ORIGINAL ARTICLE

Fungal Infections Associated with Contaminated Methylprednisolone Injections

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ABSTRACT

BACKGROUND

Fungal infections are rare complications of injections for treatment of chronic pain. In September 2012, we initiated an investigation into fungal infections associated with injections of preservative-free methylprednisolone acetate that was purchased from a single compounding pharmacy.

METHODS

Three lots of methylprednisolone acetate were recalled by the pharmacy; examination of unopened vials later revealed fungus. Notification of all persons potentially exposed to implicated methylprednisolone acetate was conducted by federal, state, and local public health officials and by staff at clinical facilities that administered the drug. We collected clinical data on standardized case-report forms, and we tested for the presence of fungi in isolates and specimens by examining cultures and performing polymerase-chain-reaction assays and histopathological and immunohistochemical testing.

RESULTS

By October 19, 2012, more than 99% of 13,534 potentially exposed persons had been contacted. As of July 1, 2013, there were 749 reported cases of infection in 20 states, with 61 deaths (8%). Laboratory evidence of *Exserohilum rostratum* was present in specimens from 153 case patients (20%). Additional data were available for 728 case patients (97%); 229 of these patients (31%) had meningitis with no other documented infection. Case patients had received a median of 1 injection (range, 1 to 6) of implicated methylprednisolone acetate. The median age of the patients was 64 years (range, 15 to 97), and the median incubation period (the number of days from the last injection to the date of the first diagnosis) was 47 days (range, 0 to 249); 40 patients (5%) had a stroke.

CONCLUSIONS

Analysis of data from a large, multistate outbreak of fungal infections showed substantial morbidity and mortality. The infections were associated with injection of a contaminated glucocorticoid medication from a single compounding pharmacy. Rapid public health actions included prompt recall of the implicated product, notification of exposed persons, and early outreach to clinicians.

There has been no systematic surveillance in the United States for adverse events that occur after glucocorticoid injections for the treatment of chronic musculoskeletal pain, but infection is a known, although probably rare, risk documented in the medical literature.[1-6] Infections that develop after a procedure are usually bacterial[2,7-10]; fungal infections are extremely rare.[11-14] We present data on a multistate outbreak of fungal meningitis and other infections associated with injections of preservative-free methylprednisolone acetate that was purchased from a single compounding pharmacy and describe the public health response to the outbreak.

Methods

Index Patient and Early Epidemiologic Investigation

On September 18, 2012, the Tennessee Department of Health received a report of a 56-year-old patient with aspergillus meningitis.[15] The patient had no known risk factors for fungal meningitis but had received an epidural glucocorticoid injection for lower back pain at an ambulatory surgical center 46 days earlier. By September 25, the initial investigation, led by the Tennessee Department of Health in collaboration with the Centers for Disease Control and Prevention (CDC), had identified seven additional patients with meningitis who had been treated at the same ambulatory surgical center. The cerebrospinal fluid cultures from the additional seven patients were initially negative.[16] However, the clinical presentation of these patients was similar to that of the index patient: all had a subacute onset of meningitis and marked cerebrospinal fluid pleocytosis; four had posterior circulation strokes.

All the patients, including the index patient, had received epidural glucocorticoid injections of 80 mg of methylprednisolone acetate per milliliter. All the vials of methylprednisolone acetate used for these injections had been purchased from a single compounding pharmacy, New England Compounding Center (NECC, Framingham, MA); all the injections involved methylprednisolone acetate from lot 05212012@68, 06292012@26, or 08102012@51. Other exposures common to these initial patients included contrast material, povidone–iodine, lidocaine, spinal needles, and epidural tray kits.

On September 25, 2012, NECC was informed of the investigation and the exposure of all eight patients in Tennessee to methylprednisolone acetate from three lots that had been shipped from NECC; the company reported orally that it had not previously received any reports of adverse events associated with these lots of methylprednisolone acetate. On September 26, NECC voluntarily recalled these three lots and provided the Food and Drug Administration (FDA) and the CDC with an invoice list for the 76 clinical facilities that had received these lots, dating back to May 21, 2012, the date the first lot was produced. This list was used to initiate case finding in other states. On September 27, 2012, the North Carolina Department of Health and Human Services informed the CDC of a single patient in North Carolina who had a negative cerebrospinal fluid culture and a clinical syndrome similar to that of the patients in Tennessee, including subacute meningitis; the patient had a posterior circulation stroke on September 28. This patient had also received an epidural glucocorticoid injection and had been exposed to methylprednisolone acetate from one of the three lots, as well as to the same brands of lidocaine and povidone–iodine as those used for the patients in Tennessee. The report of this additional case suggested the possibility of an exposure that was not limited to the single ambulatory surgical center in Tennessee. Because compounded medications had been the cause of several prior outbreaks,[14,17,18] methylprednisolone acetate from NECC was considered to be a likely source.

On September 28, 2012, state and local health departments, in collaboration with the clinical facilities that had received and administered methylprednisolone acetate from the three lots, initiated the process of identification and notification of exposed patients. Clinical facilities reviewed medical records to compile lists of patients who had received injections from one or more of the three lots of methylprednisolone acetate. The lot number was frequently not recorded in medical records; in those instances, facilities determined the period during which vials from the three lots of methylprednisolone acetate were likely to have been used and included all patients who had received injections of methylprednisolone acetate during that period. Clinical facilities, with help from state and local health departments and the CDC, notified pa-

tients by means of telephone calls, home visits, or letters. The objectives of the notification were to refer exposed persons who were symptomatic for immediate medical evaluation and to advise exposed persons who were asymptomatic to seek clinical follow-up in the event of future symptoms. Additional information regarding case finding and outreach efforts is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

On October 4, 2012, the FDA announced that microscopical evaluation of unopened vials of NECC methylprednisolone acetate from lot 08102012@51 revealed evidence of fungi.[19,20] The CDC and FDA announced on October 18 that the environmental mold *Exserohilum rostratum*, in addition to the nonpathogenic fungi *Rhodotorula laryngis* and *Rhizopus stolonifer*, had been recovered from unopened vials of methylprednisolone acetate from lot 08102012@51.[20,21] *E. rostratum* was subsequently identified in vials from lot 06292012@26, and evidence of *E. rostratum* DNA in lot 05212012@68 was reported to the CDC by the New York State Public Health laboratory.[21] Other fungi were also subsequently identified from vials of methylprednisolone acetate during the course of the outbreak, including *Cladosporium cladosporioides* from lot 08102012@51, *R. laryngis* from lot 06292012@26, and *Paecilomyces formosus* from lot 05212012@68.[21] Several bacillus species of bacteria were also identified from lot 08102012@51.[21]

For the purposes of this analysis, a case was defined according to the presence of any of the following conditions at the time of clinical presentation in a person who had been exposed to one of the three lots of methylprednisolone acetate (05212012@68, 06292012@26, or 08102012@51) produced by NECC after May 21, 2012: meningitis of unknown cause that developed after an epidural or paraspinal injection; posterior circulation stroke due to presumed meningitis (without a cardioembolic source and without documentation of a normal cerebrospinal fluid profile) after an epidural or paraspinal injection; clinician-diagnosed osteomyelitis, abscess, or other infection of unknown cause in the spinal or paraspinal structures at or near the site of injection after an epidural or paraspinal injection; or clinician-diagnosed osteomyelitis or worsening inflammatory arthritis of a peripheral joint diagnosed after a peripheral-joint injection, without a known cause. Clinically diagnosed meningitis was defined as signs or symptoms of meningitis and a cerebrospinal fluid profile with pleocytosis (>5 white cells per cubic millimeter), accounting for the presence of red cells (i.e., subtracting 1 white cell for every 500 red cells present).

MICROBIOLOGIC INVESTIGATION

Clinical specimens from case patients, primarily cerebrospinal fluid or joint fluid, were evaluated at the CDC by means of polymerase-chain-reaction (PCR) assays, with the use of broad-range, internal transcribed spacer (ITS) region fungal primers.[22-25] (PCR for fungal detection is a research test. It has not been cleared or approved by the FDA, and the performance characteristics have not been established. The results of this test should not be used for diagnosis, treatment, or assessment in clinical practice.) Sequencing of amplified fungal DNA and DNA extracted from fungal isolates was performed for the identification of fungal species.[25] Histopathological and immunohistochemical testing of tissue from autopsy or biopsy specimens, as well as PCR testing and DNA sequencing, were also performed at the CDC.[26] In addition, microbiologic testing of specimens from case patients was performed at local, state, and reference laboratories.

INVESTIGATION OVERSIGHT AND DATA COLLECTION

This investigation was part of an emergency public health response; as such, it was not considered to be research that required review by an institutional review board or informed consent from the patients. Clinical data were collected with the use of a standardized case-report form developed for the outbreak.

STATISTICAL ANALYSIS

All analyses were performed with the use of SAS software, version 9.3 (SAS Institute). The incubation period was calculated as the number of days from the last injection to the date of diagnosis. For case patients with multiple diagnoses, an incubation period was calculated for each diagnosed infection. The date of diagnosis was defined in the following way: for patients with meningitis as the date of the initial lumbar puncture yielding cerebrospinal fluid that met the case criteria, for patients with stroke as the date of the stroke,

for patients with spinal or paraspinal infections as the date of imaging that revealed those infections, and for patients with peripheral-joint infections as the date of arthrocentesis. National and state-specific attack rates were calculated as the number of case patients divided by the total number of exposed persons. National attack rates were calculated with data from all cases; state-specific attack rates were calculated with data from cases involving injections in non-peripheral joints only. Persons exposed to both types of injections (peripheral-joint and non-peripheral-joint injections) were included in both denominator categories. Lot-specific attack rates were also calculated (for details see the Supplementary Appendix).

RESULTS

EPIDEMIOLOGIC INVESTIGATION

On the basis of records provided by NECC, we determined that the three lots of methylprednisolone acetate comprised 17,675 vials that had been distributed to 76 facilities in 23 states. An active review of records by clinical facilities and state and local health departments identified 13,534 persons who had potentially been exposed to medication from at least one of the three lots: 12,068 (89%) had been exposed through epidural, spinal, or paraspinal injections, and 1648 (12%) through peripheral-joint or other injections. By October 19, 2012, state health departments reported that approximately 99% of the persons potentially exposed to these lots of methylprednisolone acetate had been contacted at least once.

As of July 1, 2013, a total of 749 cases had been identified in 20 states, according to the interval case counts that the states send to the CDC; 61 case patients (8%) had died. Of the 749 patients with infections, 323 (43%) had spinal or paraspinal infections only, 233 (31%) had meningitis only, 151 (20%) had meningitis and concurrent spinal or paraspinal infections, 33 (4%) had peripheral-joint infections only, 7 (1%) had stroke due to presumed meningitis, and 2 (<1%) had spinal or paraspinal infections and concurrent peripheral-joint infections.

Data from case-report forms were available for 728 case patients (97%) as of July 1, 2013: a total of 310 of these patients (43%) had spinal or paraspinal infections only, 229 (31%) had meningitis only, 148 (20%) had meningitis and concurrent spinal or paraspinal infections, 32 (4%) had septic arthritis after a peripheral-joint injection (Table 1), 7 (1%) met the case definition for stroke due to presumed meningitis, and 2 (<1%) had spinal or paraspinal infections and concurrent peripheral-joint infections. The median age of these patients was 64 years (range, 15 to 97), and 432 (59%) were women. A total of 60 patients (8%) had underlying immunosuppression (Table 1). Data on symptoms were available for 701 case patients (96%). The most commonly reported symptoms among case patients with meningitis only were headache (in 88%) and neck stiffness (in 49%); the most commonly reported symptoms among case patients with spinal or paraspinal infections only were back pain (in 63%) and headache (in 36%). A total of 84% of the case patients with peripheral-joint infections only (i.e., with no other site of infection) reported joint pain (Table 1).

The CDC received reports of stroke in 40 case patients (5%). In 7 patients, the stroke was due to presumed meningitis (lumbar puncture was never performed). A total of 33 patients had a stroke in addition to documented meningitis; data on the timing of the stroke were available for 32 of these patients: 12 had a stroke before or at the same time as the diagnosis of meningitis, and 20 had a stroke after the diagnosis of meningitis. Data on the type of stroke were available for 34 case patients; 24 strokes were ischemic, 6 were hemorrhagic, and 4 were both. Among the 28 case patients for whom the location of the stroke was known, 27 (96%) had strokes that involved the posterior circulation.

Data on antifungal treatment were available for 476 of the 728 case patients (65%) for whom case-report forms were available: 301 (63%) received voriconazole alone, 173 (36%) received both voriconazole and amphotericin B, and 2 (<1%) received amphotericin B alone. The earliest date of the onset of symptoms was July 7, 2012, in a patient who had a spinal or paraspinal infection; the first case patient with documented meningitis had an onset of symptoms on July 16, 2012. At the outset of this outbreak, most case patients received a diagnosis of meningitis; however by mid-October, spinal or paraspinal infections became the predominant diagnosis in case pa-

Table 1. Characteristics of Patients with Fungal Infections Associated with Contaminated Lots of Methylprednisolone Acetate.*

Characteristic	All Cases† (N=728)	Meningitis Only (N=229)	Spinal or Paraspinal Infection Only (N=310)	Meningitis and Spinal or Paraspinal Infection (N=148)	Peripheral-Joint Infection Only (N=32)
Demographic and clinical data					
Female sex — no. (%)	432 (59)	134 (59)	184 (59)	90 (61)	19 (59)
Age — yr					
Median	64	58	65	67	62
Range	15–97	15–97	26–91	23–90	43–86
Interquartile range	53–74	48–71	56–75	57–74	52–72
Immunosuppressed — no. (%)	60 (8)	21 (9)	23 (7)	13 (9)	2 (6)
Initial symptoms — no./total no. (%)					
Headache	428/701 (61)	201/229 (88)	102/284 (36)	NA	4/31 (13)
Back pain	319/701 (46)	55/229 (24)	180/284 (63)	NA	2/31 (6)
Neck pain or stiffness	211/701 (30)	112/229 (49)	47/284 (17)	NA	5/31 (16)
Fever	140/701 (20)	72/229 (31)	21/284 (7)	NA	3/31 (10)
Photophobia	107/701 (15)	65/229 (28)	15/284 (5)	NA	0
Joint pain	51/701 (7)	2/229 (1)	22/284 (8)	NA	26/31 (84)
Exposure data					
Lot exposure known — no./total no. (%)	536/728 (74)	149/229 (65)	244/310 (79)	124/148 (84)	14/32 (44)
Exposed to lot 05212012@68	74/536 (14)	40/149 (27)	19/244 (8)	12/124 (10)	1/14 (7)
Exposed to lot 06292012@26	429/536 (80)	109/149 (73)	202/244 (83)	101/124 (81)	13/14 (93)
Exposed to lot 08102012@51	95/536 (18)	28/149 (19)	41/244 (17)	24/124 (19)	0
Exposed to only one lot	474/536 (88)	121/149 (81)	224/244 (92)	111/124 (90)	14/14 (100)
05212012@68	43/474 (9)	23/121 (19)	12/224 (5)	6/111 (5)	1/14 (7)
06292012@26	376/474 (79)	85/121 (70)	186/224(83)	90/111 (81)	13/14 (93)
08102012@51	55/474 (12)	13/121 (11)	26/224 (12)	15/111 (14)	0
Procedures involving methylprednisolone acetate during the outbreak period — no./patient					
Median	1	1	1	1	2
Range	1–6	1–4	1–6	1–3	1–4
Type of injection known — no./total no. (%)	705/728 (97)	221/229 (97)	298/310 (96)	145/148 (98)	32/32 (100)
Epidural or paraspinal injection	665/705 (94)	220/221 (99.5)	295/298 (99)	142/145 (98)	0
Peripheral-joint or other injection	20/705 (3)	0	0	0	20/32 (62)
Both	20/705 (3)	1/221 (<1)	3/298 (1)	3/145 (2)	12/32 (38)
Treatment and outcome					
Antifungal treatment documented — no./total no. (%)	476/728 (65)	151/229 (66)	212/310 (68)	91/148 (61)	21/32 (66)
Voriconazole monotherapy	301/476 (63)	95/151 (63)	143/212 (67)	42/91 (46)	20/21 (95)
Amphotericin monotherapy	2/476 (<1)	1/151 (1)	1/212 (<1)	0	0
Voriconazole and amphotericin	173/476 (36)	55/151 (36)	68/212 (32)	49/91 (54)	1/21 (5)
Development of stroke — no./total no. (%)‡	40/728 (5)	21/229 (9)	0	12/148 (8)	0
Ischemic	24/34 (71)	12/18 (67)	0	6/9 (67)	0
Hemorrhagic	6/34 (18)	5/18 (28)	0	0	0
Both	4/34 (12)	1/18 (6)	0	3/9 (33)	0

Table 1. (Continued.)

Characteristic	All Cases*† (N=728)	Meningitis Only (N=229)	Spinal or Paraspinal Infection Only (N=310)	Meningitis and Spinal or Paraspinal Infection (N=148)	Peripheral-Joint Infection Only (N=32)
Laboratory data					
Initial lumbar puncture results					
White-cell count — cells/mm³			NA		NA
Median	83	23		319	
Range	6–15,400	6–12,745		6–15,400	
Interquartile range	12–850	10–594		49–1487	
Glucose — mg/dl			NA		NA
Median	53	56		46	
Range	3–249	3–249		7–151	
Interquartile range	41–64	45–66		36–60	
Protein — mg/dl					
Median	84	64	NA	115	NA
Range	13–2830	13–2830		17–1000	
Interquartile range	47–141	42–114		73–197	
Initial joint aspirate results					
White-cell count — cells/mm³	NA	NA	NA		
Median					515
Range					11–24,000
Interquartile range					45–1954
Evidence of fungus — no.	169	57	54	51	7
Documented by PCR only	85	30	18	33	4
Documented by culture only	33	12	16	5	0
Documented by histopathological assessment only	0	0	0	0	0
Documented by >1 technique	51	15	20	13	3
Exserohilum species	153	49	50	47	7

* Included are data as of July 1, 2013. Cases are classified according to the case definition met. To convert the values for glucose to millimoles per liter, multiply by 0.05551. NA denotes not applicable, and PCR polymerase chain reaction.
† Included are cases in patients with meningitis, patients with stroke who did not undergo lumbar puncture, patients with spinal or paraspinal infections, and patients with peripheral-joint infections, as well as patients who met multiple case definitions.
‡ Information on the type of stroke was not available for some of the persons in whom stroke developed.

tients (Fig. 1). Among the 728 case patients with available data on the incubation period (the interval from the date of the last injection to the date of the initial diagnosis), the median incubation period was 47 days (range, 0 to 249). Incubation periods were calculated for each syndrome (Fig. 2); the incubation period was longest among patients with peripheral-joint infections (median, 65 days [range, 22 to 190]) and shortest among patients who had a stroke without documented meningitis (i.e., in whom a lumbar puncture was not performed) (median, 24 days [range, 3 to 157]). Among the patients who met the case definition for meningitis, the median white-cell count in the first cerebrospinal fluid sample was 83 cells per cubic millimeter (range, 6 to 15,400), the median glucose concentration was 53 mg per deciliter (range, 3 to 249) (2.9 mmol per liter [range, 0.2 to 13.8]), and the median protein level was 84 mg per deciliter (range, 13 to 2830) (Table 1). Among the 16 case patients with peripheral-joint infections and available data on synovial fluid analysis, the median white-cell count was 515 cells per cubic millimeter (range, 11 to 24,000).

Lot-specific exposure data were available for

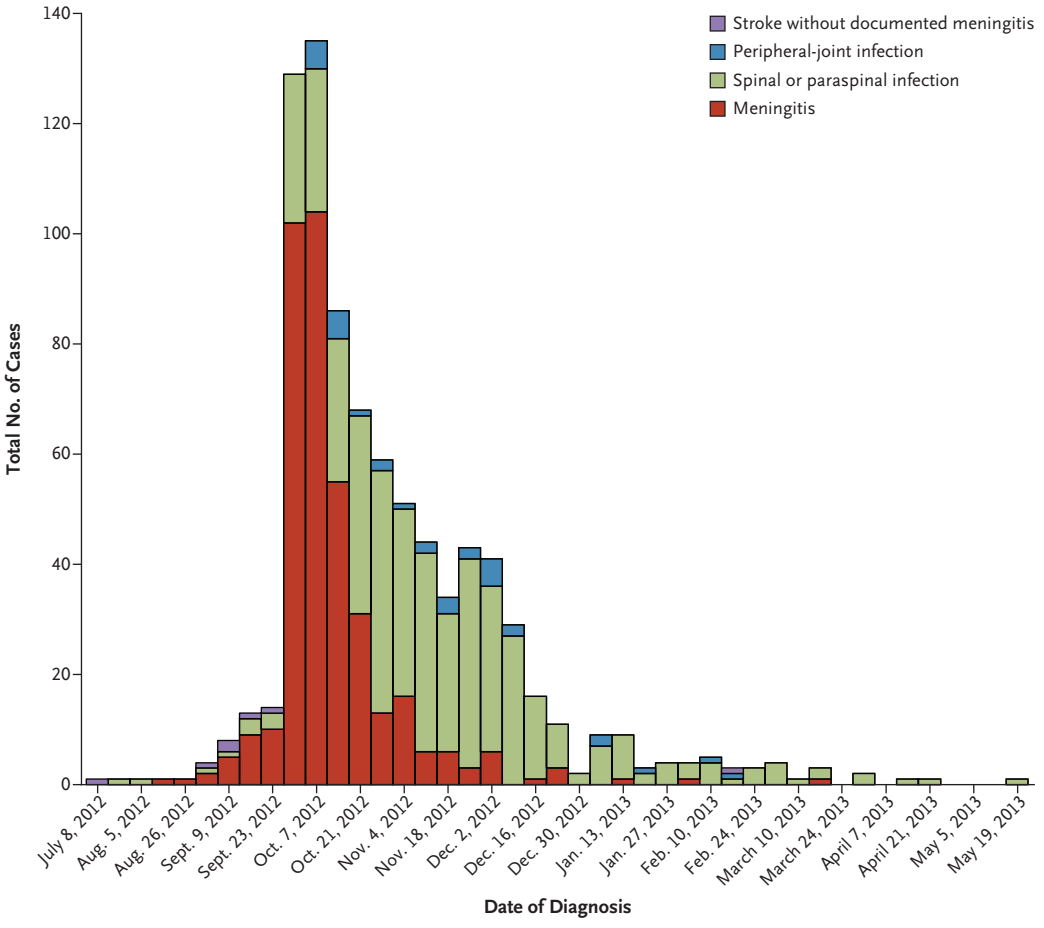

Figure 1. Fungal Infections Associated with Contaminated Lots of Methylprednisolone Acetate, According to Date of Diagnosis.

Included are data as of July 1, 2013. Data on the date of diagnosis were available for 710 cases comprising 844 diagnoses. For patients meeting two case definitions, two dates of diagnoses are included. A median of 5 days elapsed between the onset of symptoms and the reporting of cases to the Centers for Disease Control and Prevention.

536 of the 728 case patients (74%) for whom case-report forms were available (Table 1). Using case counts from July 1, 2013, we calculated the overall attack rate (i.e., the rate for any fungal infection meeting the case definition) as 5.5 cases per 100 exposed persons (Table 2). The overall attack rate for nonperipheral-joint infections (meningitis, stroke due to presumed meningitis, and spinal or paraspinal infections) was 5.9 cases per 100 exposed persons, but the rate varied widely by state, ranging from 0 to 18 cases per 100 exposed persons (Table 2).

NECC shipped a total of 11,622 ml of the 05212012@68 lot of methylprednisolone acetate, 10,774 ml of the 06292012@26 lot, and 7092 ml of the 08102012@51 lot. On the basis of data from case-report forms received as of July 1, 2013, the lot-specific attack rates were estimated to be 6 cases per 1000 ml of methylprednisolone acetate used from lot 05212012@68, 40 cases per 1000 ml from lot 06292012@26, and 22 cases per 1000 ml from lot 08102012@51 (Table 3).

MICROBIOLOGIC INVESTIGATION

As of July 1, 2013, the CDC had received specimens from 519 case patients; for 173 of the case patients from whom specimens were obtained (33%), there was laboratory evidence supportive of a fungal infection: direct detection of fungal DNA in 87 fluid or tissue specimens (50%), a

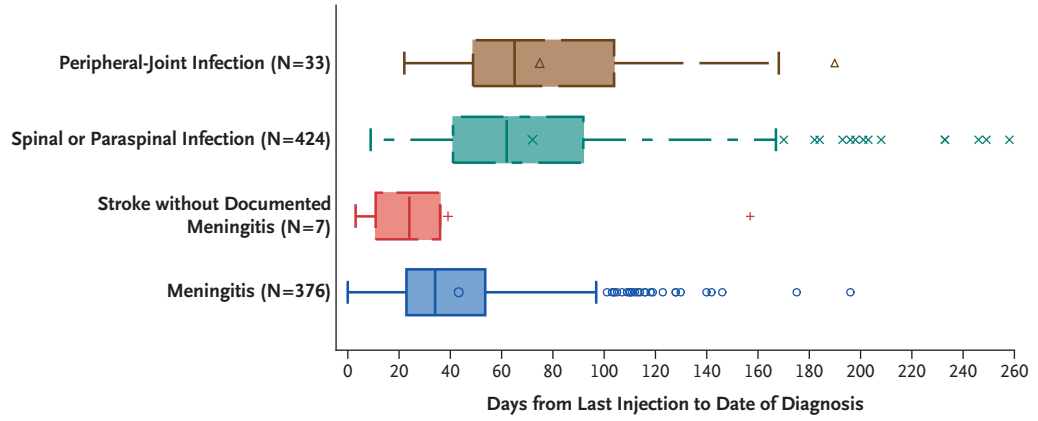

Figure 2. Box Plot of Incubation Periods for Cases of Fungal Infections Associated with Contaminated Lots of Methylprednisolone Acetate, According to Syndrome.

Included are data as of July 1, 2013. The box-plot graph shows the number of days from the last injection to the date of diagnosis, according to syndrome. The width of the box indicates the interquartile range, the vertical bar within the box indicates the median, the circle within the box indicates the mean, and the horizontal line with brackets indicates the range of observations, excluding the outliers, which are represented by additional circles beyond the range. Data were available for a total of 710 cases comprising 844 diagnoses. For patients meeting two case definitions, two incubation periods are included, one for each diagnosis.

fungal isolate with identification confirmed by DNA sequencing in 33 (19%), and evidence from the use of multiple techniques in 53 (31%). A total of 153 case patients had evidence of *E. rostratum*, and 1 case patient had histopathological evidence of invasive disease due to *Aspergillus fumigatus*. Evidence of other fungi of unknown clinical significance was present in 22 case patients, 6 of whom (27%) also had evidence of *E. rostratum* (further details are available in the Supplementary Appendix). For 9 case patients, laboratory evidence of fungal infection was available only from testing at outside laboratories: nonspecific fungal growth was reported for 1 patient, histopathological evidence was reported for 6, and direct DNA detection of fungus in fluid or tissue specimens was reported for 2.

DISCUSSION

We describe epidemiologic and laboratory data from a multistate outbreak of fungal infections associated with injection of contaminated methylprednisolone acetate from a single compounding pharmacy. These infections comprise the largest outbreak of health care–associated infections reported to date in the United States. This investigation was a collaboration among federal, state, and local public health officials, as well as staff at clinical facilities, all of whom worked rapidly to contact patients and to collect, aggregate, and disseminate clinical and laboratory data, which helped guide interim diagnostic and treatment decisions.

At the outset of this investigation, when patients had been identified only at a single ambulatory surgical center in Tennessee, our hypotheses about the source of the outbreak included both the possibility of contamination at the center and the chance that this could be part of a broader event involving product contamination at the point of production. Facility-specific contamination had resulted in a previous outbreak of aspergillus meningitis in Sri Lanka, which was traced back to contaminated spinal needles stored in damp closets.[11] Although fungal meningitis is extremely rare in immunocompetent hosts, sporadic cases have been reported after epidural injection, probably owing to breaks in aseptic technique during the procedure.[12] The subsequent report of a case in North Carolina suggested that this was not a facility-specific problem and that widespread contamination might have occurred. The FDA announcement on October 4, 2012, of visible fungal contamination in unopened vials of methylprednisolone acetate compounded at NECC confirmed the leading hypothesis that contaminated methyl-

Table 2. National Attack Rates for All Infections and National and State-Specific Attack Rates for Meningitis and Spinal or Paraspinal Infections, as of July 1, 2013.*

Description	No. of Cases	Persons Potentially Exposed†	No. of Cases/100 Persons Potentially Exposed (95% CI)
National attack rate, all infections	749	13,534	5.5 (5.1–5.9)
National attack rate, meningitis and spinal or paraspinal infections‡	716	12,068	5.9 (5.5–6.4)
State-specific attack rate, meningitis and spinal or paraspinal infections‡§			
Florida	25	1,034	2.4 (1.6–3.5)
Georgia	1	180	0.6 (0.03–2.7)
Idaho	1	47	2.1 (0.1–10.5)
Illinois	2	238	0.8 (0.1–2.8)
Indiana	91	1,362	6.7 (5.4–8.2)
Maryland	26	1,057	2.5 (1.6–3.5)
Michigan	239	1,727	13.8 (12.3–15.5)
Minnesota	12	843	1.4 (0.8–2.4)
New Hampshire	9	601	1.5 (0.7–2.8)
New Jersey	50	638	7.8 (5.9–10.1)
New York	1	405	0.2 (0.01–1.2)
North Carolina	18	100	18 (11.4–26.5)
Ohio	20	328	6.1 (3.9–9.1)
Pennsylvania	1	720	0.1 (0.01–0.7)
Rhode Island	3	266	1.1 (0.3–3.1)
South Carolina	3	231	1.3 (0.3–3.5)
Tennessee	151	1,010	14.9 (12.7–17.5)
Texas	2	58	3.5 (0.6–11.4)
Virginia	54	645	8.4 (6.4–10.7)
West Virginia	7	121	5.8 (2.6–11.1)

* The attack rate is the number of cases per 100 persons potentially exposed. CI denotes confidence interval.
† For the attack rate of all infections, this category includes all persons who received any type of glucocorticoid injection (peripheral-joint or nonperipheral-joint injection). For the attack rate of meningitis and spinal or paraspinal infections, this category includes persons who received an epidural or spinal or paraspinal injection.
‡ Included are persons who had meningitis, stroke due to presumed meningitis, and spinal or paraspinal infections.
§ Cases were attributed to the state in which the patient received the injection, not the state of residence. Persons potentially exposed to implicated methylprednisolone acetate were reported in California and Connecticut, but there were no cases in those states. Implicated methylprednisolone was shipped to Nevada, but no persons in that state were reported to have been exposed, and there were no cases.

prednisolone acetate from NECC was causing serious fungal illness in patients who had received an injection with this medication.

One critical component of the public health response was the rapid, active outreach targeting both patients and clinicians. Anecdotal data collected during the first week of the outbreak indicated that many of the initial patients had mild-to-moderate symptoms that ordinarily would not have prompted urgent medical evaluation.[16] There was added concern that many clinicians would be unable to make a diagnosis of meningitis caused by molds because of the low yield of traditional diagnostic methods, such as culturing.[27-29] Therefore, there was a considerable potential for missed diagnoses in exposed patients if direct intervention to alert patients and clinicians did not occur. In addition, given the fact that the initial nine patients had poor outcomes, including death and posterior circulation stroke, rapid

notification could allow for early diagnosis and treatment, which could reduce the risk of poor outcomes.

The extent of the contamination of the three lots of methylprednisolone acetate is not known. We identified at least two organisms in patients, *E. rostratum* and *A. fumigatus*, that caused infection. Additional fungi, most of which are common environmental molds but rarely cause human disease,[30-36] were identified in specimens from case patients, as well as in the product,[21] but are of unclear clinical significance. Some of these organisms, when injected into a sterile site, might have contributed to the disease by causing inflammatory reactions without true infection.

Despite the magnitude of potential exposure to contaminated methylprednisolone acetate — with more than 13,000 persons exposed — disease has developed in a relatively small proportion of exposed persons, to date. In addition, state-specific attack rates have varied widely, from 0 to 18 cases per 100 exposed persons; lot-specific attack rates have also varied considerably. Because all states achieved near-complete notification of exposed persons, the wide range of attack rates observed is unlikely to be due to large differences in case-finding methods. Rather, differences in the degree of contamination, the receipt dates and storage times of the lots, and injection practices might have contributed to the varying attack rates observed in different facilities and states. The longest incubation period in a 2002 outbreak of fungal meningitis after injection of contaminated glucocorticoids was 116 days,[14] reflecting the subacute nature of some fungal infections of the central nervous system. In this outbreak, we also observed lengthy incubation periods; in some case patients, the diagnosis was made more than 8 months after their last injection. As of July 2013, a few additional cases (1 to 2 per month) continue to be reported in this outbreak; continued vigilance for disease among exposed patients is still warranted.

The clinical course for case patients remains uncertain. Although many case patients have completed antifungal therapy and their conditions are currently stable or improved, relapses of infection are possible.[37] Continued vigilance for recrudescence of infection among known case patients, even after the resolution of symptoms and normalization of cerebrospinal fluid variables, is warranted. Further study of the most effective antifungal therapy and duration of treatment, as well as long-term outcomes in case patients, will be helpful for informing clinical guidance.

Table 3. Lot-Specific Attack Rate for All Infections, as of July 1, 2013.*

Lot Number	No. of Cases†	Total Amount of Methylprednisolone Acetate Used	No. of Cases/1000 ml of Methylprednisolone Acetate (95% CI)†
		ml	
Primary analysis			
05212012@68	74	11,622	6 (4.8–7.8)
06292012@26	429	10,665	40 (37–44)
08102012@51	95	4,304	22 (18–27)
Sensitivity analysis‡			
05212012@68	283	11,622	24 (21–27)
06292012@26	638	10,665	60 (55–65)
08102012@51	304	4,304	71 (63–79)

* The attack rate is the number of cases per 1000 ml of methylprednisolone acetate.
† Included are cases in persons exposed to the indicated lot; some persons had exposure to more than one lot.
‡ In the sensitivity analysis, all cases for which the lot exposure could not be determined were assigned to each lot, in order to assess the maximum possible attack rate for each lot.

There are several limitations of this investigation. First, we lacked lot-specific data on exposure for many patients, which prevented the exact calculation of lot-specific attack rates. This also made it impossible, in many facilities, to enumerate the exact number of patients exposed to the three lots of methylprednisolone acetate; the numbers presented here are estimates that took into account the time during which the implicated lots of methylprednisolone acetate were in use at clinics and the number of patients who underwent procedures during that time. Second, when estimating the rate of use, we assumed that the use of methylprednisolone acetate ceased within 4 days after the recall and that all methylprednisolone acetate used at each clinic came from NECC. These assumptions might not be true for each facility; some facilities might have stopped using methylprednisolone acetate earlier or later than 4 days after the recall or they might have used methylprednisolone acetate from other manufacturers at the same time that they were using methylprednisolone acetate from NECC. Third, some data, particularly data on symptom onset, are subject to recall bias. Finally, our investigation was also subject to the limitations of existing diagnostic assays to detect fungal infections.

Our findings have two important implica-

tions. First, it is imperative that steps are taken to ensure that compounded medications that are labeled as sterile are safe and uncontaminated. The consequences of contamination of a widely distributed, compounded medication used for injection can be devastating, as was shown in the current outbreak. Compounded medications were the source of several outbreaks before the outbreak described here,[14,17,18] and other contamination issues with compounding pharmacies have occurred since this outbreak.[38,39] Understanding how to prevent contamination of products is essential for public health and the public confidence in the health care delivery system. Second, the large-scale public health efforts undertaken in this investigation required a strong public health infrastructure and collaboration among clinicians and public health officials at the state, local, and federal levels. These efforts played a critical role not only in alerting the public to an evolving health threat, but also in collecting, aggregating, and disseminating information in real time, with the information used both to understand the scope and source of the outbreak and to drive efforts to reduce further morbidity and mortality.

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.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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