Multistate Outbreak of Fungal Meningitis and Other Infections Associated with Contaminated Steroid Injections

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"… 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 taking care of patients

Response Objectives

- **Prevent severe illness and deaths due to fungal meningitis and other infections in patients exposed to contaminated steroid injections by:**
  - Notifying all exposed patients (~14,000)
    - Referring for evaluation if symptomatic
    - Educating to recognize symptoms in future
  - Developing and distributing diagnostic and treatment guidance
  - Providing advanced testing at CDC laboratories
  - Conducting surveillance to identify risk exposures
  - Coordinating with FDA to identify contaminated medication

Key Early Time Points

September 18

- Tennessee Department of Health contacted about a patient with culture-confirmed *Aspergillus fumigatus* meningitis who received epidural steroid injection at a pain clinic on July 30

September 18-25

- TN DOH in consultation with CDC investigates additional culture-negative meningitis cases who received epidural steroid injections at the same pain clinic
- Multiple common exposures identified, including to at least one of three lots of methylpredisolone acetate (MPA) compounded by New England Compounding Center (NECC)
- Communications with FDA and MA Board of Pharmacy

September 26

- NECC voluntarily recalls three lots of MPA
  - 17,000 vials distributed to 75 facilities in 23 states

Key Early Time Points (2)

September 26

- Efforts to identify cases in other states initiated
  - NC reports a case late the next day

October 3

- FDA identifies by microscopy fungal contamination in a sealed vial of MPA
- NECC ceases compounding and broadens recall

October 4

- FDA recommends that all health care professionals cease use and remove from their pharmaceutical inventory **any** product produced by NECC

October 2-6

- *Exserohilum rostratum* identified in patient samples by VA DOH and CDC

Fungi Confirmed in Patients

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

Laboratory Testing of Unopened MPA Vials

- **Identified 3 Fungi and confirmed by DNA sequencing in vials from 2 of 3 lots:**
  - *Exserohilum rostratum*
  - *Rhodotorula laryngis*
    - Not known human pathogen; no growth at 37C
  - *Rhizopus stolonifer* (in one slant)
    - Not known human pathogen; no growth at 37C

Fungal Meningitis and Other Infections

(as of December 10, 2012)

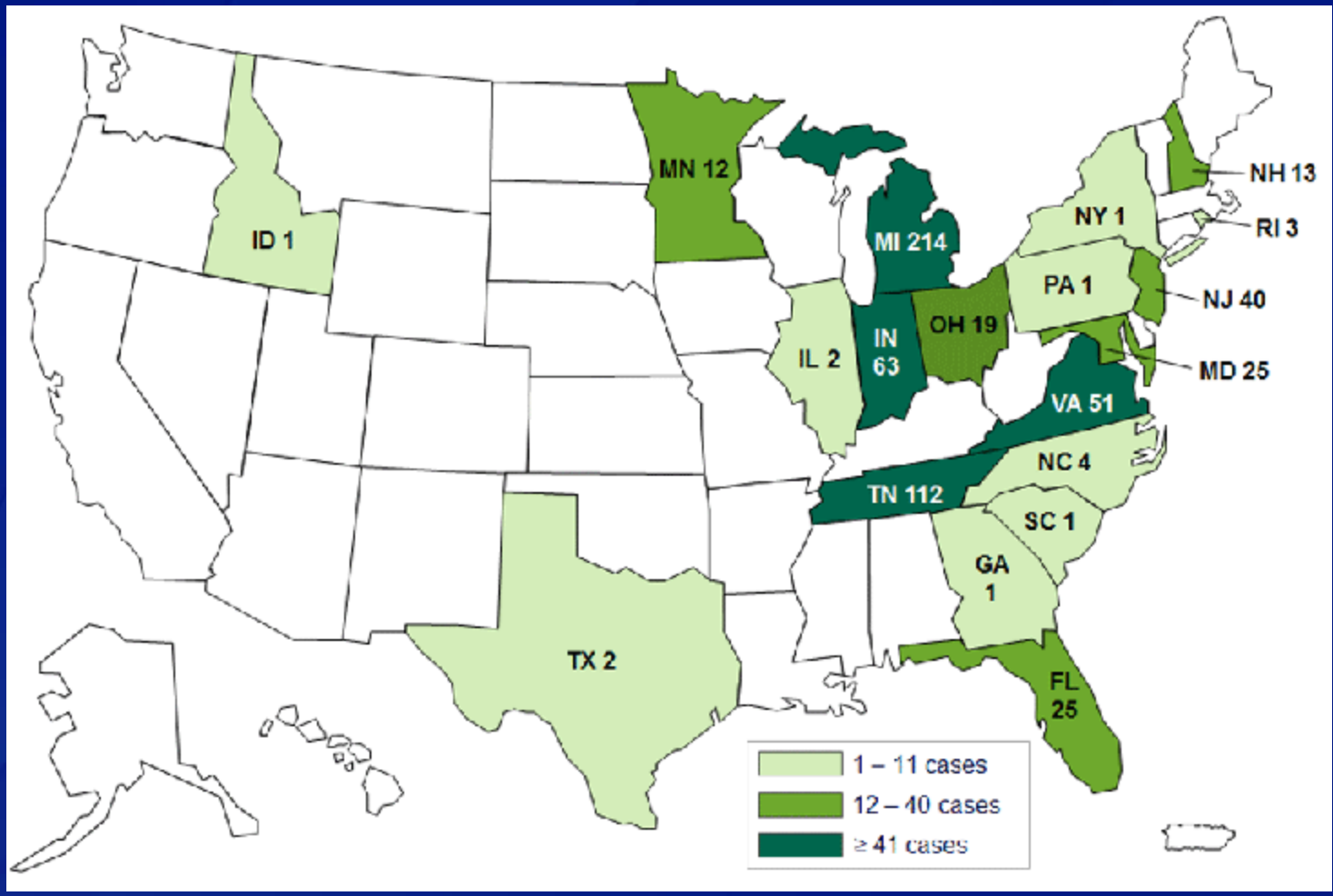
State	Total Case Counts	Meningitis (with or without other infection) *	Stroke without Lumbar Puncture only	Paraspinal/Spinal Infection only	Peripheral Joint Infection only	Paraspinal/Spinal + Peripheral Joint Infection	Deaths
Florida (FL)	25	20	3	2	0	0	3
Georgia (GA)	1	1	0	0	0	0	0
Idaho (ID)	1	1	0	0	0	0	0
Illinois (IL)	2	2	0	0	0	0	0
Indiana (IN)	63	49	1	13	0	0	6
Maryland (MD)	25	24	0	1	0	0	2
Michigan (MI)	214	64	1	133	15	1	10
Minnesota (MN)	12	10	0	2	0	0	0
North Carolina (NC)	4	3	0	1	0	0	1
New Hampshire (NH)	13	9	0	0	4	0	0
New Jersey (NJ)	40	38	0	2	0	0	0
New York (NY)	1	0	0	1	0	0	0
Ohio (OH)	19	16	0	3	0	0	0
Pennsylvania (PA)	1	1	0	0	0	0	0
Rhode Island (RI)	3	2	0	1	0	0	0
South Carolina (SC)	1	1	0	0	0	0	0
Tennessee (TN)	112	76	3	31	2	0	13
Texas (TX)	2	2	0	0	0	0	0
Virginia (VA)	51	49	0	2	0	0	2
TOTALS	**590**	**368**	**8**	**192**	**21**	**1**	**37**

*Some patients with meningitis had other infections diagnosed in addition; the majority of these other infections were spinal/paraspinal infections, although one patient had both meningitis and a peripheral joint infection. The patient with meningitis and a peripheral joint infection had both a joint injection and a spinal/paraspinal injection.

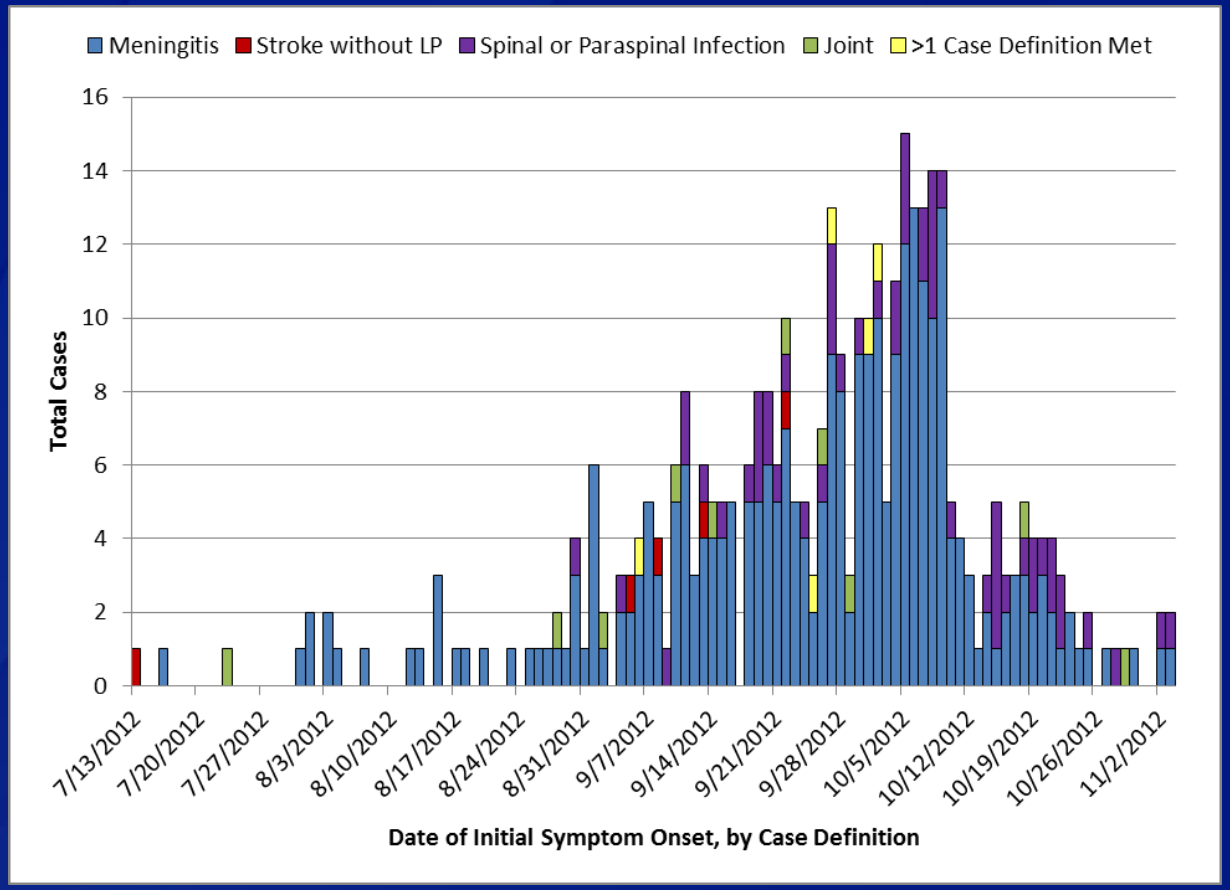
Case counts by state are based on the state where the procedure was performed, not the state of residence.

Fungal Meningitis and Other Infections

(as of December 10, 2012)

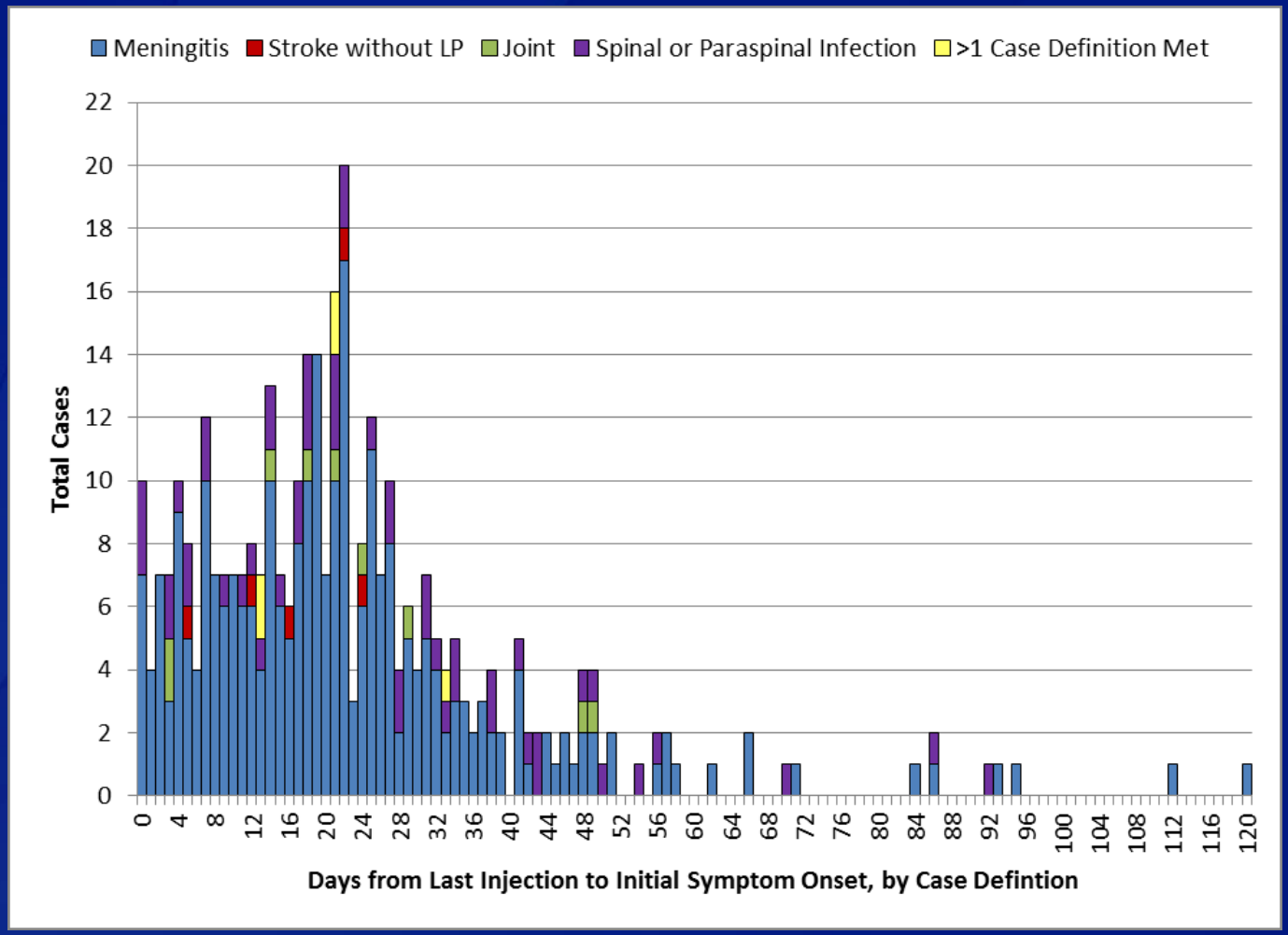


Fungal Infections Associated with Contaminated Lots of MPA, by Date of Initial Symptom Onset and Presenting Syndrome (n=356)



Source: Smith RM et al. Fungal infections associated with contaminated methylprednisolone injections . N Engl J Med (in press).

Incubation period in days (from last injection to initial symptom onset), by presenting syndrome (n=346)



Patient UPDATE FROM NEJM Characteristics

Characteristic (N=180)*	No.	(%)
Median Age (range) *years*		
Female	117	65
Presentation		
Meningitis	170	94
Stroke without lumbar puncture	4	2
Epidural abscess or osteomyelitis	3	2
Peripheral joint	2	1
More than one case definition	1	1
Death	12	9

**As of October 24, preliminary data available for 180/317 (57%) patients*

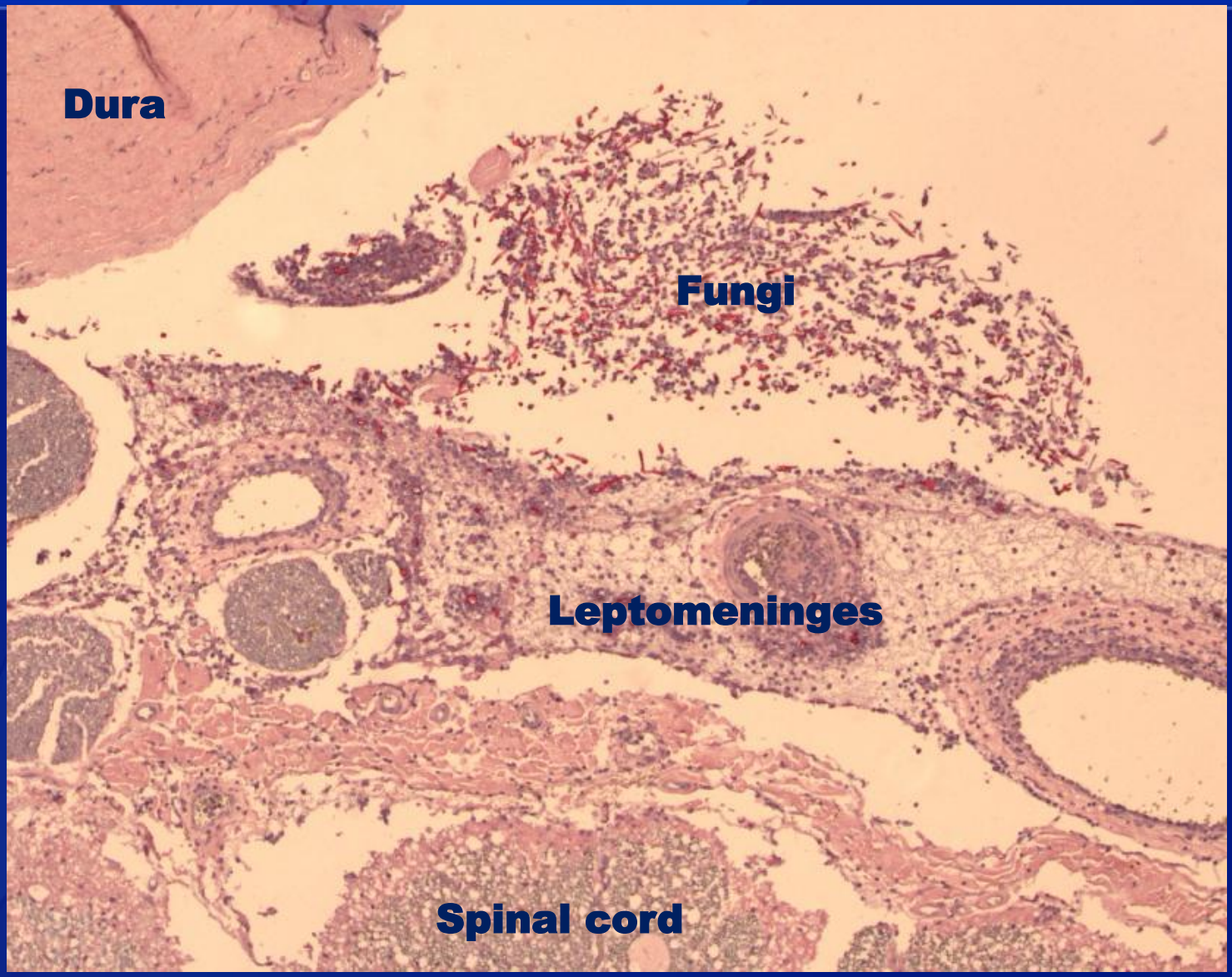
Meningitis Patient Characteristics and Symptoms (N=300)

Median age 64 years (16-92); 61% female
Median incubation period 19 days (0-120)

Symptom	n	%
Headache	251	85
Neck pain/stiffness	117	39
Fever	95	32
Photophobia	66	22

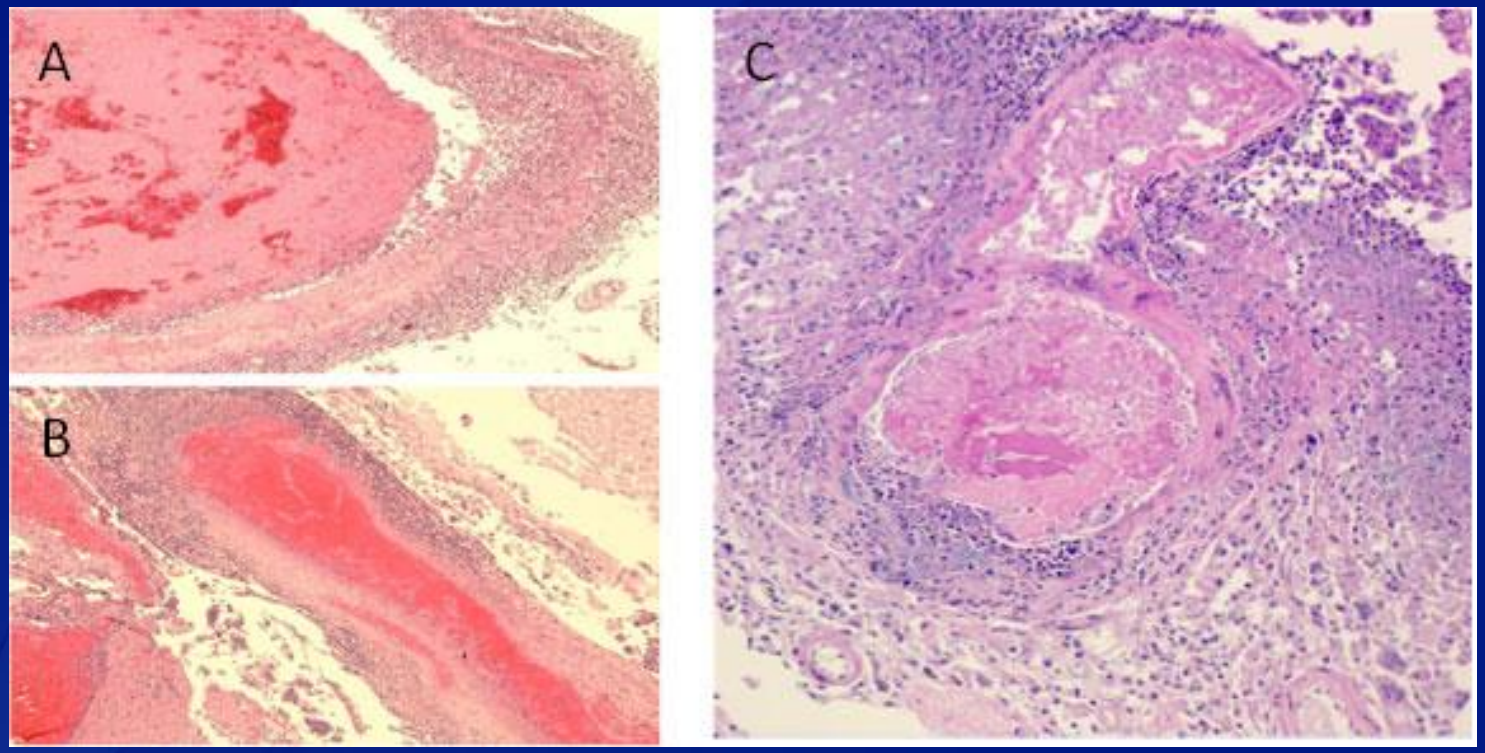
Many patients with meningitis had only a few mild symptoms, but had CSF pleocytosis

Source: Smith RM et al. Fungal infections associated with contaminated methylprednisolone injections . N Engl J Med (in press).



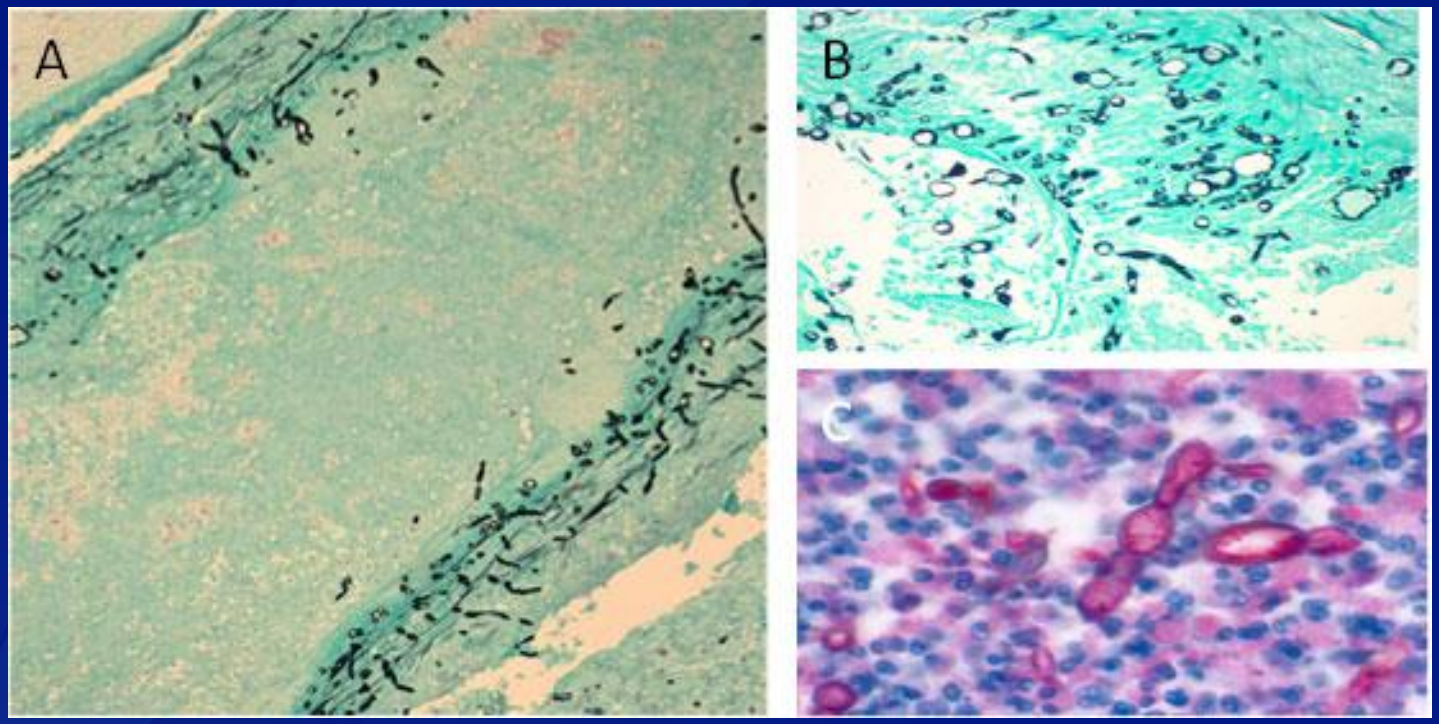
Courtesy Infectious Diseases Pathology Branch, Division of High-Consequence Pathogens and Pathology, CDC

Disease Caused by Fungus in Brain Tissue



Major histopathologic findings in clinical cases of meningitis show evidence of necrotizing, suppurative vasculitis with thrombosis (A and B). These findings are seen in many cases involving a branch of the basilar artery (C), which are consistent with the clinical findings.

Fungus in Brain Tissue



Fungal hyphae (black) can be visualized with silver stain within vessel walls (A) and in area of necrosis in basilar artery (B). Using a polyfungal immunohistochemistry reagent, fungal hyphae (red) is also seen in the purulent exudate in spinal meningitis (C).

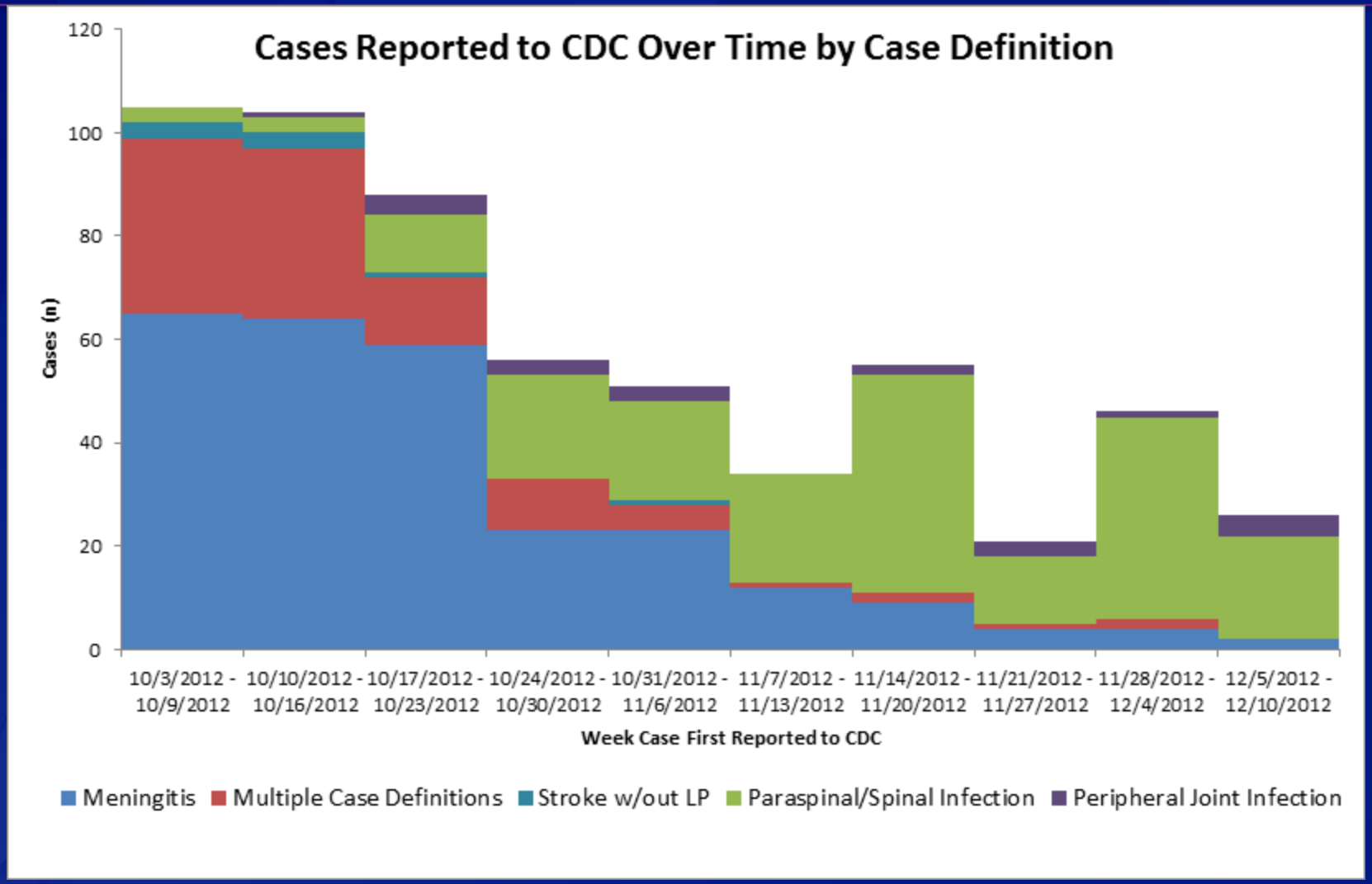
Navigating Uncharted Waters

- Very limited diagnostic tools
  - CDC lab developed PCR assay, optimized for CSF
- Extremely limited clinical experience
  - Convened clinical mycology group to provide advice about diagnosis and treatment to inform CDC guidance. Met frequently (sometimes daily).
- Clinical course unknown
  - Recruited group of ID specialist volunteers to provide ongoing consultation to treating physicians
  - Continue to stay in close contact with centers treating large numbers of patients
  - Keep surveillance strong to detect potential later infection manifestations

Interim Diagnostic and Treatment Guidance Early October, 2012

- Clinicians should be aware of the atypical presentation of meningitis in this outbreak, and should consider performing lumbar puncture if patients have mild symptoms and have received a steroid injection originating from one of the three implicated lots of MPA.
- Consult an infectious disease physician to assist with diagnosis, management and follow-up.
- Initiate empiric antifungal therapy with voriconazole in addition to routine empiric treatment to cover bacterial pathogens
- Consider adding liposomal amphotericin B if patient presents with severe disease or deteriorates on voriconazole
- Adequate duration of therapy unknown but likely a minimum of 3 months
- Empiric antifungal therapy not recommended

Evolving Clinical Picture



Health Alert Network Advisory

November 20, 2012

- Epidural abscess and other clinical syndromes being diagnosed in exposed patients
- Patients, including those being treated for meningitis, who have new or worsening symptoms at or near injection site need MRI
- Low threshold for repeat MRI if worsening or localizing symptoms
- For patients being treated for meningitis, strongly consider MRI of injection site 2-3 weeks after meningitis diagnosis
- Early consultation with neurosurgeon in addition to initiation of antifungal therapy

Health Alert Network Update

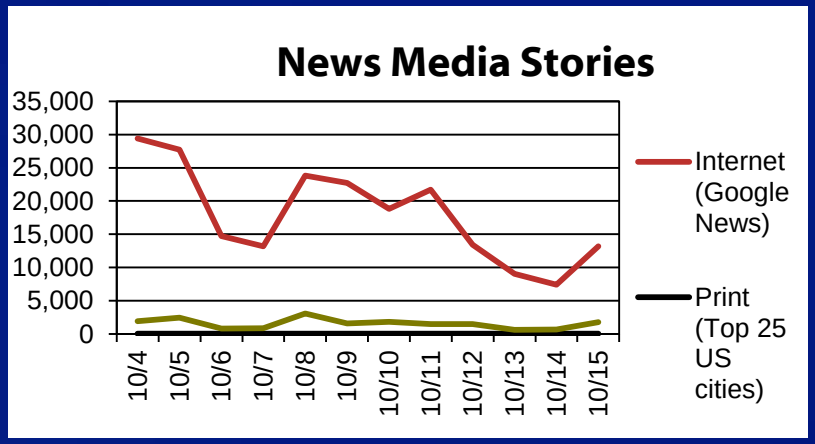
December 3, 2012

- Additional contamination found in NECC products
  - betamethasone, cardioplegia, and triamcinolone solutions
- *Bacillus* and fungal species
  - *Aspergillus tubingensis*, *Aspergillus fumigatus*, *Cladosporium* species, *Penicillium* species
  - Some can be human pathogens
- Effect on patients clinically is unknown
- No reports of laboratory-confirmed cases associated with these contaminated products
- No change in clinical guidance

Multistate Fungal Meningitis Outbreak 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



CDC Emergency Operations Center Activated for Multistate Fungal Meningitis Outbreak

Dr. John Jernigan, Clinical Team Co-lead, and Dr. Rachel Smith, Surveillance Team, listen to the latest updates regarding the 2012 fungal meningitis outbreak.

Dr. Benjamin Park, Surveillance Team Lead, updates the Incident Manager and colleagues on CDC activities in response to the 2012 fungal meningitis outbreak.

Pharmacy Compounding

Papyrus Ebers, c. 1552 BC

[Medicine] for Blindness: Eyes of the Pig

"Remove [these] and place in water…red ocher…a fermentation product of honey, finely grind, make a uniform mass, pour into the ear of the man, so that he immediately becomes healthy. Do it and you will see: a successful method…"

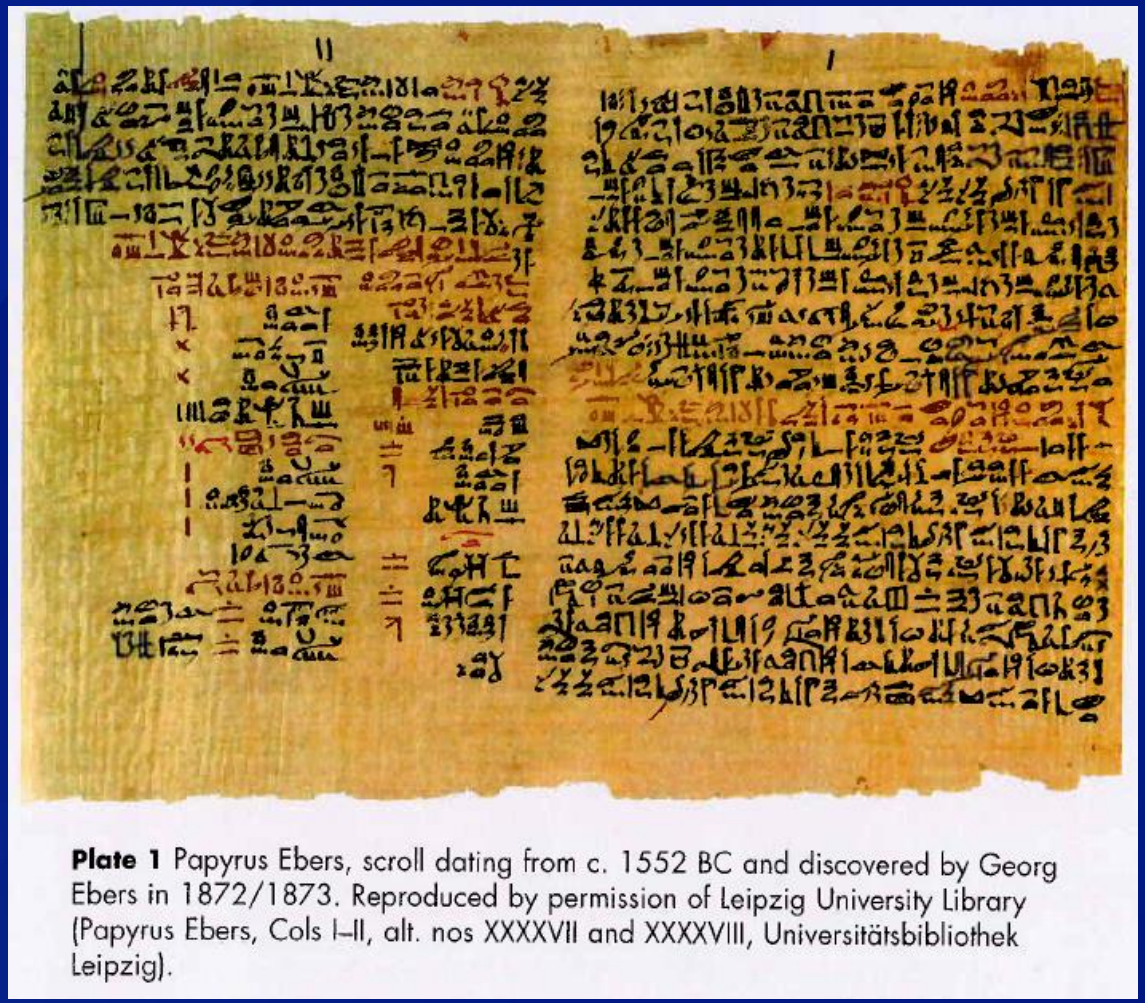
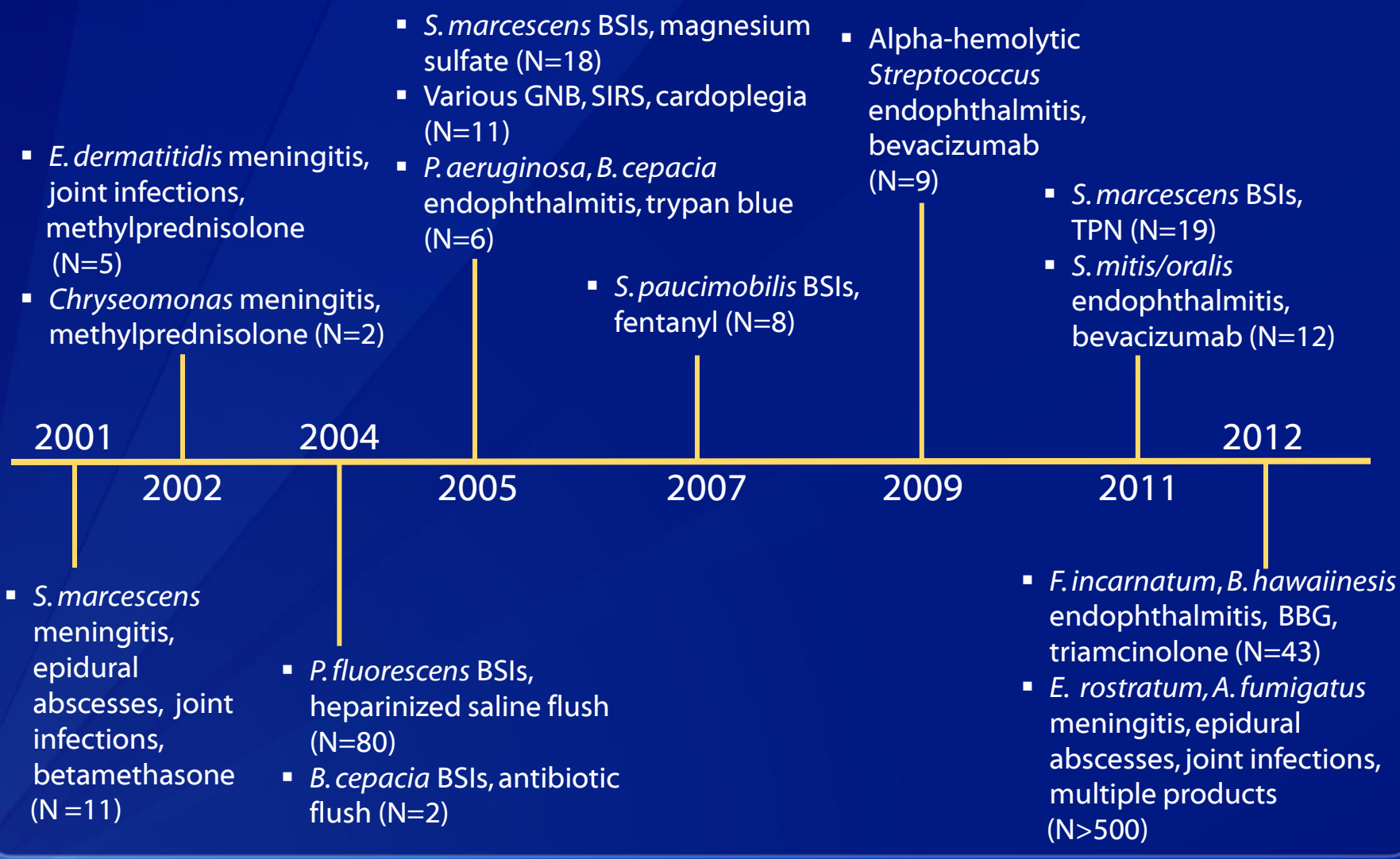


Plate 1 Papyrus Ebers, scroll dating from c. 1552 BC and discovered by Georg Ebers in 1872/1873. Reproduced by permission of Leipzig University Library (Papyrus Ebers, Cols I–II, alt. nos XXXXVII and XXXXVIII, Universitätsbibliothek Leipzig).

http://dianabuja.wordpress.com/2012/08/01/eyes-and-the-papyrus-ebers/

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

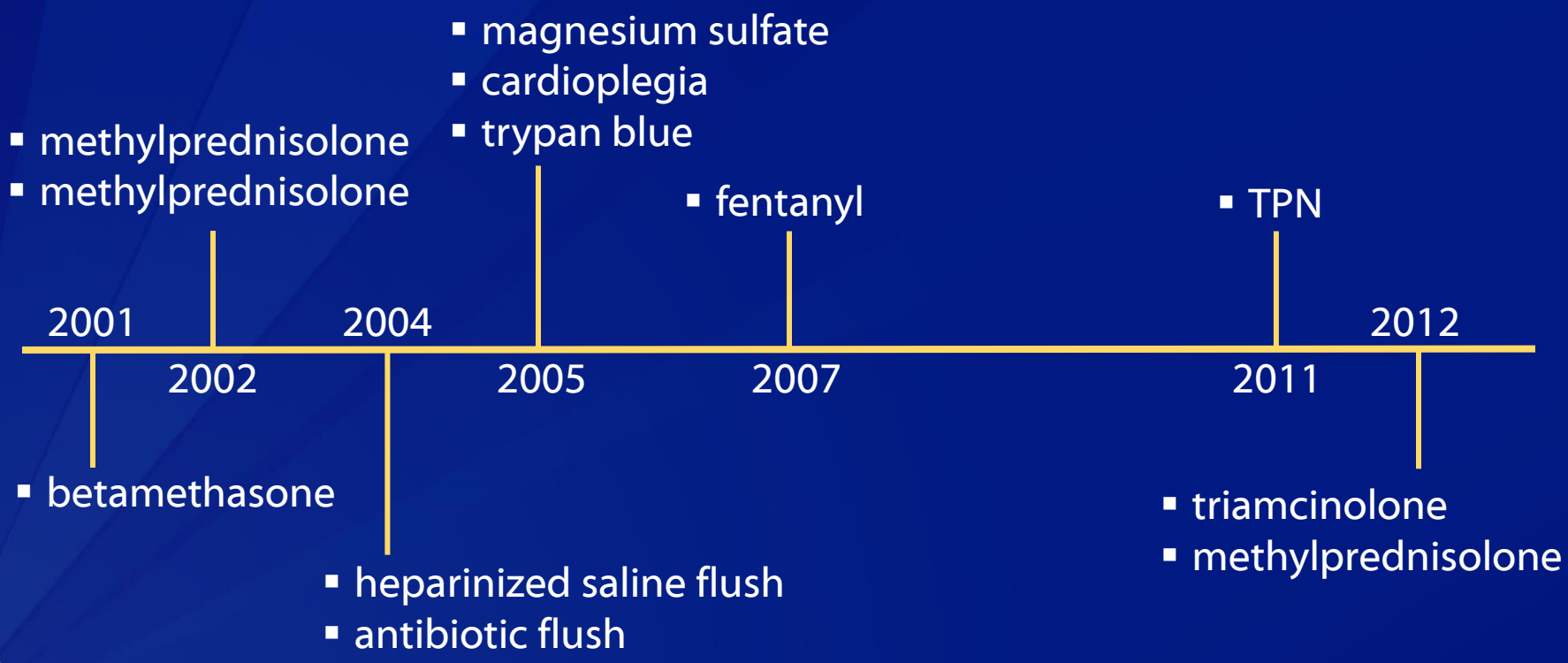


BBG Brilliant Blue-G; BSI Bloodstream infection; GNB Gram negative bacteria; SIRS Systemic Inflammatory Response Syndrome; TPN Total parenteral nutrition

Pharmacy Compounding
Product Scope

Compounding Pharmacy Investigations
Challenges – Detection

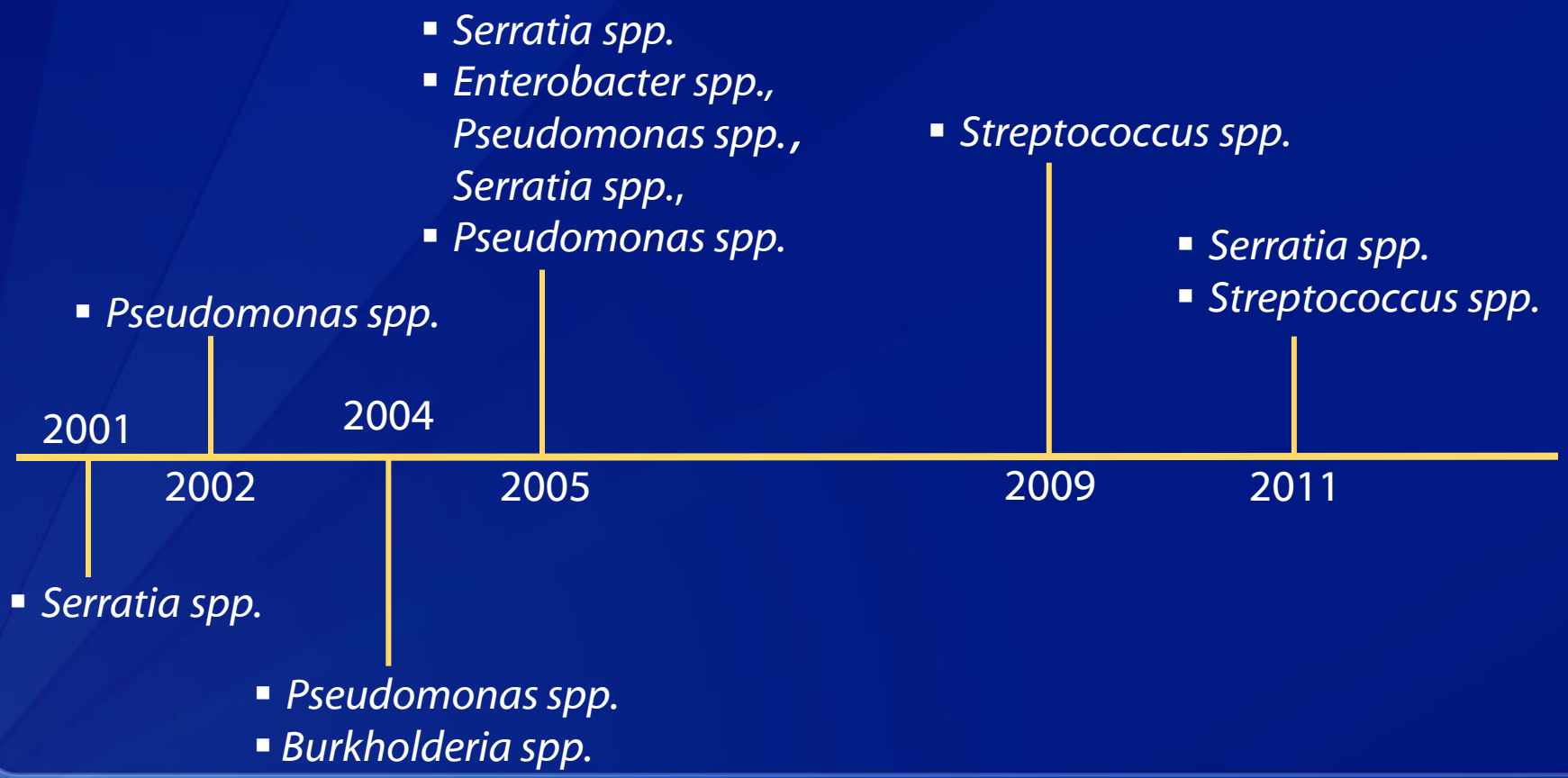
- **Contaminated product may not be readily recognized as potential source of infection**



TPN Total parenteral nutrition

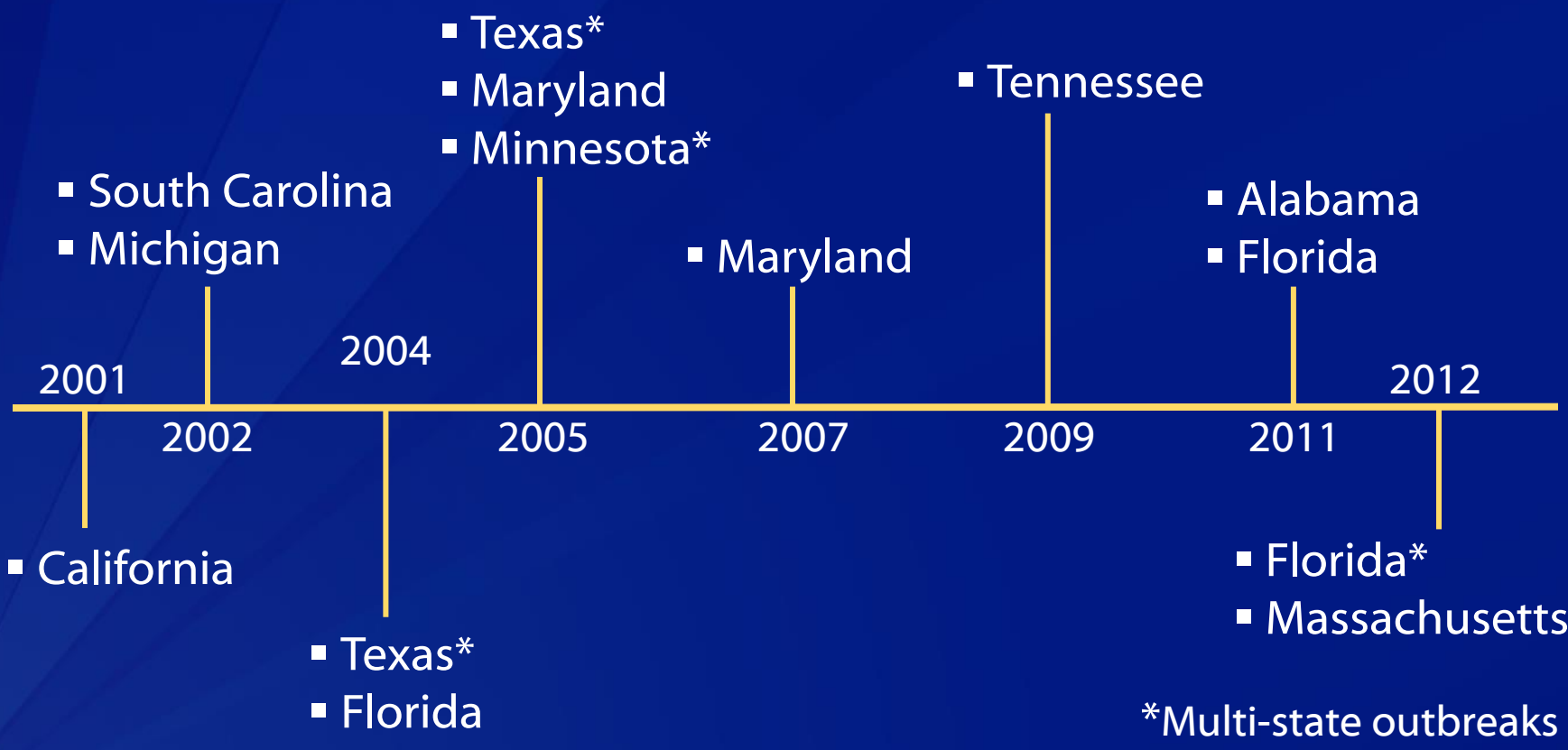
Compounding Pharmacy Investigations
Challenges – Detection

- **Low index of suspicion if organism is common cause of healthcare-associated infections**



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

States Where Implicated Pharmacies Have Been Located



*Multi-state outbreaks

35 Days of EOC Activation… and the Response Continues

- 2 new websites with hundreds of updates
- Daily case counts
- 8 Health Alert Network notices
- 4 New treatment guidelines
- Patient information in English and Spanish
- New lab results web pages
- Dozens of new partner organizations established
- Rapid social media responses
- Regular updates to 245 clinical groups and professional societies
- 4 COCA calls (reaching >5000 clinicians)
- Medscape video (reaching >15,000 clinicians)
- Hundreds of CDC INFO calls answered
- New clinical connection hotline
- Hundreds of media queries answered
- 2 press conferences

A Few Observations

- Pivotal role of state health departments
  - Sounding the alarm
  - Contacting 14,000 patients
  - Ongoing surveillance providing vital information
- CDC role with the states
  - Majority of outbreak responders directly supported by CDC's financial and in kind support to states
    - Key role of Emerging Infections Program, Epidemiology and Laboratory Capacity cooperative agreement, and HAI coordinators
  - Laboratory training
  - Leadership
  - Keeping everyone moving in the same direction

A Few Observations (2)

- CDC's laboratories again proved critical
  - Assay development
  - Ability to identify rare or obscure pathogens
    - Assist FDA in identification of what's in the vials
  - Surge capacity to backstop the states
  - To date tested over 800 human clinical specimens from 26 states
- CDC filled huge gap in clinical expertise and knowledge to optimize the quality and timeliness of guidance about diagnosis and treatment
  - Hub for characterizing and sharing clinical experience
  - Convene "best minds" in mycology to provide advice
  - Real time updating of guidance as new information becomes available
- Communication was key

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
- Clinical syndrome is rare and determination of optimal treatment as well as rates of adverse events related to treatment may have to be continually revised for the duration of the treatment of affected patients
- Proper practices in compounding pharmacies may prevent such outbreaks in the future