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Epidemiological Effectiveness and Cost of a Fungal Meningitis Outbreak Response in New River Valley, Virginia: Local Health Department and Clinical Perspectives

Dr. Nargesalsadat Dorratojtaj, PhD, Dr. Margaret L. O'Dell, MD, Ms. Paige Bordwine, MPH, Dr. Thomas M. Kerkering, MD, Dr. Kerry J. Redican, PhD, and Dr. Kaja M. Abbas, PhD

Department of Population Health Sciences, Virginia Tech, Blacksburg, Virginia (Drs Dorratojtaj, Redican, Abbas); New River Health District, Virginia Department of Health, Christiansburg, Virginia (Dr O'Dell, Ms Bordwine); Division of Infectious Diseases, Virginia Tech Carilion School of Medicine, Roanoke, Virginia (Dr Kerkering)

Abstract

Objective—We evaluated the effectiveness and cost of a fungal meningitis outbreak response in the New River Valley of Virginia during 2012–2013 from the perspective of the local public health department and clinical facilities. The fungal meningitis outbreak affected 23 states in the United States with 751 cases and 64 deaths in 20 states; there were 56 cases and 5 deaths in Virginia.

Methods—We conducted a partial economic evaluation of the fungal meningitis outbreak response in New River Valley. We collected costs associated with the local health department and clinical facilities in the outbreak response and estimated the epidemiological effectiveness by using disability-adjusted life years (DALYs) averted.

Results—We estimated the epidemiological effectiveness of this outbreak response to be 153 DALYs averted among the patients, and the costs incurred by the local health department and clinical facilities to be \$30,413 and \$39,580, respectively.

Conclusions—We estimated the incremental cost-effectiveness ratio of \$198 per DALY averted and \$258 per DALY averted from the local health department and clinical perspectives, respectively, thereby assisting in impact evaluation of the outbreak response by the local health department and clinical facilities.

Keywords

cost-effectiveness analysis; fungal meningitis outbreak; local health department; clinical; New River Valley; Virginia

Correspondence and reprint requests to Kaja M. Abbas, Department of Population Health Sciences, Virginia Tech, Blacksburg, VA 24061 (kaja.abbas@vt.edu).

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Fungal meningitis occurs in individuals infected by the predominant pathogen *Exserohilum rostratum*, which spreads in the spinal cord through the bloodstream and leads to swelling of the protective membrane of the spinal cord or brain. Fungal meningitis is not contagious and is not transmitted directly between people. The pathogen can be found in soil, water, food, air, and vegetation. People exposed to this fungal pathogen generally experience no adverse effects. However, immunocompromised people are at higher risk for developing fungal infection and symptomatic effects. Symptoms include meningitis, encephalitis, and stroke. During the multistate fungal meningitis outbreak in the United States during 2012–2013, exposed patients with mild symptoms of fever, headache, back pain, or other relevant symptoms were also tested.¹

Multistate Fungal Meningitis Outbreak

In September 2012, the Tennessee Department of Health confirmed cases of *Aspergillus fumigatus* meningitis following epidural steroid injection. After Tennessee, 19 other states reported cases caused by the predominant pathogen *Exserohilum rostratum*.² The cause of the multistate fungal meningitis outbreak was traced to fungal-contaminated lots of preservative-free methylprednisolone acetate that were used in the epidural steroid injections and were produced in a compounding pharmacy, the New England Compounding Center in Framingham, Massachusetts.³ More than 13,000 patients had received the fungal-contaminated epidural steroid injections in 23 states and were at risk of developing fungal meningitis. The outbreak was the largest outbreak associated with steroid injections.⁴ There were 751 cases and 64 deaths in 20 states as of October 23, 2013; additional cases are not anticipated.⁵

Fungal Meningitis Case Definition

The Centers for Disease Control and Prevention (CDC) defined a probable fungal meningitis case as a patient who had received the fungal-contaminated epidural injections after May 21, 2012, with symptoms of meningitis, stroke, spinal infections, osteomyelitis, or arthritis of peripheral joints. Probable cases with evidence of the fungal pathogen in culture, histopathology, or molecular assay were also defined as confirmed cases.

Fungal Meningitis Outbreak in Virginia

Virginia reported the fourth highest number of cases with 56 cases and 5 deaths. Two clinical facilities in Virginia had administered these fungal-contaminated injections, with one facility located in New River Valley and the other facility located in neighboring Roanoke. New River Health District personnel conducted disease surveillance, case reporting, and referral of probable cases to clinical facilities for diagnostics, treatment, or hospitalization.

Clinical Response

The CDC released treatment guidelines, and voriconazole therapy was the recommended treatment.⁵ Confirmed cases in Virginia were prescribed similar treatment, and voriconazole therapy improved prognosis among the treated patients.⁶

Multi-sectoral Public Health Response

The multistate fungal meningitis outbreak was controlled through a multi-sectoral public health response, as illustrated in Figure 1. The outbreak response required effective coordination between patients and immediate caregivers; treatment administered through hospitals, clinics, and pharmacies; and a systematic effort between the public health agencies at the local, state, and federal levels. The outbreak was widely publicized after October 4, 2013, and the multisectoral public health response by CDC and its partners averted 3150 methylprednisolone acetate injections, 153 cases of meningitis or stroke, and 124 deaths, in comparison to the 60-day case-fatality rates and clinical characteristics of fungal meningitis patients diagnosed before October 4, 2013.⁷

New River Health District

New River Health District is one of 35 local health districts of the Virginia Department of Health in Virginia and includes the counties of Floyd, Giles, Montgomery, Pulaski, and the city of Radford.⁸ It is among 11 health districts in Virginia with residents who were injected with fungal-contaminated epidural steroids. In this study, “local health department” refers to New River Health District.

Study Objective

The objective of this study was to evaluate the effectiveness and cost of the fungal meningitis outbreak response in the New River Valley of Virginia from the perspectives of the local public health department and clinical facilities.

Related Studies

In a related study, we conducted an economic evaluation of the fungal meningitis outbreak response in New River Valley from the local public health department perspective.⁹ In this article, we extend the prior study to include the cost estimates from the clinical response to evaluate the effectiveness and cost of the fungal meningitis outbreak response in New River Valley from both the clinical and local public health department perspectives. We also conducted a systematic review of the clinical response, outbreak investigation, and epidemiology of the fungal meningitis outbreak in the United States.¹⁰ The multi-sectoral public health response to the fungal meningitis epidemic from the hospitals, clinics, pharmacies, and the public health system at the local, state, and federal levels led to an efficient epidemiological investigation to trace the outbreak source and rapid implementation of multiple response plans. The systematic review reaffirmed the effective execution of a multi-sectoral public health response and efficient delivery of the core functions of public health assessment, policy development, and service assurances to improve population health.

Public Health Significance

The multistate fungal meningitis outbreak affected Virginia with 56 cases and 5 deaths. Impact evaluation of the outbreak response in New River Valley can assist the local health department and clinical facilities in optimization and prioritization of limited resources.

METHODS

Surveillance and Outbreak Investigation by New River Health District

The timeline of the fungal meningitis outbreak response by the New River Health District and clinical facilities in New River Valley was from October 2012 to March 2013. A total of 91 patients were exposed to the fungal-contaminated epidural steroids and were followed up for further assistance. The local health department implemented the surveillance system for follow-up with the affected patients on the basis of guidelines from the CDC. Figure 2 shows the surveillance and outbreak response process implemented by the New River Health District. When the multistate outbreak was confirmed by the CDC, personnel from New River Health District visited the clinical facilities in New River Valley and Roanoke where the exposed patients received the fungal-contaminated epidural steroid injections and collected their information. The local health department personnel were in continuous contact with the state health department and the CDC to get the updated information regarding the probable symptoms and updated case definition. The health district epidemiologist and volunteers then contacted patients and screened them for specific clinical symptoms. Patients with symptoms specific to fungal meningitis were referred to their local clinical facility for further lab tests. The epidemiologist contacted the patients' physicians or local emergency department to provide information about probable patients who may get admitted with confirmed symptoms. The epidemiologist also provided up-to-date information and recommendations for managing symptomatic patients in the clinical facilities. If the results of the lab test met the case definition, the patient was referred to the local hospital for further medical care. If the patient did not have any further symptoms, the local health department personnel continued to follow up with the patient for 6 months after the last dose of the contaminated injection.

Cost and Effectiveness of the Fungal Meningitis Outbreak Response

Cost and effectiveness of the fungal meningitis outbreak response by the New River Health District and clinical facilities were compared to the do-nothing alternative (scenario of no intervention). We assessed effectiveness by the combined epidemiological impact of morbidity and mortality by using the metric of disability-adjusted life years (DALYs) averted.¹¹

Do-Nothing Alternative

Fungal meningitis is a rare disease, and the last recorded outbreak prior to the 2012–2013 outbreak was in 2002 with 5 cases.¹² Health departments currently do not include fungal meningitis in their list of diseases or health conditions as part of the reportable disease or sentinel surveillance process and case-reporting activities. Therefore, we evaluated the fungal meningitis outbreak response in comparison to the do-nothing alternative in this economic evaluation.

Costs

We estimated the direct cost incurred by the New River Health District for the fungal meningitis outbreak response on the basis of the total hours spent by the local health department personnel involved in the outbreak response and corresponding hourly wages.

The outbreak response team in the local health department includes the epidemiologist, health district director, planner, environmental health manager, clerical staff, administrative staff, nurse epidemiologist, and volunteers. Data were provided by the New River Health District. Direct cost incurred by the clinical facilities was estimated on the basis of the total cost of clinical care for the patients exposed to fungal-contaminated epidural steroid injections.

Epidemiological Effectiveness

Effectiveness measures the epidemiological impact of the fungal meningitis outbreak response, using the metric of DALYs.¹¹ DALYs measures the burden of (disease) fungal meningitis as a combined metric of the epidemiological impacts of morbidity and mortality. Morbidity impact was measured by years of life lost due to disability (YLD), and mortality impact was measured by years of life lost due to premature mortality (YLL). Disability weight was used to quantify the disease severity on a scale of 0 (equivalent of perfect health) to 1 (equivalent of death).¹³ DALYs are the primary health metric used to measure the disease burden in the Global Burden of Diseases, Injuries and Risk Factors Study,^{14–17} which includes data and analytics on premature death and disability from more than 300 diseases and injuries in 188 countries, by age and sex, from 1990 to 2015, allowing comparisons over time, across age groups, and among populations.

The equations for YLD, YLL, and DALY are below:

$$YLD = \text{Number of incident cases} * \text{Disability weight} * \text{Average duration of disease} \quad (\text{Eq 1})$$

$$YLL = \text{Number of incident cases} * \text{Case fatality rate} * (\text{Life expectancy} - \text{Age of death}) \quad (\text{Eq 2})$$

$$DALY = YLD + YLL \quad (\text{Eq 3})$$

Cost-Effectiveness

Cost-effectiveness was measured by using the incremental cost-effectiveness ratio (ICER). The ICER is computed as the ratio of the difference in costs and the difference in effectiveness (burden of disease) of the fungal meningitis outbreak response by the local health department and clinical facilities compared to the do-nothing alternative. The equations for ICER are below:

$$ICER = \frac{\text{Cost (outbreak response)} - \text{Cost (do-nothing alternative)}}{\text{Effectiveness (outbreak response)} - \text{Effectiveness (do-nothing alternative)}} \quad (\text{Eq 4})$$

$$ICER = \frac{Cost (outbreak response) - Cost (do-nothing alternative)}{Burden of disease (do-nothing alternative) - Burden of disease (outbreak response)}$$

(Eq 5)

Ethics Approval

Ethics approval for this study was received from the institutional review boards of Virginia Tech and the Virginia Department of Health.

RESULTS

Time Horizon

We conducted the economic evaluation of the fungal meningitis outbreak response in New River Valley by using the time horizon of October 2012 to March 2013.

Discount Rate

No discount rate was used because the time horizon of the study was less than a year.

Decision Tree

Figure 3 illustrates the decision tree to compare the fungal meningitis outbreak response of the local health department and clinical/hospital facilities with the do-nothing alternative. In the outbreak response branch, positively diagnosed patients may receive treatment while negatively diagnosed patients do not receive treatment with corresponding costs and health benefits. Positively diagnosed patients may recover with treatment or die from fungal meningitis. The recovery rate of positively diagnosed patients with treatment was 90.32%.⁵ On the do-nothing branch, the positively diagnosed patients have a case fatality rate of 100%. There are no available or recorded estimates of case fatality rate among untreated fungal meningitis patients. The 100% case fatality rate among untreated fungal meningitis patients is based on the input of TMK (infectious disease physician who led the clinical response to the fungal meningitis outbreak in New River Valley) that fungal meningitis, if left untreated, leads to a fatal outcome.

Cost: Local Health Department

Table 1 includes the distribution of costs among the local health department personnel of the New River Health District who were involved in the fungal meningitis outbreak response. The hours spent by the personnel in the outbreak response and the corresponding hourly wages were provided by the New River Health District. We estimated that \$30,413.20 was spent by the local health department in response to the fungal meningitis outbreak in New River Valley.

Cost: Clinical

Table 2 includes the distribution of costs of clinical care for patients who received fungal-contaminated epidural steroid injections in New River Valley. Among the 91 exposed patients, 12 lumbar punctures and 14 cerebrospinal fluid cultures were done, and 9 patients were admitted to clinical facilities in Montgomery, Salem, and Pulaski counties or Roanoke city. The average length of stay in these clinical facilities was 2.5 days with a range of between 0 and 11 days for hospitalized patients. These data were obtained from the hospital records and patients' files. We estimated the cost associated with lumbar puncture of outpatients from the study by Tung et al,¹⁸ the cost of cerebrospinal fluid cultures of outpatients from the study by Barenfanger et al,¹⁹ and the cost of hospitalization of inpatients from the hospital records data. We estimated that \$39,579.84 was spent by the clinical facilities in response to the fungal meningitis outbreak in New River Valley.

Cost: Local Health Department and Clinical

The local health department incurred a cost of \$30,413.20 and the clinical facilities incurred a cost of \$39,579.84 for a combined cost of \$69,993.04 in the fungal meningitis out-break response in New River Valley from October 2012 to March 2013.

Disability Weight

Disability weight specific to fungal meningitis is not available, because it is a novel and rare disease. Bacterial meningitis and fungal meningitis have similar symptoms.²⁰ Thereby, we used the disability weight of 0.615 for bacterial meningitis^{13,21} as the disability weight for fungal meningitis.

Years of Life Lost Due to Disability

None of the 91 patients in the New River Health District met the case definition of fungal meningitis as defined by CDC. Using the average attack rate of 8.6% for fungal meningitis in Virginia among the patients who had received the contaminated epidural steroid injections, it was estimated that there would be 7.785 potential cases in New River Valley, as illustrated in Table 3. The average duration of treatment is 4 months for recovered patients, whereas the average duration of treatment among the fatal patients was near null. Using Eq 1, 90.32% of patients who survived the fungal meningitis due to intervention were getting treatment for 4 months on average. Patients who recovered from successful treatment lost 1.427 DALYs to account for the morbidity impact caused by fungal meningitis during the treatment duration. Thereby, we estimated the YLD to be -1.427 DALYs averted due to the fungal meningitis outbreak response compared to the do-nothing alternative.

Years of Life Lost Due to Premature Mortality

The case fatality rate of fungal meningitis patients was 9.678% with treatment, whereas it is 100% without treatment. The average life expectancy in Virginia is 79 years,²³ whereas the average age of patients in Virginia who were injected with fungal-contaminated epidural steroids was 57 years. Using Eq 2, we estimated the YLL to be 154.69 DALYs averted due to the fungal meningitis outbreak response compared to the do-nothing alternative.

Epidemiological Effectiveness (DALY = YLD + YLL)

Using Eq 3, we estimated the total DALYs to be 153.26 DALYs averted due to the fungal meningitis outbreak response compared to the do-nothing alternative. The computations of YLDs, YLLs, and DALYs are illustrated in Table 4.

Cost-Effectiveness

Using Eq 4, the ICERs from the local health department perspective, clinical facilities perspective, and total (including both local health department and clinical facilities perspectives) were computed to be \$198.43, \$258.24, and \$456.67, respectively, per DALY averted due to the fungal meningitis outbreak response compared to the do-nothing alternative.

Uncertainty and Sensitivity Analysis

We conducted sensitivity analysis for the duration of treatment, attack rate, and disability weight.

Duration of Treatment—We estimated that treatment duration had an average of 4 months with a range of (1.5 months, 18 months). The corresponding impact on the ICER was (\$197.29, \$205.21) per DALY averted from the local health department perspective, (\$256.76, \$267.06) per DALY averted from the clinical perspective, and (\$454.05, \$472.26) per DALY averted from the local health department and clinical perspectives.

Attack Rate—We estimated the attack rate to be 8.6% (range: 1%, 17%) depending on the epidural injection lot. We tested 6 potential scenarios if all the epidural injections administered to the patients in New River Valley had come from the 6 different lot numbers, as shown in Table 3. The corresponding impact on the ICER was (\$1697.58, \$99.86) per DALY averted from the local health department perspective, (\$2209.23, \$129.96) per DALY averted from the clinical perspective, and (\$3906.81, \$229.81) per DALY averted from the local health department and clinical perspectives.

Disability Weight—We estimated the disability weight for fungal meningitis to be 0.615 with a 95% confidence interval of (0.613, 0.616). The corresponding impact on the ICER was (\$198.43, \$198.44) per DALY averted from the local health department perspective, (\$258.23, \$258.24) per DALY averted from the clinical perspective, and (\$456.66, \$456.68) per DALY averted from the local health department and clinical perspectives.

DISCUSSION

Local health departments conducted disease surveillance, case reporting, and referral of probable cases to clinical facilities for diagnostics, treatment, and/or hospitalization during the 2012–2013 multistate fungal meningitis outbreak in the United States. We estimated the total direct costs incurred by New River Health District and clinical facilities for the fungal meningitis outbreak response to be \$69,993.04. We estimated a morbidity impact of –1.427 DALYs for YLD averted and a mortality impact of 154.69 DALYs for YLL averted, for a combined morbidity and mortality impact (burden of fungal meningitis) of 153.26 DALYs

averted for epidemiological effectiveness of the fungal meningitis outbreak response compared to the do-nothing alternative. We estimated the ICER of the fungal meningitis outbreak response in New River Valley to be \$198.43, \$258.24, and \$456.67 per DALY averted from the local health department, clinical, and combined local health department and clinical perspectives, respectively, compared to the do-nothing alternative.

Partial Economic Evaluation

Although the fungal meningitis outbreak response required a coordinated effort by the CDC, the Food and Drug Administration (FDA), and state and local health departments and included the clinical response of diagnosis and treatment, this analysis was only from the local health department and clinical perspectives. While epidemiological effectiveness among patients in New River Valley was a combined result of the coordinated effort of the health departments (local, state, and federal) and the clinical facilities (laboratories and hospitals), the cost calculations included only the costs incurred by the local health department and hospitals or clinics. Owing to this asymmetry in the boundaries of calculation of effectiveness and costs, this study was a partial economic evaluation of the fungal meningitis outbreak response in New River Valley.

Limitations

New River Health District and the Virginia Department of Health currently do not use a threshold to judge whether an intervention or public health program is cost-effective, and correspondingly we do not infer whether the fungal meningitis outbreak response was cost-effective. The cost calculations did not include indirect costs incurred by New River Health District or clinical facilities. Scientific studies and clinical knowledge on fungal meningitis are lacking, because it is a relatively rare disease. Thereby, the disability weight of fungal meningitis was estimated by using the disability weight of bacterial meningitis, because both diseases have common symptoms. There were variations in the cost calculations among the different clinical facilities in New River Valley. While the fungal meningitis outbreak response required a coordinated effort by the CDC, the FDA, and state and local health departments,^{24,25} the focus of this economic evaluation was only from the local health department and clinical perspectives.

CONCLUSIONS

Economic evaluation of the fungal meningitis outbreak response in New River Valley assists the local health department and clinical facilities to analyze the costs and epidemiological effectiveness of the outbreak response compared to the do-nothing alternative. We estimated the epidemiological effectiveness to be 153.26 DALYs averted, and the ICER to be \$456.67 per DALY averted from the local health department and clinical perspective. The DALY metric provides a uniform metric to estimate and compare the burden of different diseases, and the ICER (\$/DALY averted) provides a uniform metric to evaluate and compare the impact of different disease control and prevention programs, thereby assisting in the prioritization of public health programs.

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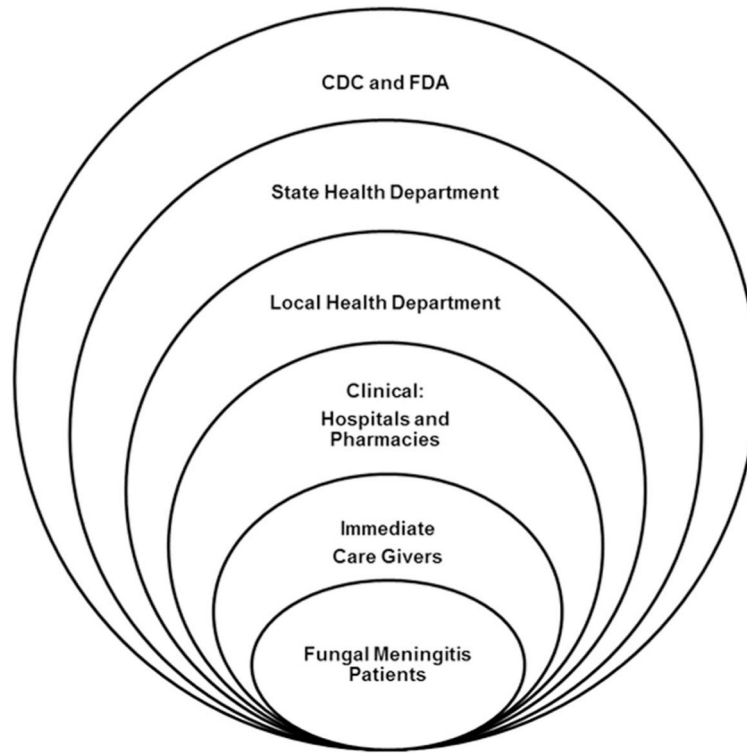


FIGURE 1. Multi-sectoral Response to the Fungal Meningitis Outbreak

The multistate fungal meningitis outbreak was controlled through effective coordination between patients and immediate caregivers; treatment administered through hospitals, clinics and pharmacies; and a systematic effort between the public health agencies at the local, state, and federal levels. Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration.

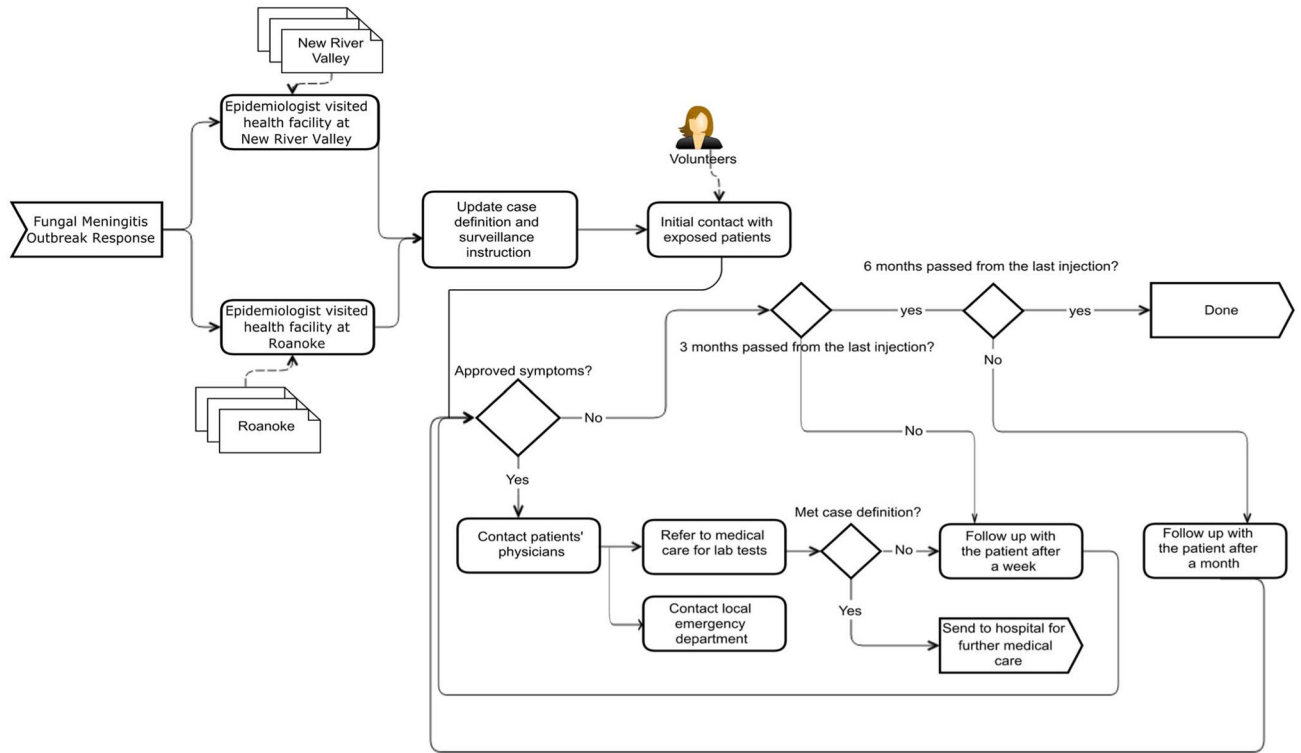


FIGURE 2. Fungal Meningitis Outbreak Response in New River Valley, Virginia
 New River Valley patients who were administered fungal-contaminated epidural injections in the 2 clinical facilities of New River Valley and Roanoke were contacted by personnel of New River Health District. Exposed patients were followed up weekly for 3 months and monthly for another 3 months. Symptomatic patients were referred to lab tests, and positively diagnosed patients were referred to hospitals for treatment.

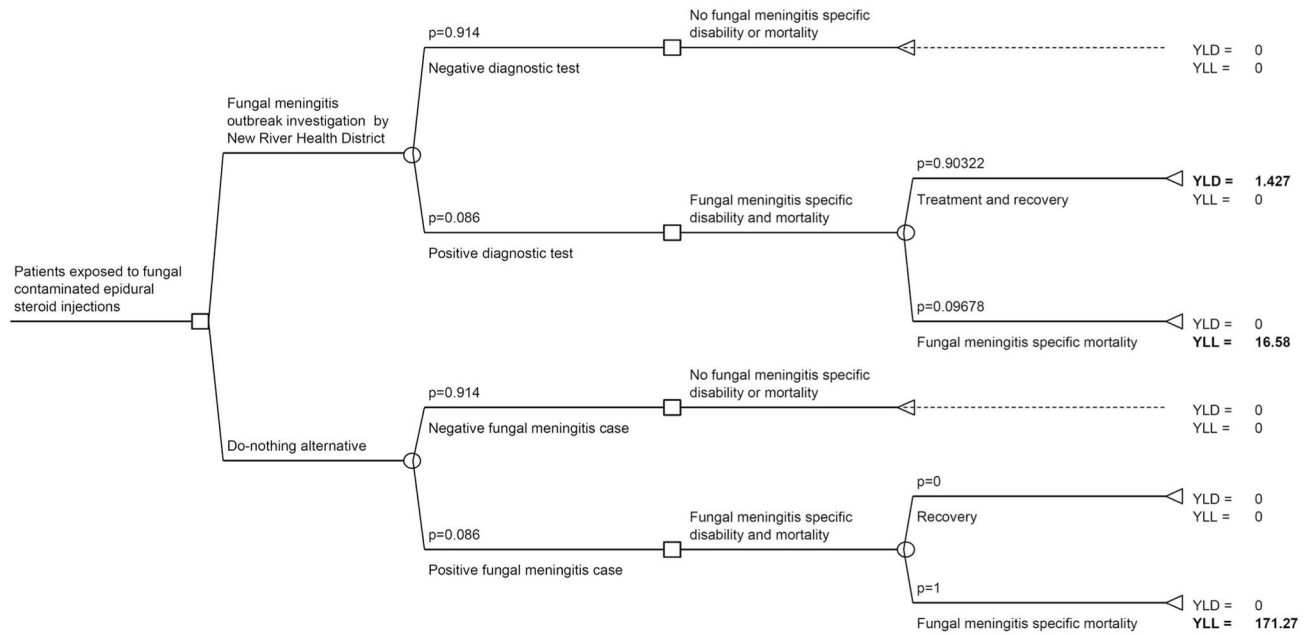


FIGURE 3. Decision Tree Comparing the Fungal Meningitis Outbreak Investigation in New River Health District With the Do-Nothing Alternative

Positively diagnosed patients from the outbreak investigation had a 90% survival rate with treatment compared to a 100% mortality rate with the do-nothing alternative. The disability-adjusted life years (DALY) or lost years of healthy life associated with the outbreak investigation was 18 DALYs compared to 171 DALYs associated with the do-nothing alternative. Thereby, 153 DALYs were averted as a result of the fungal meningitis outbreak response in New River Valley, compared to the do-nothing alternative. Abbreviations: YLD, years of life lost due to disability; YLL, years of life lost due to premature mortality.

TABLE 1

Local Health Department Costs: Costs Expended by the New River Health District to Control the Fungal Meningitis Outbreak in New River Valley

New River Health District Personnel	Total No. of Hours	Hourly Wage	Cost
Epidemiologists	386	\$43.39	\$16,748.54
Health District Director	70.5	\$95.70	\$6,746.85
Planner	32	\$48.71	\$1,558.72
Environmental Health Manager	12	\$42.58	\$510.96
Clerical	12	\$31.07	\$372.84
Administration	8	\$20.04	\$160.32
Nurse Epidemiologist	16	\$35.97	\$575.52
Volunteers	143	\$26.15	\$3,739.45
Total cost			\$30,413.20

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TABLE 2

Clinical Costs: Cost of Clinical Care in Local Clinical Facilities to Control the Fungal Meningitis Outbreak in New River Valley

Type of Cost	No. of Patients	Average Unit Cost	Cost
Hospital admission	9	\$3,908.11	\$35,173.00
Lumbar puncture	12	\$285.57	\$3,426.84
Cerebrospinal fluid culture	14	\$70.00	\$980.00
Total cost			\$39,579.84

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TABLE 3Potential Cases of Fungal Meningitis in New River Valley^a

Lot #	Patients in New River Valley Receiving Injection Lot	Virginia Attack Rate, ^b %	Potential Cases in New River Valley
06292012 only	45	14.44	6.498
06292012 with other lot	7	14.61	1.023
05212012 only	24	1.1	0.264
08102012 only	3	0	0
05212012 + 08102012	0	17	0
05212012 with other lot	12	0	0
Total	91		7.785

^aFungal meningitis attack rate for different injected lots. Potential attack rate of fungal meningitis in the New River Valley was extracted from lot numbers and Virginia attack rate.

^bSource: Virginia Department of Health.²²

TABLE 4

Epidemiological Effectiveness of the Fungal Meningitis Outbreak Response^a

Parameter	Estimation
Number of potential cases (proxy for incident cases)	7.785
Disability weight	0.615 (95% CI: 0.613, 0.616)
Average duration of treatment of recovered patients (proxy for average duration of disease)	0.33 years (mean: 4 months; range: 1.5–18 months)
Average duration of treatment of fatal patients	~0 years (range: 1–8 days; 1 outlier case: 44 days)
YLD (outbreak response)	1.427 DALYs
YLD (no response)	0 DALYs
YLD (averted)	YLD (no response) – YLD (outbreak response) = 0 – 1.427 = -1.427 DALYs averted (=1.427 DALYs)
Case fatality rate	
Outbreak response	9.678%
No outbreak response	100%
Average life expectancy in Virginia	79 years
Average age of patients (proxy for average age of death)	57 years
YLL (outbreak response)	16.58 DALYs
YLL (no response)	171.27 DALYs
YLL (averted)	YLL (no response) – YLL (outbreak response) = 171.27 – 16.58 = 154.69 DALYs averted
DALYs (averted)	YLD (averted) + YLL (averted) = -1.427 + 154.69 = 153.26 DALYs averted

^a Abbreviations: DALY, disability-adjusted life year (1 DALY equals 1 lost year of healthy life; DALY = YLD + YLL); YLD, years lost due to disability (YLD = number of incident cases × disability Weight × average duration of disease); YLL, years of life lost due to premature death [YLL = number of incident cases × case fatality rate × (life expectancy - age of death)].

Effectiveness of the fungal meningitis outbreak response in New River Valley was measured by DALYs averted. DALYs is a combined measure of morbidity (YLD) and mortality (YLL).