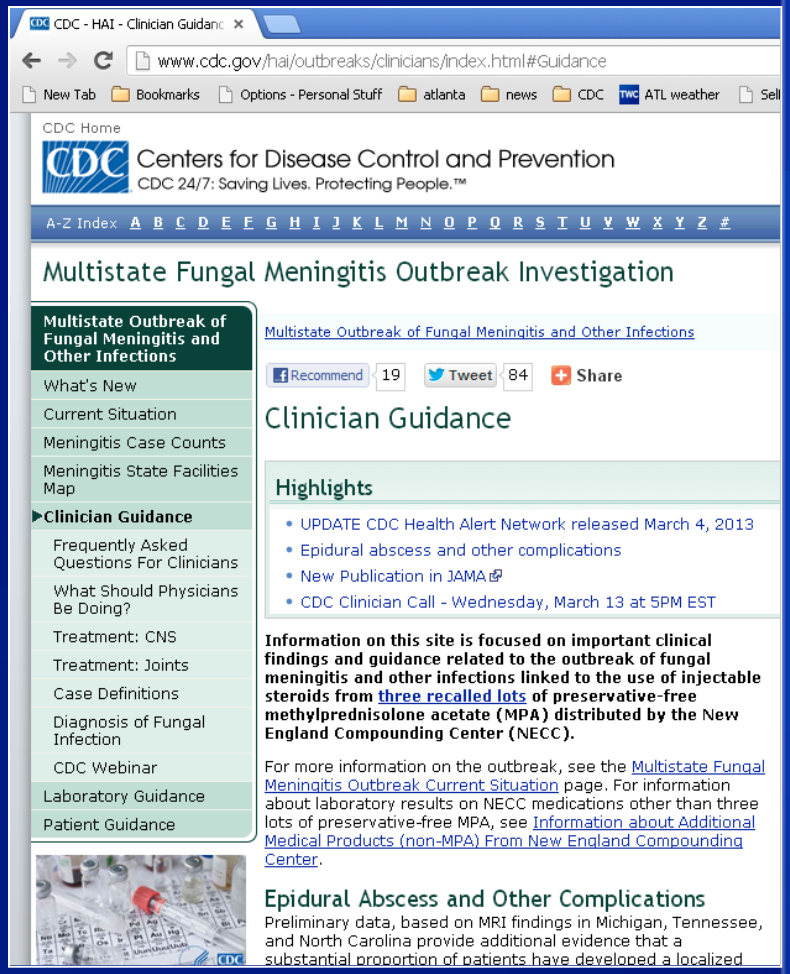
Patient Notification

- **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

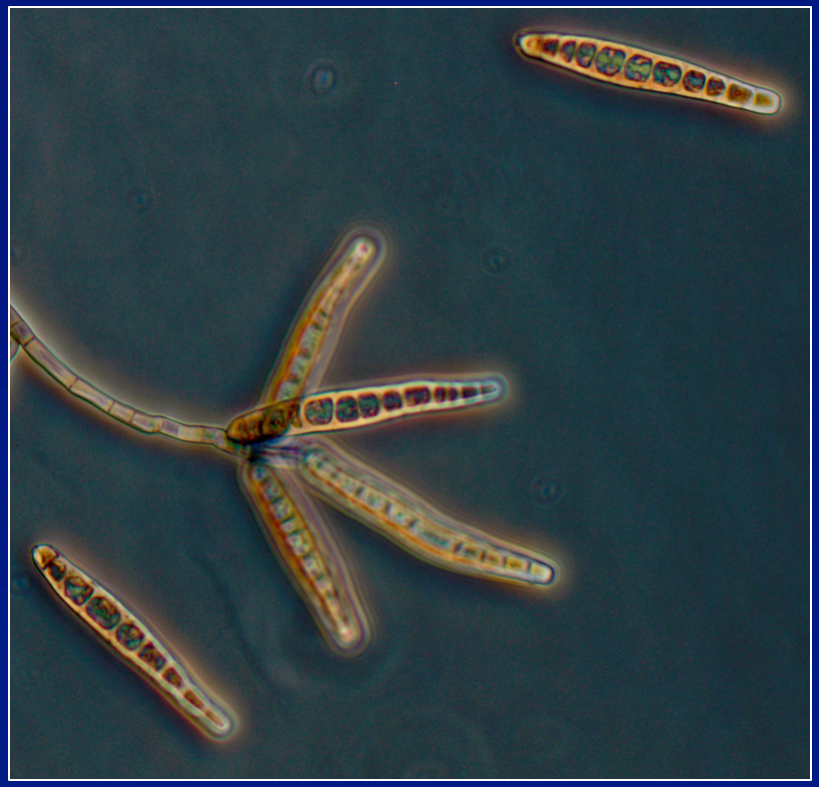
Development of Clinical Guidance

- **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



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

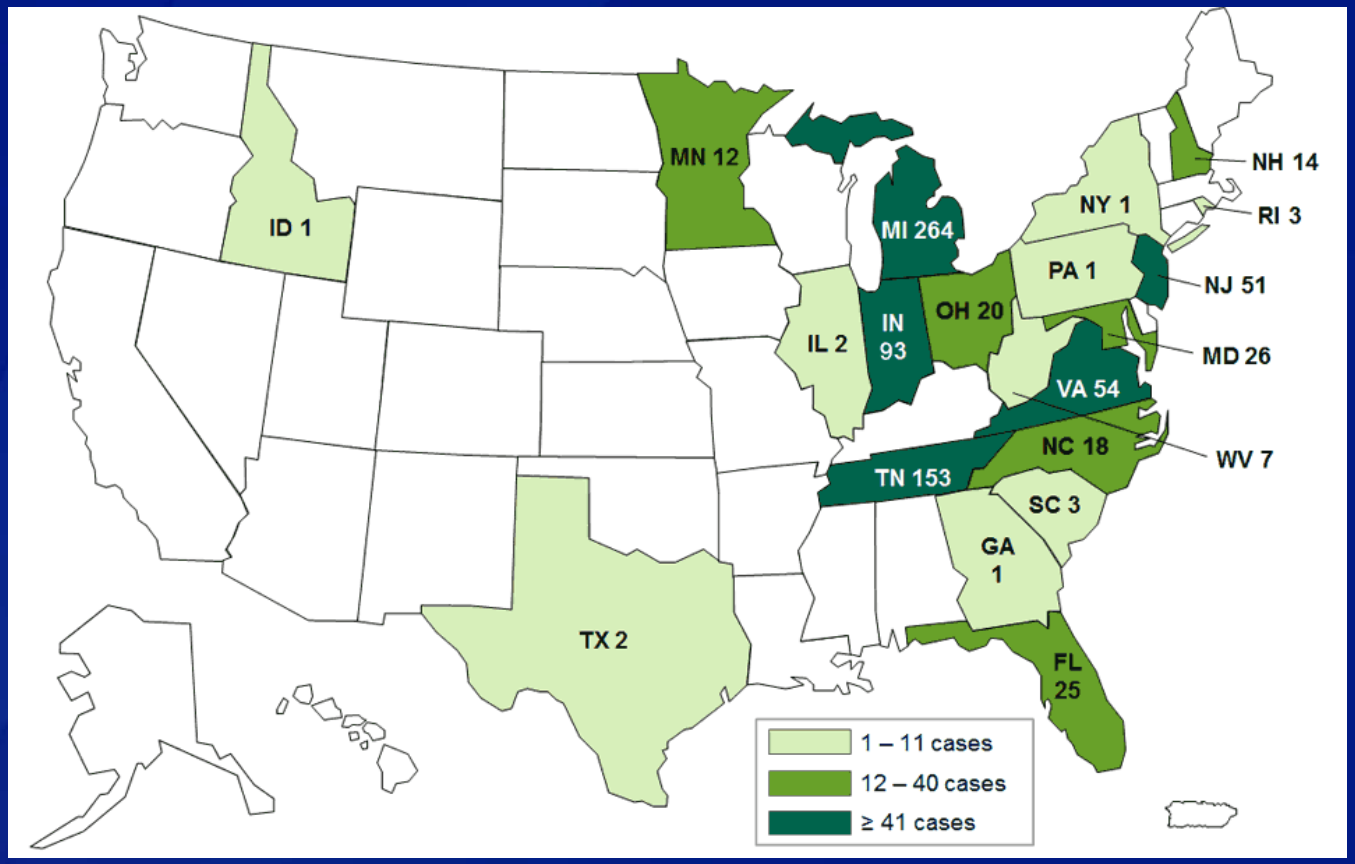


Exserohilum rostratum

Lockhart SR et al, **Preliminary Laboratory Report of Fungal Infections Associated with Contaminated Methylprednisolone Injections**. J Clin Microbiol August 2013 vol. 51 no. 8 2654-2661

OUTBREAK STATUS

Final Case Count reported on October 23, 2013



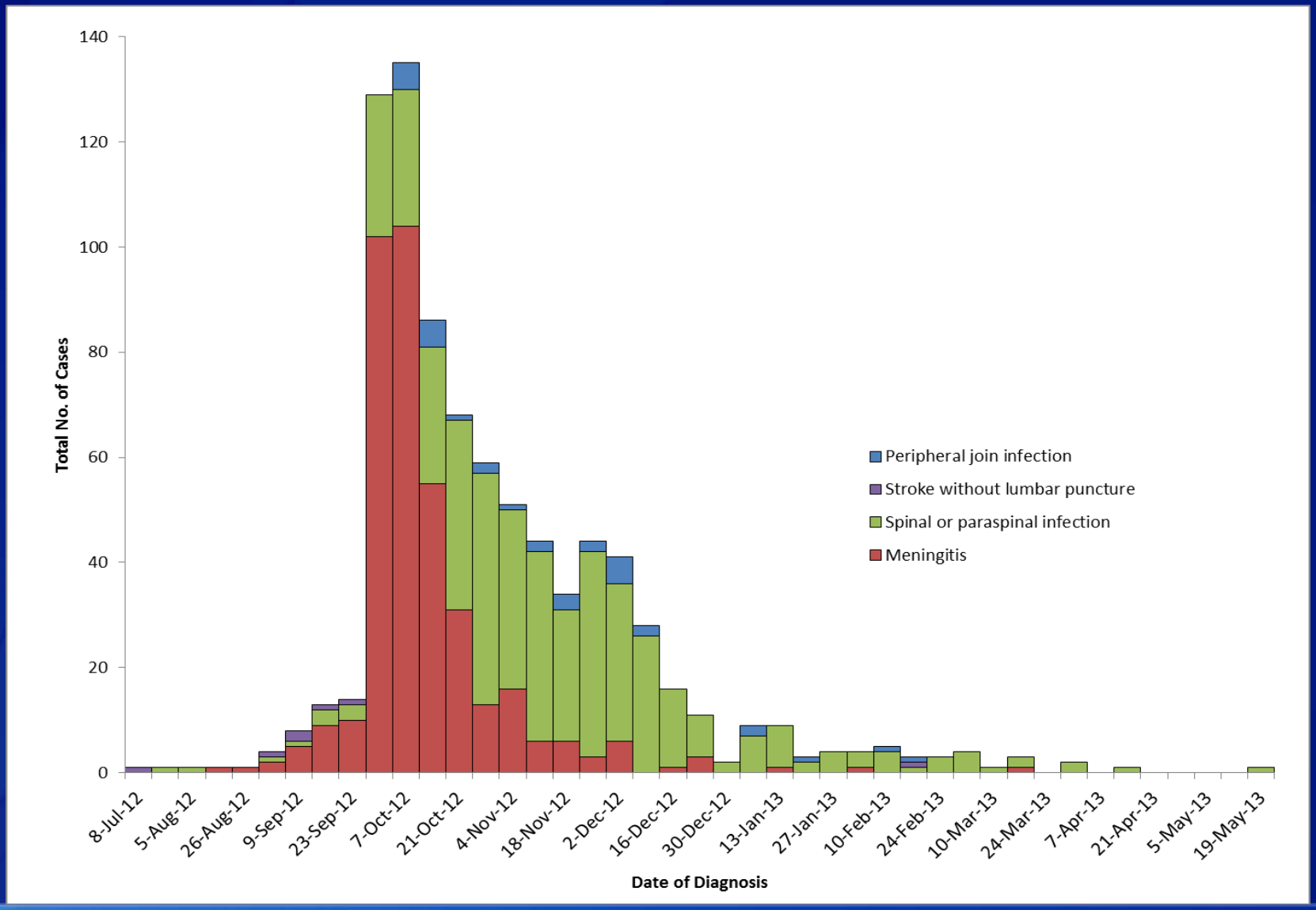
751 cases in 20 states

64 deaths

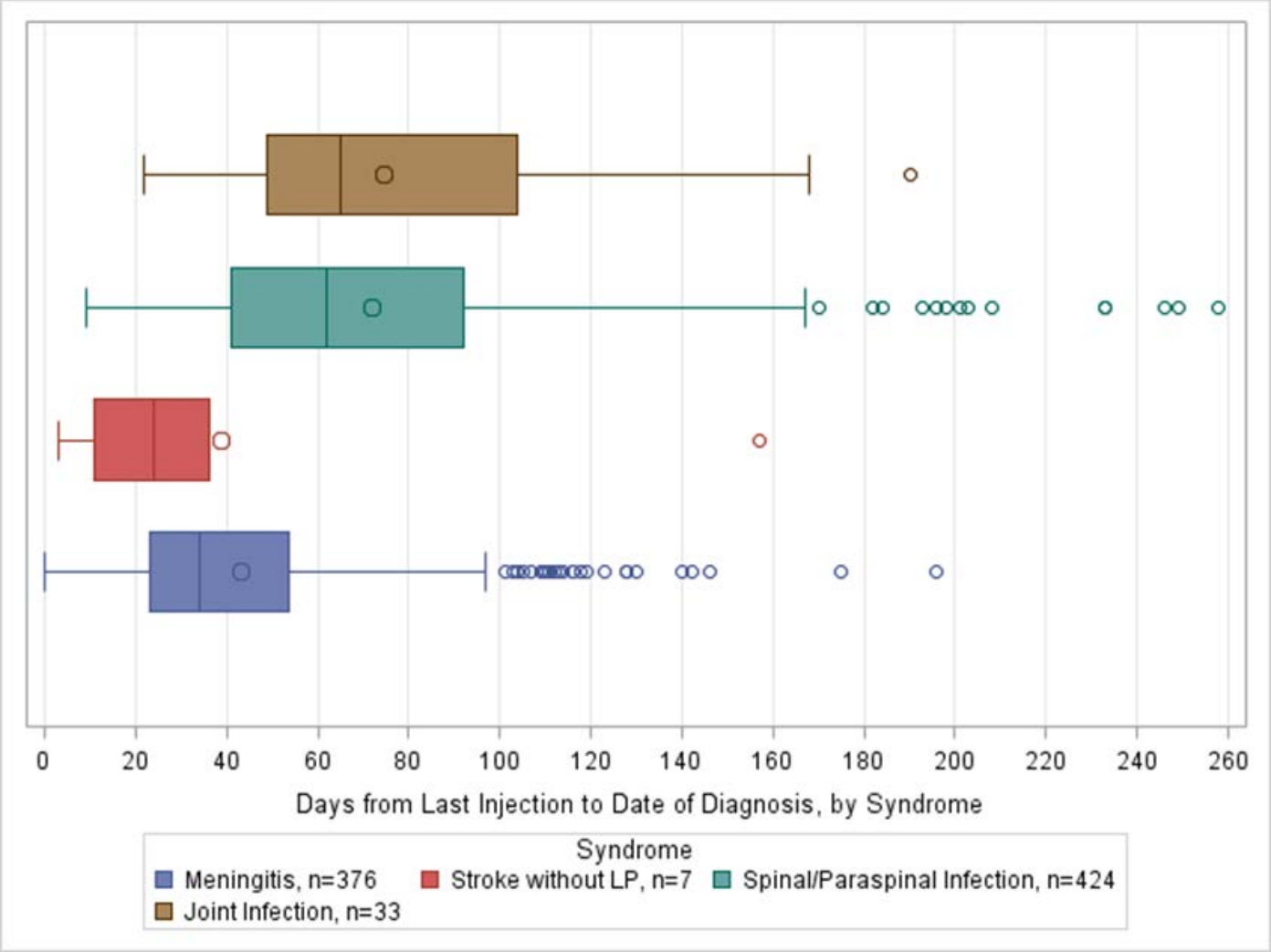
Sites of infection

- **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



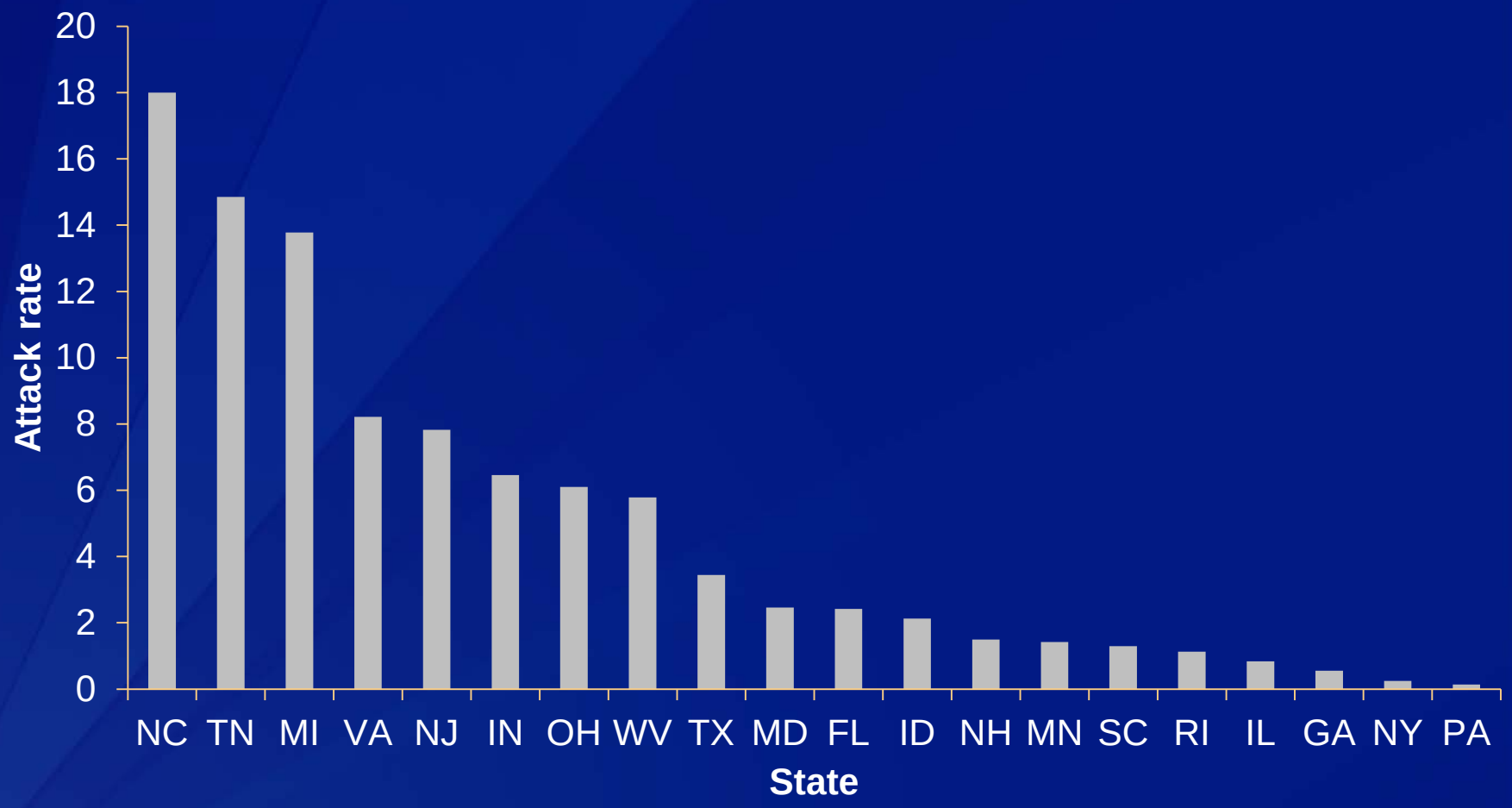
Median incubation to first diagnosis: 47 days (0-249)

National attack rates

Injection type	Cases	Exposed	Attack rate*
All injections	751	13,534	5.5
Epidural/paraspinal injections	718	12,069	5.9
Peripheral joint injections	35	1,648	2.1

*** Per 100 persons exposed**

State-specific attack rates

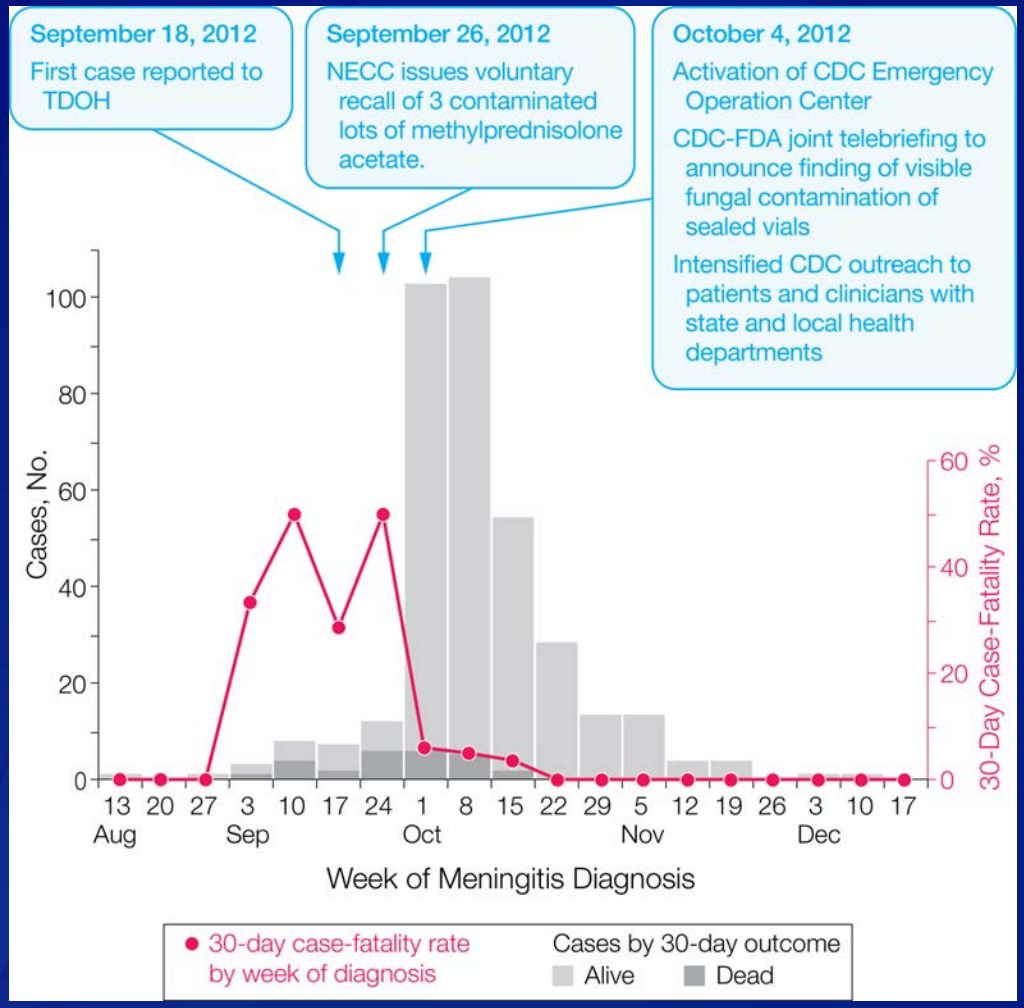


States with exposures but no cases: CT, CA and NV

Did we achieve our goals?

- Early diagnosis
- Reduction in poor outcomes

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.

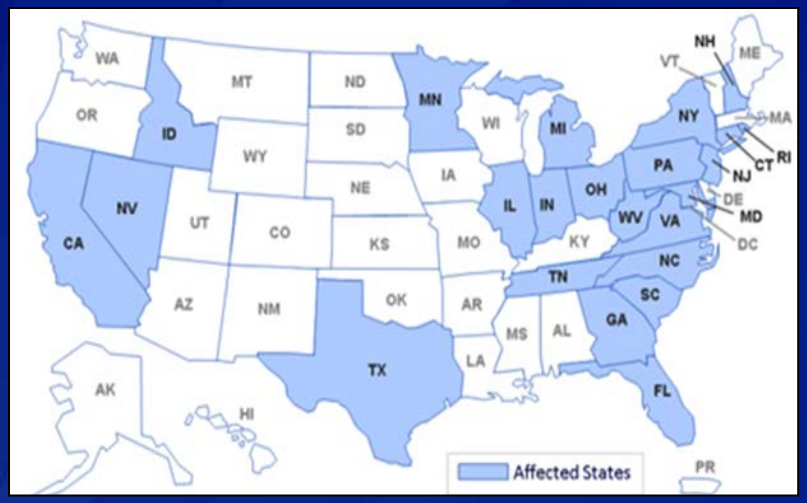
Public health efforts led to early diagnosis

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

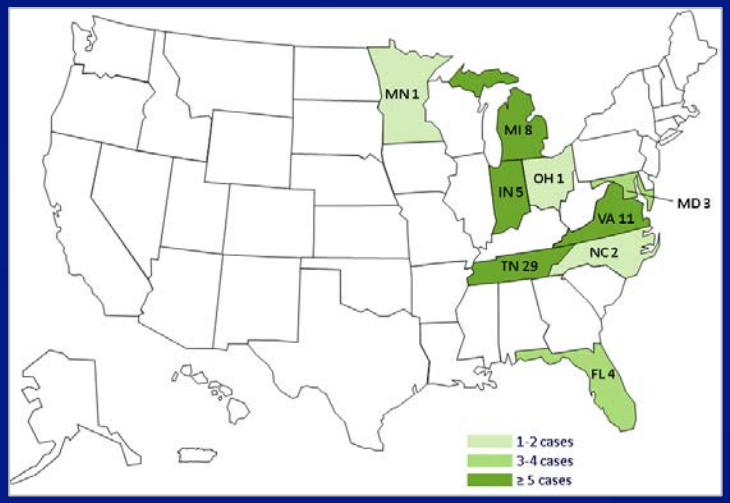
LESSONS LEARNED

Detection of outbreaks

- **Fungal diagnostics make identification difficult**
- **Wide distribution of contaminated products**
  - Small clusters of disease across states, difficult to link together



Distribution of NECC MPA



Cases of MPA-associated illness
On October 6

- http://www.cdc.gov/hai/outbreaks/meningitis-facilities-map.html
- http://www.cdc.gov/hai/outbreaks/meningitis-map.html#casecount_table

Patient notification

- **Often difficult to identify who got a specific medication**
  - Products from multiple manufacturers may be in use
  - Lot numbers may not be recorded
- **Best way to notify patients**
  - Letter
  - Phone calls
  - Home visits
- **Risk communication strategies**
  - Often before risk is fully realized

Identification of outbreak source

- **Contaminated products may not be readily recognized as source of infection**
- **Compounding practices cannot always be observed, re-created**
- **Multiple infection control breaches can occur**
  - Difficult to pinpoint exact source of contamination
- **Unused product may not be available to test**
  - Recovery of organisms may be difficult

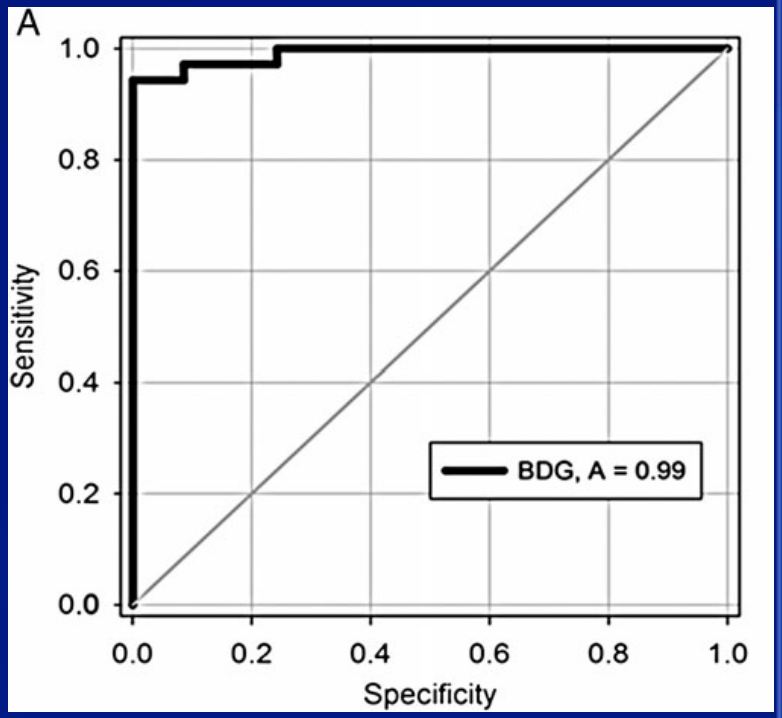
Overall Keys to Success

- **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

LOOKING FORWARD

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

Long term follow-up study

- **Study to track long term outcomes of case-patients**
  - Antifungal medications
  - Side effects
  - Outcomes including relapse, treatment failure
- **CDC, UAB and Mycoses Study Group**
- **Enrollment, data collection is ongoing**
  - Submission of latebreaker abstract to ICAAC 2014

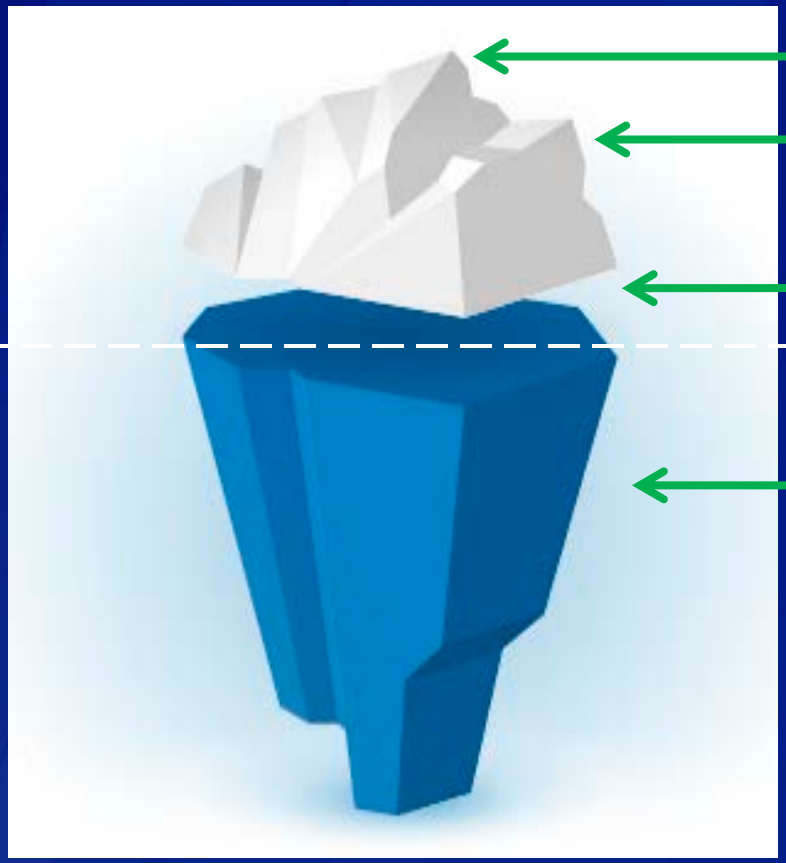
Relapses?

- 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

What About Compounding?



Outbreaks

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

FDA “Warning Letters”

?

CDC investigations related to compounding pharmacies, 2001 - present

- *S. marcescens* in magnesium sulfate
- Gram negative bacteria in cardioplegia solution
- *P. aeruginosa*, *B. cepacia* in trypan blue
- *E. dermatitidis* in methylprednisolone
- *Chryseomonas* in methylprednisolone
- *S. paucimobilis* in fentanyl
- Alpha-hemolytic *Streptococcus* in bevacizumab
- *Neosartorya, Hamigera* in magnesium sulfate
- *S. marcescens* in TPN
- *S. mitis/oralis* in bevacizumab

2001 2002 2004 2005 2007 2009 2011 2012 2013

- *S. marcescens* in betamethasone
- *P. fluorescens* in heparinized saline flush
- *B. cepacia* in antibiotic flush
- *F. incarnatum*, *B. hawaiinesis* in Brilliant blue-G dye, triamcinolone
- *E. rostratum* in methylprednisolone

Attention Turned to Compounding Industry

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 <u>voluntary</u>

The Future?

- **Outbreak is over**
  - No new cases since summer 2013
- **Patients face tremendous anxiety**
  - CDC-INFO/phone duty inquiries
  - Infected and exposed
- **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!

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.