



Fungal Meningitis: A Lesson in Preparing for the Unexpected

Denise Pettit, Ph.D.

North Carolina State Laboratory of Public Health

Email: dee.pettit@dhhs.nc.gov

Phone: (919-807-8940)

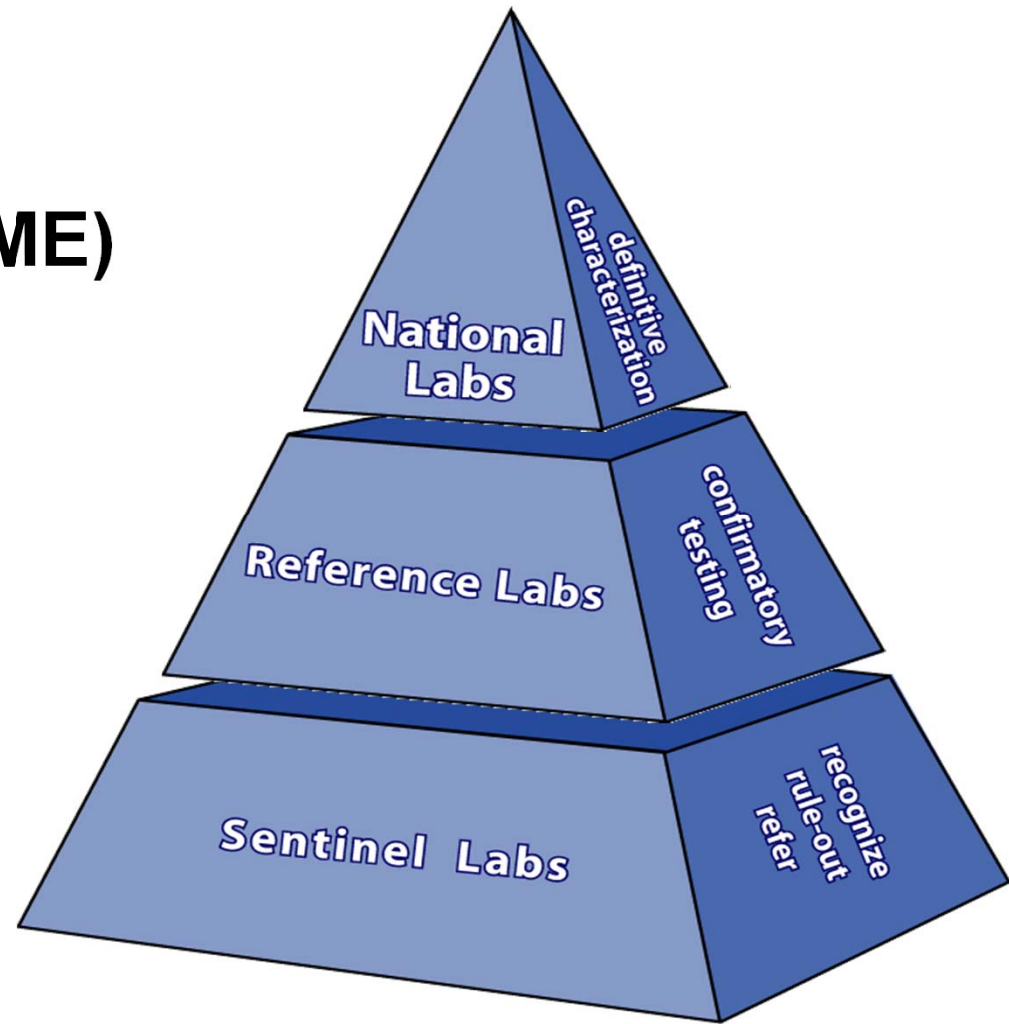


Benefits of PHL Preparedness

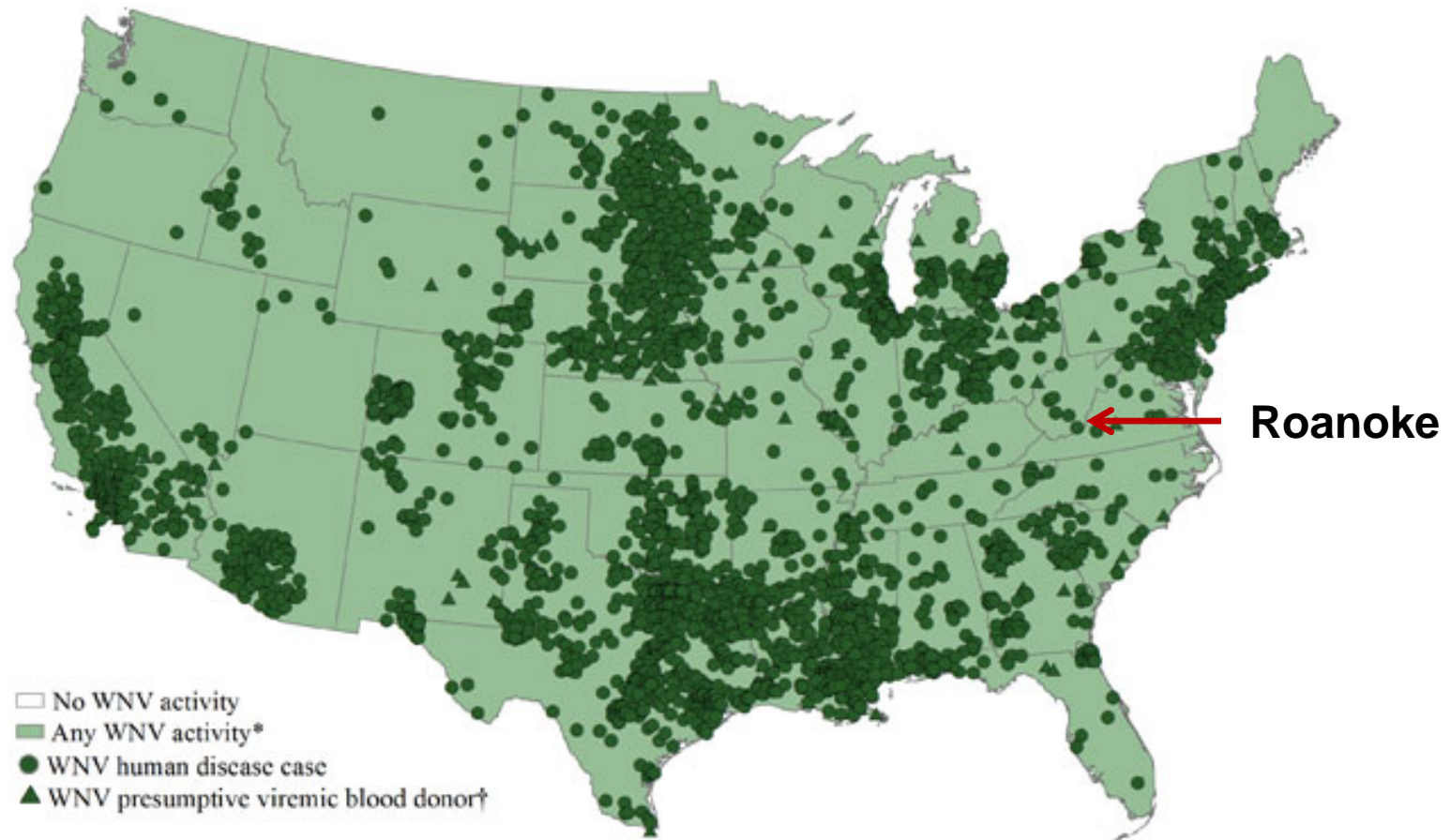
- **An intentional attack with a biological agent**
- **Outbreaks**
 - Known endemic disease
 - New or reemerging infectious disease
- **Establish and maintain partnerships to leverage resources**

The Laboratory Response Network

- Clinical/hospital
- Public health (OCME)
- Military
- Veterinary
- Agriculture
- Food
- Environmental



WNV Activity 2012



Virginia: 17 neuroinvasive cases, 9 non-neuroinvasive cases, 2 asymptomatic blood donors, and 3 fatalities. Highest numbers since 2003.

Rapidly Fatal Meningitis

09-12-12

Severe headache, Photophobia, Neck pain (cervical disk disease), Nausea,
No fever or respiratory symptoms

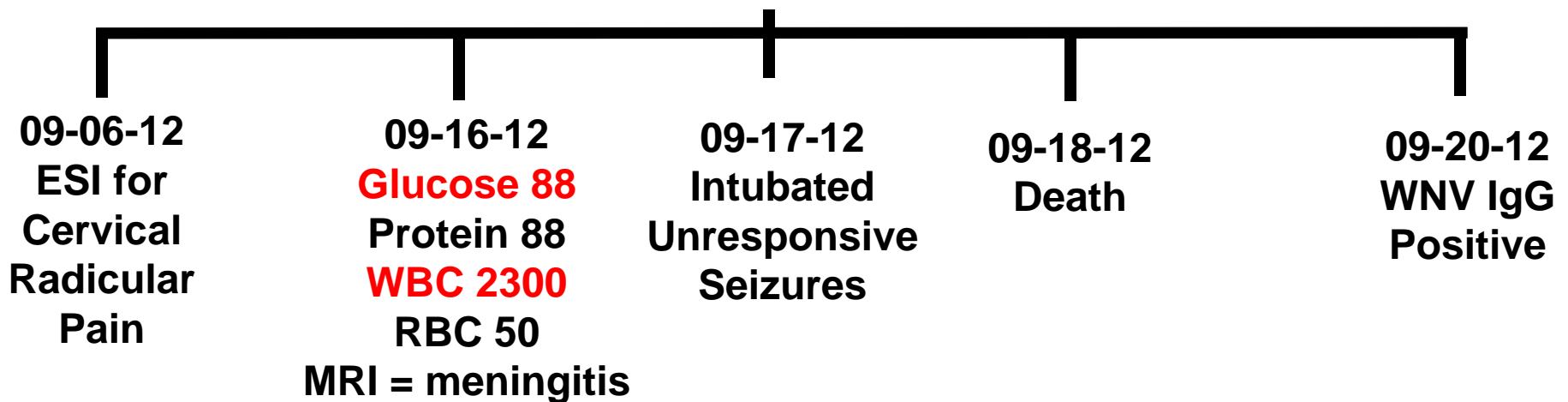


Table 1. Typical CSF Findings in Patients With and Without Meningitis

Parameter	Normal	Bacterial Meningitis	Viral Meningitis	Fungal Meningitis	Tuberculous
Opening pressure (mm H ₂ O)	<180	200-500	NA	>250 (<i>Cryptococcus</i> sp)	NA
WBC count (mm ³)	0-5	100-20,000 (mean 800)	5-500 (mean 80)	20-2,000 (mean 100)	5-2,000 (mean 200)
WBC differential	No predominance	>80% PMN	>50% L, <20% PMN	>50% L	>80% L
Protein (mg/dL)	15-50	100-500	30-150	40-150	>50
Glucose (mg/dL)	45-100 (2/3 of serum)	≤40 (<40% of serum)	30-70	30-70	<40
Gram stain (% +)	NA	60-90	-	-	37-87 (AFB)

+: positive; -: negative; AFB: acid-fast bacilli; CSF: cerebrospinal fluid; L: lymphocytes; NA: not applicable; PMN: polymorphonuclear white blood cells. Source: References 9, 10.

Post-Mortem Analysis

- R/O West Nile Virus Encephalitis
- OCME Specimen Collection
 - Neural tissue (formalin fixed, fresh frozen, room temp)
 - Cultures initiated at DCLS
 - Viral cultures negative
 - Bacterial cultures positive for *P. acnes*
 - Tissues sent to CDC Infectious Disease Pathology Branch
- Hospital laboratory all remaining specimens and culture plates
 - Serum: WNV IgM Neg, **WNV IgG Pos**
 - CSF culture had **black mold (environmental contaminant)**
- Neuropathological findings suggestive of stroke
- Initiation of **culture at the local level** provided the only fungal isolate in this investigation

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:
 Contributor's instructions for distributing this report.

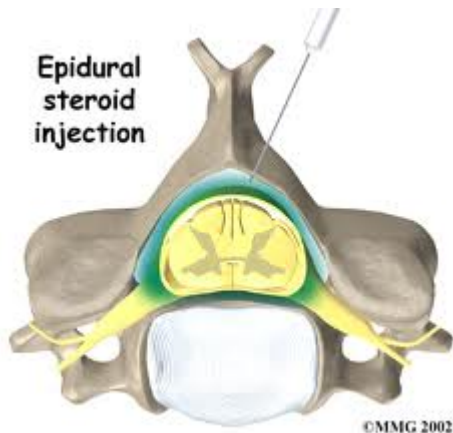
Release outside of Epi-X as needed

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.

Description:

On 9/18/2012, the Tennessee Department of Health was notified of a patient with culture-confirmed *Aspergillus fumigatus* meningitis following epidural steroid injection (ESI) at a TN ambulatory surgical center.



Six additional patients with clinically-diagnosed meningitis were identified.

Symptoms of meningitis, including headache, stiff neck, and fatigue, developed within 1-4 weeks post-injection.

Two patients presented with additional focal neurological deficits (strokes).

All had a similar cerebrospinal fluid (CSF) profile (low glucose, elevated protein and high, neutrophil-predominant, white cell count); CSF cultures on the 6 subsequent patients are negative to date.

Patients have generally received antibacterial antibiotics without improvement.

All patients received one or more ESIs during 7/30 to 9/18/2012.

All patients received injections of preservative-free methylprednisolone, preservative free normal saline, lidocaine, and skin prep with povidone-iodine.

Six of the patients received injections of omnipaque, a contrast material.

To understand the scope of this cluster and identify possible etiologies, we are seeking information on patients with clinical meningitis or possible neurologic infection (epidural abscess, spinal osteomyelitis, etc.), following epidural injections since July 1.

An epidemiological study is ongoing in collaboration with the ambulatory surgical center, state and federal public health partners.

Because *Aspergillus* meningitis can be difficult to diagnose, clinicians should consider this diagnosis in any patient presenting with similar signs and symptoms of neurologic infection post-ESI.

Diagnosis of *Aspergillus* meningitis should be sought by evaluating CSF for *Aspergillus* (galactomannan) antigen; fungal cultures of CSF should also be sent, preferably following centrifugation concentration. Do not discard any remaining CSF.

Empiric treatment with amphotericin B or voriconazole should be considered if *Aspergillus* meningitis is suspected.

State and local health departments are asked to disseminate this advisory widely to appropriate clinicians in their respective jurisdictions.

Public health officials who learn of suspected cases of clinical meningitis or other neurologic infection (i.e. epidural abscess, spinal osteomyelitis, etc.) with symptom onset within 1 month of epidural injection since July 1, are asked to contact Dr. Marion Kainer on 615-741-7247 or marion.kainer@tn.gov.

Unknown - Insufficient Data

Type of Cases:

Human

Number of Cases:

Actual
 Total Ill or Injured: 7
 Hospitalized: 7

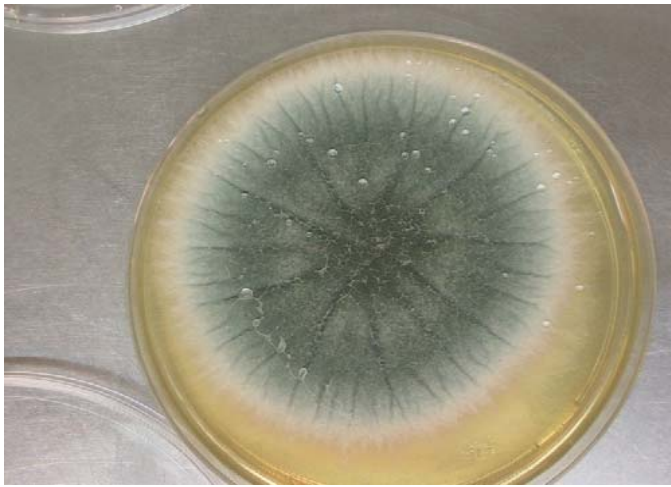


Fungal Infections

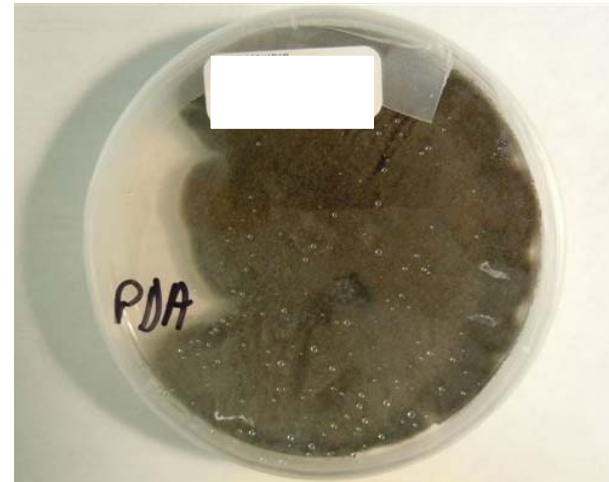
Signs and Symptoms

- Fever
- New or **worsening headache**
- Stiff neck**
- Nausea** and vomiting
- Photophobia**
- Altered mental status
- New weakness or numbness in any part of the your body
- Increased pain, redness or swelling at your injection site
- “**Black mold**”

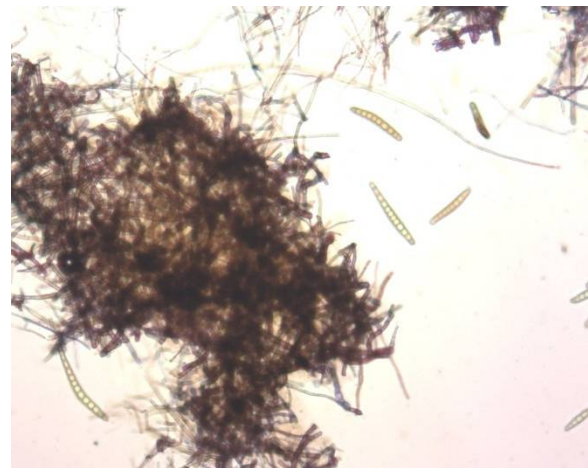
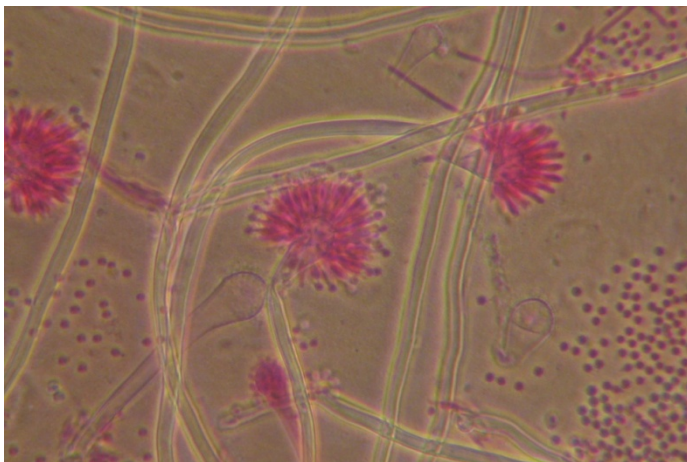
Aspergillus Vs “The Unknown”



Aspergillus



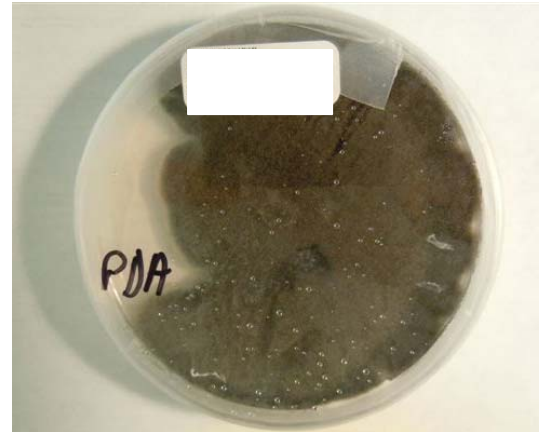
VA Isolate



Aspergillus Vs *Exserohilum*



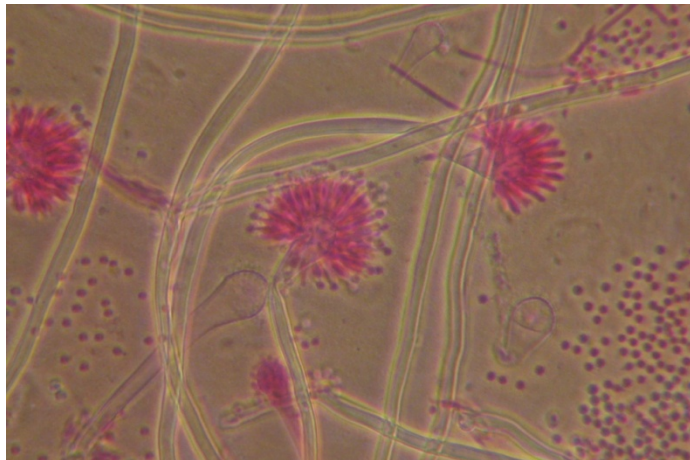
Aspergillus



VA Isolate



Exserohilum





Rapidly Fatal Meningitis

- IDPB-CDC Report
 - Polyfungal immunohistochemistry **Positive**
 - Immunohistochemical staining for *Aspergillus* sp. **Negative**
 - Molecular evidence of *P. acnes*
- CDC Mycology Branch
 - Preparedness training to SPHLs
 - PCR and sequencing of ribosomal DNA ITS-2 regions
 - Neural tissue **Positive**
 - CSF Negative
 - *Exserohilum rostratum* identified
- Final Diagnosis: *E. rostratum* meningitis



Case Definitions

- **Fungal meningitis of sub-acute onset following ESI after May 21, 2012**
- **Posterior circulation stroke following ESI after May 21, 2012**
- **Evidence of spinal osteomyelitis or epidural abscess at the site of injection**
- **Septic arthritis or osteomyelitis of a peripheral joint following SI**



Clinical Lab Guidance

- Use case definitions
- Collect ≥ 5 ml CSF and 2 – 3 ml serum from meningitis cases
- Testing
 - CSF analysis (Cell CT/Dif, Glu, Protein)
 - Perform Gram stain, bacterial and fungal cultures, and AFB smears
 - Hold cultures for 4 weeks to enhance recovery of fungal agents
 - Send CSF and serum for *Aspergillus* galactomannan analysis



Shifting Mindsets

- **Culture Isolates**

- *Aspergillus fumigatus* (TENN)

- *Exserohilum rostratum*

- *Propionibacterium acnes*

- **Encourage an open mindset**



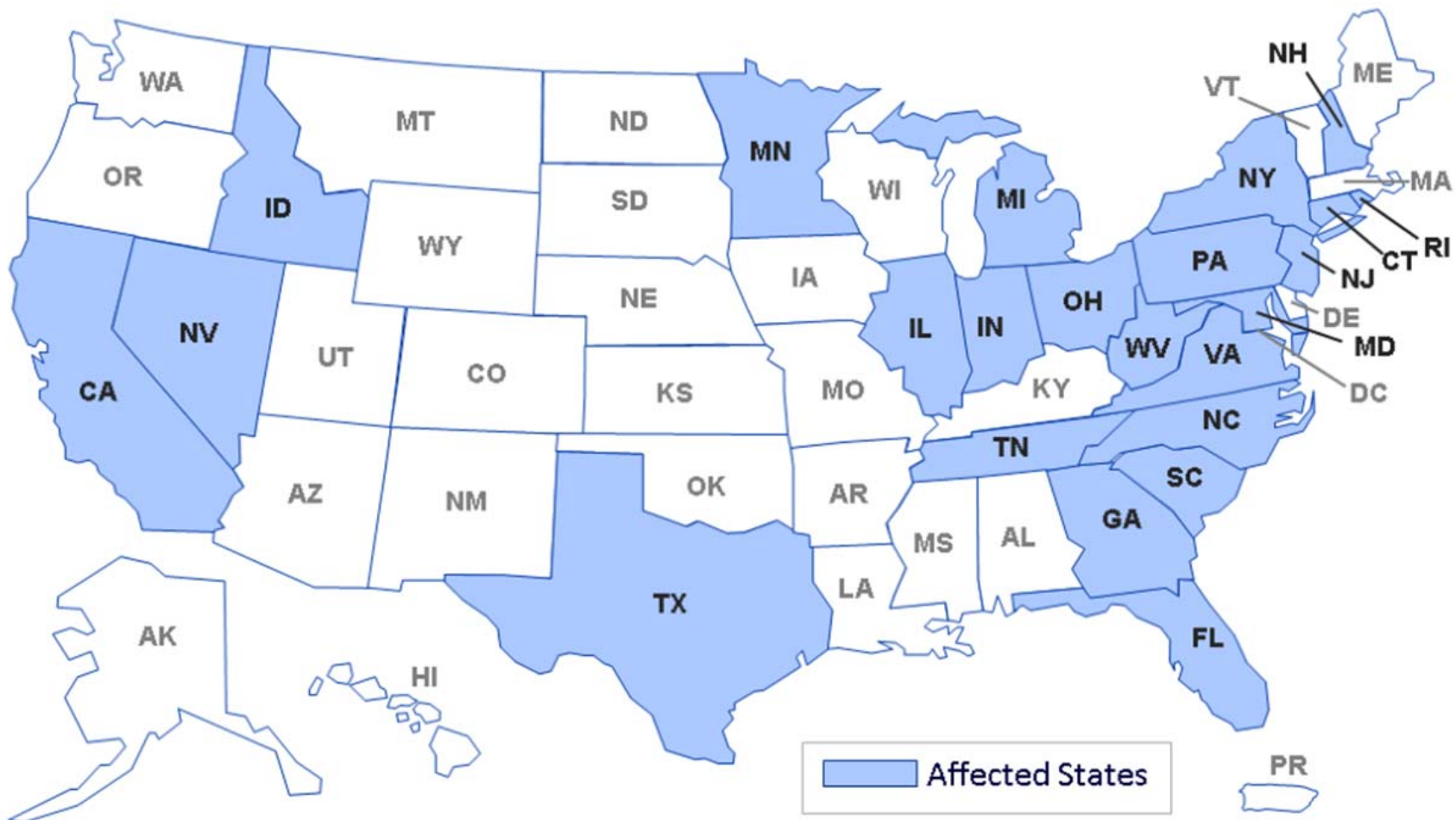
NECC Preservative-free Methylprednisolone vials

- ❑ FDA and CDC analysis
- ❑ *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

NECC MPA Healthcare Facilities



23 states, 76 facilities, and 17,675 vials



Clinical Challenges

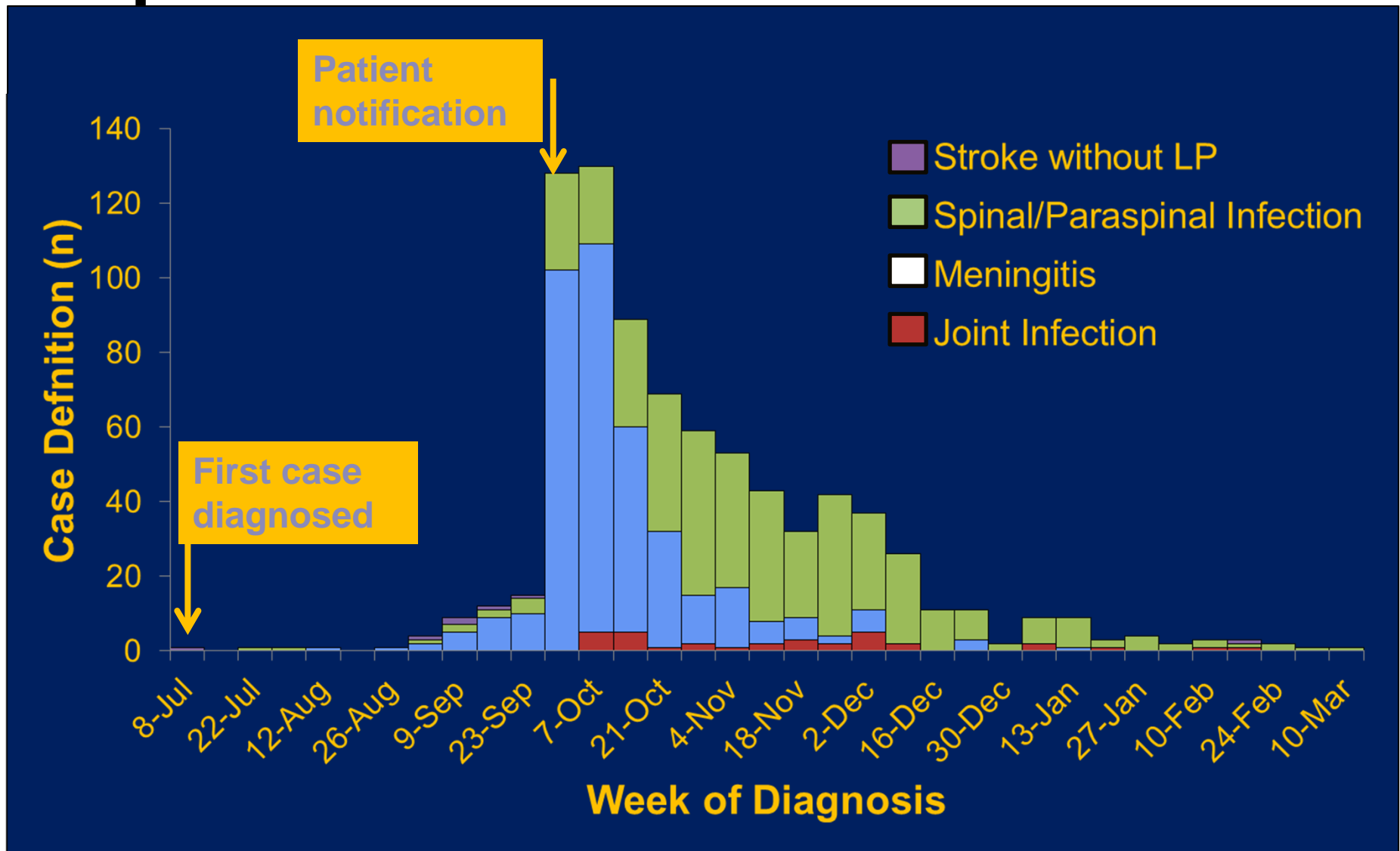
- **Patient notifications resulted in hundreds of patients seeking medical care in Virginia**
- **Many physicians had never seen or treated fungal meningitis**
- **Often difficult for patients to distinguish new symptoms from baseline symptoms**
- **Diagnostic test not without risk**



Support Services

- Weekly patient evaluations with LP
- Specimens with a WBC >5
- Complete all necessary paperwork for CDC submission
- Quickly identified the need for data management and unique specimen id to determine date of collection
- Specimen storage
- Specimen tracking
- Spreadsheet-based reporting
- Verbal reports on positives
- Laboratory reports as they evolved

Epidemic curve*



*n=814 case definition diagnoses among 702 cases



Case-patient characteristics (n=696)

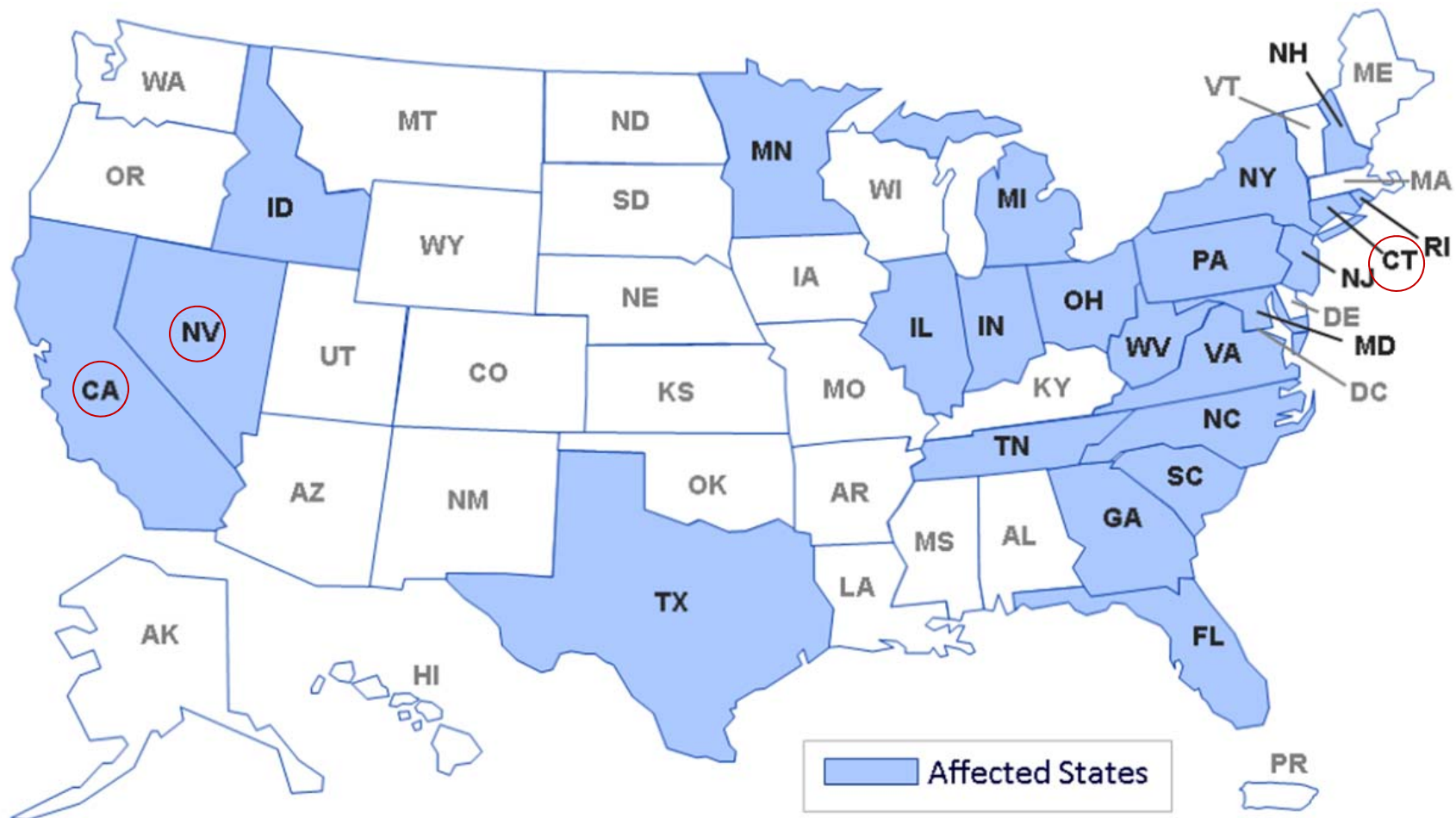
Characteristic	n	%
Median age, years (range)	63	(16-97)
Female (%)	415	(59)
Median no. injections (range)	1	(1-6)
MPA lot exposure known		
Lot 5	70	(10)
Lot 6	417	(59)
Lot 8	91	(13)



Case-patient Laboratory Results

Result	No.	(%)
Case-patients with specimens at CDC	495	(67)
Positive result	167	(34)
<i>Exserohilum</i> sp.	148	(89)
<i>Cladosporium</i> sp.	6	(4)
Other fungi	12	(7)
Laboratory-confirmed outside CDC	31	(4)
All laboratory-confirmed case-patients	198	(27)

NECC MPA Healthcare Facilities



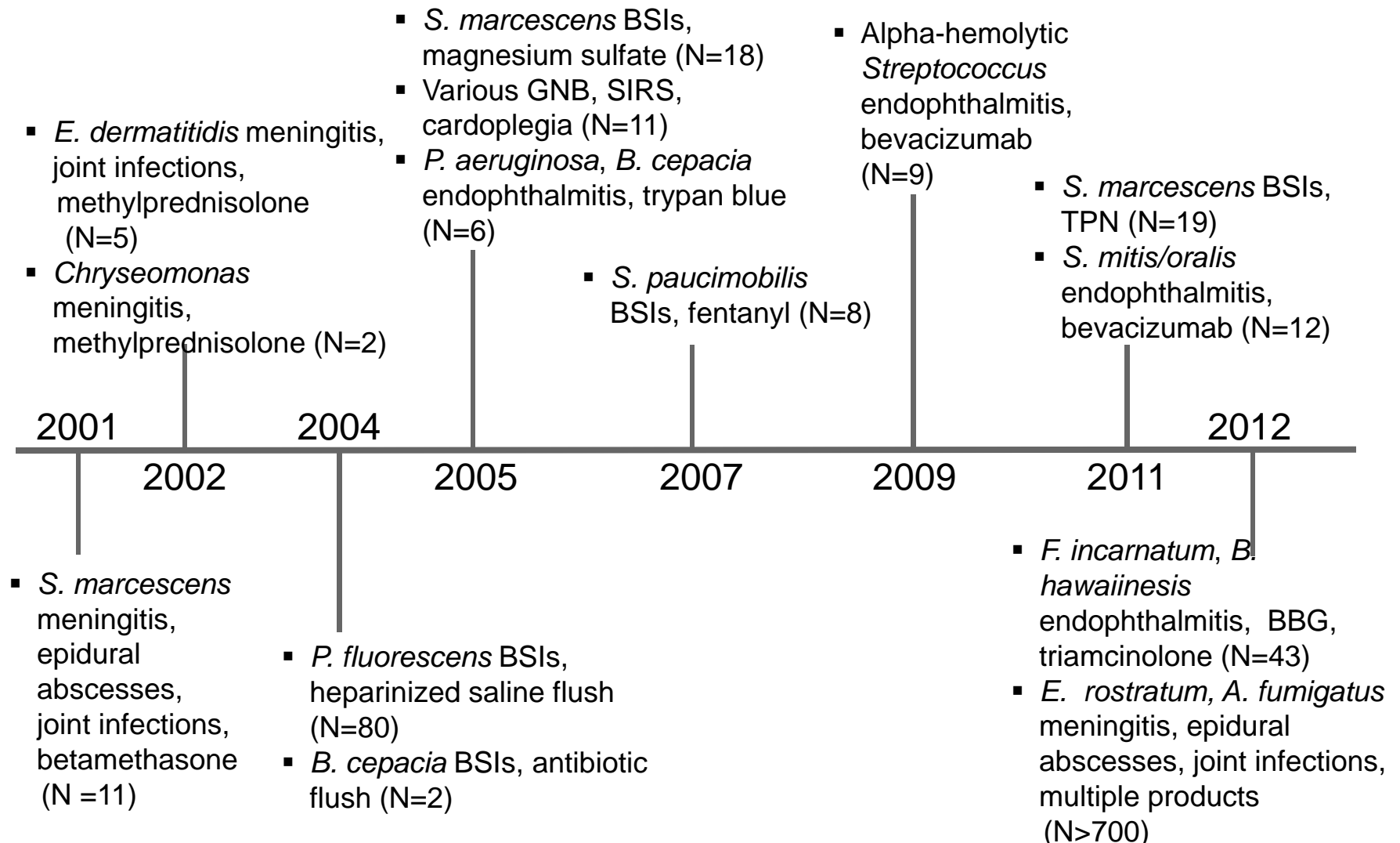
23 states, 76 facilities, and 17,675 vials



Compounding Pharmacies

- **Prepare customized medications that are not commercially available (prescription required)**
- **Regulated by the state boards of pharmacy**
- **Exempt from good manufacturing practice**
- **Products are not evaluated for clinical safety and efficacy**

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



BBG Brilliant Blue-G; BSI Bloodstream infection; GNB Gram negative bacteria; SIRS Systemic Inflammatory Response Syndrome; TPN Total parenteral nutrition

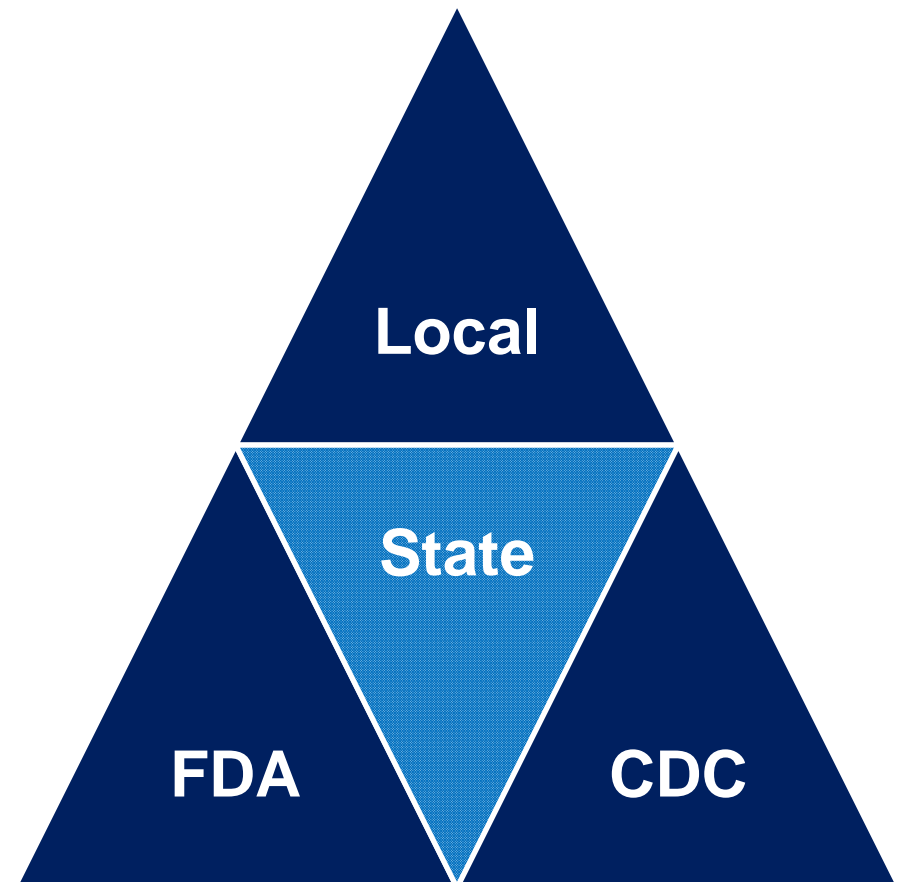


NECC

- Recalled more than 2,000 products in addition to MPA and ceased operations in October 2012
- Filed for Chapter 11 bankruptcy in Dec. 2012
- Multitude of bacterial and fungal organisms were isolated from NECC products labeled as sterile
- Highlighted regulatory questions for compounding pharmacies

Summary

- Collaboration among multiple laboratories facilitated a rapid and effective response
 - Initiation of culture at the clinical lab
 - CDC Mycology Branch Training
- *Exserohilum rostratum* was identified in the patients and in the MPA compounded at the NECC
- Largest outbreak of health-care associated infections in the US
- Patients are still at risk and cases continue to be reported





Acknowledgements

■ Administrative

- Dr. Tom York
- Managers/Directors
- Administrative support staff

■ Fungal Meningitis Team

- Beverly Jones
- Carol Campus
- Karen Schnell
- Mary Reid
- Marlene Frazier
- Mary Kate Yost Daljev
- Susan Downer
- Willie Andrews

■ CDC

- Dr. Mary Brandt
- Dr. Shawn Lockhart
- Dr. Anne Purfield
- Dr. Diana Blau
- Dr. Sherif Zaki

■ Bioterrorism Response Team

- Emergency Mgmt Duty Officers
- Sean Kelly
- Ellen Basinger
- Dr. LaToya Griffin-Thomas
- Emily Hopkins
- Jo Ann Jellison
- Elaine McCaffery

NCSLPH



Denise Pettit, Ph.D.
**North Carolina State Laboratory of
Public Health**
Email: dee.pettit@dhhs.nc.gov
Phone: (919-807-8940)

CDC Recognizes Virginia Contribution



Dr. Tom Frieden @DrFriedenCDC

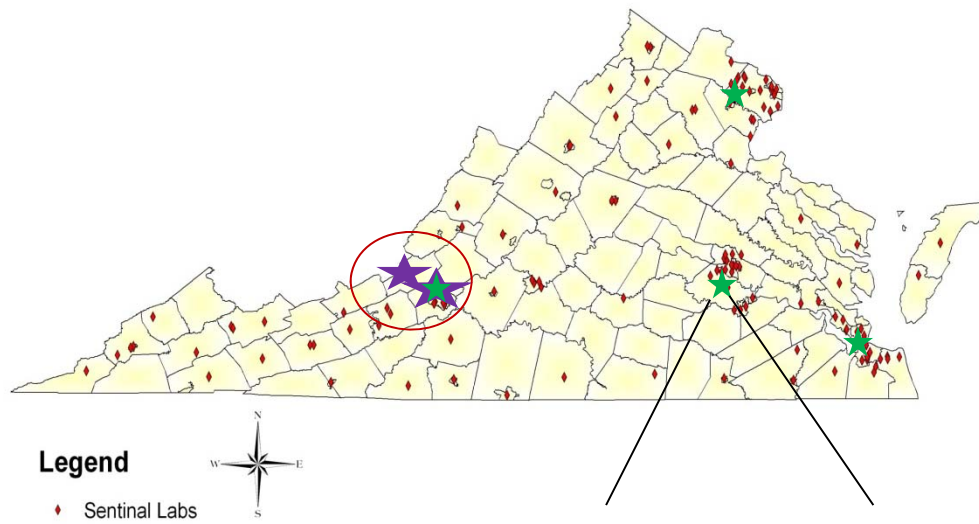
11 Oct

Kudos to VA state PH lab for 1st identifying *Exserohilum*, a black mold/fungus, in current [#meningitis](#) outbreak. [go.usa.gov/Ykb9](https://www.go.usa.gov/Ykb9)

 Retweeted by CDC_eHealth

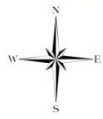
Expand

Facility Locations Virginia



Legend

◆ Sentinel Labs



- >130 sentinel labs ◆ ★
- 4 ME District Offices ★
- Emergency courier



DCLS



OCME



Rapidly Fatal Meningitis

- **CSF Bac Ag Panel**
 - Lyme
 - H. influenzae*
 - S. pneumoniae*
 - Grp B Strep
 - Cryptococcus*
- **Culture**
 - CSF – NSG after 3 days
 - HSV and VZV



Suspect Case

- **A person who has developed an infection of a normally sterile site following use of a product labeled as sterile prepared by the NECC**